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Novel Therapies Issue

The International Myeloma Foundation *(IMF) presents this edition of Citings, our premiere publication featuring the most up-to-date information on myeloma treatment, focused on the novel therapies currently under study and in use. This edition corresponds with articles published between May and September 2010.*

It is our hope that CITINGS will be a valuable tool in keeping you informed on the latest developments in myeloma treatment. Please feel free to contact us at (800) 452-CURE (2873) or visit us on the web at www.myeloma.org.

– Susie Novis, President, IMF

Novel Therapies Publications

September 2010

Pathological adaptive responses of Schwann cells to endoplasmic reticulum stress in bortezomib-induced peripheral neuropathy.

Shin YK, Jang SY, Lee HK, Jung J, Suh DJ, Seo SY, Park HT.

Glia. 2010 Sep 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20830808

The authors' observations suggest that the pathological adaptive responses of Schwann cells to bortezomib-induced endoplasmic reticulum stress may, in part, participate in the development of bortezomib-induced peripheral neuropathy.

Bortezomib, a proteasome inhibitor, has been considered as a promising anticancer drug in the treatment of recurrent multiple myeloma and some solid tumors. The bortezomib-induced peripheral neuropathy (BIPN) is a prominent cause of dose-limiting toxicities after bortezomib treatment. In this study, we found that BIPN in a mouse model is characterized by acute but transient endoplasmic reticulum (ER) damages to Schwann cells. These damaged Schwann cells exhibit abnormal outcomes from healing processes such as the myelination of Remak bundles. A morphometric analysis of polymyelinated Remak bundles revealed that the pathological myelination was not related to the axonal parameters that regulate the normal myelination process during development. In addition, demyelinating macrophages were focally infiltrated within endoneurium of the sciatic nerve. To identify the mechanism underlying these pathologies, we applied a gene microarray analysis to bortezomib-treated primary Schwann cells and verified the changes of several gene expressions in bortezomib-treated sciatic nerves. The analysis showed that bortezomib-induced ER stress was accompanied by the activation of several protective molecular chaperones and the down-regulation of myelin gene expression. ER stress inducers such as thapsigargin and bredelfin A also suppressed the mRNA expression of myelin gene P0 at transcriptional levels. In addition, the expression of chemokines such as the macrophage chemoattractants Ccl3 and Cxcl2 was significantly increased in Schwann cells in response to bortezomib and ER stress inducers. Taken together, these observations suggest that the pathological adaptive responses of Schwann cells to bortezomib-induced ER stress may, in part, participate in the development of BIPN.

Funded by unrestricted educational grants from Celgene Corporation and Onyx Pharmaceuticals.

Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM).

Lacy MQ, Hayman SR, Gertz MA, Short KD, Dispenzieri A, Kumar S, Greipp PR, Lust JA, Russell SJ, Dingli D, Zeldenrust S, Fonseca R, Bergsagel PL, Roy V, Mikhael JR, Stewart AK, Laumann K, Allred JB, Mandrekar SJ, Rajkumar SV, Buadi F.

Leukemia. 2010 Sep 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20827286

The authors find that the combination of pomalidomide and dexamethasone is highly active and well tolerated in patients with lenalidomide-refractory myeloma.

Patients with multiple myeloma progressing on current therapies have limited treatment options. Pomalidomide (CC4047), an immunomodulatory drug, has significant activity in relapsed myeloma and previous studies suggest activity in lenalidomide refractory disease. To better define its efficacy in this group, we treated a cohort of lenalidomide refractory patients. Pomalidomide was given orally (2 mg) daily, continuously in 28-day cycles along with dexamethasone (40 mg) given weekly. Responses were assessed by the International Myeloma Working Group Criteria. Thirty-four patients were enrolled. The best response was very good partial response in 3 (9%), partial response (PR) in 8 (23%), best responses (MR) in 5 (15%), stable disease in 12 (35%) and progressive disease in 6 (18%), for an overall response rate of 47%. Of the 14 patients that were considered high risk, 8 (57%) had responses including 4 PR and 4 MR. The median time to response was 2 months and response duration was 9.1 months, respectively. The median overall survival was 13.9 months. Toxicity was primarily hematologic, with grade 3 or 4 toxicity seen in 18 patients (53%) consisting of anemia (12%), thrombocytopenia (9%) and neutropenia (26%). The combination of pomalidomide and dexamethasone (Pom/dex) is highly active and well tolerated in patients with lenalidomide-refractory myeloma.

A phase I study of bortezomib in combination with doxorubicin and intermediate-dose dexamethasone (iPAD therapy) for relapsed or refractory multiple myeloma.

Takamatsu Y, Sunami K, Hata H, Nagafuji K, Choi I, Higuchi M, Uozumi K, Masaki Y, Tamura K; The Kyushu Hematology Organization for Treatment Study Group (K-HOT).

Int J Hematol. 2010 Sep 8. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20824401

The authors conduct a dose finding study of bortezomib in combination with a fixed dose of doxorubicin and intermediate-dose dexamethasone (iPAD therapy) in patients with relapsed or refractory myeloma and conclude that bortezomib at the dose of 1.0 mg/m² is recommended.

Bortezomib and doxorubicin have synergistic activity against myeloma cells *in vitro*. We underwent a dose finding study of bortezomib in combination with a fixed dose of doxorubicin and intermediate-dose dexamethasone (iPAD therapy) in patients with relapsed or refractory myeloma. Bortezomib was administered on days 1, 4, 8 and 11 at a dose of 1.0 and 1.3 mg/m² in cohorts 1 and 2, respectively. Doxorubicin 9 mg/m² was given by rapid intravenous infusion on days 1-4, and dexamethasone 20 mg on days 1-2, 4-5, 8-9 and 11-12. Treatment was repeated at a 3-week interval and the dose-limiting toxicity (DLT), defined as grade 4 hematological toxicity lasting more than 5 days and/or grade 3 or higher non-hematological toxicity, was evaluated. In cohort 1, 2 of 6 patients developed DLTs including grade 4 hyponatremia and grade 3 infection with appropriate neutrophil counts. No DLT was observed in the remaining 4 patients, indicating that this dose was tolerable. In cohort 2, 3 of 5 patients developed DLTs including grade 4 thrombocytopenia lasting more than 5 days, grade 3 hepatic transaminase elevation and grade 3 ileus, indicating that this dose was intolerable. It is concluded that bortezomib at the dose of 1.0 mg/ m² is recommended in combination with doxorubicin and intermediate-dose dexamethasone.

Bortezomib Plus Dexamethasone Is Superior to Vincristine Plus Doxorubicin Plus Dexamethasone As Induction Treatment Prior to Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: Results of the IFM 2005-01 Phase III Trial.

Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, Lenain P, Hulin C, Facon T, Casassus P, Michallet M, Maisonneuve H, Benboubker L, Maloisel F, Petillon MO, Webb I, Mathiot C, Moreau P.

J Clin Oncol. 2010 Sep 7. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20823406

The authors compare efficacy and safety of bortezomib plus dexamethasone versus vincristine plus doxorubicin plus dexamethasone (VAD) as induction before stem-cell transplantation in previously untreated myeloma. They find that bortezomib plus dexamethasone significantly improves post induction and post-transplantation complete response (CR)/nearCR and at least very good partial response rates compared with VAD, and results in a trend for longer progression free survival. They conclude that bortezomib plus dexamethasone should therefore be considered a standard of care in this setting.

PURPOSE: To compare efficacy and safety of bortezomib plus dexamethasone and vincristine plus doxorubicin plus dexamethasone (VAD) as induction before stem-cell transplantation in previously untreated myeloma. PATIENTS AND METHODS: Four hundred eighty-two patients were randomly assigned to VAD (n = 121), VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation (n = 121), bortezomib plus dexamethasone (n = 121), or bortezomib plus dexamethasone plus DCEP (n = 119), followed by autologous stem-cell transplantation. Patients not achieving very good partial response (VGPR) required a second transplantation. The primary end point was post-induction complete response/near complete response (CR/nCR) rate. Results Post induction CR/nCR (14.8% v 6.4%), at least VGPR (37.7% v 15.1%), and overall response (78.5% v 62.8%) rates were significantly higher with bortezomib plus dexamethasone versus VAD; CR/nCR and at least VGPR rates were higher regardless of disease stage or adverse cytogenetic abnormalities. Response rates were similar in patients who did and did not receive DCEP. Post first transplantation, CR/nCR (35.0% v 18.4%) and at least VGPR (54.3% v 37.2%) rates remained significantly higher with bortezomib plus dexamethasone. Median progression-free survival (PFS) was 36.0 months versus 29.7 months (p = .064) with bortezomib plus dexamethasone versus VAD; respective 3-year survival rates were 81.4% and 77.4% (median follow-up, 32.2 months). The incidence of severe adverse events appeared similar between groups, but hematologic toxicity and deaths related to toxicity (zero v seven) were more frequent with VAD. Conversely, rates of grade 2 (20.5% v 10.5%) and grades 3 to 4 (9.2% v 2.5%) peripheral neuropathy during induction through first transplantation were significantly higher with bortezomib plus dexamethasone. CONCLUSION: Bortezomib plus dexamethasone significantly improved post-induction and post-transplantation CR/nCR and at least VGPR rates compared with VAD and resulted in a trend for longer PFS. Bortezomib plus dexamethasone should therefore be considered a standard of care in this setting.

Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis.

Lamm W, Willenbacher W, Lang A, Zojer N, Müldür E, Ludwig H, Schauer-Stalzer B, Zielinski CC, Drach J.

Ann Hematol. 2010 Sep 7. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20821326

This retrospective evaluation confirms the activity of bortezomib/dexamethasone in patients with AL amyloidosis and suggests that patients achieving a complete response have a marked benefit for survival.

Bortezomib-dexamethasone (Btz/Dex) is an active regimen in patients with multiple myeloma and has been used in few patients with amyloidosis. Here, we report a retrospective evaluation of the efficacy and toxicity of Btz/Dex in 26 patients with AL amyloidosis (AL). Eighteen patients (69%) received Btz/Dex as first-line treatment. Organs most frequently involved were kidneys (100%) and heart (35%); five patients (19%) had less than two organs involved. The overall response rate was 54% (14 of 26 patients), with eight patients (31%) achieving a hematologic complete remission (CR). All patients who reached a CR received Btz/Dex as first-line therapy. Median time to response was 7.5 weeks. Improvement in organ function was noticed in three patients (12%). Median progression-free survival (PFS) and overall survival (OS) was 5.0 and 18.7 months, respectively; in CR patients, however, median PFS and OS have not yet been reached. Toxicities were manageable, with hematological side effects being most common. No grade 3/4 neuropathy was observed. Our results confirm the activity of bortezomib/dexamethasone in patients with AL amyloidosis and suggest that patients achieving a CR have a marked benefit for survival.

Light Chain-Induced Acute Renal Failure Can Be Reversed by Bortezomib-Doxorubicin-Dexamethasone in Multiple Myeloma: Results of a Phase II Study.

Ludwig H, Adam Z, Hájek R, Greil R, Tóthová E, Keil F, Autzinger EM, Thaler J, Gisslinger H, Lang A, Egyed M, Womastek I, Zojer N.

J Clin Oncol. 2010 Sep 7. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20823423

The authors assess the efficacy of bortezomib-doxorubicin-dexamethasone (BDD) therapy in patients with myeloma with light chain-induced acute renal failure. They find that BDD induces a high rate of myeloma and renal responses and that treatment is well tolerated.

PURPOSE: To assess the efficacy of bortezomib-doxorubicin-dexamethasone (BDD) therapy in patients with multiple myeloma with light chain-induced acute renal failure. PATIENTS AND METHODS: Sixty-eight patients with light chain-induced acute renal failure and glomerular filtration rate (GFR) less than 50 mL/min received bortezomib (1.0 mg/m² on days 1, 4, 8, and 11), doxorubicin (9 mg/m² on days 1 and 4), and dexamethasone (40 mg on days 1, 4, 8, and 11); if well tolerated after two cycles, bortezomib could be increased to 1.3 mg/m² and doxorubicin administered on days 1, 4, 8, and 11. RESULTS: By intent-to-treat analysis a myeloma response was obtained in 72% of 18 previously and 50 not previously treated patients (complete response [CR]/near CR [nCR], 38%; very good partial response [VGPR], 15%; partial response [PR], 13%; minor response [MR], 6%). Renal response was achieved in 62% of patients (renal CR, 31%; renal PR, 7%; renal MR, 24%). Median GFR increased from 20.5 to 48.4 mL/min. GFR improvement correlated with tumor response; the greatest increase to 59.6 mL/min was seen in the group of patients with CR/nCR/VGPR. Median progression-free survival was 12.1 months. One- and 2-year survival rates were 72% and 58%, respectively. Survival did not differ between patients with and without renal response but was inferior in previously treated patients ($p < 0.001$). In multivariate analysis, baseline GFR and tumor response correlated with renal response, and pretreatment status, lactate dehydrogenase, and myeloma response correlated with survival. The most common grade 3 or 4 toxicities were infection (19.1%), thrombocytopenia (14.7%), neutropenia (14.7%), fatigue/weakness (10.3%), and polyneuropathy (8.8%). CONCLUSION: BDD induced a high rate of myeloma and renal responses, and treatment was well tolerated.

Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma.

Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Björkstrand B, Carlson K, Dahl IM, Forsberg K, Gulbrandsen N, Haukås E, Hjertner O, Hjorth M, Karlsson T, Knudsen LM, Nielsen JL, Linder O, Mellqvist UH, Nesthus I, Rolke J, Strandberg M, Sørbø JH, Wisløff F, Juliusson G, Turesson I; Nordic Myeloma Study Group.

Blood. 2010 Sep 2; 116(9):1405-12. [Epub 2010 May 6.]

http://www.ncbi.nlm.nih.gov/pubmed/20448107

In this double-blind, placebo-controlled study, 363 patients with untreated myeloma are randomized to receive either melphalan, prednisone and thalidomide (MPT) or melphalan, prednisone, and placebo (MP). The authors find that MPT has a significant antimyeloma effect, but this does not translate into improved survival.

In this double-blind, placebo-controlled study, 363 patients with untreated multiple myeloma were randomized to receive either melphalan, prednisone and thalidomide (MPT) or melphalan, prednisone, and placebo (MP). The dose of melphalan was 0.25 mg/kg and prednisone was 100 mg given daily for 4 days every 6 weeks until plateau phase. The dose of thalidomide/placebo was escalated to 400 mg daily until plateau phase and thereafter reduced to 200 mg daily until progression. A total of 357 patients were analyzed. Partial response was 34% and 33%, and very good partial response or better was 23% and 7% in the MPT and MP arms, respectively ($p < .001$). There was no significant difference in progression-free or overall survival, with median survival being 29 months in the MPT arm and 32 months in the MP arm. Most quality of life outcomes improved equally in both arms, apart from constipation, which was markedly increased in the MPT arm. Constipation, neuropathy, non-neuropathy neurologic toxicity, and skin reactions were significantly more frequent in the MPT arm. The number of thromboembolic events was equal in the 2 treatment arms. In conclusion, MPT had a significant antimyeloma effect, but this did not translate into improved survival. This trial was registered at www.clinicaltrials.gov as #NCT00218855.

PI3K/p110{delta} is a novel therapeutic target in multiple myeloma.

Ikeda H, Hideshima T, Fulciniti M, Perrone G, Miura N, Yasui H, Okawa Y, Kiziltepe T, Santo L, Vallet S, Cristea D, Calabrese E, Görgün G, Raje NS, Richardson P, Munshi NC, Lannutti BJ, Puri KD, Giese NA, Anderson KC.

Blood. 2010 Sep 2;116(9):1460-8. [Epub 2010 May 26.]

http://www.ncbi.nlm.nih.gov/pubmed/20505158

The authors find that combined CAL-101 with bortezomib induces synergistic cytotoxicity against myeloma cells.

In this study, we demonstrate expression and examined the biologic sequelae of PI3K/p110delta signaling in multiple myeloma (MM). Knockdown of p110delta by small interfering RNA caused significant inhibition of MM cell growth. Similarly, p110delta specific small molecule inhibitor CAL-101 triggered cytotoxicity against LB and INA-6 MM cell lines and patient MM cells, associated with inhibition of Akt phosphorylation. In contrast, CAL-101 did not inhibit survival of normal peripheral blood mononuclear cells. CAL-101 overcame MM cell growth conferred by IL-6, IGF-1, and bone marrow stromal cells (BMSCs) coculture. Interestingly, inhibition of p110delta potently induced autophagy. The in vivo inhibition of p110delta with IC488743 was evaluated in two murine xenograft models of human MM: SCID mice bearing human MM cells subcutaneously; and the SCID-hu model, in which human MM cells are injected within a human bone chip implanted subcutaneously in SCID mice. IC488743 significantly inhibited tumor growth and prolonged host survival in both models. Finally, combined CAL-101 with bortezomib induced synergistic cytotoxicity against MM cells. Our studies therefore show that PI3K/p110delta is a novel therapeutic target in MM and provide the basis for clinical evaluation of CAL-101 to improve patient outcome in MM.

A modified regimen of pegylated liposomal doxorubicin, bortezomib, and dexamethasone is effective and well tolerated in the treatment of relapsed or refractory multiple myeloma.

Waterman GN, Yellin O, Swift RA, Mapes R, Eades B, Ackerman E, Berenson JR.

Ann Hematol. 2010 Sep 1. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20809423

This retrospective study evaluates the efficacy and safety of the combination of a more frequent low-dose schedule of pegylated liposomal doxorubicin (PLD), bortezomib, and intravenous dexamethasone (DVD) for patients with relapsed/refractory myeloma, many of whom were previously treated with bortezomib. The authors find that DVD appears to represent a well-tolerated regimen with a high response rate for the treatment of this patient group.

Preclinical and clinical studies have demonstrated synergy between bortezomib and pegylated liposomal doxorubicin (PLD) for relapsed/refractory (R/R) multiple myeloma (MM) patients compared to bortezomib as a single agent. This retrospective study evaluated the efficacy and safety of a more frequent low-dose schedule of PLD, bortezomib, and intravenous dexamethasone (DVD) for patients with R/R MM, many of whom were previously treated with bortezomib. Twenty-eight patients with R/R MM were treated, and 23 (83%) had been previously treated with >/=1 bortezomib-containing regimen. Treatment consisted of dexamethasone 40 mg intravenously, bortezomib 1.0 mg/m^2, and PLD 5.0 mg/m^2 on days 1, 4, 8, and 11 of a 28-day cycle for a maximum of eight cycles. Patients ranged from 33 to 81 years of age (median, 67) and had received 1-14 prior therapies (median, 5). At baseline, ten, nine, and nine patients were in stages I, II, and III, respectively, as defined by the International Staging System, and eight (29%) patients had elevated serum creatinine levels. The overall response rate was 61%, which included one (4%) complete response, three (11%) very good partial responses, eight (29%) partial responses, and five (18%) minimal responses. Of the 23 patients who had previously received bortezomib, 12 (52%) responded. The regimen was well tolerated with only six patients (21%) who showed worsening of their baseline peripheral neuropathy (PN). One patient discontinued this regimen due to an adverse event (grade II PN). DVD appears to represent a well-tolerated regimen with a high response rate for the treatment of R/R MM patients.

Bortezomib, doxorubicin, and dexamethasone combination therapy followed by thalidomide and dexamethasone consolidation as a salvage treatment for relapsed or refractory multiple myeloma: analysis of efficacy and safety.

Lee SS, Suh C, Kim BS, Chung J, Joo YD, Ryoo HM, Do YR, Jin JY, Kang HJ, Lee GW, Lee MH, Shim H, Kim K, Yoon SS, Bang SM, Kim HY, Lee JJ, Park J, Lee DS, Lee JH; Korean Multiple Myeloma Working Party.

Ann Hematol. 2010 Sep;89(9):905-12. [Epub 2010 Mar 27.]

http://www.ncbi.nlm.nih.gov/pubmed/20349060

The authors conduct a phase II study with bortezomib, doxorubicin, and dexamethasone (PAD) followed by thalidomide and dexamethasone (TD) in patients with relapsed myeloma. They find the treatment regimen to be very effective and tolerable.

We conducted a phase II study with bortezomib, doxorubicin, and dexamethasone (PAD) followed by thalidomide and dexamethasone (TD) in patients with relapsed multiple myeloma (MM). Forty patients were enrolled between November 2005 and October 2007, with follow-up continuing until January 2009. Efficacy could be assessed in 37 patients. The overall response rate to PAD followed by TD was 83.6%: complete response 51.4%, near-complete response 13.4%, very good partial remission 5.4%, and partial response 13.4%. The median follow-up was 27 months (range 13-39). The median progression-free survival (PFS) from the start of treatment was 18 months (95% CI, 9.7-26.2 months), with a 1-year PFS rate of 56.9% and 3-year PFS rate of 25.7%. Median overall survival was 35.1 months (95% CI, 18.5-51.7), with a 1-year survival rate of 75% and 3-year survival rate of 27.3%. One hundred seventy-eight PAD cycles (median 6, range 1-6) in 38 patients were assessable for safety. The most common hematologic toxicity was thrombocytopenia, with grade 3-4 in 35.8%. Sensory neuropathy occurred at grade 2 in 26.3% and grade 3 in 10.3%. Two hundred TD treatment cycles (median 4, range 0-12 cycles) were administered. Most adverse events were of mild degree and manageable. PAD followed by TD in patients with relapsed MM is very effective and tolerable.

Combined proteasome and histone deacetylase inhibition: A promising synergy for patients with relapsed/refractory multiple myeloma.

Jagannath S, Dimopoulos MA, Lonial S.

Leuk Res. 2010 Sep;34(9):1111-8. [Epub 2010 May 15.]

http://www.ncbi.nlm.nih.gov/pubmed/20472288

This review examines the potential of combined bortezomib and HDAC inhibition in the treatment of relapsed/refractory myeloma.

Multiple myeloma (MM) is an incurable disease characterized by the accumulation of malignant plasma cells in the bone marrow. Recently, an improved understanding of the biology of the disease has led to the development of targeted agents such as the proteasome inhibitor bortezomib and the immunomodulatory agents thalidomide and lenalidomide; however, MM remains incurable. The combination of bortezomib and an HDAC inhibitor synergistically induces MM cell apoptosis and may be of value in the treatment of patients with relapsed/refractory MM. This review examines the potential of combined proteasome and HDAC inhibition in the treatment of relapsed/refractory MM.

Improved survival of multiple myeloma patients with late relapse after high-dose treatment and stem cell support, a population-based study of 348 patients in Denmark in 1994-2004*.

Vangsted AJ, Klausen TW, Andersen NF, Abildgaard N, Gang AO, Gregersen H, Vogel U, Gimsing P.

Eur J Haematol. 2010 Sep;85(3):209-16. [Epub 2010 May 5.]

http://www.ncbi.nlm.nih.gov/pubmed/20477864

This Danish retrospective study analyzes if myeloma patients with early relapse after high-dose chemotherapy with stem cell support (HDT) benefit from new treatment strategies. The authors find that improved survival is only observed among patients with late relapse after HDT, and that this may be because of increased use of salvage HDT, improved supportive care, and introduction of new drugs, including thalidomide, lenalidomide, and bortezomib.

ABSTRACT OBJECTIVE: To analyse if patients with early relapse after high-dose chemotherapy with stem cell support (HDT) benefit from new treatment strategies in a population-based setting. METHODS: We conducted a retrospective study of relapse treatment and survival in 348 patients undergoing HDT in Denmark in 1994-2004. Patients were divided into two groups according to time-to-treatment failure (i) within 18 months after HDT and (ii) later than 18 months after HDT. The fraction of patients surviving 3 yr after first relapse was evaluated in relation to calendar periods for introduction of new drugs: before the introduction of thalidomide (1995-1999), before the introduction of bortezomib and lenalidomide (2000-2002) and when patients had access to all treatment modalities (2003-2008). RESULTS: Two hundred and forty-three patients suffered from relapse which required treatment. The median follow-up time was 91.4 months (60-158.8 months) and overall survival was 56.3 months after HDT. The fraction of patients alive 3 yr after first relapse increased in the periods after the year 2000 for patients with late relapse: 1995-1999, 36%; 2000-2002, 57%; and 2003-2008, 72% ($p = 0.03$), in contrast to patients with early relapse: 1995-1999, 25%; 2000-2002, 33%; and 2003-2008, 31% ($p = 0.7$). CONCLUSION: Improved survival was only observed among patients with late relapse after HDT and this may be because of increased use of salvage HDT, improved supportive care and introduction of new drugs.

Lenalidomide efficacy in bortezomib-resistant myeloma.

Gozzetti A, Crupi R, Defina M, Bocchia M.

Nat Rev Clin Oncol. 2010 Sep;7(9).

http://www.ncbi.nlm.nih.gov/pubmed/20824907

Comment on: Nat Rev Clin Oncol. 2010 May;7(5):289-94.

Lenalidomide for bortezomib-resistant multiple myeloma.
Briani C, Berno T, Campagnolo M, Zambello R.
Nat Rev Clin Oncol. 2010 Sep;7(9).
http://www.ncbi.nlm.nih.gov/pubmed/20824906
Comment on: Nat Rev Clin Oncol. 2010 May;7(5):289-94.

Lenalidomide plus dexamethasone vs. lenalidomide plus melphalan and prednisone: a retrospective study in newly diagnosed elderly myeloma.
Gay F, Vincent Rajkumar S, Falco P, Kumar S, Dispenzieri A, Petrucci MT, Gertz MA, Boccadoro M, Keith Stewart A, Palumbo A.
Eur J Haematol. 2010 Sep;85(3):200-8. [Epub 2010 May 8.]
http://www.ncbi.nlm.nih.gov/pubmed/20477865
This retrospective study shows that both melphalan-prednisone-lenalidomide and lenalidomide/dexamethasone are efficacious regimens for elderly myeloma patients.

