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VELCADE® (bortezomib) Issue

Welcome to the International Myeloma Foundation's (IMF) special edition of CITINGS, our premiere publication featuring the most up-to-date information on myeloma treatment. This issue focuses on VELCADE (bortezomib), the first of a new class of drugs called proteasome inhibitors. In this issue, we provide a list of references to the latest published studies on bortezomib from both national and international medical journals and publications from the first quarter of this year.

We hope that CITINGS provides a detailed and informative update of the VELCADE literature. Please feel free to contact the IMF at (800) 452-CURE or www.myeloma.org

– Susie Novis, President, IMF

VELCADE (bortezomib) Publications 1st Quarter, 2009

Bortezomib is associated with better health-related quality of life than high-dose dexamethasone in patients with relapsed multiple myeloma: results from the APEX study.

Lee SJ, Richardson PG, Sonneveld P, Schuster MW, Irwin D, San Miguel JF, Crawford B, Massaro J, Dhawan R, Gupta S, Anderson KC.

Br J Haematol. 2008 Nov;143(4):511-9.

http://www.ncbi.nlm.nih.gov/pubmed/18986387?ordinalpos=81&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report on a questionnaire that finds bortezomib is associated with significantly better multidimensional health-related quality of life compared with dexamethasone, consistent with the better clinical outcomes seen with bortezomib.

Health-related quality of life (HRQL) was prospectively measured during the phase III APEX trial of bortezomib versus dexamethasone in relapsed multiple myeloma patients. The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core (QLQ-C30) and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (NTX) side-effects questionnaires were administered at baseline and every 6 weeks up to 42 weeks. Patients receiving bortezomib (1.3 mg/m(2), days 1, 4, 8 and 11 for eight 3-week cycles, then days 1, 8, 15 and 22 for three 5-week cycles; n = 296) demonstrated significantly better mean Global Health Status over the study versus patients receiving dexamethasone (40 mg/d, days 1-4, 9-12, and 17-20 for four 5-week cycles, then days 1-4 only for five 4-week cycles; n = 302), plus significantly better physical health, role, cognitive, and emotional functioning scores, lower dyspnoea and sleep symptom scores, and better NTX questionnaire score, using multiple imputation to account for missing data. Results were similar using available-data analyses. Sensitivity analyses suggested that improved HRQL with bortezomib is at least partially explained by improved survival. These results show that bortezomib was associated with significantly better multidimensional HRQL compared with dexamethasone, consistent with the better clinical outcomes seen with bortezomib.

Overexpression of carboxylesterase-2 results in enhanced efficacy of topoisomerase I inhibitor, irinotecan (CPT-11), for multiple myeloma.

Yano H, Kayukawa S, Iida S, Nakagawa C, Oguri T, Sanda T, Ding J, Mori F, Ito A, Ri M, Inagaki A, Kusumoto S, Ishida T, Komatsu H, Inagaki H, Suzuki A, Ueda R.

Cancer Sci. 2008 Nov;99(11):2309-14. [Epub 2008 Sep 1.]

http://www.ncbi.nlm.nih.gov/pubmed/18771527?ordinalpos=83&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors investigate the therapeutic potential of CPT-11 and find when a combination of CPT-11 and bortezomib is administered, subcutaneous tumors completely disappear. They therefore conclude that clinical trials on CPT-11 in patients with relapsed or refractory myeloma are warranted.