ABSTRACT BACKGROUND: The goal of this retrospective study was to compare the efficacy and toxicity of lenalidomide-dexamethasone (len/dex) vs. melphalan-prednisone-lenalidomide (MPR) as upfront therapy for newly diagnosed elderly myeloma patients. METHODS: Data from 51 patients enrolled in Italy in a phase I/II trial and treated with MPR, were analyzed and compared with data from 38 patients, seen at the Mayo Clinic, treated with len/dex and enrolled in phase II/III trials. RESULTS: On intent-to-treat analysis, time to progression (median: 24.7 vs. 27.5 months in MPR and len/dex groups, respectively, p = 0.903), progression-free survival (median: 24.7 vs. 27.5 months in MPR and len/dex groups, respectively, p = 0.926) and overall survival (2-year overall survival: 86.2% in MPR vs. 89.1% in len/dex, p = 0.730) were not significantly different between the 2 groups. Results were confirmed when the analysis was restricted to MPR and len/dex matched pair mates. Hematologic grade 3-4 toxicities were more common with MPR (neutropenia: 66.7% vs. 21.1%, P < 0.001; thrombocytopenia: 31.4% vs. 2.6%, p < 0.001). Grade 3-4 gastrointestinal events (13.2% vs. 3.9%, p = 0.132), thrombotic events (13.2% vs. 5.9%, p = 0.279) and fatigue (10.5% vs. 3.9%, p = 0.395) were more common with len/dex. CONCLUSIONS: Results show that both MPR and len/dex are efficacious regimens for elderly myeloma patients. Randomized trials are needed to confirm these results.

Monitoring bortezomib therapy in multiple myeloma: screening of cyclin D1, D2, and D3 via reliable real-time polymerase chain reaction and association with clinico-pathological features and outcome.
Ngo BT, Felthaus J, Hein M, Follo M, Wider D, Ihorst G, Engelhardt M, Wäsch R.
Leuk Lymphoma. 2010 Sep;51(9):1632-42.
http://www.ncbi.nlm.nih.gov/pubmed/20578819
This study is the first to suggest that overexpressed cyclin D1 in myeloma is an independent prognostic marker associated with a more durable response to bortezomib.

Cyclins D1, D2, and D3 (CCND1, 2, 3) are regulated by proteasomal degradation. Their overexpression in multiple myeloma (MM) has prognostic value. We performed this pilot study to analyze a possible association between CCND1-3 overexpression and response to treatment with the proteasome inhibitor bortezomib, since a specific prognostic marker for bortezomib response has not been reported, but would be ideal in order to predict who benefits most from bortezomib in times of several potentially efficient therapeutic options. Bone marrow (BM) specimens of 20/47 consecutive patients were available for reliable CCND1-3 analyses by real-time PCR. With CCND1 overexpression in 9/20 patients, the risk for progression after bortezomib treatment was significantly decreased (HR 0.102, 95% CI 0.021-0.498, p = 0.0048) and progression-free survival substantially prolonged (p = 0.0011). Our study is the first to suggest that overexpressed CCND1 in MM is an independent prognostic marker associated with a more durable response to bortezomib. These preliminary results warrant a larger study.

Multiple myeloma: management of adverse events.

Gay F, Palumbo A.

Med Oncol. 2010 Sep;27(3):646-53. [Epub 2009 Jul 7.]

http://www.ncbi.nlm.nih.gov/pubmed/19582597

The authors focus on frequency and management of main adverse events in newly diagnosed and relapsed myeloma patients and provide guidelines for dose reductions and supportive therapy, including with lenalidomide.

The combination of conventional chemotherapy or dexamethasone with new drugs, such as immunomodulatory agents and proteasome inhibitors, has substantially changed the treatment paradigm of myeloma patients. New drugs have been incorporated in pre-transplant induction regimens and post-transplant consolidation and maintenance strategies for young patients; in elderly patients, standard melphalan and prednisone (MP) plus thalidomide or plus bortezomib are now considered standards of care, and ongoing trials are assessing if lenalidomide plus standard MP or plus low-dose dexamethasone may be other options. The efficacy of these drugs needs to be balanced against their toxicity. Different drugs have a different toxicity profile. The choice for the best treatment strategy for every single patient should be based on results of scientific randomized studies but tailored to account for patient's biological age, comorbidities, and the expected toxicity profile of different regimens. Prompt dose reduction and accurate management of treatment-related toxicity can greatly reduce early discontinuation rate and significantly improve treatment efficacy. This chapter will focus on frequency and management of main adverse events in newly diagnosed and relapsed myeloma patients and will provide guidelines for dose reductions and supportive therapy.

Thalidomide maintenance treatment increases progression-free but not overall survival in elderly patients with myeloma.

Ludwig H, Adam Z, Tóthová E, Hájek, R, Labar B, Egyed M, Spicka I, Gisslinger H, Drach J, Kuhn I, Hinke A, Zojer N.

Haematologica. 2010 Sep;95(9):1548-54. [Epub 2010 Apr 23.]

http://www.ncbi.nlm.nih.gov/pubmed/20418244

This study assesses the impact of thalidomide-interferon in comparison to interferon (IFN) maintenance therapy in elderly patients with myeloma. The authors find that thalidomide plus interferon maintenance therapy increases progression-free survival, but not overall survival, and is associated with slightly more toxicity than maintenance with IFN alone.

BACKGROUND: Thalidomide maintenance therapy after stem cell transplantation resulted in increased progression-free survival (PFS) and overall survival (OS) in few trials, but its role in non-transplant eligible patients with multiple myeloma (MM) remains unclear. This study assessed the impact of thalidomide-interferon in comparison to interferon maintenance therapy in elderly patients with MM. DESIGN and METHODS: Of 289 elderly patients with MM who were randomized to thalidomide- dexamethasone or melphalan-prednisolone induction therapy, 137 finally completed 9 cycles of induction therapy with stable disease or better and thereby qualified for maintenance treatment. Of these, 128 have been randomized to either thalidomide-interferon or interferon alone. Primary study endpoints were PFS and response rates, secondary endpoints were OS, toxicity and Quality-of-life. RESULTS: Thalidomide-interferon maintenance therapy led to a significantly longer PFS compared to interferon (27.7 vs. 13.2 months, p = 0.0068), but OS was similar in both groups (52.6 vs. 51.4 months, p = 0.81) and did not differ between patients aged >/=75 years or younger (p = 0.39). Survival after disease progression tended to be shorter in patients on thalidomide-interferon maintenance therapy (p = 0.056). PFS and OS tended to be shorter in patients with adverse cytogenetic (FISH) findings compared to the standard risk group but differences were not significant (p = 0.084 and p = 0.082, respectively). There was more neuropathy (p = 0.0015), constipation (p = 0.0004), skin toxicity (p = 0.0041) and elevated creatinine (p = 0.026) in patients on thalidomide-interferon. CONCLUSIONS: Thalidomide plus interferon maintenance therapy increased PFS, but not OS and was associated with slightly more toxicity than maintenance with IFN alone.

Therapeutic approaches for newly diagnosed multiple myeloma patients in the era of novel drugs.
Morabito F, Gentile M, Mazzone C, Bringhen S, Vigna E, Lucia E, Recchia AG, Raimondo FD, Musto P, Palumbo A.
Eur J Haematol. 2010 Sep;85(3):181-91. [Epub 2010 May 17.]

http://www.ncbi.nlm.nih.gov/pubmed/20491882

The authors report updated data for the front-line therapy of myeloma, examining the role of new drugs (including thalidomide, lenalidomide, and bortezomib) either when administered as induction therapy before for autologous stem cell transplantation in younger patients or when combined with alkylating agents for the treatment of older patients.

ABSTRACT: The treatment of newly diagnosed multiple myeloma (MM) has evolved rapidly over recent years. The availability of new effective drugs with novel mechanisms of action such as thalidomide, lenalidomide, and bortezomib in the last decade have resulted in a new scenario expected to impact favourably on the outcome of MM patients. The introduction of new drugs in the treatment of patients eligible for autologous stem cell transplantation (ASCT) has allowed for a significant increase of complete response rate with a positive impact on progression-free survival. In patients not eligible for ASCT, randomized trials have shown that both thalidomide and bortezomib when combined with melphalan and prednisone (MP) are superior to MP and are now considered the standard of care. Ongoing trials are assessing if MP plus lenalidomide or the combination of lenalidomide plus dexamethasone should be considered an attractive treatment option, while additional studies are needed to determine the role of routine maintenance or consolidation therapy with these new drugs. This new therapeutic armamentarium on the light of adequate prophylaxis and supportive care allows clinicians to greatly improve the survival perspectives for both young and elderly patients. In this review, we report updated data for the front-line therapy of MM, examining the role of new drugs either when administered as induction therapy before ASCT in younger patients or when combined with alkylating agents for the treatment of older patients. The most relevant papers on therapy of MM published from November 1982 to January 2010 (selected through PubMed) and recent meeting abstracts were used as sources for this review.

August 2010

Efficacy and safety of once weekly bortezomib in multiple myeloma patients.
Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, Gentili S, Patriarca F, Nozzoli C, Levi A, Guglielmelli T, Benevolo G, Callea V, Rizzo V, Cangialosi C, Musto P, De Rosa L, Liberati AM, Grasso M, Falcone AP, Evangelista A, Cavo M, Gaidano G, Boccadoro M, Palumbo A.
Blood. 2010 Aug 31. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20807892

The authors find that, for this protocol, the reduction to once-weekly bortezomib infusions does not impact the efficacy of the regimen.

In a recent phase III trial, bortezomib-melphalan-prednisone-thalidomide followed by maintenance treatment with bortezomib-thalidomide (VMPT-VT) demonstrated superior efficacy compared with VMP. To decrease neurologic toxicities, the protocol was amended and patients in both arms received once-weekly instead of the initial twice-weekly bortezomib infusions: 372 patients received once-weekly and 139 twice-weekly bortezomib. This post-hoc analysis assessed the impact of the schedule change on clinical outcomes and safety. Long-term outcomes appeared similar: 3-year progression-free survival rate was 50% in the once-weekly and 47% in the twice-weekly group ($p = 1.00$), and 3-year overall survival rate was 88% and 89%, respectively ($p = .54$). The complete response rate was 30% in the once-weekly and 35% in the twice-weekly group ($p = .27$). Non-hematologic grade 3/4 adverse events were reported in 35% of once-weekly patients and 51% of twice-weekly patients ($p = .003$). The incidence of grade 3/4 peripheral neuropathy was 8% in the once-weekly and 28% in the twice-weekly group ($p < .001$); 5% of patients in the once-weekly and 15% in the twice-weekly group discontinued therapy due to PN ($p < .001$). This improvement in safety did not appear to impact efficacy.

European Myeloma Network: the 3rd Trialist Forum Consensus Statement from the European experts meeting on multiple myeloma.

Engelhardt M, Udi J, Kleber M, Spencer A, Rocci A, Knop S, Bruno B, Bringhen S, Pérez-Simón JA, Zweegman S, Driessen C, Patriarca F, Gramatzki M, Terpos E, Sezer O, Kropff M, Straka C, Johnsen HE, Waage A, Boegsted M, Lokhorst H, Hájek R, Morgan G, Boccadoro M, Ludwig H, Cavo M, Polliack A, Sonneveld P, Einsele H, Palumbo A.

Leuk Lymphoma. 2010 Aug 31. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20807087

The authors address the use of novel therapies for the pre- and post-transplant settings of patients with myeloma.

Over the past two decades, not only treatment options, but also the diagnosis, staging, and risk assessment of multiple myeloma (MM), have undergone significant development, partially due to a deeper understanding of MM pathogenesis. Conventional cytogenetics and fluorescence *in situ* hybridization are routinely assessed in MM, and when combined with ISS stage may attain an even better predictive potential. In order to achieve even more effective and individualized therapies, one crucial goal is the identification of genes and gene combinations that predict for response or resistance to chemotherapy. High-dose chemotherapy with autologous stem cell transplant (SCT) still remains the standard therapy for younger patients, with novel agents now being included in both pre-transplant regimens and post-transplant consolidation/maintenance approaches. Similarly, novel agents are also being incorporated into allogeneic SCT for selected patients. In the treatment of elderly patients with MM, novel agents have been successfully incorporated into less intensive regimens, including melphalan/prednisone, low-dose dexamethasone, and cyclophosphamide/dexamethasone. While second-generation proteasome inhibitors are currently being intensively investigated, the subcutaneous administration of bortezomib, being equivalent to the established i.v. route, is now entering clinical practice. Supportive care remains a crucial aspect in the management of MM. The European Myeloma Network Trialist Group aims to address these contemporary aspects in MM.

A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma.

Chauhan D, Singh AV, Aujay M, Kirk CJ, Bandi M, Ciccarelli B, Raje N, Richardson P, Anderson KC.

Blood. 2010 Aug 30. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20805366

The authors find that ONX 0912 enhances anti-myeloma activity of bortezomib and lenalidomide.

Bortezomib therapy has proven successful for the treatment of relapsed, relapsed/refractory, and newly diagnosed multiple myeloma (MM). At present, bortezomib is available as an intravenous (IV) injection and its prolonged treatment is associated with toxicity and development of drug-resistance. Here we show that the novel proteasome inhibitor ONX 0912, a tripeptide epoxyketone, inhibits growth and induces apoptosis in MM cells resistant to conventional and bortezomib therapies. The anti-MM activity of ONX-0912 is associated with activation of caspase-8, caspase-9, caspase-3, and PARP, as well as inhibition of migration of MM cells and angiogenesis. ONX 0912, like bortezomib, predominantly inhibits chymotrypsin-like activity of the proteasome and is distinct from bortezomib in its chemical structure. Importantly, ONX 0912 is orally bioactive. In animal tumor model studies, ONX 0912 significantly reduced tumor progression and prolongs survival. Immunostaining of MM tumors from ONX 0912-treated mice showed growth inhibition, apoptosis, and a decrease in associated angiogenesis. Finally, ONX 0912 enhances anti-MM activity of bortezomib, lenalidomide, dexamethasone, or pan-HDAC inhibitor. Taken together, our study provides the rationale for clinical protocols evaluating ONX 0912, either alone or in combination, to improve patient outcome in MM.

Total Therapy 3 for multiple myeloma: prognostic implications of cumulative dosing and premature discontinuation of VTD maintenance components, bortezomib, thalidomide, and dexamethasone, relevant to all phases of therapy.

van Rhee F, Szymonifka J, Anaissie E, Nair B, Waheed S, Alsayed Y, Petty N, Shaughnessy JD Jr, Hoering A, Crowley J, Barlogie B.

Blood. 2010 Aug 26;116(8):1220-7. [Epub 2010 May 25.]

http://www.ncbi.nlm.nih.gov/pubmed/20501894

The authors find that the absence of adverse effects on post-relapse survival of dosing of any bortezomib-thalidomide-dexamethasone components— and a benefit from bortezomib— supports the use up-front of all active agents in a dose-dense and dose-intense fashion, as practiced in Total Therapy 3, toward maximizing myeloma survival.

The impact of cumulative dosing and premature drug discontinuation (PMDD) of bortezomib (V), thalidomide (T), and dexamethasone (D) on overall survival (OS), event-free survival (EFS), time to next therapy, and post-relapse survival in Total Therapy 3 were examined, using time-dependent methodology, relevant to induction, peri-transplantation, consolidation, and maintenance phases. Univariately, OS and EFS were longer in case higher doses were used of all agents during induction, consolidation (except T), and maintenance (except V and T). The favorable OS and EFS impact of D induction dosing provided the rationale for examining the expression of glucocorticoid receptor NR3C1, top-tertile levels of which significantly prolonged OS and EFS and rendered outcomes independent of D and T dosing, whereas T and D, but not V, dosing was critical to outcome improvement in the bottom-tertile NR3C1 setting. PMDD of V was an independent highly adverse feature for OS (hazard ratio = 6.44; $P < .001$), whereas PMDD of both T and D independently imparted shorter time to next therapy. The absence of adverse effects on post-relapse survival of dosing of any VTD components and indeed a benefit from V supports the use up-front of all active agents in a dose-dense and dose-intense fashion, as practiced in Total Therapy 3, toward maximizing myeloma survival.

Treatment of patients with relapsed/refractory multiple myeloma with lenalidomide and dexamethasone with or without bortezomib: prospective evaluation of the impact of cytogenetic abnormalities and of previous therapies.

Dimopoulos MA, Kastritis E, Christoulas D, Migkou M, Gavriatopoulou M, Gkotzamanidou M, Iakovaki M, Matsouka C, Mparmparoussi D, Roussou M, Efstathiou E, Terpos E.

Leukemia. 2010 Aug 26. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20739955

The authors find that the presence of cytogenetic abnormalities is an important adverse prognostic factor for patients with relapsed/refractory myeloma, but resistance to previous thalidomide, elevated lactate dehydrogenase, and presence of extramedullary disease remain of major prognostic importance; the outcome of patients with del17p remains extremely poor even with a bortezomib-lenalidomide-dexamethasone combination.

We prospectively studied the impact of several cytogenetic abnormalities (CAs) in patients with relapsed/refractory myeloma who received lenalidomide and dexamethasone (RD) with or without the addition of bortezomib (V). On the basis of the presence of previous neuropathy, 50 patients were treated with RD and 49, without preexisting neuropathy, with VRD. The overall response rate was 63%, similar for RD and VRD. Poor risk cytogenetics were associated with lower response rates in RD ($p = 0.01$), but not in VRD ($p = 0.219$). The median progression-free survival (PFS) was similar for RD (9 months) and VRD (7 months). The median overall survival (OS) for all patients was 16 months, with no differences between RD or VRD regimens. Poor risk cytogenetics, especially del17p, resistance to previous thalidomide, elevated lactate dehydrogenase (LDH) and presence of extramedullary disease were associated with inferior response to therapy and shorter PFS and OS. The impact of other CAs on OS was more pronounced in RD. In conclusion, the presence of CAs is an important adverse prognostic factor for patients with relapsed/refractory myeloma, but resistance to previous thalidomide, elevated LDH and presence of extramedullary disease remain of major prognostic importance. The outcome of patients with del17p remains extremely poor even with VRD combination.

A Phase I/II Trial Combining High Dose Melphalan and Autologous Transplant with Bortezomib for Multiple Myeloma: A Dose and Schedule Finding Study.

Lonial S, Kaufman J, Tighiouart M, Nooka A, Langston A, Heffner LT, Torre C, McMillan S, Renfroe H, Harvey RD, Lechowicz MJ, Khoury HJ, Flowers C, Waller EK.

Clin Cancer Res. 2010 Aug 25. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20739431

The authors find that use of bortezomib in conjunction with high dose melphalan is safe, with data suggesting improved efficacy. They recommend a single dose of bortezomib administered after high dose melphalan, and schedule for future clinical investigation.

PURPOSE: We performed a randomized phase I/II trial designed to evaluate the safety and efficacy of combining the proteasome inhibitor bortezomib with high dose melphalan as the conditioning for high dose therapy and autologous transplant for myeloma. EXPERIMENTAL DESIGN: Enrolled patients were limited to those who did not achieve a very good partial remission following one or more induction regimens, and were randomized to receive a single escalating dose of bortezomib (1.0mg/m², 1.3mg/m², or 1.6mg/m²) either 24 hours before or 24 hours after high-dose melphalan. Dose escalation was based upon the Escalation With Overdose Control(EWOC), a Bayesian statistical model. Bone marrow aspirates were collected before initiation of therapy and at the time of transplant to evaluate which sequence resulted in maximal plasma cell apoptosis, and response to transplant was assessed by IMWG criteria. RESULTS: Among 39 randomized patients, 20 received bortezomib after melphalan and 19 received bortezomib before melphalan. Toxicities and post-transplant hematopoietic recovery rates were similar between arms. The overall response rate for all patients was 87%, with 51% achieving a VGPR or better. Pharmacodynamic studies demonstrated greater plasma cell apoptosis among patients who received bortezomib following melphalan. CONCLUSIONS: The use of bortezomib in conjunction with high dose melphalan is safe, with data suggesting improved efficacy. A single dose of bortezomib administered after high dose melphalan is the recommended dose and schedule for future clinical investigation.

Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial.

Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, de Paz R, García-Laraña J, Bengoechea E, Martín A, Mediavilla JD, Palomera L, de Arriba F, González Y, Hernández JM, Sureda A, Bello JL, Bargay J, Peñalver FJ, Ribera JM, Martín-Mateos ML, García-Sanz R, Cibeira MT, Ramos ML, Vidriales MB, Paiva B, Montalbán MA, Lahuerta JJ, Bladé J, San Miguel JF.

Lancet Oncol. 2010 Aug 23. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20739218

The authors find that reduced-intensity induction with a bortezomib-based regimen, followed by maintenance, is a safe and effective treatment for elderly myeloma patients.

BACKGROUND: Bortezomib plus melphalan and prednisone (VMP) is significantly better than melphalan plus prednisone alone for elderly patients with untreated multiple myeloma; however, toxic effects are high. We investigated a novel and less intensive bortezomib-based regimen to maintain efficacy and to reduce toxic effects. METHODS: Between March, 2006, and October, 2008, 260 patients with untreated multiple myeloma, 65 years and older, from 63 Spanish centres, were randomly assigned to receive six cycles of VMP (n = 130) or bortezomib plus thalidomide and prednisone (VTP; n = 130) as induction therapy, consisting of one cycle of bortezomib twice per week for 6 weeks (1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32), plus either melphalan (9 mg/m^2 on days 1-4) or daily thalidomide (100 mg), and prednisone (60 mg/m^2 on days 1-4). The first cycle was followed by five cycles of bortezomib once per week for 5 weeks (1.3 mg/m^2 on days 1, 8, 15, and 22) plus the same doses of melphalan plus prednisone and thalidomide plus prednisone. 178 patients completed the six induction cycles and were randomly assigned to maintenance therapy with bortezomib plus prednisone (n = 87) or bortezomib plus thalidomide (n = 91), consisting of one conventional cycle of bortezomib for 3 weeks (1.3 mg/m² on days 1, 4, 8, and 11) every 3 months,

plus either prednisone (50 mg every other day) or thalidomide (50 mg per day), for up to 3 years. Treatment codes were generated with a computerised random number generator, and neither participants nor study personnel were masked to treatment. The primary endpoint was response rate in induction and maintenance phases. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, #NCT00443235. FINDINGS: In the induction phase, 105 (81%) patients in the VTP group and 104 (80%) in the VMP group achieved partial responses or better (p = 0.9), including 36 (28%) and 26 (20%) complete remissions, respectively (p = 0.2). Treatment with VTP resulted in more serious adverse events (40 [31%] vs. 20 [15%], p=0.01) and discontinuations (22 [17%] vs. 15 [12%], p=0.03) than did treatment with VMP. The most common toxicities (grade 3 or worse) were infections (one [1%] in the VTP group vs. nine [7%] in the VMP group), cardiac events (11 [8%] vs. 0), and peripheral neuropathy (nine [7%] vs. 12 [9%]). After maintenance therapy, the complete remission rate was 42% (40 [44%] patients in complete remission in the bortezomib plus thalidomide group, 34 [39%] in the bortezomib plus prednisone group). No grade 3 or worse haematological toxicities were recorded during maintenance therapy; two (2%) patients in the bortezomib plus prednisone group and six (7%) in the bortezomib plus thalidomide group developed peripheral neuropathy. INTERPRETATION: Reduced-intensity induction with a bortezomib-based regimen, followed by maintenance, is a safe and effective treatment for elderly patients with multiple myeloma. FUNDING: PETHEMA (Spanish Program for the Treatment of Hematologic Diseases).

Bortezomib Plus Thalidomide for Newly Diagnosed Multiple Myeloma in China.
Chen SL, Jiang B, Qiu LG, Yu L, Zhong YP, Gao W.
Anat Rec (Hoboken). 2010 Aug 23. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20734318

This phase II study seeks to determine the efficacy and safety of combined bortezomib and thalidomide as initial treatment for newly diagnosed patients with myeloma in China. The authors find that bortezomib in combination with thalidomide is a very effective regimen for newly diagnosed myeloma patients, with manageable toxicities.

The aim of this phase II study was to determine the efficacy and safety of combined bortezomib and thalidomide (VT) regime as initial treatment for newly diagnosed patients with multiple myeloma (MM) in China. Thirty-four patients have been enrolled in this study and were planned to receive VT regime up to eight 21-day cycles. Bortezomib (1.3 mg/m²) was given intravenously on days 1, 4, 8, and 11, while oral thalidomide (100 mg/day) was given on days 1 to 21. The primary end point was clinical response; the secondary end point was safety. Among 34 patients enrolled, 26 patients were able to complete the planned eight cycles of therapy. After eight cycles, the overall response rate was 100% (complete response 31%; near-complete response 23%; partial response 42%; minimal response 4%). The best response occurred within the first four cycles in 96% of patients. Adverse events included hematologic (53%), peripheral neuropathy (38%), fatigue (35%), gastrointestinal (45%), and fever (32%). Grade 3 non-hematologic adverse events included four patients (12%) with renal failure associated with tumor-lysis syndrome, one patient (3%) with peripheral sensory and motor neuropathy that improved with VT dose reduction, and one patient (3%) with hypotension. One patient (3%) experienced Grade 4 thrombocytopenia. No patient experienced deep venous thrombosis, while 1 patient (3%) died due to acute renal failure. In conclusion, Bortezomib in combination with thalidomide is a very effective regimen for newly diagnosed MM patients and the toxicities are manageable.

Optimising bortezomib in newly diagnosed multiple myeloma.
Rajkumar SV.
Lancet Oncol. 2010 Aug 23. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20739219

No abstract available.

Lenalidomide in combination with melphalan and dexamethasone in patients with newly-diagnosed AL amyloidosis: a multicenter phase I/II dose escalation study.

Moreau P, Jaccard A, Benboubker L, Royer B, Leleu X, Bridoux F, Salles G, Leblond V, Roussel M, Alakl M, Hermine O, Planche L, Harousseau JL, Fermand JP.

Blood. 2010 Aug 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20724537

The authors find that lenalidomide 15 mg/day plus melphalan-dexamethasone is a new effective combination therapy in patients with newly diagnosed AL amyloidosis.

New treatment options are required for primary systemic AL amyloidosis (AL). This phase I /II dose-escalation study aimed to determine the maximum tolerated dose (MTD) of lenalidomide in combination with melphalan and dexamethasone (M-dex), and to assess the efficacy and tolerability of this therapy for patients with de novo AL. Twenty-six patients were enrolled across 4 cohorts: M-dex plus lenalidomide 5, 10, 15 and 20 mg once daily on days 1-21 in a 28-day cycle. No DLT was observed in cohort n degrees 1, 2 and 3. Four patients / 7 in cohort n degrees 4, M-dex + lenalidomide 20 mg/day, experienced dose-limiting toxicity. 15 mg lenalidomide was defined as MTD. A complete hematologic response was achieved in 42% at the dose of 15 mg of lenalidomide / day. After a median follow-up of 19 months, estimated 2-year overall survival and event-free survival (EFS) were 80.8% and 53.8%, respectively. Hematologic and organ responses were both associated with superior EFS rates (p = .0001). A higher EFS was also observed in patients whose free light chains decreased by more than 50% during therapy (p = .019). Lenalidomide 15 mg/day plus M-dex is a new effective combination therapy in patients with newly diagnosed AL. This study is registered at http://clinicaltrials.gov as #NCT00621400.

Combination therapy of bortezomib with novel targeted agents: an emerging treatment strategy.

Wright JJ.

Clin Cancer Res. 2010 Aug 15;16(16):4094-104. [Epub 2010 Aug 3.]

http://www.ncbi.nlm.nih.gov/pubmed/20682705

The author discusses clinical trials evaluating combinations of targeted agents with bortezomib, with the objective of enhancing its single agent activity in hematologic malignancies (including myeloma), as well as expanding its efficacy in solid tumors.

Clinical trials evaluating combinations of targeted agents with bortezomib, the first-in-class proteasome inhibitor, have been initiated, with the objective of enhancing its single agent activity in hematologic malignancies (myeloma, mantle cell lymphoma), as well as expanding its efficacy in solid tumors. In most cases, preclinical studies have provided a supportive rationale for designing these doublet combination studies. Novel, small molecule-targeted agents being investigated with bortezomib in clinical trials include protein deacetylase inhibitors, kinase inhibitors, farnesyltransferase inhibitors, heat-shock protein 90 inhibitors, pan-Bcl-2 family inhibitors, and other classes of targeted inhibitors. Preliminary clinical data, available from a number of ongoing trials, suggest that most of these combinations are well tolerated and some have promising clinical efficacy that will require subsequent confirmation. Translational studies, conducted as part of the trials, may provide important insights into the putative mechanism of action delineated by preclinical studies of the combinations. The emergence of novel proteasome inhibitors may also expand the opportunities for optimizing these combination therapies. There is potential for an increasingly broad clinical trials program to investigate this therapeutic approach in a range of tumor types, as well as to consider additional agents in sequence or in combination.

The efficacy and safety of lenalidomide plus dexamethasone in relapsed and/or refractory multiple myeloma patients with impaired renal function.

Dimopoulos M, Alegre A, Stadtmauer EA, Goldschmidt H, Zonder JA, de Castro CM, Masliak Z, Reece D, Olesnyckyj M, Yu Z, Weber DM.

Cancer. 2010 Aug 15;116(16):3807-14.

http://www.ncbi.nlm.nih.gov/pubmed/20564094

This retrospective analysis finds that, with careful monitoring of the CL(Cr) level and adverse events as well as appropriate dose adjustments, lenalidomide plus dexamethasone is an effective and well tolerated treatment option for patients with multiple myeloma who have renal impairment.

BACKGROUND:: In patients with multiple myeloma, renal impairment (RI) at the time of diagnosis is associated with poor survival. To the authors' knowledge, the current retrospective analysis presented is the first to assess the impact of various degrees of renal dysfunction on safety and efficacy outcomes in a large cohort of patients with relapsed and/or refractory multiple myeloma who received treatment with lenalidomide plus dexamethasone. METHODS:: Three hundred fifty-three patients from two large phase III trials were randomized to receive lenalidomide (25 mg) plus dexamethasone (40 mg). For the purpose of this analysis, RI was defined according to the calculated creatinine clearance (CL(Cr)) level as follows: mild or no RI (CL(Cr) >/= 60 mL/minute), moderate RI (CL(Cr) from >/= 30 mL/minute to <60 mL/minute), and severe RI (CL(Cr) <30 mL/minute). RESULTS:: The RI subgroups did not differ significantly in terms of the overall response rate (range, 50%-64%) or response quality (very good partial response or better, 27%-37%). In all RI subgroups, the time to progression and progression-free survival did not differ significantly compared with the mild or no RI group. Patients with RI experienced an increased incidence of thrombocytopenia, required more frequent lenalidomide dose reduction or interruption, and had shorter overall survival than patients with mild or no RI (p = .006). Lenalidomide plus dexamethasone led to improvement in renal function in the majority of patients. CONCLUSIONS:: The results from this study indicated that, with careful monitoring of the CL(Cr) level and adverse events as well as appropriate dose adjustments, lenalidomide plus dexamethasone is an effective and well tolerated treatment option for patients with multiple myeloma who have RI.

Bortezomib Plus Dexamethasone Induction Improves Outcome of Patients With t(4;14) Myeloma but Not Outcome of Patients With del(17p).

Avet-Loiseau H, Leleu X, Roussel M, Moreau P, Guerin-Charbonnel C, Caillot D, Marit G, Benboubker L, Voillat L, Mathiot C, Kolb B, Macro M, Campion L, Wetterwald M, Stoppa AM, Hulin C, Facon T, Attal M, Minvielle S, Harousseau JL.

J Clin Oncol. 2010 Aug 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20644101

The authors find that short-term bortezomib induction improves outcome of patients with t(4;14) but not the outcome of patients with del(17p). However, both abnormalities remain prognostic factors predicting both event-free survival and overall survival despite bortezomib induction.

PURPOSE: Cytogenetics is an important prognostic parameter in multiple myeloma (MM). Patients presenting with either t(4;14) or del(17p) are known to have a short event-free survival (EFS) and overall survival (OS). Some preliminary data suggest that bortezomib is able to overcome these prognostic parameters. PATIENTS and METHODS: A series of 507 patients with newly diagnosed MM who received four cycles of bortezomib-dexamethasone induction therapy before high-dose melphalan were analyzed for both t(4;14) and del(17p). RESULTS: We found that both t(4;14) and del(17p) remain prognostic parameters, even in the context of bortezomib treatment. However, it is important to note that bortezomib significantly improves the prognosis (in terms of both EFS and OS) of patients with t(4;14), compared with patients treated with vincristine, doxorubicin, and dexamethasone induction therapy. In contrast, no improvement was observed for del(17p) patients. CONCLUSION: Short-term bortezomib induction improves outcome of patients with t(4;14) but not the outcome of patients with del(17p). However, both abnormalities remain prognostic factors predicting both EFS and OS despite bortezomib induction.

Kidney dysfunction during lenalidomide treatment for AL amyloidosis.

Specter R, Sanchorawala V, Seldin DC, Shelton A, Fennessey S, Finn KT, Zeldis JB, Dember LM.

Nephrol Dial Transplant. 2010 Aug 5. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20693160

The authors aim to characterize alterations in kidney function among patients with AL amyloidosis undergoing treatment with lenalidomide. They find that among patients with AL amyloidosis, worsening of kidney function occurs frequently during lenalidomide treatment; while a causal role of the drug has not been established, these findings suggest that kidney function should be monitored closely during treatment with this drug.

BACKGROUND: Lenalidomide is an immunomodulatory agent used to treat plasma cell dyscrasias. We previously observed worsening of kidney function in a high proportion of patients with AL amyloidosis during lenalidomide treatment. The objective of this study is to characterize alterations in kidney function among patients with AL amyloidosis undergoing treatment with lenalidomide. METHODS: This is a secondary analysis of an ongoing clinical trial at a single referral centre. Forty-one patients with AL amyloidosis received lenalidomide with or without dexamethasone in monthly cycles. Kidney dysfunction was defined as >/= 50% increase in serum creatinine. Severe kidney dysfunction was defined as >/= 100% increase in serum creatinine. Recovery of renal function was defined as a return of serum creatinine to within 25% of the pre-treatment value or discontinuation of dialysis. RESULTS: Twenty-seven of 41 patients (66%) developed kidney dysfunction during lenalidomide treatment. The kidney dysfunction was severe in 13 of these patients (32%); four of whom required initiation of dialysis (10%). The median time to kidney dysfunction after starting lenalidomide was 44 days (interquartile range 15-108 days). Four of eight patients without underlying renal amyloidosis developed kidney dysfunction. Patients with severe kidney dysfunction were older and had a higher frequency of underlying renal amyloidosis, greater urinary protein excretion, and lower serum albumin. Recovery of renal function occurred in 12 patients (44%). CONCLUSIONS: Among patients with AL amyloidosis, worsening of kidney function occurs frequently during lenalidomide treatment. While a causal role of the drug has not been established, our findings suggest that kidney function should be monitored closely during treatment with this drug.

Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.

Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, Avigan DE, Xie W, Ghobrial IM, Schlossman RL, Mazumder A, Munshi NC, Vesole DH, Joyce R, Kaufman JL, Doss D, Warren DL, Lunde LE, Kaster S, Delaney C, Hideshima T, Mitsiades CS, Knight R, Esseltine DL, Anderson KC.

Blood. 2010 Aug 5;116(5):679-86. [Epub 2010 Apr 12.]

http://www.ncbi.nlm.nih.gov/pubmed/20385792

This phase I/II study, the first prospective evaluation of lenalidomide-bortezomib-dexamethasone in front-line myeloma, finds that the combination demonstrates favorable tolerability and is highly effective in the treatment of newly diagnosed myeloma.

This phase I/II study is the first prospective evaluation of lenalidomide-bortezomib-dexamethasone in front-line myeloma. Patients (n = 66) received eight 3-week cycles of bortezomib 1.0-1.3 mg/m² (days 1, 4, 8, 11), lenalidomide 15-25 mg (days 1-14), and dexamethasone 40 or 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12). Responding patients proceeded to maintenance or transplant. Phase II dosing was determined to be bortezomib 1.3 mg/m², lenalidomide 25 mg, and dexamethasone 20 mg. Most common toxicities included sensory neuropathy (80%) and fatigue (64%), with only 27%/2% and 32%/3% grade 2/3, respectively. Additionally, 32% reported neuropathic pain (11%/3% grade 2/3). Grade 3/4 hematologic toxicities included lymphopenia (14%), neutropenia (9%), and thrombocytopenia (6%). Thrombosis was rare (6% overall) and no treatment-related mortality was seen. Rate of partial response was 100% in both the phase II population and overall, with 74% and 67% each achieving very good partial response or better. Twenty eight patients (42%) proceeded to transplant. With median follow-up of 21 months, estimated 18-month progression-free and overall survival for the combination treatment with/without transplant was 75% and 97%, respectively. Lenalidomide-bortezomib-dexamethasone demonstrates favorable tolerability and is highly effective in the treatment of newly diagnosed myeloma. This study is registered at http://clinicaltrials.gov as #NCT00378105.

No influence of the polymorphisms CYP2C19 and CYP2D6 on the efficacy of cyclophosphamide, thalidomide, and bortezomib in patients with Multiple Myeloma.

Vangsted AJ, Søeby K, Klausen TW, Abildgaard N, Andersen NF, Gimsing P, Gregersen H, Vogel U, Werge T, Rasmussen HB.

BMC Cancer. 2010 Aug 4;10:404.

http://www.ncbi.nlm.nih.gov/pubmed/20684753

The authors explore the potential influence of different polymorphisms in the CYP enzymes on the outcome of myeloma treatment. They find that there is no association between functional CYP2C19 and CYP2D6 alleles and treatment outcome in myeloma patients treated with cyclophosphamide, thalidomide or bortezomib; a larger number of patients treated with bortezomib are needed to determine the role of CYP2D6 alleles in treatment outcome.

BACKGROUND: The response to treatment varies among patients with multiple myeloma and markers for prediction of treatment outcome are highly needed. Bioactivation of cyclophosphamide and thalidomide, and biodegradation of bortezomib, is dependent on cytochrome P450 metabolism. We explored the potential influence of different polymorphisms in the CYP enzymes on the outcome of treatment. METHODS: Data was analyzed from 348 patients undergoing high-dose treatment and stem cell support in Denmark in 1994 to 2004. Clinical information on relapse treatment in 243 individual patients was collected. The patients were genotyped for the non-functional alleles CYP2C19*2 and CYP2D6*3, *4, *5 (gene deletion), *6, and CYP2D6 gene duplication. RESULTS: In patients who were treated with bortezomib and were carriers of one or two defective CYP2D6 alleles there was a trend towards a better time-to-next treatment. We found no association between the number of functional CYP2C19 and CYP2D6 alleles and outcome of treatment with cyclophosphamide or thalidomide. Neither was the number of functional CYP2C19 and CYP2D6 alleles associated with neurological adverse reactions to thalidomide and bortezomib. CONCLUSION: There was no association between functional CYP2C19 and CYP2D6 alleles and treatment outcome in multiple myeloma patients treated with cyclophosphamide, thalidomide or bortezomib. A larger number of patients treated with bortezomib are needed to determine the role of CYP2D6 alleles in treatment outcome.

Recent advances of IMiDs in cancer therapy.

Li S, Gill N, Lentzsch S.

Curr Opin Oncol. 2010 Aug 4. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20689431

The authors provide a review on the recent advances in the development of IMiDs, including newly established guidelines for venous thromboembolism prophylaxis and stem cell mobilization failure associated with lenalidomide treatment.

PURPOSE OF REVIEW: Immunomodulatory derivatives of thalidomide (IMiDs) have been used for the treatment of myelodysplastic syndrome and multiple myeloma; however, the mechanism of action of IMiDs is largely unknown. The purpose of this review is to provide an overview of recent findings on the mechanism of action of IMiDs, its use as a new treatment modality for various hematologic malignancies, and problems associated with stem cell mobilization after lenalidomide treatment. RECENT FINDINGS: Recent clinical trials revealed lenalidomide as a promising new agent for the treatment of follicular non-Hodgkin's lymphoma (NHL) and also diffuse large B-cell lymphoma. Pomalidomide was shown to be even more effective in refractory multiple myeloma than lenalidomide. New guidelines for the management of venous thromboembolism have been established. The chemokine receptor 4 (CXCR4) inhibitor, AMD-3100, is recommended for patients who have received lenalidomide and failed to mobilize stem cells after G-SCF and cyclophosphamide. Preclinical studies investigated the pleiotropic functions of IMiDs, with a particular focus on immune modulation, their effects on new targets, stem cells and disruption of plasma cell microenvironment interactions. SUMMARY: More and more indications for the use of IMiDs in hematologic malignancies have been identified. In order to establish better clinical usage of IMiDs, it is of utmost importance to clarify the antitumor mechanism of IMiDs. Here, we provide a review on the recent advances in the development of IMiDs. New guidelines for venous thromboembolism prophylaxis and stem cell mobilization failure associated with lenalidomide treatment have been established.

Bortezomib added to high-dose melphalan as pre-transplant conditioning is safe in patients with heavily pre-treated multiple myeloma.

Thompson PA, Prince HM, Seymour JF, Ritchie D, Stokes K, Burbury K, Wolf M, Peinert S, Joyce T, Harrison SJ.
Bone Marrow Transplant. 2010 Aug 2. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20676149

No abstract available.

Immunoglobulin D multiple myeloma: response to therapy, survival, and prognostic factors in 75 patients.

Kim MK, Suh C, Lee DH, Min CK, Kim SJ, Kim K, Moon JH, Yoon SS, Lee GW, Kang HJ, Kim SH, Choi CW, Eom HS, Kwak JY, Kim HJ, Mun YC, Bang SM, Lee K, Shin HJ, Lee JH; Korean Multiple Myeloma Working Party.
Ann Oncol. 2010 Aug 2. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20682550

To analyze the clinical features, outcomes including efficacy of treatment, and prognostic factors of patients with immunoglobulin D multiple myeloma (IgD MM, 75 patients diagnosed with IgD MM are selected from the Korean Myeloma Registry database. Sixteen patients receive first-line chemotherapy including bortezomib or thalidomide, with an overall response rate of 81%. The authors conclude, however, that despite positive initial response, survival after relapse is dismal.

BACKGROUND: To analyze the clinical features, outcomes including efficacy of treatment, and prognostic factors of patients with immunoglobulin D multiple myeloma (IgD MM). Design and methods: Seventy-five patients diagnosed with IgD MM were selected from the Korean Myeloma Registry database (www.myeloma.or.kr). RESULTS: Median age was 57 years and the main presenting features were bone pain (77%). Renal function impairment and hypercalcemia were present in 40 (53%) and 20 (27%) patients. Sixty-seven patients (89%) had lambda light chains. Forty-eight patients (64%) were of stage III by International Staging System. Twenty-six patients (53%) had chromosomal abnormalities mostly by conventional cytogenetics. Thirty-nine patients (54%) were treated with vincristine, adriamycin, and dexamethasone chemotherapy; the overall response rate (ORR) of 56%. Sixteen patients (22%) received first-line chemotherapy including new drugs (bortezomib or thalidomide), with an ORR of 81%. At a median follow-up time of 28.6 months, median overall survival (OS) was 18.5 months. Age, extramedullary plasmacytoma, del(13) or hypoploidy, serum beta² microglobulin level, and platelet count were significant prognostic factors for OS.

CONCLUSIONS: IgD MM is an aggressive disease that is usually detected at an advanced stage. Despite a positive initial response, survival after relapse was dismal. Intensive treatment strategies before and following stem cell transplantation may improve outcomes in younger patients.

Access to thalidomide for the treatment of multiple myeloma in Canada: physician behaviours and ethical implications.

Minuk L, Sibbald R, Peng J, Bejaimal S, Chin-Yee I.

Curr Oncol. 2010 Aug;17(4):11-9.

http://www.ncbi.nlm.nih.gov/pubmed/20697510

The authors conclude that the current lack of access to thalidomide in Canada is a concerning problem for patients and health care providers dealing with myeloma. They state that regulatory changes at the federal level (Health Canada) need to be re-examined to promptly resolve this issue.

BACKGROUND: Multiple myeloma is an incurable malignancy. Since the late 1990s, its management has changed with the introduction of novel agents. Thalidomide, which is often called a "novel" therapy, has significantly prolonged survival in multiple myeloma and is considered worldwide to be part of standard of care in this disease. However, thalidomide is not approved in Canada, leading to problems with drug access for patients.

METHODS: Our study surveyed Canadian hematologists on their thalidomide prescribing practices and difficulties with drug access. We address some of the ethical issues facing patients and their doctors who are unable to obtain or afford the drug, and who therefore resort to alternative means such as illegal importation. RESULTS: Of the 411 Canadian hematologists contacted, 122 completed the survey, 97 reported that they did not treat myeloma, and 192 did not respond. Assuming that all non-responders treat myeloma, our estimated overall response rate from physicians who treat this disease was 39%. Survey participants indicated that, in Canada, access to thalidomide is a major issue for physicians and myeloma patients alike, and that 81% of respondents are dissatisfied or very dissatisfied with the drug access process. Many physicians felt that the special access process for thalidomide is unduly onerous, influences treatment decisions, and invades patient privacy. We found that 20% of physicians were unaware of the legal implications of obtaining thalidomide from other countries and that at least 23% overtly or covertly support patients in obtaining the drug from a non-Health-Canada-approved source. CONCLUSIONS: The current lack of access to thalidomide in Canada is a concerning problem for patients and health care providers dealing with myeloma. Regulatory changes at the federal level (Health Canada) need to be re-examined to promptly resolve this issue.

The addition of cyclophosphamide to lenalidomide and dexamethasone in multiply relapsed/refractory myeloma patients; a phase I/II study.

Schey SA, Morgan GJ, Ramasamy K, Hazel B, Ladon D, Corderoy S, Jenner M, Phekoo K, Boyd K, Davies FE.

Br J Haematol. 2010 Aug;150(3):326-33. [Epub 2010 Jun 10.]

http://www.ncbi.nlm.nih.gov/pubmed/20553268

This phase I/II dose escalation study finds that lenalidomide, cyclophosphamide and dexamethasone is a safe, effective combination in relapsed myeloma inducing a high response rate, warranting further investigation in phase III trials.

Summary We report the results of a phase I/II dose escalation study to determine the maximum tolerated dose (MTD) of cyclophosphamide when combined with lenalidomide and dexamethasone in relapsed/refractory myeloma. Thirty-one patients were enrolled in cohorts of 3, at five dose levels of cyclophosphamide to a maximum of 700 mg on days 1 and 8 of a 28-d cycle. Patients received lenalidomide 25 mg days 1-21 and dexamethasone 20 mg orally days 1-4 and 8-11. The MTD was 600 mg cyclophosphamide, days 1 and 8. Grade 3/4 haematological complications occurred in 26% of patients, grade 3/4 infection in 3% (both at 700 mg cyclophosphamide), with thromboembolic complications in 6% of patients. Overall complete response (CR) rate was 29%, very good partial response rate 7% and partial response rate 45% giving an overall response rate of 81%. After 21 months median follow-up, projected 2-year progression-free survival was 56%, with 80% overall survival at 30 months. Ten further patients were treated at MTD with a 40% CR rate. No dose reductions for any study drugs or deaths occurred during cycles 1-9. Lenalidomide, cyclophosphamide and dexamethasone is a safe, effective combination in relapsed myeloma inducing a high response rate, warranting further investigation in phase III trials.

Bortezomib-based therapy as induction regimen of an autograft program in front-line treatment of multiple myeloma with end-stage renal disease.

Siniscalchi A, Dentamaro T, Perrotti A, Tatangelo P, de Fabritiis P, Caravita T.

Ann Hematol. 2010 Aug;89(8):821-2. [Epub 2009 Dec 2.]

http://www.ncbi.nlm.nih.gov/pubmed/19953253

No abstract available.

Bortezomib-resistant myeloma cell lines: a role for mutated PSMB5 in preventing the accumulation of unfolded proteins and fatal ER stress.

Ri M, Iida S, Nakashima T, Miyazaki H, Mori F, Ito A, Inagaki A, Kusumoto S, Ishida T, Komatsu H, Shiotsu Y, Ueda R.

Leukemia. 2010 Aug;24(8):1506-12. [Epub 2010 Jun 17.]

http://www.ncbi.nlm.nih.gov/pubmed/20555361

To investigate the underlying mechanisms associated with acquired resistance to bortezomib, the authors establish two bortezomib-resistant myeloma cell lines. They find that a fraction of myeloma cells may acquire bortezomib resistance by suppressing apoptotic signals through the inhibition of unfolded protein accumulation and subsequent excessive ER stress by a mutation of the PSMB5 gene.

Bortezomib is an effective agent for treating multiple myeloma (MM). To investigate the underlying mechanisms associated with acquired resistance to this agent, we established two bortezomib-resistant MM cell lines, KMS-11/BTZ and OPM-2/BTZ, the 50% inhibitory concentration values of which were respectively 24.7- and 16.6-fold higher than their parental cell lines. No activation of caspase and BH3-only proteins such as Noxa was noted in bortezomib-resistant cells after exposure to the drug. The accumulation of polyubiquitinated proteins was reduced in bortezomib-resistant cells compared with the parental cells, associated with avoidance of catastrophic ER stress as assessed by downregulation of CHOP expression. These resistant MM cells have a unique point mutation, G322A, in the gene encoding the proteasome beta5 subunit (PSMB5), likely resulting in conformational changes to the bortezomib-binding pocket of this subunit. KMS-11 parental cells transfected to express mutated PSMB5 also showed reduced bortezomib-induced apoptosis compared with those expressing wild-type PSMB5 or the parental cells. Expression of mutated PSMB5 was associated with the prevention of the accumulation of unfolded proteins. Thus, a fraction of MM cells may acquire bortezomib resistance by suppressing apoptotic signals through the inhibition of unfolded protein accumulation and subsequent excessive ER stress by a mutation of the PSMB5 gene.

Consensus guidelines for the optimal management of adverse events in newly diagnosed, transplant-ineligible patients receiving melphalan and prednisone in combination with thalidomide (MPT) for the treatment of multiple myeloma.

Palumbo A, Davies F, Kropff M, Bladé J, Delforge M, Leal da Costa F, García-Sanz R, Schey S, Facon T, Morgan G, Moreau P.

Ann Hematol. 2010 Aug;89(8):803-11. [Epub 2010 Mar 16.]

http://www.ncbi.nlm.nih.gov/pubmed/20232066

This article outlines both evidence- and consensus-based recommendations discussed by a panel of experts in order to provide a practical guide for physicians addressing the effective management of newly diagnosed, transplant-ineligible myeloma patients receiving thalidomide therapy.