Multiple myeloma (MM) remains an incurable disease and further development of novel agents is needed. Because constitutive expression of topoisomerase I (TopoI) in MM cells and the efficacy of SN-38, an active metabolite of irinotecan (CPT-11), have been reported, we investigated the therapeutic potential of CPT-11. Of the eight MM cell lines analyzed, four showed 50% inhibitory concentration values of less than 2 microg/mL for CPT-11 and less than 2 ng/mL for SN-38. This efficacy was partly explained by the high expression level of human carboxylesterase-2 (hCE-2) in MM cells. Interestingly, high expression of hCE-2 represented the nature of normal plasma cells, suggesting that hCE-2 could efficiently generate SN-38 within the plasma cells. As expected, higher sensitivity to CPT-11 was observed in hCE-2-overexpressing U266 cells than mock U266 cells. On the other hand, the expression levels of hCE-1, TopoI, UGT1A and ABCG2 did not seem to be associated with the sensitivity of MM cells to CPT-11. In a murine xenograft model inoculated s.c. with RPMI8226 cells, administration of CPT-11 alone significantly reduced the tumor volume. When a combination of CPT-11 and bortezomib was administered, the subcutaneous tumors completely disappeared. Thus, clinical trials on CPT-11 in patients with relapsed or refractory MM are warranted.

Stromal cells in bone marrow play important roles in pro-inflammatory cytokine secretion causing fever following bortezomib administration in patients with multiple myeloma.

Maruyama D, Watanabe T, Heike Y, Nagase K, Takahashi N, Yamasaki S, Waki F, Yokoyama H, Kim SW, Kobayashi Y, Aizawa S, Tobinai K.

Int J Hematol. 2008 Nov;88(4):396-402. [Epub 2008 Nov 7.]

http://www.ncbi.nlm.nih.gov/pubmed/18989635?ordinalpos=90&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Although this investigation is a preliminary study with a small number of patients, results suggest that pro-inflammatory cytokines causing bortezomib-associated fever are secreted from bone marrow stromal cells rather than myeloma cells.

Bortezomib blocks the activation of nuclear factor-kappaB-mediated pro-inflammatory cytokines, however, systemic inflammatory symptoms following bortezomib administration have been reported, although their mechanisms remain elusive. Serum samples were obtained from five patients, who participated in a phase I/II study of Japanese patients with relapsed or refractory multiple myeloma (MM), and developed cyclic fever following bortezomib administration, to measure cytokine levels. Significant correlations between interleukin (IL)-6 or interferon (IFN)-gamma and the body temperature were observed in two patients each. Furthermore, we found that IL-6 elevation was not observed after the addition of bortezomib to any examined MM cells alone, but was noted in a case of bone marrow stromal cells (BMSCs) of macrophage origin alone or co-cultured with MM cells. Similarly, a marked increase in IFN-gamma levels was induced by adding bortezomib to BMSCs of fibroblast origin. Although this investigation was a preliminary study with a small number of patients, our results suggested that pro-inflammatory cytokines causing bortezomib-associated fever were secreted from BMSCs rather than MM cells.

Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma.

Jagannath S, Barlogie B, Berenson JR, Siegel DS, Irwin D, Richardson PG, Niesvizky R, Alexanian R, Limentani SA, Alsina M, Esseltine DL, Anderson KC.

Br J Haematol. 2008 Nov;143(4):537-40. [Epub 2008 Sep 6.]

http://www.ncbi.nlm.nih.gov/pubmed/18783399?ordinalpos=82&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors present updated survival analyses after prolonged follow-up of a study that had previously demonstrated substantial activity with two dose levels of bortezomib, alone or with dexamethasone, in relapsed or refractory myeloma.

The Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST) demonstrated substantial activity with two dose levels of bortezomib (1.0 and 1.3 mg/m(2)), alone or with dexamethasone, in relapsed or refractory multiple myeloma. We present updated survival analyses after prolonged follow-up (median >5 years). One- and 5-year survival rates were 82% and 32%,

respectively, in the 1.0 mg/m(2) group (n = 28), and 81% and 45%, respectively, in the 1.3 mg/m(2) group (n = 26). Notable survival, response, and time-to-progression data suggest that a bortezomib starting dose of 1.3 mg/m(2) is preferred. If bortezomib dose reduction is required, the 1.0 mg/m(2) dose still offers patients a substantial survival benefit.

Bortezomib-induced cutaneous lesions in multiple myeloma patients: a case report.

Rodríguez-Martín M, Sáez-Rodríguez M, García-Bustínduy M, Martín-Herrera A, Noda-Cabrera A.