Thalidomide has received approval from the European Agency for the Evaluation of Medicinal Products for the treatment of newly diagnosed multiple myeloma (MM) patients older than 65 years or ineligible for transplant. The results of five phase III trials assessing thalidomide in combination with melphalan and prednisone (MPT) have demonstrated significantly improved response rates compared with melphalan and prednisone (MP) alone. Additionally, two of these studies showed that survival was extended by approximately 18 months in patients treated with MPT compared with MP alone. Thalidomide, in combination with MP, is associated with adverse events (AEs) including peripheral neuropathy and venous thromboembolism. In order to optimize the efficacy of MPT, a good awareness of

these AEs is imperative. This manuscript outlines both evidence- and consensus-based recommendations discussed by a panel of experts, to provide a practical guide for physicians addressing the effective management of newly diagnosed, transplant-ineligible MM patients receiving thalidomide therapy.

Consensus statement from European experts on the diagnosis, management, and treatment of multiple myeloma: from standard therapy to novel approaches.

Engelhardt M, Kleber M, Udi J, Wäsch R, Spencer A, Patriarca F, Knop S, Bruno B, Gramatzki M, Morabito F, Kropff M, Neri A, Sezer O, Hájek R, Bunjes D, Boccadoro M, Straka C, Cavo M, Polliack A, Einsele H, Palumbo A.

Leuk Lymphoma. 2010 Aug;51(8):1424-43.

http://www.ncbi.nlm.nih.gov/pubmed/20509769

This report reviews recent clinical advances in the treatment strategies available for myeloma, including the use of thalidomide, lenalidomide, and bortezomib, and provides an overview of the state of the art management of patients with myeloma.

Treatment for multiple myeloma (MM) has changed beyond recognition over the past two decades. During the early 1980s, MM inevitably resulted in a slow progressive decline in quality of life until death after about 2 years, while today patients can expect a 50% chance of achieving a complete remission, median survival of 5 years, and a 20% chance of surviving longer than 10 years. An international expert opinion meeting (including members of the GIMEMA and DSMM study groups) was held in 2009. One of the outcomes of the meeting was the development of a consensus statement outlining contemporary optimal clinical practice for the treatment of MM. The international panel recommended that the state of the art therapy for MM should comprise: (a) evidence-based supportive care, (b) effective and well-tolerated chemotherapeutic regimens, (c) autologous hematopoietic stem cell transplant (ASCT) for patients suitable for intensive conditioning therapy, and (d) evidence-based incorporation of novel anti-MM agents. Maintenance strategies have also become increasingly important for the prolongation of remission after front-line therapies. In addition, improved understanding of the biology of MM has led to the development of novel biological therapeutic agents such as thalidomide, lenalidomide, bortezomib, and others. These agents specifically target intracellular mechanisms and interactions, such as those within the bone marrow microenvironment, and have been integrated into MM treatment. This report reviews recent clinical advances in the treatment strategies available for MM and provides an overview of the state of the art management of patients with MM.

Hematology: Is thalidomide combination a new option for myeloma?

Palumbo A.

Nat Rev Clin Oncol. 2010 Aug;7(8):425-6.

http://www.ncbi.nlm.nih.gov/pubmed/20668477

No abstract available.

Inhibition of the ubiquitin-proteasome system by natural products for cancer therapy.

Tsukamoto S, Yokosawa H.

Planta Med. 2010 Aug;76(11):1064-74. [Epub 2010 Feb 25.]

http://www.ncbi.nlm.nih.gov/pubmed/20186654

The authors review natural products targeting the ubiquitin-proteasome system as well as synthetic compounds with potent inhibitory effects, including the use of lenalidomide.

The ubiquitin-proteasome system plays a critical role in selective protein degradation and regulates almost all cellular events such as cell cycle progression, signal transduction, cell death, immune responses, metabolism, protein quality control, development, and neuronal function. The recent approval of bortezomib, a synthetic proteasome inhibitor, for the treatment of relapsed multiple myeloma has opened the way to the discovery of drugs targeting the proteasome and ubiquitinating and deubiquitinating enzymes as well as the delivery system. To date, various synthetic and natural products have been reported to inhibit the components of the ubiquitin-proteasome system. Here, we review natural products targeting the ubiquitin-proteasome system as well as synthetic compounds with potent inhibitory effects.

Melphalan, prednisone, and thalidomide versus thalidomide, dexamethasone, and pegylated liposomal doxorubicin regimen in very elderly patients with multiple myeloma: a case-match study.

Offidani M, Leoni P, Bringhen S, Corvatta L, Larocca A, Gentili S, Oliva S, Polloni C, Galieni P, Catarini M, Alesiani F, Mele A, Brunori M, Blasi N, Ferranti M, Visani G, Boccadoro M, Palumbo A.

Leuk Lymphoma. 2010 Aug;51(8):1444-9.

http://www.ncbi.nlm.nih.gov/pubmed/20496998

The authors find that thalidomide, dexamethasone, and pegylated liposomal doxorubicin can be considered a therapeutic option in very elderly myeloma patients, since it induces a faster and deeper response than that obtained with melphalan, prednisone, thalidomide, and has a similar safety profile.

The outcome of patients with multiple myeloma (MM) aged over 75 years remains poor, and the best therapeutic approach has still to be defined. We compared the response, toxicity, and outcome of 34 very elderly patients with MM receiving thalidomide, dexamethasone, and pegylated liposomal doxorubicin (ThaDD) to those of 34 patients matched for age, International Staging System (ISS), and creatinine who received melphalan, prednisone, thalidomide (MPT). ThaDD resulted in a significantly higher response: >/=PR (87.5% vs. 61.5%, p = 0.009) and >/=VGPR (55.5% vs. 29.5%; p = 0.03). No statistical differences were detected in terms of median probability of progression-free survival (PFS) and overall survival (OS) between the two treatments. Patients treated with MPT had more neutropenia, neuropathy, and heart toxicity, whereas thromboembolism resulted more frequently in patients receiving ThaDD. Therapy discontinuation occurred in 9% and 14.5% of patients treated with ThaDD and MPT, respectively. ThaDD can be considered a therapeutic option in very elderly patients with MM since it induces a faster and deeper response than that obtained with MPT, having similar safety profile.

Prediction of treatment efficacy by the M-protein reduction rate after the first cycle of VAD therapy for multiple myeloma.

Momma Y, Shinagawa A, Katsura T, Yoshida C, Chikatsu N, Kudo D, Komeno T.

Rinsho Ketsueki. 2010 Aug;51(8):685-9.

http://www.ncbi.nlm.nih.gov/pubmed/20805676

The findings of this retrospective study suggest that a change from conventional to novel therapeutic drugs (such as bortezomib and thalidomide) in refractory cases of myeloma can be a beneficial treatment strategy.

In recent years, novel drugs for multiple myeloma such as bortezomib and thalidomide have been shown to be effective. However, in Japan, these drugs are indicated only for patients with relapsed or refractory multiple myeloma. There are no established criteria for the definition of refractory cases, and it is often difficult to determine when treatment methods should be changed for those cases. Therefore, we performed a retrospective study to investigate whether treatment responses can be predicted in the early stage of VAD therapy. After the first and third cycles of VAD, the M-protein reduction rate was evaluated. As a result, it was estimated with a 50% probability that an M-protein reduction rate of 87.6% (lower limit of the 95% CI, 73.9%) after the first cycle of VAD can predict a reduction of 90% after the third cycle. The progression-free survival period was slightly longer in the group achieving 90% M-protein reduction after the third cycle than in the group who did not achieve this rate (3.3 vs. 2.2 years, p=0.09). These findings suggest that a change from conventional to novel therapeutic drugs in refractory cases identified by the responses to the first cycle of VAD can be a beneficial treatment strategy.

Primary therapy with single agent bortezomib as induction, maintenance and re-induction in patients with high-risk myeloma: results of the ECOG E2A02 trial.

Dispenzieri A, Jacobus S, Vesole DH, Callandar N, Fonseca R, Greipp PR.

Leukemia. 2010 Aug;24(8):1406-11. [Epub 2010 Jun 10.]

http://www.ncbi.nlm.nih.gov/pubmed/20535147

As the first to prospectively explore single agent bortezomib as primary therapy (induction, maintenance and re-induction) without consolidative autologous stem cell transplant in a cohort selected to have high-risk multiple myeloma, the authors find that in high-risk patients, upfront bortezomib results in response rates that are comparable to those reported for unselected cohorts, but that single agent bortezomib is not sufficient as primary therapy.

Single agent bortezomib results in response rates of 51% in patients with newly diagnosed multiple myeloma and is touted to be especially effective in high-risk disease. We are the first to prospectively explore single agent bortezomib as primary therapy (induction, maintenance and re-induction) without consolidative autologous stem cell transplant in a cohort selected to have high-risk multiple myeloma. Patients received eight cycles of induction, followed by maintenance bortezomib every other week, indefinitely. Patients relapsing on maintenance had the full induction schedule resumed. On an intention-to-treat basis, the response rate (>/=partial response) was 48%. Among seven patients who progressed on maintenance bortezomib and received re-induction, two responded to the treatment. With a median follow-up of 48.2 months, 1- and 2-year overall survival probabilities were 88% (95% confidence interval (CI) 79-98%) and 76% (95% CI 60-86%), respectively. Median progression-free survival was 7.9 months (95% CI 5.8-12.0). Twenty-three and thirty-four patients had >/=grade 3 hematological and non-hematological toxicity, respectively, with treatment-emergent neuropathy in 7% with motor grade 1-2, 56% with sensory grade 1-2 and 2% with grade 3, and in 14% with neuropathic pain grade 1-2 and 2% with grade 3. In high-risk patients, up-front bortezomib results in response rates that are comparable to those reported for unselected cohorts, but single agent bortezomib is not sufficient as primary therapy.

The proteasome inhibitor bortezomib disrupts tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expression and natural killer (NK) cell killing of TRAIL receptor-positive multiple myeloma cells.

Feng X, Yan J, Wang Y, Zierath JR, Nordenskjöld M, Henter JI, Fadeel B, Zheng C.

Mol Immunol. 2010 Aug;47(14):2388-96. [Epub 2010 Jun 9.]

http://www.ncbi.nlm.nih.gov/pubmed/20542572

The authors show that proteasome inhibition by bortezomib disrupts of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expression and TRAIL dependent and/or independent pathway-mediated killing of myeloma cells, suggesting that bortezomib may potentially hamper NK-dependent immunosurveillance against tumors in patients treated with this drug.

Bortezomib, a potent 26S proteasome inhibitor, is approved for the treatment of multiple myeloma (MM) and clinical trials are under way to evaluate its efficacy in other malignant diseases. However, cytotoxic effects of bortezomib on immune-competent cells have also been observed. In this study, we show that bortezomib downregulates cell surface expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on primary human interleukin (IL)-2-activated natural killer (NK) cells. Pharmacological inhibition of the transcription factor, NF-kappaB also profoundly decreased TRAIL expression, suggesting that NF-kappaB is involved in the regulation of TRAIL expression in activated human NK cells. Furthermore, perforin-independent killing of the human MM cell lines RPMI8226 and U266 by NK cells was markedly suppressed following bortezomib treatment. In addition, blocking cell surface-bound TRAIL with a TRAIL antibody impaired NK cell-mediated lysis of the TRAIL-sensitive MM cell line, RPMI8226. In conclusion, the proteasome is likely to be involved in the regulation of TRAIL expression in primary human IL-2-activated NK cells. Proteasome inhibition by bortezomib disrupts TRAIL expression and TRAIL dependent and/or independent pathway-mediated killing of myeloma cells, suggesting that bortezomib may potentially hamper NK-dependent immunosurveillance against tumors in patients treated with this drug.

Tanespimycin with bortezomib: activity in relapsed/refractory patients with multiple myeloma.

Richardson PG, Badros AZ, Jagannath S, Tarantolo S, Wolf JL, Albitar M, Berman D, Messina M, Anderson KC.

Br J Haematol. 2010 Aug;150(4):428-37. [Epub 2010 Jul 7.]

http://www.ncbi.nlm.nih.gov/pubmed/20618338

This phase II, open-label multicentre study compares 1.3 mg/m² bortezomib + three doses of tanespimycin: 50, 175 and 340 mg/m² in heavily pretreated patients with relapsed and refractory myeloma. The authors observe antitumour activity, with promising response rates.

Summary Tanespimycin (17-allylamino-17-demethoxygeldanamycin, 17-AAG) disrupts heat shock protein 90 (HSP90), a key molecular chaperone for signal transduction proteins critical to myeloma growth, survival and drug resistance. In previous studies, tanespimycin monotherapy was well tolerated and active in heavily pretreated patients with relapsed/refractory multiple myeloma (MM). Preclinical data have shown antitumour synergy between tanespimycin and bortezomib, with more pronounced intracellular accumulation of ubiquitinated proteins than either drug alone, an effect attributed to the synergistic suppression of chymotryptic activity in the 20S proteasome. HSP70 induction has been observed in all phase I tanespimycin studies in which it has been measured, with several separate reports of HSP70 overexpression protecting against peripheral nerve injury. In this phase II, open-label multicentre study, we compared 1.3 mg/m² bortezomib + three doses of tanespimycin: 50, 175 and 340 mg/m² in heavily pretreated patients with relapsed and refractory MM and measured HSP70 expression and proteasome activity levels in plasma of treated patients. The study was closed prematurely for resource-based reasons, precluding dose comparison. Nonetheless, antitumour activity was observed, with promising response rates and promising severity of peripheral neuropathy.

Thalidomide-dexamethasone as induction therapy before autologous stem cell transplantation in patients with newly diagnosed multiple myeloma and renal insufficiency.

Tosi P, Zamagni E, Tacchetti P, Ceccolini M, Perrone G, Brioli A, Pallotti MC, Pantani L, Petrucci A, Baccarani M, Cavo M.

Biol Blood Marrow Transplant. 2010 Aug;16(8):1115-21. [Epub 2010 Mar 1.]

http://www.ncbi.nlm.nih.gov/pubmed/20197100

The authors aim to evaluate the efficacy and the toxicity of thalidomide-dexamethasone as induction therapy before autologous peripheral blood stem cell (PBSC) transplantation in patients with newly diagnosed myeloma with renal insufficiency. They find thalidomide-dexamethasone is effective and safe in this patient group, and that given the relationship between recovery of renal function and response to induction treatment, more intensive thalidomide + bortezomib regimens could be explored to rescue higher numbers of patients.

The aim of this study was to evaluate the efficacy and the toxicity of thalidomide-dexamethasone (Thal-Dex) as induction therapy before autologous peripheral blood stem cell (PBSC) transplantation in patients with newly diagnosed multiple myeloma (MM) with renal insufficiency. The study included 31 patients with a baseline creatinine clearance value < or = 50 mL/min, 7 of whom required chronic hemodialysis. Patients received 4 months of Thal-Dex, followed by PBSC collection and subsequent transplantation. After induction, a partial response (PR) or greater was obtained in 23 patients (74%), including 8 (26%) who achieved a very good PR. Renal function improved more frequently in patients achieving a PR or greater (82%, vs. 37% in patients achieving less than a PR; p = .04). Twenty-six patients underwent PBSC mobilization; in 17 of these patients (65%), >4 x 10^6 CD34(+) cells/kg were collected. Double autologous transplantation was performed in 15 patients, and a single autologous transplantation was performed in 7 patients. After a median of 32 months of follow-up, median event-free survival was 30 months, and median survival was not determined. According to our data, Thal-Dex is effective and safe in patients with newly diagnosed MM and renal insufficiency. Given the relationship between recovery of renal function and response to induction treatment, more intensive Thal + bortezomib regimens could be explored to rescue higher numbers of patients.

July 2010

Histone deacetylases are critical targets of bortezomib-induced cytotoxicity in multiple myeloma.

Kikuchi J, Wada T, Shimizu R, Izumi T, Akutsu M, Mitsunaga K, Noborio-Hatano K, Nobuyoshi M, Ozawa K, Kano Y, Furukawa Y.

Blood. 2010 Jul 22;116(3):406-17. [Epub 2010 Mar 29.]

http://www.ncbi.nlm.nih.gov/pubmed/20351311

The authors show that histone deacetylases (HDACs) are critical targets of bortezomib, which specifically down-regulate the expression of class I HDACs (HDAC1, 2 and 3) in myeloma cell lines and primary myeloma cells at the transcriptional level, accompanied by reciprocal histone hyperacetylation. These results suggest that bortezomib targets HDACs via distinct mechanisms from conventional HDAC inhibitors, providing a novel molecular basis and rationale for the use of bortezomib in myeloma treatment.

Bortezomib is now widely used for the treatment of multiple myeloma (MM); however, its action mechanisms are not fully understood. Despite the initial results, recent investigations have indicated that bortezomib does not inactivate nuclear factor-kappaB activity in MM cells, suggesting the presence of other critical pathways leading to cytotoxicity. In this study, we show that histone deacetylases (HDACs) are critical targets of bortezomib, which specifically down-regulated the expression of class I HDACs (HDAC1, HDAC2, and HDAC3) in MM cell lines and primary MM cells at the transcriptional level, accompanied by reciprocal histone hyperacetylation. Transcriptional repression of HDACs was mediated by caspase-8-dependent degradation of Sp1 protein, the most potent transactivator of class I HDAC genes. Short-interfering RNA-mediated knockdown of HDAC1 enhanced bortezomib-induced apoptosis and histone hyperacetylation, whereas HDAC1 overexpression inhibited them. HDAC1 overexpression conferred resistance to bortezomib in MM cells, and administration of the HDAC inhibitor romidepsin restored sensitivity to bortezomib in HDAC1-overexpressing cells both in vitro and in vivo. These results suggest that bortezomib targets HDACs via distinct mechanisms from conventional HDAC inhibitors. Our findings provide a novel molecular basis and rationale for the use of bortezomib in MM treatment.

Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma.

Görgün G, Calabrese E, Soydan E, Hideshima T, Perrone G, Bandi M, Cirstea D, Santo L, Hu Y, Tai YT, Nahar S, Mimura N, Fabre C, Raje N, Munshi N, Richardson P, Anderson KC.

Blood. 2010 Jul 22. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20651070

The authors examine the in vitro immunomodulatory effects of immunomodulatory agents (IMiDs) on cytokine signaling triggered by interaction of effector cells with myeloma cells and bone marrow stromal cells. Their data demonstrate that modulation of suppressor of cytokine signaling 1 may enhance immune response and efficacy of IMiDs in myeloma.

The bone marrow (BM) microenvironment consists of extracellular-matrix and the cellular compartment including immune cells. Multiple myeloma (MM) cell and BM accessory cell interaction promotes MM survival via both cell-cell contact and cytokines. Immunomodulatory agents (IMiDs) target not only MM cells, but also MM cell-immune cell interactions and cytokine signaling. Here we examined the in vitro immunomodulatory effects of IMiDs on cytokine signaling triggered by interaction of effector cells with MM cells and BMSCs. IMiDs diminished IL-2, IFNgamma and IL-6 regulator suppressor of cytokine signaling (SOCS)1 expression in immune (CD4T, CD8T, NKT, NK) cells from both BM and PB of MM patients. Additionally, coculture of MM cells with healthy PBMCs induced SOCS1 expression in effector cells; conversely, treatment with IMiDs downregulated the SOCS1 expression. SOCS1 negatively regulates IL-6 signaling and is silenced by hypermethylation in MM cells. To define the mechanism of inhibitory-cytokine signaling in effector cells and MM cells, we next analysed the interaction of immune cells with MM cells that were epigenetically modified to re-express SOCS1; IMiDs induced more potent CTL responses against SOCS1 re-expressing-MM cells than unmodified MM cells. These data therefore demonstrate that modulation of SOCS1 may enhance immune response and efficacy of IMiDs in MM.

Activity and safety of lenalidomide and dexamethasone in multiple myeloma patients requiring dialysis: a Spanish multicenter retrospective study.

de la Rubia J, Roig M, Ibáñez A, García I, Vera JA, Aguilar C, Del Campo R, González N, Martínez R, Palomera L, Picón I, Rodríguez JN, Sanz MA.

Eur J Haematol. 2010 Jul 21. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20662900

This retrospective analysis of 15 myeloma patients who required dialysis at the time of lenalidomide administration suggest that lenalidomide-based regimens can be used in myeloma patients requiring dialysis, with a good response rate.

Lenalidomide is an immunomodulating agent indicated for the treatment of relapsed multiple myeloma (MM). However, experience in patients with MM and dialysis support is limited. We underwent a retrospective analysis in 15 patients with MM who required dialysis at the time of lenalidomide administration. In 14 cases lenalidomide was given in combination with dexamethasone. Patients were given a median of 8 cycles (range, 1-28) of treatment. Neutropenia was the toxicity most commonly observed (10 patients) and 2 patients died due to infectious complications. Overall and complete response rate was 60% and 29%, respectively. These results suggest that lenalidomide-based regimens can be used in MM patients requiring dialysis, with a good response rate. The high incidence of neutropenia and infectious complications highlights the need of a close monitoring of these patients.

Effect of noncompetitive proteasome inhibition on bortezomib resistance.

Li X, Wood TE, Sprangers R, Jansen G, Franke NE, Mao X, Wang X, Zhang Y, Verbrugge SE, Adomat H, Li ZH, Trudel S, Chen C, Religa TL, Jamal N, Messner H, Cloos J, Rose DR, Navon A, Guns E, Batey RA, Kay LE, Schimmer AD.

J Natl Cancer Inst. 2010 Jul 21;102(14):1069-82. [Epub 2010 May 26.]

http://www.ncbi.nlm.nih.gov/pubmed/20505154

The authors hypothesize that proteasome inhibitors that act through a noncompetitive mechanism might overcome some forms of bortezomib resistance and find that 5-amino-8-hydroxyquinoline can overcome some forms of bortezomib resistance in vitro.

BACKGROUND: Bortezomib and the other proteasome inhibitors that are currently under clinical investigation bind to the catalytic sites of proteasomes and are competitive inhibitors. We hypothesized that proteasome inhibitors that act through a noncompetitive mechanism might overcome some forms of bortezomib resistance. METHODS: 5-amino-8-hydroxyquinoline (5AHQ) was identified through a screen of a 27-compound chemical library based on the quinoline pharmacophore to identify proteasome inhibitors. Inhibition of proteasome activity by 5AHQ was tested by measuring 7-amino-4-methylcoumarin (AMC) release from the proteasome substrate Suc-LLVY-AMC in intact human and mouse leukemia and myeloma cells and in tumor cell protein extracts. Cytotoxicity was assessed in 5AHQ-treated cell lines and primary cells from myeloma and leukemia patients using AlamarBlue fluorescence and MTS assays, trypan blue staining, and annexin V staining. 5AHQ-proteasome interaction was assessed by nuclear magnetic resonance. 5AHQ efficacy was evaluated in three leukemia xenograft mouse models (9-10 mice per group per model). All statistical tests were two-sided. RESULTS: 5AHQ inhibited the proteasome when added to cell extracts and intact cells (the mean concentration inhibiting 50% [IC(50)] of AMC release in intact cells ranged from 0.57 to 5.03 microM), induced cell death in intact cells from leukemia and myeloma cell lines (mean IC(50) values for cell growth ranged from 0.94 to 3.85 microM), and preferentially induced cell death in primary myeloma and leukemia cells compared with normal hematopoietic cells. 5AHQ was equally cytotoxic to human myelomonocytic THP1 cells and to THP1/BTZ500 cells, which are 237-fold more resistant to bortezomib than wild-type THP1 cells because of their overexpression and mutation of the bortezomib-binding beta5 proteasome subunit (mean IC(50) for cell death in the absence of bortezomib, wild-type THP1: 3.7 microM, 95% confidence interval = 3.4 to 4.0 microM; THP1/BTZ500: 6.6 microM, 95% confidence interval = 5.9 to 7.5 microM). 5AHQ interacted with the alpha subunits of the 20S proteasome at noncatalytic sites. Orally administered 5AHQ inhibited tumor growth in all three mouse models of leukemia without overt toxicity (e.g.,

OCI-AML2 model, median tumor weight [interquartile range], 5AHQ vs. control: 95.7 mg [61.4-163.5 mg] vs. 247.2 mg [189.4-296.2 mg], p = .002). CONCLUSIONS: 5AHQ is a noncompetitive proteasome inhibitor that is cytotoxic to myeloma and leukemia cells in vitro and inhibits xenograft tumor growth in vivo. 5AHQ can overcome some forms of bortezomib resistance in vitro.

Bortezomib Plus Dexamethasone Induction Improves Outcome of Patients With t(4;14) Myeloma but Not Outcome of Patients With del(17p).

Avet-Loiseau H, Leleu X, Roussel M, Moreau P, Guerin-Charbonnel C, Caillot D, Marit G, Benboubker L, Voillat L, Mathiot C, Kolb B, Macro M, Campion L, Wetterwald M, Stoppa AM, Hulin C, Facon T, Attal M, Minvielle S, Harousseau JL.

J Clin Oncol. 2010 Jul 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20644101

The authors find that short-term bortezomib induction improves outcome of myeloma patients with t(4;14) but not the outcome of patients with del(17p). However, both abnormalities remain prognostic factors predicting both event-free survival and overall survival despite bortezomib induction.

PURPOSE: Cytogenetics is an important prognostic parameter in multiple myeloma (MM). Patients presenting with either t(4;14) or del(17p) are known to have a short event-free survival (EFS) and overall survival (OS). Some preliminary data suggest that bortezomib is able to overcome these prognostic parameters. PATIENTS and METHODS: A series of 507 patients with newly diagnosed MM who received four cycles of bortezomib-dexamethasone induction therapy before high-dose melphalan were analyzed for both t(4;14) and del(17p). Results We found that both t(4;14) and del(17p) remain prognostic parameters, even in the context of bortezomib treatment. However, it is important to note that bortezomib significantly improves the prognosis (in terms of both EFS and OS) of patients with t(4;14), compared with patients treated with vincristine, doxorubicin, and dexamethasone induction therapy. In contrast, no improvement was observed for del(17p) patients. CONCLUSION: Short-term bortezomib induction improves outcome of patients with t(4;14) but not the outcome of patients with del(17p). However, both abnormalities remain prognostic factors predicting both EFS and OS despite bortezomib induction.

Betulinic acid suppresses STAT3 activation pathway through induction of protein tyrosine phosphatase SHP-1 in human multiple myeloma cells.

Pandey MK, Sung B, Aggarwal BB.

Int J Cancer. 2010 Jul 15;127(2):282-92.

http://www.ncbi.nlm.nih.gov/pubmed/19937797

This study finds that betulinic acid enhances the apoptosis induced by thalidomide (from 10 to 55%) and bortezomib (from 5 to 70%) in myeloma cells.

STAT3 activation has been associated with survival, proliferation and invasion of various human cancers. Whether betulinic acid, a pentacyclic triterpene, can modulate the STAT3 pathway, was investigated in human multiple myeloma (MM) cells. We found that betulinic acid inhibited constitutive activation of STAT3, Src kinase, JAK1 and JAK2. Pervanadate reversed the betulinic acid-induced downregulation of STAT3 activation, suggesting the involvement of a protein tyrosine phosphatase (PTP). Furthermore, betulinic acid induced the expression of the PTP SHP-1 and silencing of the SHP-1 gene abolished the ability of betulinic acid to inhibit STAT3 activation and rescued betulinic acid-induced cell death. Betulinic acid also downregulated the expression of STAT3-regulated gene products such as bcl-xL, bcl-2, cyclin D1 and survivin. This correlated with an increase in apoptosis as indicated by an increase in the sub-G1 cell population and an increase in caspase-3-induced PARP cleavage. Consistent with these results, overexpression of constitutive active STAT3 significantly reduced the betulinic acid-induced apoptosis. Betulinic acid also enhanced the apoptosis induced by thalidomide (from 10 to 55%) and bortezomib (from 5 to 70%) in MM cells. Overall, our results suggest that betulinic acid downregulates STAT3 activation through upregulation of SHP-1, and this may have potential in sensitization of STAT3 over-expressing tumors to chemotherapeutic agents.

XBP1s levels are implicated in the biology and outcome of myeloma mediating different clinical outcomes to thalidomide-based treatments.

Bagratuni T, Wu P, Gonzalez de Castro D, Davenport EL, Dickens NJ, Walker BA, Boyd K, Johnson DC, Gregory W, Morgan GJ, Davies FE.

Blood. 2010 Jul 15;116(2):250-3. [Epub 2010 Apr 26.]

http://www.ncbi.nlm.nih.gov/pubmed/20421453

This study highlights the importance of XBP1 in myeloma, its significance as an independent prognostic marker and as a predictor of thalidomide response.

Immunoglobulin production by myeloma plasma cells depends on the unfolded protein response for protein production and folding. Recent studies have highlighted the importance of IRE1alpha and X box binding protein 1 (XBP1), key members of this pathway, in normal B-plasma cell development. We have determined the gene expression levels of IRE1alpha, XBP1, XBP1UNSPLICED (XBP1u), and XBP1SPLICED (XBP1s) in a series of patients with myeloma and correlated findings with clinical outcome. We show that IRE1alpha and XBP1 are highly expressed and that patients with low XBP1s/u ratios have a significantly better overall survival. XBP1s is an independent prognostic marker and can be used with beta^2 microglobulin and t(4;14) to identify a group of patients with a poor outcome. Furthermore, we show the beneficial therapeutic effects of thalidomide in patients with low XBP1s/u ratios. This study highlights the importance of XBP1 in myeloma and its significance as an independent prognostic marker and as a predictor of thalidomide response.

Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with non-intensive therapy: analysis of the phase III VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone.

Harousseau JL, Palumbo A, Richardson PG, Schlag R, Dimopoulos MA, Shpilberg O, Kropff M, Kentos A, Cavo M, Golenkov A, Komarnicki M, Mateos MV, Esseltine DL, Cakana A, Liu K, Deraedt W, van de Velde H, San Miguel JF.

Blood. 2010 Jul 13. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20628153

The results of this analysis highlight that complete response is an important treatment goal and support prolonged bortezomib-melphalan-prednisone therapy to achieve maximal response.

The phase III VISTA study in newly diagnosed multiple myeloma patients ineligible for high-dose therapy demonstrated that bortezomib-melphalan-prednisone (VMP) was superior to melphalan-prednisone across all efficacy endpoints. This analysis assessed the prognostic impact of response on time-to-event parameters in the intent-to-treat population. Patients received nine 6-week cycles of treatment. Time to progression (TTP), time to next therapy (TNT), and treatment-free interval (TFI) were associated with quality of response. By EBMT criteria, complete response (CR) was associated with significantly longer TTP (HR = 0.45, p = 0.004), TNT (HR = 0.46, p = 0.0004), and TFI (HR = 0.38, p < 0.0001) versus partial response, but there was no significant difference in OS (HR = 0.87, p = 0.54); similar differences were seen with CR versus very good partial response by uniform criteria. Quality of response improved with prolonged VMP treatment, with 28% of CRs achieved during cycles 5-9. CR duration appeared similar among patients with 'early' (cycles 1-4) and 'late' CRs (cycles 5-9) and among patients receiving 9 versus <9 cycles of bortezomib within VMP. These results highlight that CR is an important treatment goal and support prolonged VMP therapy to achieve maximal response. This study was registered at http://clinicaltrials.gov as NCT00111319.

High incidence of arterial thrombosis in young patients treated for multiple myeloma: results of a prospective cohort study.

Libourel EJ, Sonneveld P, van der Holt B, de Maat MP, Leebeek FW.

Blood. 2010 Jul 8;116(1):22-6. [Epub 2010 Mar 25.]

http://www.ncbi.nlm.nih.gov/pubmed/20339094

This prospective study evaluates the risk of arterial thrombosis in 195 consecutive patients aged 18 to 65 years with newly diagnosed myeloma. All patients are treated with 3 cycles of vincristine/ doxorubicin/ dexamethasone, thalidomide/ doxorubicin/ dexamethasone or bortezomib/ doxorubicin/ dexamethasone, followed by high-dose melphalan and autologous stem cell transplantation. The authors find that patients have an increased risk for arterial thrombotic events during and after induction chemotherapy.

This prospective study evaluated the risk of arterial thrombosis in 195 consecutive patients aged 18 to 65 years with newly diagnosed multiple myeloma (MM). All patients were treated with 3 cycles of VAD (vincristine, doxorubicin, and dexamethasone) or TAD (thalidomide-AD) or PAD (bortezomib-AD) in national trials, followed by high-dose melphalan and autologous stem cell transplantation. For a period of 522 patient-years, 11 of the 195 patients (5.6%) developed arterial thrombosis. The highest incidence was seen during induction chemotherapy courses. Median age at onset of arterial thrombosis was 59 years (range, 43-65 years). Hypertension and smoking were significantly associated with arterial thrombosis with a relative risk of 11.7 (2.23-61.2) and 15.2 (1.78-130), respectively. Factor VIII levels (FVIII:C) correlated significantly with age (p = .02) and higher International Scoring System (ISS) stage (p = .001). A higher FVIII:C was associated with arterial thrombosis (hazard ratio [HR] = 1.85; 95% confidence interval [CI] = 0.99-3.47) after adjustment for age, ISS score, and assigned treatment arm. MM patients have an increased risk for arterial thrombotic events during and after induction chemotherapy. Hypertension, smoking, and high factor VIII levels, possibly reflecting disease activity, contribute to the risk of arterial thrombosis.

Assessing lenalidomide for treating multiple myeloma, myelofibrosis, and myelodysplastic syndrome.

[Article in Spanish]

Hernández Prats C, Romero Iborra F, Arroyo Domingo E, Castillo Valero I, Réal Panisello M, Sánchez Casado MI.

Farm Hosp. 2010 Jul 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20615740

The authors find that lenalidomide is well-tolerated and produces sustained clinical benefits, especially in myeloma patients.

OBJECTIVE: Lenalidomide (LDM) is an immunomodulatory and anti-angiogenic drug which has been shown to be effective in several haematological disorders (multiple myeloma [MM], myeloid metaplasia with myelofibrosis [MF] and myelodysplastic syndrome [MDS]). The objective of this study is to evaluate the effectiveness and tolerability of LDM in our patients. METHOD: Retrospective observational study which included patients at our hospital who were monitored by the haematology unit, diagnosed with MM, MF and MDS and candidates for LDM treatment. Treatment effectiveness was assessed after approximately 4 cycles of treatment. RESULTS: Between February 2007 and March 2008, 16 patients were listed as candidates for receiving treatment with LDM (50% female/50% male, with a mean age of 69.6 years); of these candidates, 3 never initiated treatment. Five of the six patients with MM treated at our hospital obtained some sort of response (83.3%). Of the 4 patients with MF, 2 (66.6%) experienced some sort of response to treatment. Of the 6 patients diagnosed with MDS, treatment was initiated in 3, and it had to be suspended in 2 cases due to different reasons. Treatment only had to be suspended in two of the 13 patients who began it (15.4%) due to adverse effects (AE). CONCLUSION: LDM is well-tolerated and produces sustained clinical benefits, especially in MM and MF. More studies are needed for in-depth examination of treatment duration, new indications and the use of treatments combined with other drugs.

Proteasome inhibitors: Dozens of molecules and still counting.

de Bettignies G, Coux O.

Biochimie. 2010 Jul 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20615448

The authors discuss the success of bortezomib as a new drug for the treatment of myeloma, and the ongoing clinical trials to evaluate the effect of several other proteasome inhibitors in various human pathologies, which illustrate the interest for human health of these compounds.

The discovery of the proteasome in the late 80's as the core protease of what will be then called the ubiquitin-proteasome system, rapidly followed by the development of specific inhibitors of this enzyme, opened up a new era in biology in the 90's. Indeed, the first proteasome inhibitors were instrumental for understanding that the proteasome is a key actor in most, if not all, cellular processes. The recognition of the central role of this complex in intracellular proteolysis in turn fuelled an intense quest for novel compounds with both increased selectivity towards the proteasome and better bioavailability that could be used in fundamental research or in the clinic. To date, a plethora of molecules that target the proteasome have been identified or designed. The success of the proteasome inhibitor bortezomib as a new drug for the treatment of Multiple Myeloma, and the ongoing clinical trials to evaluate the effect of several other proteasome inhibitors in various human pathologies, illustrate the interest for human health of these compounds.

Bortezomib, thalidomide, and dexamethasone as induction therapy for patients with symptomatic multiple myeloma: a retrospective study.

Kaufman JL, Nooka A, Vrana M, Gleason C, Heffner LT, Lonial S.

Cancer. 2010 Jul 1;116(13):3143-51.

http://www.ncbi.nlm.nih.gov/pubmed/20564642

This single-center retrospective study determines the efficacy of bortezomib, thalidomide, and dexamethasone (BTD) as induction for patients with myeloma who are eligible for autologous stem cell transplantation (ASCT). The authors find BTD to be highly effective and well tolerated as induction for myeloma patients who are eligible for ASCT. Long-term outcomes appeared to be similar with or without ASCT consolidation.

BACKGROUND: This single-center retrospective study determined the efficacy of bortezomib, thalidomide, and dexamethasone (BTD) as induction for patients with multiple myeloma (MM) who were eligible for autologous stem cell transplantation (ASCT). METHODS: Patients with symptomatic MM who had received BTD induction before stem cell collection at Winship Cancer Institute were included. BTD induction comprised up to 8 3-week cycles of bortezomib 1.3 mg/m^2 on Days 1, 4, 8, and 11; thalidomide 100 mg daily; and dexamethasone 40 mg on Days 1 through 4 and Days 9 through 12. Stem cell mobilization involved granulocyte-colony-stimulating factor and/or cyclophosphamide. Response was assessed according to European Group for Blood and Marrow Transplantation criteria. RESULTS: Review of medical records identified 44 eligible patients (34 patients who were treated in the front-line setting and 10 patients who were treated for recurrent disease) who received a median of 4 BTD cycles. The overall response rate (ORR) was 91%, which included a greater than or equal to very good partial response (> or = VGPR) rate of 57% (including 20% stringent complete responses/complete response [sCR/CR] rate). In front-line patients, the ORR was 94%, which included a 56% > or = VGPR rate (24% sCR/CR). The median CD34-positive stem cell collection was 10.67 x 10^6/kg. The ORR after ASCT in 34 patients who were evaluable for response was 100%, including a 76% > or = VGPR rate (53% sCR/CR). Among all 44 patients, the median progression-free survival (PFS) was 27.4 months. The median overall survival (OS) was not reached after a median follow-up of 25 months, and the 2-year OS rate was 82%. There were no significant differences in PFS (27.4 months vs. 23.5 months) or in 2-year survival (80% vs. 90%) between patients who did and did not undergo ASCT, respectively. Twenty patients (45%) developed neuropathy, including 4 (9%) with grade 3 neuropathy episodes, and 1 patient developed deep vein thrombosis. CONCLUSIONS: BTD was highly effective and well tolerated as induction for MM patients who were eligible for ASCT. Long-term outcomes appeared to be similar with or without ASCT consolidation.

Erratum to: Lenalidomide plus dexamethasone treatment in Japanese patients with relapsed/refractory multiple myeloma.

Iida S, Chou T, Okamoto S, Nagai H, Hatake K, Murakami H, Takagi T, Shimizu K, Lau H, Takeshita K, Takatoku M, Hotta T.

Int J Hematol. 2010 Jul 1. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20593310

No abstract available.

Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study.

Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H, Zweegman S, van Marwijk Kooy M, van der Griend R, Lokhorst H, Sonneveld P; Dutch-Belgium Cooperative Group HOVON.

J Clin Oncol. 2010 Jul 1;28(19):3160-6. [Epub 2010 Jun 1.]

http://www.ncbi.nlm.nih.gov/pubmed/20516439

The authors investigate the efficacy, toxicity, and effects on quality of life of melphalan-prednisone-thalidomide (MP-T), and demonstrate that thalidomide improves the response rate and very good partial response in elderly patients with newly diagnosed myeloma; MP-T also results in a better event-free survival, progression-free survival and overall survival.

PURPOSE: For several decades, the treatment of elderly patients with multiple myeloma (MM) has consisted of melphalan and prednisone (MP). The Dutch-Belgium Hemato-Oncology Cooperative Group (HOVON) investigated the efficacy of thalidomide added to MP (MP-T) in a randomized phase III trial. The objective of this study was to investigate the efficacy, toxicity, and effects on quality of life of MP-T. PATIENTS AND METHODS: A randomized phase III trial compared standard MP with MP-T (thalidomide 200 mg/d) in newly diagnosed patients with multiple myeloma older than age 65 years. Maintenance therapy with thalidomide 50 mg/d was administered to patients after MP-T until relapse. The primary end point was event-free survival (EFS); response rate, overall survival (OS), and progression-free survival (PFS) were secondary end points. RESULTS: An intent-to-treat analysis of 333 evaluable patients showed significantly higher response rates in MP-T-treated patients compared with MP-treated patients a response (> or = partial response: 66% v 45%, respectively; p < .001; and > or = very good partial response [VGPR]: 27% v 10%, respectively; p < .001). EFS was 13 months with MP-T versus 9 months with MP (p < .001). OS was 40 months with MP-T versus 31 months with MP (p = .05). CONCLUSION: This study demonstrates that thalidomide improves the response rate and VGPR in elderly patients with newly diagnosed MM. MP-T also results in a better EFS, PFS, and OS.

Bone marrow stromal cells from multiple myeloma patients uniquely induce bortezomib resistant NF-kappaB activity in myeloma cells.

Markovina S, Callander NS, O'Connor SL, Xu G, Shi Y, Leith CP, Kim K, Trivedi P, Kim J, Hematti P, Miyamoto S.

Mol Cancer. 2010 Jul 6;9(1):176. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20604947

The authors report that bone marrow stromal cells specifically derived from myeloma patients are capable of further activating bortezomib-resistant NF-kappaB activity in myeloma cells.

ABSTRACT: BACKGROUND: Components of the microenvironment such as bone marrow stromal cells (BMSCs) are well known to support multiple myeloma (MM) disease progression and resistance to chemotherapy including the proteasome inhibitor bortezomib. However, functional distinctions between BMSCs in MM patients and those in disease-free marrow are not completely understood. We and other investigators have recently reported that NF-kappaB activity in primary MM cells is largely resistant to the proteasome inhibitor bortezomib, and that further enhancement of NF-kappaB by BMSCs is similarly resistant to bortezomib and may mediate resistance to this therapy. The mediating factor(s) of this bortezomib-resistant NF-kappaB activity is induced by BMSCs is not currently understood. RESULTS: Here we report that BMSCs specifically derived from MM patients are capable of further activating bortezomib-

resistant NF-kappaB activity in MM cells. This induced activity is mediated by soluble proteinaceous factors secreted by MM BMSCs. Among the multiple factors evaluated, interleukin-8 was secreted by BMSCs from MM patients at significantly higher levels compared to those from non-MM sources, and we found that IL-8 contributes to BMSC-induced NF-kappaB activity. CONCLUSIONS: BMSCs from MM patients uniquely enhance constitutive NF-kappaB activity in MM cells via a proteinaceous secreted factor in part in conjunction with IL-8. Since NF-kappaB is known to potentiate MM cell survival and confer resistance to drugs including bortezomib, further identification of the NF-kappaB activating factors produced specifically by MM-derived BMSCs may provide a novel biomarker and/or drug target for the treatment of this commonly fatal disease.

Bortezomib, dexamethasone, cyclophosphamide and lenalidomide combination for newly diagnosed multiple myeloma: phase I results from the multicenter EVOLUTION study.

Kumar SK, Flinn I, Noga SJ, Hari P, Rifkin R, Callander N, Bhandari M, Wolf JL, Gasparetto C, Krishnan A, Grosman D, Glass J, Sahovic EA, Shi H, Webb IJ, Richardson PG, Rajkumar SV.

Leukemia. 2010 Jul;24(7):1350-6. [Epub 2010 May 27.]

http://www.ncbi.nlm.nih.gov/pubmed/20508619

This phase I study determines that cyclophosphamide in combination with bortezomib, dexamethasone and lenalidomide is well tolerated and highly active in untreated myeloma patients, with a maximum tolerated dose of 500 mg/mc.

This phase I study (Clinicaltrials.gov #NCT00507442) was conducted to determine the maximum tolerated dose (MTD) of cyclophosphamide in combination with bortezomib, dexamethasone and lenalidomide (VDCR) and to assess the safety and efficacy of this combination in untreated multiple myeloma patients. Cohorts of three to six patients received a cyclophosphamide dosage of 100, 200, 300, 400 or 500 mg/m² (on days 1 and 8) plus bortezomib 1.3 mg/m² (on days 1, 4, 8 and 11), dexamethasone 40 mg (on days 1, 8 and 15) and lenalidomide 15 mg (on days 1-14), for eight 21-day induction cycles, followed by four 42-day maintenance cycles (bortezomib 1.3 mg/m², on days 1, 8, 15 and 22). The MTD was the cyclophosphamide dose below which more than one of six patients experienced a dose-limiting toxicity (DLT). Twenty-five patients were treated. Two DLTs were seen, of grade 4 febrile neutropenia (cyclophosphamide 400 mg/m^2) and grade 4 herpes zoster despite anti-viral prophylaxis (cyclophosphamide 500 mg/m²). No cumulative hematological toxicity or thromboembolic episodes were reported. The overall response rate was 96%, including 20% stringent complete response (CR), 40% CR/near-complete response and 68% >or=very good partial response. VDCR is well tolerated and highly active in this population. No MTD was reached; the recommended phase II cyclophosphamide dose in VDCR is 500 mg/m², which was the highest dose tested.

Bortezomib plus intermediate-dose dexamethasone and thalidomide in elderly untreated patients with multiple myeloma: a Chinese experience.

Guo H, Zhou X, Jiang Y, Yang G, Sun C, Zhuang Y, Sun H, Lu M, Qian X, Chen F, Mao J, Chen H, Xia J, Shen Y.

Am J Hematol. 2010 Jul;85(7):499-501.

http://www.ncbi.nlm.nih.gov/pubmed/20575036

This preliminary experience in Chinese patients indicates that bortezomib-dexamethasone-thalidomide is highly effective in elderly untreated patients with myeloma, even in patients with poor prognostic features.

Bortezomib has proven to be active in patients with multiple myeloma (MM), including elderly patients. The aim of this study was to evaluate the efficacy and toxicity of bortezomib in combination with intermediate-dose dexamethasone (Dex) and thalidomide in untreated MM patients aged > or = 65 years in a Chinese single center. In this study, 18 patients were treated with bortezomib at 1.3 mg/m² IV on Days 1, 4, 8, and 11 and Dex at 20 mg/day IV on Days 1-4 and 8-11 simultaneously. Thalidomide at dose of 100 mg/day was given everyday. The mean number of cycles of bortezomib treatment was 2.06. Three patients (17%) achieved a complete response (CR), four (22%) a very good partial response (VGPR), and nine (50%) a PR, resulting in an overall response rate of 89%. The median time to response was 22 days (range 14-50 days). The duration of response was significantly longer in patients achieving a CR/VGPR with respect to those achieving only a PR (8.5 vs. 4.2 months, p = 0.03). Grade 3-4 toxicities occurring in

patients comprised weakness, thrombocytopenia, diarrhea, infection, and neuropathy. Only one patient suffered from deep vein thrombosis. This preliminary experience in Chinese patients indicated that bortezomib-Dex-thalidomide is highly effective in elderly untreated patients with MM, even in patients with poor prognostic features.

Calcium channel blocker verapamil enhances endoplasmic reticulum stress and cell death induced by proteasome inhibition in myeloma cells.

Meister S, Frey B, Lang VR, Gaipl US, Schett G, Schlötzer-Schrehardt U, Voll RE.

Neoplasia. 2010 Jul;12(7):550-61.

http://www.ncbi.nlm.nih.gov/pubmed/20651984

The authors find that verapamil increases the antimyeloma effect of bortezomib, and that therefore the combination of bortezomib with verapamil may improve the efficacy of proteasome inhibitor therapy.

The proteasome inhibitor bortezomib is clinically approved for the treatment of multiple myeloma. However, long-term remissions are difficult to achieve, and myeloma cells often develop secondary resistance to proteasome inhibitors. We recently demonstrated that the extraordinary sensitivity of myeloma cells toward bortezomib is dependent on their extensive immunoglobulin synthesis, thereby triggering the terminal unfolded protein response (UPR). Here, we investigated whether verapamil, an inhibitor of the multidrug resistance (MDR) gene product, can enhance the cytotoxicity of bortezomib. The combination of bortezomib and verapamil synergistically decreased the viability of myeloma cells by inducing cell death. Importantly, bortezomib-mediated activation of major UPR components was enhanced by verapamil. The combination of bortezomib and verapamil resulted in caspase activation followed by poly(ADP-ribose) polymerase cleavage, whereas nuclear factor kappaB (NF-kappaB) activity declined in myeloma cells. Also, we found reduced immunoglobulin G secretion along with increased amounts of ubiquitinylated proteins within insoluble fractions of myeloma cells when using the combination treatment. Verapamil markedly induced reactive oxygen species production and autophagic-like processes. Furthermore, verapamil decreased MDR1 expression. We conclude that verapamil increased the antimyeloma effect of bortezomib by enhancing ER stress signals along with NF-kappaB inhibition, leading to cell death. Thus, the combination of bortezomib with verapamil may improve the efficacy of proteasome inhibitory therapy.

Drug interaction between itraconazole and bortezomib: exacerbation of peripheral neuropathy and thrombocytopenia induced by bortezomib.

Iwamoto T, Ishibashi M, Fujieda A, Masuya M, Katayama N, Okuda M.

Pharmacotherapy. 2010 Jul;30(7):661-5.

http://www.ncbi.nlm.nih.gov/pubmed/20575631

The authors find that itraconazole appears to exacerbate peripheral neuropathy and thrombocytopenia induced by bortezomib; however, the mechanism of this drug interaction is unknown. Clinicians should closely monitor for bortezomib-induced adverse effects when itraconazole, or any other potent CYP3A4 inhibitor, is administered concomitantly with bortezomib.

STUDY OBJECTIVE: To investigate whether a drug interaction exists between bortezomib and the cytochrome P450 (CYP) 3A4 inhibitor itraconazole and/or the CYP2C19 inhibitor lansoprazole that results in increased severity of bortezomib-induced peripheral neuropathy and thrombocytopenia. DESIGN: Retrospective medical record review. SETTING: Hematology-oncology ward of a university-affiliated hospital in Japan. PATIENTS: Six adults with relapsed multiple myeloma who received intravenous bortezomib plus oral dexamethasone as the first course of a 21-day cycle between July 2007 and December 2008. Four of the six patients were treated concomitantly with itraconazole or lansoprazole: two with itraconazole, one with lansoprazole, and one with both itraconazole and lansoprazole. MEASUREMENTS AND MAIN RESULTS: Using the National Cancer Institute's Common Terminology Criteria for Adverse Events, we identified the presence and graded the severity of peripheral neuropathy and thrombocytopenia before and during each patient's first 21-day course of bortezomib plus dexamethasone therapy. All three patients who received itraconazole experienced new or worsening peripheral neuropathy; they also experienced grade 4 thrombocytopenia. The patient who received lansoprazole alone, as well as the two patients who did not receive

itraconazole or lansoprazole, had no changes in either adverse effect. We also evaluated the relationship between peripheral neuropathy and bortezomib plus dexamethasone therapy by using the Naranjo adverse drug reaction probability scale, and a probable relationship was found. We further assessed whether a drug interaction between bortezomib and itraconazole and/or lansoprazole had occurred involving the CYP3A4 and/or the CYP2C19 pathways, respectively-resulting in increased severity of the bortezomib-induced peripheral neuropathy and thrombocytopenia-by using the Horn drug interaction probability scale. We found that the occurrence of this drug interaction was strongly supported. CONCLUSIONS: Itraconazole appears to exacerbate peripheral neuropathy and thrombocytopenia induced by bortezomib; however, the mechanism of this drug interaction is unknown. Clinicians should closely monitor for bortezomib-induced adverse effects when itraconazole, or any other potent CYP3A4 inhibitor, is administered concomitantly with bortezomib.