Dermatol Online J. 2008 Nov 15;14(11):14.

http://www.ncbi.nlm.nih.gov/pubmed/19094852?ordinalpos=71&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report on a case of cutaneous lesions induced by bortezomib in a patient with relapsed myeloma.

Proteasome inhibitors are emerging as a promising class of anti-cancer therapeutic agents. Bortezomib (PS341) is the first proteosome inhibitor with clinical significance. It acts by blocking vital functions of tumoral cells in myeloma, inducing apoptosis. Its toxicity is usually manageable. Gastrointestinal symptoms, peripheral neuropathy, neuropathic pain and thrombocytopenia are described as the most common side effects. We report on a case of cutaneous lesions induced by bortezomib in a patient with relapsed multiple myeloma (MM).

In vitro activity of bortezomib in cultures of patient tumour cells-potential utility in haematological malignancies.

Wiberg K, Carlson K, Aleskog A, Larsson R, Nygren P, Lindhagen E.

Med Oncol. 2008 Nov 18. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19016012?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the in vitro activity of bortezomib with regard to tumor-type specificity and possible mechanisms of drug resistance in 115 samples of tumor cells from patients and in a cell-line panel, using the short-term fluorometric microculture cytotoxicity assay. Their data support the current use of bortezomib, including in the treatment of myeloma, but also points to its potential utility in other tumor types and in combination with cytotoxic drugs.

Bortezomib represents a new class of anti-cancer drugs, the proteasome inhibitors. We evaluated the in vitro activity of bortezomib with regard to tumour-type specificity and possible mechanisms of drug resistance in 115 samples of tumour cells from patients and in a cell-line panel, using the short-term fluorometric microculture cytotoxicity assay. Bortezomib generally showed dose-response curves with a steep slope. In patient cells, bortezomib was more active in haematological than in solid tumour samples. Myeloma and chronic myeloid leukaemia were the most sensitive tumour types although with great variability in drug response between the individual samples. Colorectal and kidney cancer samples were the least sensitive. In the cell-line panel, only small differences in response were seen between the different cell lines, and the proteasome inhibitors, lactacystin and MG 262, showed an activity pattern similar to that of bortezomib. The cell-line data suggest that resistance to bortezomib was not mediated by MRP-, PgP, GSH-; tubulin and topo II-associated MDR. Combination experiments indicated synergy between bortezomib and arsenic trioxide or irinotecan. The data support the current use of bortezomib but also points to its potential utility in other tumour types and in combination with cytotoxic drugs.

Bortezomib administered pre-auto-SCT and as maintenance therapy post transplant for multiple myeloma: a single institution phase II study.

Uy GL, Goyal SD, Fisher NM, Oza AY, Tomasson MH, Stockerl-Goldstein K, Dipersio JF, Vij R.

Bone Marrow Transplant. 2008 Nov 24. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19029964?ordinalpos=65&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors conduct a study in 40 patients with bortezomib given sequentially pre-auto-stem cell transplant (ASCT) and as maintenance therapy post ASCT.

The appropriate induction therapy before and the role of maintenance therapy after auto-SCT for patients with multiple myeloma remain areas of active investigation. We conducted a study in 40 patients with bortezomib given sequentially pre-auto-SCT and as maintenance therapy post auto-SCT. Pre-transplant bortezomib was administered for two cycles followed by high-dose melphalan 200 mg/m(2) with auto-SCT of G-CSF-mobilized PBMCs. Post transplant bortezomib was administered weekly for 5 out of 6 weeks for six cycles. No adverse effects were observed on stem cell mobilization or engraftment. An overall response rate of 83% with a CR+very good partial remission (VGPR) of 50% was observed with this approach. Three-year Kaplan-Meier estimates of disease-free survival and overall survival (OS) were 38.2 and 63.1%, respectively. Bortezomib reduced CD8(+) cytotoxic T cell and CD56(+) natural killer cell PBL subsets and was clinically associated with high rates of viral reactivation to varicella zoster.

The combination of bortezomib, melphalan, dexamethasone and intermittent thalidomide is an effective regimen for relapsed/refractory myeloma and is associated with improvement of abnormal bone metabolism and angiogenesis.

Terpos E, Kastritis E, Roussou M, Heath D, Christoulas D, Anagnostopoulos N, Eleftherakis-Papaiakovou E, Tsionos K, Croucher P, Dimopoulos MA.

Leukemia. 2008 Dec;22(12):2247-56. [Epub 2008 Sep 4.]

http://www.ncbi.nlm.nih.gov/pubmed/18769451?ordinalpos=59&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the combination of bortezomib, melphalan, dexamethasone and intermittent thalidomide is an active and well-tolerated regimen for relapsed/refractory myeloma, affecting abnormal bone remodeling and angiogenesis.

This phase 2 study aimed to determine the efficacy and safety of the combination of bortezomib, melphalan, dexamethasone and intermittent thalidomide (VMDT) and its effect on bone remodeling and angiogenesis in relapsed/refractory myeloma. Bortezomib (1.0 mg/m(2)) was given on days 1, 4, 8, 11, oral melphalan (0.15 mg/kg) on days 1-4, whereas thalidomide (100 mg per day) and dexamethasone (12 mg/m(2)) were administered on days 1-4 and 17-20 of a 28-day cycle, for four cycles. Patients without disease progression continued for up to eight cycles. VMDT effect on bone remodeling was evaluated by measuring osteoclast regulators (soluble receptor activator of nuclear factor-kappa B ligand/osteoprotegerin ratio, osteopontin, macrophage inflammatory protein-1alpha), dickkopf-1 protein, bone resorption and formation markers, whereas its effect on angiogenesis was assessed by measuring serum vascular endothelial growth factor, angiogenin, angiopoietin-2 and basic fibroblast growth factor, after four cycles and at the study end. A total of 62 patients were enrolled. The overall response rate was 66%: CR 13%, vgPR 27% and PR 26%. Median time to response was 35 days and median time to progression was 9.3 months. Common adverse events included cytopenias, peripheral neuropathy and infections. No patient experienced deep-vein thrombosis. VMDT reduced angiogenic cytokines, osteoclast regulators, dickkopf-1 and bone resorption. We conclude that VMDT with intermittent thalidomide is an active and well-tolerated regimen for relapsed/refractory myeloma, affecting abnormal bone remodeling and angiogenesis.

Delayed complete remission in a patient with multiple myeloma.

Ria R, Vacca A, Mangialardi G, Dammacco F.

Eur J Clin Invest. 2008 Dec;38(12):966-8.

http://www.ncbi.nlm.nih.gov/pubmed/19021723?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report a strikingly positive, late response to bortezomib in conjunction with pegylated liposomal doxorubicin in a 79-year old woman with myeloma.

We report a strikingly positive, late response to bortezomib in conjunction with pegylated liposomal doxorubicin in a 79-year old woman with multiple myeloma (MM). The patient obtained a partial remission after eight courses of therapy and a complete remission about 10 months after the end of therapy. This delayed complete remission may be similar to the spontaneous regression reported for other malignancies such as melanoma or lymphoma. We postulate that the immune response and a persistent anti-angiogenic effect of bortezomib could well explain the delayed complete remission in our patient.

New drugs in multiple myeloma: mechanisms of action and phase I/II clinical findings.

Ocio EM, Mateos MV, Maiso P, Pandiella A, San-Miguel JF.

Lancet Oncol. 2008 Dec;9(12):1157-65.

http://www.ncbi.nlm.nih.gov/pubmed/19038762?ordinalpos=55&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors review some of the new, targeted therapeutic strategies under assessment in preclinical and clinical myeloma studies, including use of bortezomib.