Experiences with bortezomib in multiple myeloma - from phase II studies to daily practice.
Schmitt S, Bertsch U, Goldschmidt H.
Int J Clin Pharmacol Ther. 2010 Jul;48(7):494-6.

http://www.ncbi.nlm.nih.gov/pubmed/20557858
No abstract available.

Increased bone mineral density in a subset of patients with relapsed multiple myeloma who received the combination of bortezomib, dexamethasone and zoledronic acid.
Terpos E, Christoulas D, Kokkoris P, Anargyrou K, Gavriatopoulou M, Migkou M, Tsionos K, Dimopoulos MA.
Ann Oncol. 2010 Jul;21(7):1561-2. [Epub 2010 May 23.]

http://www.ncbi.nlm.nih.gov/pubmed/20497962
No abstract available.

Lenalidomide and dexamethasone for the treatment of refractory/relapsed multiple myeloma: dosing of lenalidomide according to renal function and effect on renal impairment.
Dimopoulos MA, Christoulas D, Roussou M, Kastritis E, Migkou M, Gavriatopoulou M, Matsouka C, Mparmparoussi D, Psimenou E, Grapsa I, Efstathiou E, Terpos E.
Eur J Haematol. 2010 Jul;85(1):1-5. [Epub 2010 Feb 20.]

http://www.ncbi.nlm.nih.gov/pubmed/20192988
The authors study the effect of the lenalidomide and dexamethasone regimen (LenDex) on renal impairment (RI) and renal reversibility. They find that with dosing of lenalidomide according to renal function, LenDex can be administered to patients with RI (who may not have other treatment options) without excessive toxicity. Furthermore, LenDex may improve the renal function in approximately 40% of patients with RI.

OBJECTIVES: Lenalidomide and dexamethasone (LenDex) is an active regimen for relapsed/refractory multiple myeloma (MM). However, there is limited data for the effect of LenDex on renal impairment (RI) and on renal reversibility. PATIENTS & METHODS: Fifty consecutive patients with relapsed/refractory MM received LenDex in 28-d cycles. Median lines of previous therapies were 2 (range: 1-6). Lenalidomide was administered on days 1-21 according to creatinine clearance (CrCl), while dexamethasone was given at a dose of 40 mg on days 1-4 and 15-18 for the first four cycles and only on days 1-4 thereafter. RESULTS: Twelve patients (24%) had RI at baseline, defined as CrCl < 50 mL/min. Most patients were pretreated with either thalidomide or bortezomib and > 50% of them were refractory to both drugs. At least partial response was documented in 60.5% and 58% of patients with and without RI. Median progression-free survival (PFS) and overall survival (OS) for all patients was 9 and 16 months, respectively. RI was not associated with an inferior PFS or OS. There were no differences in the incidence of adverse events among patients with and without RI. Three of 12 patients with RI (25%) achieved complete renal response and two (16%) achieved minor renal response with LenDex. CONCLUSIONS: We conclude that LenDex is an active treatment even in heavily pretreated MM. With dosing of lenalidomide according to renal function, LenDex can be administered to patients with RI (who may not have other treatment options) without excessive toxicity. Furthermore, LenDex may improve the renal function in approximately 40% of patients with RI.

Melphalan, prednisone, thalidomide and defibrotide in relapsed/refractory multiple myeloma: results of a multicenter phase I/II trial.

Palumbo A, Larocca A, Genuardi M, Kotwica K, Gay F, Rossi D, Benevolo G, Magarotto V, Cavallo F, Bringhen S, Rus C, Masini L, Iacobelli M, Gaidano G, Mitsiades C, Anderson K, Boccadoro M, Richardson P; Italian Multiple Myeloma Network GIMEMA.

Haematologica. 2010 Jul;95(7):1144-9. [Epub 2010 Jan 6.]

http://www.ncbi.nlm.nih.gov/pubmed/20053869

This phase I/II trial concludes that the combination of oral melphalan, thalidomide, and defibrotide shows anti-tumor activity with favorable tolerability.

BACKGROUND: Defibrotide is a novel orally bioavailable polydisperse oligonucleotide with anti-thrombotic and anti-adhesive effects. In SCID/NOD mice, defibrotide showed activity in human myeloma xenografts. This phase I/II study was conducted to identify the most appropriate dose of defibrotide in combination with melphalan, prednisone and thalidomide in patients with relapsed and relapsed/refractory multiple myeloma, and to determine its safety and tolerability as part of this regimen. DESIGN AND METHODS: This was a phase I/II, multicenter, dose-escalating, non-comparative, open label study. Oral melphalan was administered at a dose of 0.25 mg/kg on days 1-4, prednisone at a dose of 1.5 mg/kg also on days 1-4 and thalidomide at a dose of 50-100 mg/day continuously. Defibrotide was administered orally at three dose-levels: 2.4, 4.8 or 7.2 g on days 1-4 and 1.6, 3.2, or 4.8 g on days 5-35. RESULTS: Twenty-four patients with relapsed/refractory multiple myeloma were enrolled. No dose-limiting toxicity was observed. In all patients, the complete response plus very good partial response rate was 9%, and the partial response rate was 43%. The 1-year progression-free survival and 1-year overall survival rates were 34% and 90%, respectively. The most frequent grade 3-4 adverse events included neutropenia, thrombocytopenia, anemia and fatigue. Deep vein thrombosis was reported in only one patient. CONCLUSIONS: This combination of melphalan, prednisone and thalidomide together with defibrotide showed anti-tumor activity with a favorable tolerability. The maximum tolerated dose of defibrotide was identified as 7.2 g p.o. on days 1-4 followed by 4.8 g p.o. on days 5-35. Further trials are needed to confirm the role of this regimen and to evaluate the combination of defibrotide with new drugs.

Peripheral neuropathy during bortezomib treatment of multiple myeloma: a review of recent studies.

Cavaletti G, Jakubowiak AJ.

Leuk Lymphoma. 2010 Jul;51(7):1178-87.

http://www.ncbi.nlm.nih.gov/pubmed/20497001

This review discusses the clinical profile of bortezomib-induced peripheral neuropathy in the treatment of myeloma, and guidelines for its management.

Treatment-emergent peripheral neuropathy (PN) is an important dose-limiting toxicity during treatment of multiple myeloma (MM). Bortezomib-induced PN (BIPN) occurred in 37-44% of clinical trial patients with MM, with the cumulative treatment dose as its single most significant predictor. This review discusses the clinical profile of BIPN in the treatment of MM and guidelines for its management. Lower rates of BIPN observed during treatment of solid tumors compared with rates of hematologic cancers are also discussed. Several areas of research are reviewed that may improve the management of BIPN, including co-therapies with the novel heat shock protein inhibitor tanespimycin, which appears to reduce the incidence of BIPN, and recent studies with second-generation proteasome inhibitors such as carfilzomib and NPI-0052. Adherence to the National Cancer Institute dose-modification algorithm is the most effective method for mitigating BIPN. Reversal of BIPN after treatment cessation occurs in most cases, but recovery in some patients takes as long as 1.7 years, and some individuals fail to return to baseline neurologic function. BIPN can cause a significant reduction in quality of life, primarily due to severe treatment-emergent pain. Ongoing research may provide additional information about the mechanism of BIPN and strategies to reduce PN.

The proteasome inhibitor bortezomib inhibits FGF-2-induced reduction of TAZ levels in osteoblast-like cells.

Eda H, Aoki K, Kato S, Okawa Y, Takada K, Tanaka T, Marumo K, Ohkawa K.

Eur J Haematol. 2010 Jul;85(1):68-75. Epub 2010 Feb 23.

http://www.ncbi.nlm.nih.gov/pubmed/20192985

The authors' findings suggest that bortezomib inhibits fibroblast growth factor 2-induced reduction of TAZ and consequently stimulates osteogenic differentiation independently of proteasome inhibition. These findings may contribute to elucidate the osteolytic mechanism in myeloma, and to the development of new drugs for myeloma and other osteolytic diseases.

OBJECTIVES: Bortezomib (PS-341; Velcade), a proteasome inhibitor, is used as a therapeutic agent for multiple myeloma. Bortezomib has been shown to strongly induce osteoblast differentiation and elevate the levels of osteoblast-related differentiation markers in the serum of patients with myeloma. Bortezomib also reportedly increases the activity of the transcription factor, Runx2. However, the mechanism of action by which bortezomib-elevated Runx2 activity mediates osteoblast differentiation remains unclear. On the other hand, fibroblast growth factor 2 (FGF-2) is found at high levels in patients with multiple myeloma. We previously reported that FGF-2 reduces the levels of the transcriptional co-activator with PDZ-binding motif (TAZ). We therefore investigated the effects of bortezomib on TAZ protein levels in the presence of FGF-2. METHODS: Osteoblastic MC3T3-E1 cells were treated with different concentrations of bortezomib in the presence or absence of FGF-2 and various biologic responses were investigated by immunoblotting, RT-PCR, quantitative PCR, and alizarin red staining. RESULTS: We found that bortezomib inhibited FGF-2-induced reduction of TAZ levels through a pathway other than that used for proteasome inhibition, while maintaining TAZ function, which in turn, enhanced the expression of Runx2-transcribed osteogenic differentiation markers. Bortezomib also suppressed the antimineralization effect of FGF-2. CONCLUSIONS: These findings suggest that bortezomib inhibited FGF-2-induced reduction of TAZ and consequently stimulated osteogenic differentiation independently of proteasome inhibition. These findings may contribute to elucidate the osteolytic mechanism in multiple myeloma, and to the development of new drugs for multiple myeloma and other osteolytic diseases.

Ultra low dose thalidomide in myeloma revisited.

Patrick HE, Bowcock SJ.

Br J Haematol. 2010 Jul;150(2):232-4. [Epub 2010 Mar 21.]

http://www.ncbi.nlm.nih.gov/pubmed/20346009

No abstract available.

Venous thromboembolism in multiple myeloma: current perspectives in pathogenesis.

Uaprasert N, Voorhees PM, Mackman N, Key NS.

Eur J Cancer. 2010 Jul;46(10):1790-9. [Epub 2010 Apr 10.]

http://www.ncbi.nlm.nih.gov/pubmed/20385482

The authors address the relationship of immunomodulatory agents, such as thalidomide and lenalidomide, with the substantial increase of the incidence of venous thromboembolism in myeloma patients.

Patients with multiple myeloma are at increased risk of venous thromboembolism (VTE) compared to the general population. The introduction of immunomodulatory agents, such as thalidomide and lenalidomide, substantially increases the incidence of VTE in multiple myeloma patients, especially when used in combination with high-dose dexamethasone and/or anthracycline-based chemotherapy. Thromboprophylaxis is recommended for reducing VTE in patients receiving immunomodulatory agent-based regimens. On the other hand, bortezomib, a proteasome inhibitor, is not associated with an increased risk of VTE, as observed by a very low incidence of thrombotic complications in the absence of thromboprophylaxis. Currently, the mechanisms underlying the impact of these agents on VTE are not well-understood. Further studies to investigate the pathogenesis of VTE in multiple myeloma are warranted. These studies may not only yield greater insight into the pathogenesis of disease but may also define novel targets for the prevention and treatment of thromboembolic events in patients with multiple myeloma.

June 2010

Monitoring bortezomib therapy in multiple myeloma: screening of cyclin D1, D2, and D3 via reliable real-time polymerase chain reaction and association with clinico-pathological features and outcome.

Thanh-Truc Ngo B, Felthaus J, Hein M, Follo M, Wider D, Ihorst G, Engelhardt M, Wäsch R.

Leuk Lymphoma. 2010 Jun 25. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20578819

This study is the first to suggest that overexpressed cyclin D1 in myeloma is an independent prognostic marker associated with a more durable response to bortezomib.

Cyclins D1, D2, and D3 (CCND1, 2, 3) are regulated by proteasomal degradation. Their overexpression in multiple myeloma (MM) has prognostic value. We performed this pilot study to analyze a possible association between CCND1-3 overexpression and response to treatment with the proteasome inhibitor bortezomib, since a specific prognostic marker for bortezomib response has not been reported, but would be ideal to predict who benefits most from bortezomib in times of several potentially efficient therapeutic options. Bone marrow (BM) specimens of 20/47 consecutive patients were available for reliable CCND1-3 analyses by real-time PCR. With CCND1 overexpression in 9/20 patients, the risk for progression after bortezomib treatment was significantly decreased (HR 0.102, 95% CI 0.021-0.498, p = 0.0048) and progression-free survival substantially prolonged (p = 0.0011). Our study is the first to suggest that overexpressed CCND1 in MM is an independent prognostic marker associated with a more durable response to bortezomib. These preliminary results warrant a larger study.

A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma.

Görgün G, Calabrese E, Hideshima T, Ecsedy J, Perrone G, Mani M, Ikeda H, Bianchi G, Hu Y, Cirstea D, Santo L, Tai YT, Nahar S, Zheng M, Bandi M, Carrasco RD, Raje N, Munshi N, Richardson P, Anderson KC.

Blood. 2010 Jun 24;115(25):5202-13. [Epub 2010 Apr 9.]

http://www.ncbi.nlm.nih.gov/pubmed/20382844

The authors assess the in vitro and in vivo anti-myeloma activity of MLN8237, a small molecule Aurora-A kinase inhibitor. They find that combining MLN8237 with dexamethasone, doxorubicin or bortezomib induces synergistic/additive anti-myeloma activity in vitro.

Aurora-A is a mitotic kinase that regulates mitotic spindle formation and segregation. In multiple myeloma (MM), high Aurora-A gene expression has been correlated with centrosome amplification and proliferation; thus, inhibition of Aurora-A in MM may prove to be therapeutically beneficial. Here we assess the in vitro and in vivo anti-MM activity of MLN8237, a small molecule Aurora-A kinase inhibitor. Treatment of cultured MM cells with MLN8237 results in mitotic spindle abnormalities, mitotic accumulation, as well as inhibition of cell proliferation through apoptosis and senescence. In addition, MLN8237 upregulates p53 and tumor suppressor genes p21 and p27. Combining MLN8237 with dexamethasone, doxorubicin or Bortezomib induces synergistic/additive anti-MM activity in vitro. In vivo anti-MM activity of MLN8237 was confirmed using a xenograft-murine model of human-MM. Tumor burden was significantly reduced (p = 0.007) and overall survival was significantly increased (p = 0.0044) in animals treated with 30mg/kg MLN8237 for 21 days. Induction of apoptosis and cell death by MLN8237 was confirmed in tumor cells excised from treated animals by TUNEL assay. MLN8237 is currently in phase I and phase II clinical trials in patients with advanced malignancies, and our preclinical results suggest that MLN8237 may be a promising novel targeted therapy in MM.

High rate of stem cell mobilization failure after thalidomide and oral cyclophosphamide induction therapy for multiple myeloma.

Auner HW, Mazzarella L, Cook L, Szydlo R, Saltarelli F, Pavlu J, Bua M, Giles C, Apperley JF, Rahemtulla A.

Bone Marrow Transplant. 2010 Jun 21. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20562926

This retrospective review of 136 patients with newly diagnosed myeloma shows that the combination of thalidomide and oral cyclophosphamide with dexamethasone during induction therapy impairs stem cell mobilization substantially.

Novel agents are increasingly used during induction therapy for multiple myeloma (MM), but there is concern about their potential impact on stem cell mobilization. Regimens containing either thalidomide or cyclophosphamide have little or no impact on stem cell collection. In this retrospective review of 136 patients with newly diagnosed MM, we show that the combination of thalidomide and oral CY with dexamethasone (CTD) during induction therapy impaired stem cell mobilization substantially. Compared with VAD (vincristine, doxorubicin, dexamethasone) and a VAD-like induction regimen, the stem cell collection yield after CTD was decreased by 49% (median 5.0 vs. 9.8 x 10^6 CD34+cells/kg, $p < 0.001$). Following CTD, more patients failed to mobilize enough stem cells for one (25.4 vs. 5.8%, $p = 0.002$) or two (39.4 vs. 15.9%, $p = 0.002$) transplants. These results demonstrate that the combination of thalidomide and oral CY impairs stem cell mobilization and indicate that drugs with no previously reported relevant effect on stem cell mobilization can have a substantial impact when given in combination.

Reiterative survival analyses of total therapy 2 for multiple myeloma elucidate follow-up time dependency of prognostic variables and treatment arms.

Barlogie B, Anaissie E, van Rhee F, Shaughnessy JD Jr, Szymonifka J, Hoering A, Petty N, Crowley J.

J Clin Oncol. 2010 Jun 20;28(18):3023-7. [Epub 2010 May 17.]

http://www.ncbi.nlm.nih.gov/pubmed/20479421

In Total Therapy 2, after a median follow-up of 42 months, no difference was observed in overall survival between thalidomide and a control arm; at 72 months, survival was superior on the thalidomide arm in the one third exhibiting cytogenetic abnormalities. After further follow-up of 87 months, the authors examine, in reiterative analyses, the effect of increasing time intervals on clinical outcomes relevant to baseline prognostic variables and treatment randomization.

PURPOSE: In Total Therapy 2, after randomly assigning 323 patients with myeloma to thalidomide and 345 to a control arm, no difference was observed in overall survival, with a median follow-up of 42 months, although at 72 months, survival was superior on the thalidomide arm in the one third exhibiting cytogenetic abnormalities (CA). After further follow-up of 87 months, we examined, in reiterative analyses, the effect of increasing time intervals on clinical outcomes relevant to baseline prognostic variables and treatment randomization. PATIENTS AND METHODS: We investigated clinical trial end points as a function of increasing time intervals from protocol enrollment to determine consistencies of results by treatment and prognostic variables. RESULTS: The complete congruence of serial survival plots for both study arms combined attested to stable patient characteristics over the time of accrual and the quality of follow-up management. Presence of CA was associated with consistently inferior survival curves from year 3 onward. Although 80% of patients randomly assigned to thalidomide discontinued study drug after 2 years because of toxicity, its clinical benefit did not reach statistical significance until year 10. The relative ranking order in multivariate models of prognostic factors remained stable over time. Decline in initially high hazard ratio values of gene array-defined high risk is consistent with an initial crisis phase that is time limited. CONCLUSION: Reporting potentially time-sensitive features as a part of clinical trial results will enable the critical reader to judge the robustness of prognostic factors and the time sensitivity of outcome predictors, with important implications for future trial designs.

Lenalidomide plus dexamethasone treatment in Japanese patients with relapsed/refractory multiple myeloma.
Iida S, Chou T, Okamoto S, Nagai H, Hatake K, Murakami H, Takagi T, Shimizu K, Lau H, Takeshita K, Takatoku M, Hotta T.
Int J Hematol. 2010 Jun 18. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20559759

This multicenter, open-label study finds that 25 mg of lenalidomide is given safely as a single agent or in combination with dexamethasone in Japanese myeloma patients.

We conducted a multicenter, open-label study to investigate the safety, efficacy, and pharmacokinetics of lenalidomide in Japanese patients with relapsed or refractory multiple myeloma The study was composed of the "monotherapy phase", a dose-escalation phase, to determine the tolerability to single agent lenalidomide and the "combination phase" to determine the safety and obtain preliminary data on the efficacy of lenalidomide plus dexamethasone. The primary end points were the tolerability to 25 mg lenalidomide and safety. Nine and six patients were enrolled in the monotherapy phase and the combination phase, respectively. Since 25 mg of monotherapy treatment did not satisfy the DLT criteria, this dose was employed in the combination phase. The major adverse event was myelosuppression. At the planned interim analysis (median study duration, 26.3 weeks), grade 3 or grade 4 neutropenia was observed with high frequency (66.7%). However, all adverse events observed were clinically manageable. In the combination cohort, the overall response rate (>/=PR) was 100%. The pharmacokinetics of lenalidomide showed rapid absorption and elimination after both single and multiple doses. In conclusion, 25 mg of lenalidomide was given safely as a single agent or in combination with dexamethasone in Japanese patients. The good efficacy of the combination therapy was also demonstrated in this study.

Safety and efficacy of bortezomib, melphalan and low doses dexamethasone (VM-dex) in newly diagnosed patients with multiple myeloma.
Gozzetti A, Defina M, Bocchia M, Fabbri A, Marchini E, Chitarrelli I, Lauria F.
Leuk Res. 2010 Jun 15. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20557933

No abstract provided.

Polymorphisms in the multiple drug resistance protein 1 and in P-glycoprotein 1 are associated with time to event outcomes in patients with advanced multiple myeloma treated with bortezomib and pegylated liposomal doxorubicin.
Buda G, Ricci D, Huang CC, Favis R, Cohen N, Zhuang SH, Harousseau JL, Sonneveld P, Bladé J, Orlowski RZ.
Ann Hematol. 2010 Jun 8. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20532504

The authors retrospectively evaluate the influence of single nucleotide polymorphisms (SNPs) in the multiple drug resistance protein 1 (MRP1) and P-glycoprotein 1 (MDR1) genes on outcomes in relapsed and/or refractory myeloma patients treated with bortezomib or bortezomib with pegylated liposomal doxorubicin (PLD). Their findings suggest a potential role for MRP1 and MDR1 SNPs in modulating the long-term outcome of relapsed and/or refractory myeloma patients treated with PLD + bortezomib.

Single nucleotide polymorphisms (SNPs) in the multiple drug resistance protein 1 (MRP1) and P-glycoprotein 1 (MDR1) genes modulate their ability to mediate drug resistance. We therefore sought to retrospectively evaluate their influence on outcomes in relapsed and/or refractory myeloma patients treated with bortezomib or bortezomib with pegylated liposomal doxorubicin (PLD). The MRP1/R723Q polymorphism was found in five subjects among the 279 patient study population, all of whom received PLD + bortezomib. Its presence was associated with a longer time to progression (TTP; median 330 vs. 129 days; p = 0.0008), progression-free survival (PFS; median 338 vs. 129 days; p = 0.0006), and overall survival (p = 0.0045). MDR1/3435(C > T), which was in Hardy-Weinberg equilibrium, showed a trend of association with PFS (p = 0.0578), response rate (p = 0.0782) and TTP (p = 0.0923) in PLD + bortezomib

patients, though no correlation was found in the bortezomib arm. In a recessive genetic model, MDR1/3435 T was significantly associated with a better TTP (p = 0.0405) and PFS (p = 0.0186) in PLD + bortezomib patients. These findings suggest a potential role for MRP1 and MDR1 SNPs in modulating the long-term outcome of relapsed and/or refractory myeloma patients treated with PLD + bortezomib. Moreover, they support prospective studies to determine if such data could be used to tailor therapy to the genetic makeup of individual patients.

First line treatment with bortezomib rapidly stimulates both osteoblast activity and bone matrix deposition in patients with multiple myeloma, and stimulates osteoblast proliferation and differentiation in vitro.

Lund T, Søe K, Abildgaard N, Garnero P, Pedersen PT, Ormstrup T, Delaissé JM, Plesner T.

Eur J Haematol. 2010 Jun 7. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20528908

The authors find that bortezomib used as first-line treatment significantly increases collagen deposition in patients with myeloma and osteolytic lesions, but that the addition of a glucocorticoid to the treatment transiently inhibits the positive effect of bortezomib, suggesting that bortezomib may result in better healing of osteolytic lesions when used without glucocorticoids in patients that have obtained remission with a previous therapy.

ABSTRACT OBJECTIVES: The aim of the study was to investigate the effect of bortezomib on osteoblast proliferation and differentiation, as well as on bone matrix deposition for the first time in bisphosphonate-naïve, previously untreated myeloma patients. METHODS: Twenty newly diagnosed patients received four cycles of bortezomib treatment, initially as mono-therapy and then combined with a glucocorticoid from cycle two to four. Bone remodeling markers were monitored closely during treatment, and the effects of bortezomib and a glucocorticoid on immature and mature osteoblasts were studied in vitro. RESULTS: Treatment with bortezomib caused a significant increase in bone-specific alkaline phosphatase (bALP) and pro-collagen type I N-terminal propeptide (PINP), a novel bone formation marker. The addition of a glucocorticoid resulted in a transient decrease in collagen deposition. In vitro bortezomib induced osteoblast proliferation and differentiation. Differentiation but not proliferation was inhibited by glucocorticoid treatment. CONCLUSIONS: Bortezomib used as first-line treatment significantly increased collagen deposition in patients with multiple myeloma and osteolytic lesions, but the addition of a glucocorticoid to the treatment transiently inhibited the positive effect of bortezomib, suggesting that bortezomib may result in better healing of osteolytic lesions when used without glucocorticoids in patients that have obtained remission with a previous therapy. The potential bone-healing properties of single-agent bortezomib are currently being explored in a clinical study in patients who have undergone high-dose therapy and autologous stem cell transplantation.

Pharmacological properties of thalidomide and its analogues.

De Sanctis JB, Mijares M, Suárez A, Compagnone R, Garmendia J, Moreno D, Salazar-Bookaman M.

Recent Pat Inflamm Allergy Drug Discov. 2010 Jun 1;4(2):144-8.

http://www.ncbi.nlm.nih.gov/pubmed/20307255

In this review, the authors explore the current trend of the different structures, the new patents, and the possible new applications in different pathologies of thalidomide and its analogues, including lenalidomide.