The outcome of multiple myeloma has substantially improved over the past decade, mainly due to recently approved drugs, such as thalidomide, lenalidomide, and bortezomib. Nevertheless, most patients still relapse and, therefore, drugs with new mechanisms of action are urgently needed to overcome this resistance. In this Review, we discuss some of the new targeted therapeutic strategies under assessment in preclinical and clinical studies in multiple myeloma. Unfortunately, the single-agent clinical activity of most of these new drugs has been limited; nevertheless, their effectiveness might be enhanced by their rational combination with each other or with conventional agents.

New targets and treatments in multiple myeloma: Src family kinases as central regulators of disease progression.

Gertz MA.

Leuk Lymphoma. 2008 Dec;49(12):2240-5.

http://www.ncbi.nlm.nih.gov/pubmed/19052970?ordinalpos=57&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This review discuses the improved outcomes for myeloma patients provided by bortezomib, as well as on Src-dependent signalling pathways, reflecting the expanding realization of the critical and ubiquitous role of Src family kinases (SFKs) in normal and abnormal hematopoiesis.

Multiple myeloma is a malignant condition that most commonly occurs in the seventh decade of life. Recent improvements in treatment may result in a more favourable outlook for recently diagnosed patients. Multiple myeloma is an incurable clonal B-cell malignancy, which is initially responsive to conventional chemotherapy; one-third of the patients achieve complete remission but multidrug resistance eventually develops. Although autologous stem cell transplantation remains an important option, many older patients are less tolerant to the toxicity associated with conditioning treatment, as well as being intrinsically less likely to do well after transplantation. Most patients eventually relapse with or without transplantation, and salvage therapy is only moderately effective. Thalidomide and subsequently, lenalidomide and bortezomib, have demonstrated improved outcomes for these patients, as well as proving efficacious in front-line regimens. A deeper understanding of the molecular mechanisms underlying multiple myeloma has given rise to novel targeted approaches. This review will focus in particular on Src-dependent signalling pathways, reflecting the expanding realisation of the critical and ubiquitous role of Src family kinases (SFKs) in normal and abnormal hematopoiesis.

Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma.

Moreau P, Coiteux V, Hulin C, Leleu X, van de Velde H, Acharya M, Harousseau JL.

Haematologica. 2008 Dec;93(12):1908-11. [Epub 2008 Sep 2.]

http://www.ncbi.nlm.nih.gov/pubmed/18768528?ordinalpos=50&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors assess the safety and efficacy of intravenous (IV) and subcutaneous (SC) administration of bortezomib and find SC administration offers an alternative option to IV injection.

This phase I study (ClinicalTrials.gov: NCT00291538) compared pharmacokinetics and pharmacodynamics, and assessed safety and efficacy of intravenous (IV) and subcutaneous (SC) administration of bortezomib. Relapsed or refractory multiple myeloma patients were randomized to receive bortezomib by standard IV bolus (n=12) or SC injection (n=12) at the recommended dose and schedule (1.3 mg/m(2), days 1, 4, 8, 11; eight 21-day cycles). Plasma bortezomib concentration and percent 20S proteasome inhibition were measured at multiple time points on days 1 and 11, cycle 1. Systemic bortezomib exposure was similar between arms. As expected, mean maximum plasma concentration was lower and took longer to reach following SC administration. Overall 20S proteasome inhibition was similar between arms. Safety profile and response rate for the SC arm did not appear inferior to the IV arm, with good local tolerance of SC injection. Based on these exploratory findings, SC administration offers an alternative option to IV injection.

Pegylated Liposomal Doxorubicin plus Bortezomib in Relapsed or Refractory Multiple Myeloma: Efficacy and Safety in Patients with Renal Function Impairment.

Bladé J, Sonneveld P, San Miguel JF, Sutherland HJ, Hajek R, Nagler A, Spencer A, Robak T, Cibeira MT, Zhuang SH, Harousseau JL, Orlowski RZ, For The Doxil-Mmy-3001 Study Investigators.