Thalidomide and its immunomodulatory imide drugs (IMiDs) analogues CC-5013 (Revlimid, Lenalidomide) and CC-4047 (Actimid, Pomalidomide) have been used as anti-inflammatory and anticancerous drugs in the recent years. Thalidomide and IMiDs inhibit the cytokines tumour necrosis factor-alpha (TNF-alpha), interleukins (IL) 1-beta, 6, 12, and granulocyte macrophage-colony stimulating factor (GM-CSF). They also co-stimulate primary human T, NKT and NK lymphocytes inducing their proliferation, cytokine production, and cytotoxic activity. On the other hand, the compounds are anti-angiogenic, anti-proliferative, and pro-apoptotic. Thalidomide analogues have been used as inhibitors of alpha glucosidase and could be potential drugs for diabetes treatment. In this review, we explore the current trend of the different structures, the new patents, and the possible new applications in different pathologies.

Advances in treatment for relapses and refractory multiple myeloma.

Richards T, Weber D.

Med Oncol. 2010 Jun;27 Suppl 1:S25-42. [Epub 2010 Mar 6.]

http://www.ncbi.nlm.nih.gov/pubmed/20213220

This article reviews the current role for thalidomide, lenalidomide, and bortezomib-based combinations, as well as some preliminary findings for promising investigational agents currently in clinical trials for patients with relapsed and/or refractory myeloma.

Recent advances in the treatment of multiple myeloma have resulted in improved response rates and overall survival in patients with multiple myeloma. These advances are largely due to thalidomide-, lenalidomide-, and bortezomib-based combinations that have improved response rates, not only in patients with untreated disease, but also in those with relapsed and/or refractory myeloma, in some cases producing response rates up to 85%. Eventually, however, nearly all patients relapse, emphasizing a continuing role for the introduction of investigational agents that overcome drug resistance. This article will review the current role for thalidomide, lenalidomide, and bortezomib-based combinations, as well as some preliminary findings for promising investigational agents currently in clinical trials for patients with relapsed and/or refractory disease.

Bone morphogenetic proteins and receptors are over-expressed in bone-marrow cells of multiple myeloma patients and support myeloma cells by inducing ID genes.

Grcević D, Kusec R, Kovacić N, Lukić A, Lukić IK, Ivcević S, Nemet D, Seiwerth RS, Ostojić SK, Croucher PI, Marusić A.

Leuk Res. 2010 Jun;34(6):742-51. [Epub 2009 Nov 18.]

http://www.ncbi.nlm.nih.gov/pubmed/19926132

The authors find that bone morphogenetic proteins (BMPs) partially protect myeloma cells from bortezomib- and TRAIL-induced apoptosis, and conclude that BMPs may be involved in myeloma pathophysiology and serve as myeloma cell biomarkers.

We assessed the expression pattern and clinical relevance of BMPs and related molecules in multiple myeloma (MM). MM bone-marrow samples (n = 32) had increased BMP4, BMP6, ACVR1 and ACVR2A, and decreased NOG expression compared with controls (n = 15), with BMP6 having the highest sensitivity/specificity. Within MM bone-marrow, the source of BMPs was mainly CD138(+) plasma-cell population, and BMP6 and ACVR1 expression correlated with plasma-cell percentage. Using myeloma cell lines NCI H929 and Thiel we showed that BMPs induced ID1, ID2 and IL6, and suppressed CDKN1A and BAX gene expression, and BAX protein expression. Finally, BMPs partially protected myeloma cells from bortezomib- and TRAIL-induced apoptosis. We concluded that BMPs may be involved in MM pathophysiology and serve as myeloma cell biomarkers.

Bortezomib down-regulates the osterix expression by osteoblasts in the myeloma microenvironment: Implications into osteoblast function in myeloma bone disease.

Terpos E.

Leuk Res. 2010 Jun;34(6):700-1 [Epub 2010 Jan 13.]

http://www.ncbi.nlm.nih.gov/pubmed/20074800

Comment on: Leuk Res. 2010 Feb;34(2):243-9.

Comparative Efficacy of PD and VAD Regimens for Multiple Myeloma. [Article in Chinese]

Zhao Y, Jing Y, Bo J, Wang SH, Li HH, Huang WR, Zhu HY, Han XP, Gao CJ, Yu L.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2010 Jun;18(3):652-4.

http://www.ncbi.nlm.nih.gov/pubmed/20561421

The authors find that compared with conventional vincristine + adriamycin + dexamethasone chemotherapy, bortezomib + dexamethasone may improve complete response and very good partial response rates in newly diagnosed myeloma patients, and does not bring about more or worse toxicity.

This study was aimed to compare the efficacy and adverse effects of PD (bortezomib + dexamethasone) and VAD (vincristine + adriamycin + dexamethasone) as regimens for treatment of multiple myeloma patients. 21 and 31 multiple myeloma patients were enrolled in the PD and VAD groups respectively which received 2 to 5 courses of treatments, and both clinical effects and adverse reactions were observed. In the all 52 patients, 48 were newly diagnosed and the other 4 patients had accepted 1 to 2 courses of M2 or MP treatment, but didn't get PR. In 52 patients, 4, 4, 8 and 5 patients accepted 2, 3, 4 and 5 courses of PD regimen respectively, while 6, 11, 12 and 2 patients accepted 2, 3, 4 and 5 courses of VAD regimen respectively. The results indicated that the rate of good efficacy (both CR and VGPR) in PD group was 57.1%, while the rate of good efficacy in VAD group was 16.1%, there was significant difference ($p = 0.0052$). The percentage of patients who got CR, VGPR and PR in PD and VAD groups were 95.2% and 74.2% respectively, there was no significant difference ($p = 0.1108$). The incidences of adverse effects in 2 groups were similar, which included hematological toxicity, liver and kidney functional lesion, peripheral neuropathy, infection, interstitial pneumonia. It is concluded that compared with conventional VAD chemotherapy, PD may improve CR and VGPR rate in newly diagnosed patients with multiple myeloma, meanwhile it does not bring about more and worse toxicity.

Cost-effectiveness of lenalidomide in multiple myeloma.

Schey S, Higginson I.

Expert Rev Pharmacoecon Outcomes Res. 2010 Jun;10(3):229-38.

http://www.ncbi.nlm.nih.gov/pubmed/20545587

The authors discuss the importance that researchers understand the instruments used to come to decisions regarding cost-effectiveness of treatment regimens using active new agents, including myeloma, outline the models used by health economists, and assess their potential shortcomings.

Lenalidomide represents the first drug in a novel class of agents known as IMiDs. It has both a direct antimyeloma activity and an indirect effect acting through the microenvironment. In the relapsed/refractory setting, lenalidomide has been demonstrated to be highly active, producing partial and complete responses that translate into improved survival. Generally, the drug is well tolerated and more recently this agent has been used in combination with steroids, chemotherapy agents and other novel agents that have further enhanced its efficacy in clinical trials. However, the cost of this and other novel agents is significantly greater than previously used chemotherapy protocols, which in turn means that they have fallen under the scrutiny of regulatory bodies such as NICE. It is important that researchers understand the instruments used by these bodies to come to decisions regarding cost-effectiveness if patients are not to be disadvantaged by not being given access to these active new agents. This article outlines the models used by health economists and assesses their potential shortcomings. It also suggests alternative methods and identifies areas of research where improvements might be achieved.

Effect of Bortezomib on Sensitization of HL-60 Cells to TRAIL. [Article in Chinese]

Hu R, Zhang R, Li YC, Yao K, Yang Y, Hou SY, Yang W, Liu ZG.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2010 Jun;18(3):617-20.

http://www.ncbi.nlm.nih.gov/pubmed/20561413

The authors find that sub-toxic concentration of bortezomib can sensitize HL-60 cells to TNF-related apoptosis-inducing ligand and its mechanism may be related to upregulation of caspase-8 expression.

This study was aimed to explore whether bortezomib can sensitize HL-60 cells to TNF-related apoptosis-inducing ligand (TRAIL) and to investigate its possible mechanism. The HL-60 cells were treated by different concentrations of TRAIL combined with sub-toxic concentration of bortezomib. The proliferative inhibition of treated HL-60 cell was analysed by MTT assay. The cell apoptosis was determined by flow cytometry with Annexin V/PI double staining and the expression of caspase-8 was detected by Western blot. The results showed that the sub-toxic concentration of bortezomib combined with 10 ng/ml of TRAIL enhanced apoptosis of HL-60 cells, as compared with TRAIL used alone; the expression of caspase-8 increased correspondingly. It is concluded that sub-toxic concentration of bortezomib can sensitize HL-60 cells to TRAIL and its mechanism may be related to upregulation of caspase-8 expression.

Evidence for cytogenetic and fluorescence in situ hybridization risk stratification of newly diagnosed multiple myeloma in the era of novel therapies.

Kapoor P, Fonseca R, Rajkumar SV, Sinha S, Gertz MA, Stewart AK, Bergsagel PL, Lacy MQ, Dingli DD, Ketterling RP, Buadi F, Kyle RA, Witzig TE, Greipp PR, Dispenzieri A, Kumar S.

Mayo Clin Proc. 2010 Jun;85(6):532-7.

http://www.ncbi.nlm.nih.gov/pubmed/20511484

The authors study the impact of the Mayo risk-stratification model of myeloma on patient outcome in the era of novel therapies. Their findings validate the high-risk features defined by FISH and CG in the Mayo risk-stratification model for patients with myeloma predominantly treated with novel therapies based on immunomodulatory agents.

Overall survival (OS) has improved with increasing use of novel agents in multiple myeloma (MM). However, the disease course remains highly variable, and the heterogeneity largely reflects different genetic abnormalities. We studied the impact of the Mayo risk-stratification model of MM on patient outcome in the era of novel therapies, evaluating each individual component of the model-fluorescence in situ hybridization (FISH), conventional cytogenetics (CG), and the plasma cell labeling index-that segregates patients into high- and standard-risk categories. This report consists of 290 patients with newly diagnosed MM, predominantly treated with novel agents, who were risk-stratified at diagnosis and were followed up for OS. Of these patients, 81% had received primarily thalidomide (n = 50), lenalidomide (n = 199), or bortezomib (n = 79) as frontline or salvage therapies. Our retrospective analysis validates the currently proposed Mayo risk-stratification model (median OS, 37 months vs. not reached for high- and standard-risk patients, respectively; p =.003). Although the FISH or CG test identifies a high-risk cohort with hazard ratios of 2.1 (p = .006) and 2.5 (p =.006), respectively, the plasma cell labeling index cutoff of 3% fails to independently prognosticate patient risk (hazard ratio, 1.4; p = .41). In those stratified as standard-risk by one of the 2 tests (FISH or CG), the other test appears to be of additional prognostic significance. This study validates the high-risk features defined by FISH and CG in the Mayo risk-stratification model for patients with MM predominantly treated with novel therapies based on immunomodulatory agents.

The evolution and impact of therapy in multiple myeloma.
Laubach JP, Richardson PG, Anderson KC.
Med Oncol. 2010 Jun;27 Suppl 1:S1-6. [Epub 2010 Feb 19.]
http://www.ncbi.nlm.nih.gov/pubmed/20169425

This review highlights important historic landmarks as well as more recent events that have played an important role in the evolution of myeloma therapy, including the use of thalidomide, lenalidomide, and bortezomib.

Multiple myeloma is a clonal B-cell malignancy characterized by aberrant expression of plasma cells within the bone marrow, and is associated with the well known clinical manifestations anemia, bone disease, renal dysfunction, hypercalcemia, and recurrent infections. For many years, melphalan and prednisone represented the standard of care in multiple myeloma therapy, with stem cell transplantation reserved for selected patients. Treatment of the disease has evolved rapidly over the past decade, however, with the development and utilization of thalidomide, lenalidomide, and bortezomib. As a result of these developments, clinical outcomes have improved significantly. This review highlights important historic landmarks as well as more recent events that have played an important role in the evolution of myeloma therapy.

Future directions in immunomodulatory therapy.
Lonial S.
Med Oncol. 2010 Jun;27 Suppl 1:S62-6. [Epub 2009 Dec 11.]
http://www.ncbi.nlm.nih.gov/pubmed/20012563

The author discusses the roles of thalidomide, lenalidomide, and bortezomib in the management of patients with myeloma in all phases of their disease.

The role of immunomodulatory-based therapy with thalidomide or lenalidomide is clearly established in the management of patients with myeloma in all phases of their disease. Recent preclinical and clinical works have demonstrated that in addition to combination therapy with dexamethasone, there is significant activity when combined with the proteasome inhibitor bortezomib. More recent clinical studies have also demonstrated significant activity when combined with akt inhibitors, HDAC inhibitors, and even monoclonal antibodies. Further clinical development of immunomodulatory agents should continue to be based on preclinical rationale, which has resulted in a number of promising and clinically active combinations.

Management of disease- and treatment-related complications in patients with multiple myeloma.
Gay F, Palumbo A.
Med Oncol. 2010 Jun;27 Suppl 1:S43-52.
http://www.ncbi.nlm.nih.gov/pubmed/20467920

This chapter provides an overview of frequency and management of main complications related to myeloma and to the use of new drugs (including thalidomide, lenalidomide, and bortezomib) in newly diagnosed and relapsed patients.

Treatment of myeloma has dramatically changed after introduction of novel agents, such as thalidomide, lenalidomide and bortezomib, with a significant improvement in response rate and survival of patients with myeloma. For newly diagnosed patients not eligible for transplant, the standards of care are now considered melphalan and prednisone (MP) plus thalidomide and MP plus bortezomib. Ongoing randomized trials are evaluating lenalidomide plus MP and lenalidomide plus dexamethasone. For newly diagnosed patients eligible for transplant, new induction regimens included the combination of high-dose dexamethasone plus thalidomide, high-dose dexamethasone plus lenalidomide (RD) and high-dose dexamethasone plus bortezomib (VD). The combinations RD, VD and bortezomib plus pegylated-liposomal-doxorubicin have received the US Food and Drug Administration approval for the treatment of relapsed myeloma. Different efficacious regimens are therefore now available for patients with myeloma. Disease control leads to improvement of all myeloma-related complications (anemia, bone disease, immune dysfunction and renal impairment), but physicians should take into account the choice of the therapeutic strategy, the expected toxicity profile of each of these regimens, together with the patient's biologic age and comorbidities. Supportive care is an essential part of

myeloma therapy, both for the treatment of myeloma-related complications, together with anti-myeloma treatment, and for the management of treatment-emergent adverse events. This chapter will provide an overview of frequency and management of main complications related to the disease itself and to the use of new drugs in newly diagnosed and relapsed patients with myeloma.

The NF-kappaB inhibitor LC-1 has single agent activity in multiple myeloma cells and synergizes with bortezomib.

Walsby EJ, Pratt G, Hewamana S, Crooks PA, Burnett AK, Fegan C, Pepper C.

Mol Cancer Ther. 2010 Jun;9(6):1574-82. [Epub 2010 Jun 1.]

http://www.ncbi.nlm.nih.gov/pubmed/20515939

These data show that LC-1 has activity in multiple myeloma cell lines and primary multiple myeloma cells, and that LC-1 shows synergy with melphalan, bortezomib, and doxorubicin.

Multiple myeloma remains incurable with conventional therapeutics. Thus, new treatments for this condition are clearly required. In this study we evaluated the novel NF-kappaB inhibitor LC-1 in multiple myeloma cell lines and plasma cells derived from multiple myeloma patients. LC-1 was cytotoxic to multiple myeloma cell lines H929, U266, and JJN3, and induced apoptosis in a dose-dependent manner with an overall LD(50) of 3.6 micromol/L (+/-1.8) after 48 hours in culture. Primary multiple myeloma cells, identified by CD38 and CD138 positivity, had a mean LD(50) for LC-1 of 4.9 micromol/L (+/-1.6); normal bone marrow cells were significantly less sensitive to the cytotoxic effects of LC-1 (p = 0.0002). Treatment of multiple myeloma cell lines with LC-1 resulted in decreased nuclear localization of the NF-kappaB subunit Rel A and the inhibition of NF-kappaB target genes. In addition, LC-1 showed synergy with melphalan, bortezomib, and doxorubicin (combination indices of 0.72, 0.61, and 0.78, respectively), and was more effective when cells were cultured on fibronectin. These data show that LC-1 has activity in multiple myeloma cell lines and primary multiple myeloma cells, and its ability to inhibit NF-kappaB seems important for its cytotoxic effects. Furthermore, LC-1-induced transcriptional suppression of survivin and MCL1 provides a potential explanation for its synergy with conventional agents.

Single agent lenalidomide in newly diagnosed multiple myeloma: a retrospective analysis.

Baz R, Patel M, Finley-Oliver E, Lebovic D, Hussein MA, Miller KC, Wood M, Sher T, Lee K, Chanan-Khan AA.

Leuk Lymphoma. 2010 Jun;51(6):1015-9.

http://www.ncbi.nlm.nih.gov/pubmed/20367570

This retrospective analysis suggests that lenalidomide alone can induce an anti-myeloma effect in previously untreated patients who are considered poor candidates for concurrent dexamethasone.

Recently, lenalidomide and low dose dexamethasone were found to result in superior overall survival compared to lenalidomide and high dose dexamethasone. The immune suppressive effects of dexamethasone can antagonize lenalidomide immunomodulatory activity and may explain this observation. We conducted a retrospective analysis to evaluate the single agent activity of lenalidomide in newly diagnosed myeloma. Records of patients with newly diagnosed symptomatic multiple myeloma treated with single agent lenalidomide at H. Lee Moffitt Cancer Center and Roswell Park Cancer Institute were reviewed. Data were collected on disease characteristics, demographics, and treatment outcomes. Responses were assessed as per the International Myeloma Working Group criteria. From March 2007 to July 2009, 17 patients with newly diagnosed multiple myeloma were treated with single agent lenalidomide at both institutions. The median age was 70 years (range 46-84 years). Lenalidomide was generally well tolerated and no grade 4 hematologic toxicities were noted. The overall response rate (> or =partial remission) to lenalidomide alone was 47% at a median follow-up of 7 months (range 1-26). This experience suggests that lenalidomide alone can induce an anti-myeloma effect in previously untreated patients who are considered poor candidates for concurrent dexamethasone.

Stem cell collection in patients with de novo multiple myeloma treated with the combination of bortezomib and dexamethasone before autologous stem cell transplantation according to IFM 2005-01 trial.

Moreau P, Hulin C, Marit G, Caillot D, Facon T, Lenain P, Berthou C, Pégourié B, Stoppa AM, Casassus P, Michallet M, Benboubker L, Maisonneuve H, Doyen C, Leyvraz S, Mathiot C, Avet-Loiseau H, Attal M, Harousseau JL; IFM group.

Leukemia. 2010 Jun;24(6):1233-5. [Epub 2010 Apr 29.]

http://www.ncbi.nlm.nih.gov/pubmed/20428201

No abstract available.

ThaDD plus high dose therapy and autologous stem cell transplantation does not appear superior to ThaDD plus maintenance in elderly patients with de novo multiple myeloma.

Offidani M, Leoni P, Corvatta L, Polloni C, Gentili S, Savini A, Alesiani F, Brunori M, Catarini M, Visani G, Samori A, Burattini M, Centurioni R, Montanari M, Fraticelli P, Ruggieri M, Falcioni S, Galieni P.

Eur J Haematol. 2010 Jun;84(6):474-83. [Epub 2010 Mar 11.]

http://www.ncbi.nlm.nih.gov/pubmed/20331733

The results of this study suggest that in elderly myeloma patients, although ThaDD plus high-dose therapy (HDT) significantly increases complete response rate, it seems to be equivalent to ThaDD plus maintenance in terms of time to progression, progression-free response and overall survival. These results challenge the requirement for HDT consolidation in this subset of patients.

OBJECTIVES: With the aim to address the issue whether high-dose therapy (HDT) is required after new drugs combinations to improve outcome of elderly newly diagnosed multiple myeloma (MM) patients, we compared the toxicity and the outcome of ThaDD plus maintenance to those of ThaDD plus HDT-autologous stem cell transplantation (ASCT). METHODS: Sixty-two patients not eligible for HDT receiving six courses of ThaDD regimen plus maintenance with thalidomide were compared to 26 patients eligible for HDT treated with four courses of ThaDD followed by melphalan 100-200 mg/m² and ASCT. The two groups were matched for the main characteristics except for age favouring the HDT group. RESULTS AND CONCLUSIONS: Complete remission (CR) obtained with ThaDD plus maintenance was 24% whereas it was 57% after ThaDD plus HDT-ASCT ($p = 0.0232$). However, after a median follow-up of 36 months, median time to progression (TTP) and progression free survival (PFS) of the group of patients undergone HDT were not significantly different to those of patients receiving ThaDD plus maintenance (32 vs. 31 months: $p = 0.962$; 32 vs. 29 months: $p = 0.726$, respectively). Five-year overall survival (OS) was 49% in the first group and 46% in the latter one ($p = 0.404$). As expected, a significantly higher incidence of grade 3-4 neutropenia, thrombocytopenia, infections, mucositis and alopecia were observed in the ThaDD plus HDT group. Our results suggest that in elderly MM patients ThaDD plus HDT, albeit significantly increases CR rate, seems to be equivalent to ThaDD plus maintenance in terms of TTP, PFS and OS. These results challenge the requirement for HDT consolidation in this subset of patients.

Thalidomide-dexamethasone as up-front therapy for patients with newly diagnosed multiple myeloma: thrombophilic alterations, thrombotic complications, and thromboprophylaxis with low-dose warfarin.

Cini M, Zamagni E, Valdré L, Palareti G, Patriarca F, Tacchetti P, Legnani C, Catalano L, Masini L, Tosi P, Gozzetti A, Cavo M.

Eur J Haematol. 2010 Jun;84(6):484-92. [Epub 2010 Feb 23.]

http://www.ncbi.nlm.nih.gov/pubmed/20192986

The authors address the issue of pathogenesis of thalidomide-induced VTE as not well recognized and the role of prothrombotic factors, especially of thrombophilic abnormalities, as not yet determined. On the basis of their data, they do not recommend a baseline thrombophilic work up in myeloma patients receiving up-front thalidomide-dexamethasone. For these patients, fixed low-dose warfarin may be a valuable prophylaxis against VTE.

ABSTRACT BACKGROUND: Venous thromboembolism (VTE) is a major complication of myeloma therapy recently observed with the increasing use of up-front thalidomide and dexamethasone (thal-dex). The pathogenesis of thal-induced VTE is not well recognized and the role of prothrombotic factors, especially of thrombophilic abnormalities, is not yet determined. MATERIAL and METHODS: 266 patients with newly diagnosed multiple myeloma (MM) were primarily treated with thal-dex in preparation for subsequent high-dose therapy and autologous stem-cell transplantation. 190 out of these 266 patients were evaluated for thrombophilic alterations at baseline and 125 of them were also re-assessed after thal-dex therapy. RESULTS: The presence of genetic thrombophilic polymorphisms among MM patients was super-imposable to that of normal controls, and was associated with a twofold increase in the relative risk of VTE. APCR and elevated factor VIII levels were frequent, albeit transient alterations and were not associated with a significant increase in the risk of VTE. 246 patients received a thromboprophylaxis with fixed low-dose warfarin (1.25 mg/day) during thal-dex therapy. 26 of these patients (or 10.6%) had symptomatic VTE events. Their patients-years rate of VTE (35.5%) was significantly lower in comparison with the 86.2% rate recorded among the first 19 patients who initially entered the study and did not receive any kind of thromboprophylaxis ($p = 0.043$). CONCLUSIONS: On the basis of these data, a baseline thrombophilic work up is not recommended in MM patients receiving up-front thal-dex. For these patients, fixed low-dose warfarin may be a valuable prophylaxis against VTE.

May 2010

Bortezomib, dexamethasone, cyclophosphamide and lenalidomide combination for newly diagnosed multiple myeloma: phase I results from the multicenter EVOLUTION study.

Kumar SK, Flinn I, Noga SJ, Hari P, Rifkin R, Callander N, Bhandari M, Wolf JL, Gasparetto C, Krishnan A, Grosman D, Glass J, Sahovic EA, Shi H, Webb IJ, Richardson PG, Rajkumar SV.

Leukemia. 2010 May 27. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20508619

This phase I study finds that cyclophosphamide in combination with bortezomib, dexamethasone and lenalidomide is well tolerated and highly active in newly diagnosed myeloma patients.

This phase I study (Clinicaltrials.gov: #NCT00507442) was conducted to determine the maximum tolerated dose (MTD) of cyclophosphamide in combination with bortezomib, dexamethasone and lenalidomide (VDCR) and to assess the safety and efficacy of this combination in untreated multiple myeloma patients. Cohorts of three to six patients received a cyclophosphamide dosage of 100, 200, 300, 400 or 500 mg/m² (on days 1 and 8) plus bortezomib 1.3 mg/m² (on days 1, 4, 8 and 11), dexamethasone 40 mg (on days 1, 8 and 15) and lenalidomide 15 mg (on days 1-14), for eight 21-day induction cycles, followed by four 42-day maintenance cycles (bortezomib 1.3 mg/m², on days 1, 8, 15 and 22). The MTD was the cyclophosphamide dose below which more than one of six patients experienced a dose-limiting toxicity (DLT). Twenty-five patients were treated. Two DLTs were seen, of grade 4 febrile neutropenia (cyclophosphamide 400 mg/m²) and grade 4 herpes zoster despite anti-viral prophylaxis (cyclophosphamide 500 mg/m²). No cumulative hematological toxicity or thromboembolic episodes were reported. The overall response rate was 96%, including 20% stringent complete response (CR), 40% CR/near-complete response and 68% >/=very good partial response. VDCR is well tolerated and highly active in this population. No MTD was reached; the recommended phase II cyclophosphamide dose in VDCR is 500 mg/m², which was the highest dose tested.

Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance.

Nair B, van Rhee F, Shaughnessy JD Jr, Anaissie E, Szymonifka J, Hoering A, Alsayed Y, Waheed S, Crowley J, Barlogie B.

Blood. 2010 May 27;115(21):4168-73. [Epub 2010 Feb 2.]

http://www.ncbi.nlm.nih.gov/pubmed/20124509

The authors report here on the results of successor trial 2006-66, employing bortezomib-lenalidomide-dexamethasone maintenance for 3 years, versus bortezomib-thalidomide-dexamethasone in year 1 and thalidomide-dexamethasone in years 2 and 3. They conclude that robustness of the gene expression profiling risk model should be exploited in clinical trials aimed at improving the notoriously poor outcome in high-risk myeloma.

Total Therapy 3 (TT3) trial 2003-33 enrolled 303 newly diagnosed patients with multiple myeloma and was noted to provide superior clinical outcomes in comparison to predecessor trial Total Therapy 2 (TT2), especially in gene expression profiling (GEP)-defined low-risk disease. We report here on the results of successor trial 2006-66 with 177 patients, employing bortezomib-lenalidomide-dexamethasone (VRD) maintenance for 3 years versus bortezomib-thalidomide-dexamethasone (VTD) in year 1 and TD in years 2 and 3 in 2003-33 protocol. Overall survival (OS) and event-free survival (EFS) plots were super-imposable for the 2 trials, as were onset of complete response (CR) and CR duration (CRD), regardless of GEP risk. GEP-defined high-risk designation, pertinent to 17% of patients, imparted inferior OS, EFS and CRD in both protocols and, on multivariate analysis, was the sole adverse feature affecting OS, EFS and CRD. Mathematical modeling of CRD in low-risk myeloma predicted a 55% cure fraction ($p < 0.001$). Despite more rapid onset and higher rate of CR than in other molecular subgroups, CRD was inferior in CD-1 myeloma, resembling outcomes in MAF/MAFB (MF) and Proliferation (PR) entities. The robustness of the GEP risk model should be exploited in clinical trials aimed at improving the notoriously poor outcome in high-risk disease.

Impact of cytogenetics in patients with relapsed or refractory multiple myeloma treated with bortezomib: Adverse effect of 1q21 gains.

Chang H, Trieu Y, Qi X, Jiang NN, Xu W, Reece D.

Leuk Res. 2010 May 25. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20537706

The authors investigate the influence of genetic risk factors on the clinical response to bortezomib in 85 relapsed/refractory myeloma patients. Multivariate analysis confirms that 1q21 gain is an independent risk factor progression-free survival (PFS) and overall survival (OS); there was no significant difference in response rate, response duration, PFS or OS for any of the other genetic risk factors tested.

We investigated the influence of genetic risk factors on the clinical response to bortezomib in 85 relapsed/refractory multiple myeloma (MM) patients. Interphase cytoplasmic fluorescence in situ hybridization (cIg-FISH) detected del(13q), del(17p), del(1p21), t(4;14), and 1q21 gain in 38%, 22%, 26%, 18% and 39% of evaluable cases. Forty-nine patients (49%) responded to bortezomib with median progression free (PFS) and overall survivals (OS) of 5.0 and 12.6 months, respectively. Patients with 1q21 gain had a significantly shorter OS (5.3 months vs. 24.6 months, $p = 0.0006$) and PFS (2.3 months vs. 7.3 months, $p = 0.003$) than patients without such abnormality. There was no significant difference in response rate, response duration, PFS or OS for any of the other genetic risk factors tested. Multivariate analysis confirmed that 1q21 gain is an independent risk factor for PFS ($p = 0.03$) and OS ($p = 0.009$) of bortezomib-treated relapsed/refractory myeloma.

Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents.
Roussou M, Kastritis E, Christoulas D, Migkou M, Gavriatopoulou M, Grapsa I, Psimenou E, Gika D, Terpos E, Dimopoulos MA.
Leuk Res. 2010 May 24. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20510452

The authors find that bortezomib-based regimens may be the preferred treatment for newly diagnosed myeloma patients with renal impairment.

The purpose of this analysis was to assess the effect of novel agent-based regimens on the improvement of renal impairment (RI) in newly diagnosed patients with multiple myeloma. Ninety-six consecutive patients with RI received conventional chemotherapy (CC)-based regimens (n = 32), IMiDs-based regimens (n = 47) or bortezomib-based regimens (n = 17) as frontline therapy. Improvement of RI was more frequent in patients treated with novel agents (79% in IMiD- and 94% in bortezomib-treated groups versus 59% in CC-treated group; p = 0.02). Bortezomib-based regimens and CrCl > 30ml/min at baseline independently correlated with a higher probability of at least renal partial response (PRrenal) and with a shorter time to PRrenal or better. Thus bortezomib-based regimens may be the preferred treatment for newly diagnosed myeloma patients with RI.

Importance of achieving a complete response in multiple myeloma, and the impact of novel agents.
Chanan-Khan AA, Giralt S.
J Clin Oncol. 2010 May 20;28(15):2612-24. [Epub 2010 Apr 12.]

http://www.ncbi.nlm.nih.gov/pubmed/20385994

The authors review the prognostic significance of achieving complete response (CR) in myeloma and highlight the importance of CR as an increasingly realizable goal at all stages of treatment, and how this goal is informed by the advent of novel therapies, including bortezomib, thalidomide, and lenalidomide.

The goal of treatment for multiple myeloma (MM) is to improve patients' long-term outcomes. One important factor that has been associated with prolonged progression-free and overall survival is the quality of response to treatment, particularly achievement of a complete response (CR). There is extensive evidence from clinical studies in the transplant setting in first-line MM demonstrating that CR or maximal response post-transplant is significantly associated with prolonged progression-free and overall survival, with some studies demonstrating a similar association with post-induction response. Supportive evidence is also available from studies in the non-transplant and relapsed settings. With the introduction of bortezomib, thalidomide, and lenalidomide, higher rates of CR are being achieved in both first-line and relapsed MM compared with previous chemotherapeutic approaches, thereby potentially improving long-term outcomes. While standard CR by established response criteria has been shown to have differential prognostic impact compared with lesser responses, increasingly sensitive analytic techniques are now being explored to define more stringent degrees of CR or elimination of minimal residual disease (MRD), including multi-parameter flow cytometry and polymerase chain reaction. Demonstrating eradication of MRD by these techniques has already been shown to predict for improved outcomes. Here, we review the prognostic significance of achieving CR in MM and highlight the importance of CR as an increasingly realizable goal at all stages of treatment. We discuss clinical management issues and provide recommendations relevant to practicing oncologists, such as the routine use of sensitive techniques for assessment of disease status to inform evidence-based decisions on optimal patient management.

Plerixafor (Mozobil) for stem cell mobilization in patients with multiple myeloma previously treated with lenalidomide.

Micallef IN, Ho AD, Klein LM, Marulkar S, Gandhi PJ, McSweeney PA.

Bone Marrow Transplant. 2010 May 17. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/20479709

This retrospective study suggests that CD34+ hematopoietic stem cells can be successfully and predictably collected with combination plerixafor plus G-CSF for primary or secondary mobilization in the majority of myeloma patients who have been previously treated with lenalidomide.

Lenalidomide and other new agents have considerable activity in multiple myeloma (MM) and have changed the landscape of treatment. Data suggest that lenalidomide therapy before autologous hematopoietic stem cell transplantation has a detrimental effect on stem cell mobilization. This retrospective study examined the efficacy of plerixafor in combination with G-CSF among patients with MM previously treated with lenalidomide (median, 4 cycles; range, 1-20 cycles). Data were analyzed for 60 patients who received plerixafor plus G-CSF for frontline mobilization in a phase III clinical trial or an expanded access program (n = 20) or for remobilization in a compassionate use program (n = 40). The overall median number of CD34+ cells collected was 5.6 x 106 per kg (range, 0.45 x 106 -37.2 x 106). The minimum number of CD34+ cells (>/=2 x 10^6 per kg) was collected from 86.7% of patients in a median of 1 day. This minimum was collected from 100% of patients who underwent frontline mobilization and 80% of patients who underwent remobilization. These data suggest that CD34+ hematopoietic stem cells can be successfully and predictably collected with combination plerixafor plus G-CSF for primary or secondary mobilization in the majority of patients with MM who have been previously treated with lenalidomide.

Hematopoietic stem cell transplantation for multiple myeloma beyond 2010.

Bladé J, Rosiñol L, Cibeira MT, Rovira M, Carreras E.

Blood. 2010 May 6;115(18):3655-63. [Epub 2010 Mar 4.]

http://www.ncbi.nlm.nih.gov/pubmed/20203260

The authors discuss the development of novel reduced-intensity preparative regimens (including use of bortezomib) and peri- and post-transplant strategies aimed at minimizing graft-versus-host disease and enhancing the graft-versus-myeloma effect as key issues in the future treatment of myeloma.

Autologous stem cell transplantation (ASCT) is considered the gold standard in the frontline therapy of younger patients with multiple myeloma, since it results in higher complete remission (CR) rates and longer event-free survival (EFS) than conventional chemotherapy. The greatest benefit from ASCT is obtained in patients achieving CR post-transplant, the likelihood of CR being associated with the M-protein size at the time of transplant. The incorporation of novel agents results in higher pre- and post-transplant CR rates. Induction with bortezomib-containing regimens is encouraging in patients with poor-risk cytogenetics. However, longer follow-up is required to assess the impact of this increased CR on long-term survival. The results of post-transplant consolidation/maintenance with new drugs are encouraging. All the above indicate that, in the era of novel agents, high-dose therapy should be optimized rather than replaced. Due to its high transplant-related mortality, myelo-ablative allografting has been generally replaced by reduced-intensity conditioning (Allo-RIC). The best results are achieved after a debulky ASCT, with a progression-free survival plateau of 25-30% beyond 6 years from Allo-RIC. The development of novel reduced-intensity preparative regimens and peri- and -post-transplant strategies aimed at minimizing graft-versus-host disease and enhancing the graft-versus-myeloma effect are key issues.

Clinical management of myeloma – state of the art.

Harousseau JL.

Cancer Treat Rev. 2010 May;36 Suppl 2:S1-2.

http://www.ncbi.nlm.nih.gov/pubmed/20472182

In the articles included in this supplement, experts at the forefront of myeloma research provide insight into the management of patients with myeloma, and the current issues that clinicians face today regarding the best use of thalidomide, lenalidomide, and bortezomib.

In the last decade, advances in our understanding of the biology of myeloma have led to new treatment approaches that have resulted in unprecedented improvements in survival outcomes. These gains can be attributed in part to the introduction of three new active agents for the treatment of myeloma: thalidomide, lenalidomide, and bortezomib. With these treatments, however, have come new questions regarding the optimal approach to therapy, expected outcomes, and safety issues. In the articles included in this supplement, experts at the forefront of myeloma research provide insight into the management of patients with myeloma, and the current issues that clinicians face today regarding the best use of these agents.

How best to use new therapies in multiple myeloma.

Dingli D, Rajkumar SV.

Blood Rev. 2010 May;24(3):91-100. [Epub 2010 Apr 1.]

http://www.ncbi.nlm.nih.gov/pubmed/20359801

The authors summarize the key observations from recent completed and ongoing studies that determined the effect of novel therapies, including thalidomide, lenalidomide, and bortezomib, both in the setting of newly diagnosed myeloma and for relapsed disease. They also discuss their approach to the use of these agents in specific myeloma settings.

Advances in the molecular understanding of myeloma have led to the development of novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (bortezomib). When used alone, these agents have significant activity against myeloma and responses increase significantly when they are combined with additional agents including glucocorticosteroids and chemotherapeutic agents such as alkylators. There is a drive to use these novel agents in patients with newly diagnosed myeloma, where they lead to impressive response rates with increasing duration of responses. In addition, novel agents are now the mainstays of therapy for relapsed disease. In the following paper, we summarize the key observations from recent completed and ongoing studies that determined the effect of these novel therapies both in the setting of newly diagnosed myeloma and for relapsed disease. We also discuss our approach to the use of these agents in specific myeloma settings.

In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma.

Ocio EM, Vilanova D, Atadja P, Maiso P, Crusoe E, Fernández-Lázaro D, Garayoa M, San-Segundo L, Hernández-Iglesias T, de Alava E, Shao W, Yao YM, Pandiella A, San-Miguel JF.

Haematologica. 2010 May;95(5):794-803. [Epub 2009 Nov 30.]

http://www.ncbi.nlm.nih.gov/pubmed/19951978

The authors find that potent activity, together with the exclusive mechanistic profile, provides the rationale for the clinical evaluation of panobinostat and dexamethasone in combination with both bortezomib and lenalidomide in myeloma.

BACKGROUND: Combinations based on bortezomib or lenalidomide plus steroids have resulted in very high response rates in multiple myeloma. However, most patients still relapse, indicating the need for novel combination partners to increase duration of response or to treat relapsed disease. In this manuscript we have explored the antimyeloma activity of the triple combination of these well established schemes with panobinostat, a novel deacetylase inhibitor with a multi-targeted profile. DESIGN AND METHODS: The activity of these combinations was explored in vitro in cell lines by using MTT and Annexin V; ex vivo by flow cytometry; and in vivo using two different murine models

of human myeloma: one bearing a subcutaneous plasmacytoma and another with a disseminated myeloma. Moreover, gene expression profile and immunohistochemical studies were performed. RESULTS: The addition of panobinostat (LBH589) to dexamethasone and either bortezomib (PBD) or lenalidomide (PLD) resulted in clear potentiation in MM cell lines, freshly isolated plasma cells, and MM murine models. The quantification of the potency of these combinations by using the Chou-Talalay method showed synergistic combination indexes in all of them. This effect derived from the deregulation of a cluster of genes completely different to the sum of genes affected with single agents (895 and 1323 genes exclusively deregulated by PBD and PLD respectively). Functional experiments, such as Annexin V staining, cell cycle analysis, and immunohistochemical studies also supported this potentiation. Anti-myeloma efficacy was confirmed in an extramedullary plasmacytoma model and a disseminated luciferized model, in which panobinostat also provided a marked benefit in bone disease. CONCLUSIONS: The potent activity, together with the exclusive mechanistic profile, provides the rationale for the clinical evaluation of these drug combinations in MM.

Lenalidomide, melphalan, prednisone and thalidomide (RMPT) for relapsed/refractory multiple myeloma.
Palumbo A, Larocca A, Falco P, Sanpaolo G, Falcone AP, Federico V, Canepa L, Crugnola M, Genuardi M, Magarotto V, Petrucci MT, Boccadoro M.
Leukemia. 2010 May;24(5):1037-42. [Epub 2010 Apr 8.]
http://www.ncbi.nlm.nih.gov/pubmed/20376079

This multicenter, open-label, non-comparative phase II trial evaluates the safety and efficacy of salvage therapy with lenalidomide, melphalan, prednisone and thalidomide (RMPT) in patients with relapsed/refractory myeloma. The authors find that RMPT is an active salvage therapy with good efficacy and manageable side effects.

This multicenter, open-label, non-comparative phase II trial evaluated the safety and efficacy of salvage therapy with lenalidomide, melphalan, prednisone and thalidomide (RMPT) in patients with relapsed/refractory multiple myeloma (MM). Oral lenalidomide (10 mg/day) was administered on days 1-21, and oral melphalan (0.18 mg/kg) and oral prednisone (2 mg/kg) on days 1-4 of each 28-day cycle. Thalidomide was administered at 50 mg/day or 100 mg/day on days 1-28; six cycles were administered in total. Maintenance included lenalidomide 10 mg/day on days 1-21, until unacceptable adverse events or disease progression. Aspirin (100 mg/day) was given as thromboprophylaxis. A total of 44 patients with relapsed/refractory MM were enrolled and 75% achieved at least a partial response (PR), including 32% very good PR (VGPR) and 2% complete response (CR). The 1-year progression-free survival (PFS) was 51% and the 1-year overall survival (OS) from study entry was 72%. Grade 4 hematologic adverse events included neutropenia (18%), thrombocytopenia (7%) and anemia (2%). Grade 3 non-hematologic adverse events were infections (14%), neurological toxicity (4.5%) and fatigue (7%). No grade 3/4 thromboembolic events or peripheral neuropathy were reported. In conclusion, RMPT is an active salvage therapy with good efficacy and manageable side effects. This study represents the basis for larger phase III randomized trials.

Management of treatment-related adverse events in patients with multiple myeloma.
Mateos MV.
Cancer Treat Rev. 2010 May;36 Suppl 2:S24-32.
http://www.ncbi.nlm.nih.gov/pubmed/20472185

The author evaluates the incidence of treatment-related adverse events associated with thalidomide, lenalidomide, and bortezomib, and reviews the management of these adverse events with a view to delivering optimal therapeutic outcomes in patients with newly diagnosed and relapsed and/or refractory myeloma.

The introduction of novel antimyeloma therapies, including thalidomide, lenalidomide and bortezomib, has expanded treatment options for patients with multiple myeloma. These compounds alter the natural history of multiple myeloma and help improve outcomes, but have different and specific toxicity profiles. The major adverse events associated with these treatments are somnolence (thalidomide), venous thromboembolism (thalidomide and lenalidomide), myelosuppression (lenalidomide and bortezomib), gastrointestinal disturbance, and peripheral neuropathy (thalidomide and bortezomib). These adverse events are predictable, consistent, and manageable with patient monitoring, supportive care, and dose reduction and interruption where appropriate. Herein we evaluate the incidence of treatment-related adverse events associated with each of these compounds. We further review the management of these adverse events

with a view to delivering optimal therapeutic outcomes in patients with newly diagnosed and relapsed and/or refractory multiple myeloma.

Multiple myeloma: chemotherapy or transplantation in the era of new drugs.
Palumbo A, Rajkumar SV.
Eur J Haematol. 2010 May;84(5):379-90. [Epub 2010 Mar 23.]
http://www.ncbi.nlm.nih.gov/pubmed/20345446

The authors review the current results of studies incorporating novel agents, including bortezomib, thalidomide, and lenalidomide in myeloma and discuss the role of autologous stem-cell transplantation in the era of new active drugs for the treatment of this disease.

ABSTRACT OBJECTIVE: To review the current results of studies incorporating novel agents in multiple myeloma (MM) and discuss the role of autologous stem-cell transplantation (ASCT) in the era of new active drugs for the treatment of this disease. The outlook for patients with symptomatic MM is changing with the introduction of bortezomib, thalidomide, and lenalidomide into the repertoire of available chemotherapeutic agents. Compared with standard chemotherapy, a survival benefit has been reported for the first time in 30 yrs. METHODS: Articles published in English between 1969 and 2008 were identified by searching PubMed for 'myeloma', 'diagnosis', 'thalidomide', 'bortezomib', 'lenalidomide', 'dexamethasone', 'prednisone', 'doxorubicin', 'cyclophosphamide', 'melphalan', 'combination chemotherapy', and 'autologous transplantation'. RESULTS: In randomized studies, bortezomib, thalidomide, and lenalidomide have each been combined with dexamethasone, alkylating agents, or doxorubicin, and such combinations resulted in significant improvement in progression-free survival. CONCLUSIONS: The incorporation of new drugs as induction therapy along with ASCT appears to produce very good partial response rates, slightly superior to those achieved by conventional chemotherapy with new drugs. How to best optimize induction, consolidation, and maintenance therapy and how to best select and prepare patients for ASCT are still to be determined. Randomized trials are needed to directly compare the current best chemotherapeutic approach with best ASCT strategies and to guide clinical practice for patients with MM.

Multiple myeloma - current issues and controversies.
Kumar S.
Cancer Treat Rev. 2010 May;36 Suppl 2:S3-11.
http://www.ncbi.nlm.nih.gov/pubmed/20472186

The author interprets the current state of knowledge and provides a perspective on the current issues in myeloma, including those surrounding the optimal use of the use of thalidomide, lenalidomide, and bortezomib.

The outcome of patients with multiple myeloma has dramatically improved in the past decade, due to the introduction of new, more effective treatments, wider use of high-dose therapy, and better appreciation of potential complications and their management. Increasing treatment options have also raised several important questions regarding the optimal use of novel therapies such as thalidomide, lenalidomide, and bortezomib to realise their full potential and to maximise the survival of patients with myeloma. The high response rates seen with the new regimens have led to increasing debate about the goal of therapy for this disease, including the concept of cure. While we still lack definitive data answering some of these questions, we have attempted to interpret the current state of knowledge, and provide a perspective on the current issues and controversies in this disease.

Optimising patient outcomes in myeloma.

Harousseau JL.

Cancer Treat Rev. 2010 May;36 Suppl 2:S33-5.

http://www.ncbi.nlm.nih.gov/pubmed/20472187

The author discusses the nature of myeloma treatment as it evolves to be tailored to the individual patient based on the goals of therapy, patient condition, expected adverse events, and patient preference. This includes a discussion of thalidomide, lenalidomide, and bortezomib.

Multiple myeloma (MM) is an incurable disease, and the goal of therapy is to prolong survival. Newer therapies (thalidomide, lenalidomide, and bortezomib) have contributed to the recent improvements in survival. Optimal integration of these newer therapies into standard practice may be aided by better methods of risk stratification. Supplementation of existing risk stratification methods with new prognostic information, such as cytogenetic data and gene expression profiles, may improve prognostication and help to identify appropriate treatment. The advent of newer therapies has also prompted a reassessment of traditional endpoints and goals of therapy, such as complete response. While complete response correlates with survival in some cases, the correlation is not consistent across all treatment regimens and patient groups, and is therefore not always the most appropriate goal of therapy. With the aim of prolonging survival, trials are currently evaluating newer therapies as long-term maintenance therapy or as prevention therapy for patients with smouldering myeloma. Given that these patients are often asymptomatic and free of clinically active disease, success in this setting depends highly on long-term tolerability of these agents. The available evidence suggests that their adverse event profiles are distinct, predictable, and manageable with careful monitoring and intervention as appropriate. Treatment of MM should therefore be tailored to the individual patient based on the goals of therapy, patient condition, expected adverse events, and patient preference.

Palliative oncology: thalidomide.

Prommer EE.

Am J Hosp Palliat Care. 2010 May;27(3):198-204. [Epub 2009 Oct 20.]

http://www.ncbi.nlm.nih.gov/pubmed/19843880

This review describes thalidomide's use in oncology, hematology, and palliative care.

After decades of disuse because of its teratogenic effects, thalidomide has had a resurgence of use as a promising therapeutic agent for multiple myeloma. Its mechanism of action involves activation of the immune system, anti-angiogenic effects, and inhibition of cytokines. Thalidomide does not interact with the cytochrome oxidase system. It is not significantly metabolized, but it does undergo nonenzymatic hydrolysis in plasma. The resulting products are inactive. Despite the potential adverse effects of peripheral neuropathy, constipation, deep vein thrombosis, somnolence, rash, and orthostatic hypotension, thalidomide is an effective first-line agent for multiple myeloma in combination with dexamethasone or melphalan and prednisone. It has also been studied in the palliative care of patients with cytokine-based syndromes such as anorexia-cachexia syndrome. This review describes its use in oncology, hematology, and palliative care.

Presentation and risk stratification--improving prognosis for patients with multiple myeloma.

Lonial S.

Cancer Treat Rev. 2010 May;36 Suppl 2:S12-7.

http://www.ncbi.nlm.nih.gov/pubmed/20472183

The authors discusses how currently available data indicate that the use of novel therapies (including thalidomide, lenalidomide, and bortezomib) in both the induction and maintenance settings, accompanied by risk stratification, may improve prognosis for myeloma patients.

Major improvement milestones in the treatment of patients with multiple myeloma (MM) include the introduction of the melphalan/prednisone combination in the 1960s; high-dose chemotherapy supported by autologous stem cell transplant in the 1980s; and the more recent introduction of the novel agents, thalidomide, lenalidomide, bortezomib, and pegylated liposomal doxorubicin. While, historically, age and eligibility for autologous stem cell transplantation were the primary basis for treatment selection, cytogenetics and other risk stratification methods are increasingly being used to guide treatment, especially with the newer agents. This trend reflects our improved understanding of the numerous genetic and biological abnormalities that mark this complex disease. In the absence of prospective, randomised studies assessing the value of risk stratification in guiding treatment decisions, and the use of the newest therapies, results of a number of studies provide a rationale for this approach. Currently available data indicate that the use of novel therapies in both the induction and maintenance settings, accompanied by risk stratification, may improve prognosis for patients with MM. Large, prospective randomised studies are needed to confirm these early pilot studies.

Role of new treatment approaches in defining treatment goals in multiple myeloma – the ultimate goal is extended survival.

Durie BG.

Cancer Treat Rev. 2010 May;36 Suppl 2:S18-23.

http://www.ncbi.nlm.nih.gov/pubmed/20472184

The author discusses the nature of new approaches to the treatment of myeloma—including use of thalidomide, lenalidomide, and bortezomib— and that extended survival should remain the goal of these evolving therapies.

Multiple myeloma is a chronic disease for which there is currently no cure, thus, the overall goal of treatment is to improve survival. Few patients achieved a complete response (CR) with conventional chemotherapy regimens; however, this has changed with the use of high-dose therapy followed by autologous stem cell transplantation and the advent of novel therapies, such as thalidomide, lenalidomide, and bortezomib. With more patients achieving CR and studies reporting that achievement of CR correlates with survival, the role of CR as an endpoint in myeloma therapy has gained prominence. However, there is evidence that the benefit of CR is not the same with all treatment regimens, and that CR is not associated with improved survival in all patients, but mainly in poor-risk patients with more aggressive myeloma. In addition, recent evidence suggests that continued therapy with novel agents may improve the depth of response and/or prolong CR. Finally, despite improvements in response rates, time to progression, and survival achieved with novel therapies in both relapsed/refractory and newly diagnosed myeloma patients, none of the available drugs have been shown to be curative. Therefore, at this time, extended survival should remain the goal of myeloma therapy.

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