Clin Lymphoma Myeloma. 2008 Dec 1;8(6):352-355.

http://www.ncbi.nlm.nih.gov/pubmed/19064400?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors undertake a retrospective analysis of myeloma patients with renal insufficiency from a phase III trial comparing bortezomib +/– pegylated liposomal doxorubicin (PLD) in relapsed/refractory myeloma.

A retrospective analysis was undertaken of patients (n = 193) with renal insufficiency (creatinine clearance [CrCl] < 60 mL/min) from a phase III trial comparing bortezomib +/– pegylated liposomal doxorubicin (PLD) in relapsed/refractory myeloma (n = 646). The response rate (49% vs. 42%) and median time to disease progression (331 days vs. 199 days) were comparable or slightly better for patients with renal insufficiency treated with PLD/bortezomib compared with patients treated with bortezomib alone. There was a steady, clinically meaningful improvement in renal function for patients with renal insufficiency in both treatment arms. However, patients with impaired renal function were at a slightly increased risk of a drug-related serious adverse event (28% vs. 19% for CrCl < 60 and >/= 60 mL/min, respectively).

Treatment of light chain deposition disease with bortezomib and dexamethasone.

Kastritis E, Migkou M, Gavriatopoulou M, Zirogiannis P, Hadjikonstantinou V, Dimopoulos MA.

Haematologica. 2008 Dec 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19066331?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Cooperative relationship between pharmaceutical companies, academia, and media explains sharp decrease in frequency of pulmonary complications after bortezomib in Japan.

Narimatsu H, Hori A, Matsumura T, Kodama Y, Takita M, Kishi Y, Hamaki T, Yuji K, Tanaka Y, Komatsu T, Kami M.

J Clin Oncol. 2008 Dec 10;26(35):5820-3. [Epub 2008 Nov 10.]

http://www.ncbi.nlm.nih.gov/pubmed/19001340?ordinalpos=36&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Bortezomib plus melphalan and prednisone for multiple myeloma.

Avvisati G.

N Engl J Med. 2008 Dec 11;359(24):2613; author reply 2613-4.

http://www.ncbi.nlm.nih.gov/pubmed/19090032?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: N Engl J Med. 2008 Aug 28;359(9):906-17.

Bortezomib plus melphalan and prednisone for multiple myeloma.

Islam A, Ambrus JL.

N Engl J Med. 2008 Dec 11;359(24):2613; author reply 2613-4.

http://www.ncbi.nlm.nih.gov/pubmed/19073984?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: N Engl J Med. 2008 Aug 28;359(9):906-17.

Bortezomib plus melphalan and prednisone for multiple myeloma.

Tsubokura M, Kami M, Komatsu T.

N Engl J Med. 2008 Dec 11;359(24):2613; author reply 2613-4.

http://www.ncbi.nlm.nih.gov/pubmed/19090031?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: N Engl J Med. 2008 Aug 28;359(9):906-17.

Bortezomib in combination with epirubicin, dexamethasone and thalidomide is a highly effective regimen in the treatment of multiple myeloma: a single-center experience.

Lü S, Wang J, Xu X, Ni X, Huang C, Qiu H, Hu X, Yang J.

Int J Hematol. 2008 Dec 13. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19082817?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the effectiveness of bortezomib combined with epirubicin, dexamethasone, and thalidomide (BADT) for the treatment of myeloma and find BADT to be a highly effective combined regimen, with acceptable toxicity, for the treatment of multiple myeloma.

The aim of the present study was to evaluate the effectiveness of bortezomib combined with epirubicin, dexamethasone, and thalidomide (BADT) for the treatment of multiple myeloma (MM). The BADT regimen consisted of a maximum of eight 4-week cycles of: intravenous bortezomib (1.0 mg/m(2)) and intravenous epirubicin (12 mg/m(2)) on days 1, 4, 8, and 11; dexamethasone (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12; and oral thalidomide (100 mg/m(2)) on days 1-28. Twelve patients with MM were included in the study, of whom four had not been previously treated and eight had been previously treated with at least one cycle of a systemic combined regimen. All the patients completed

at least two cycles of treatment, with an average of five cycles; the complete response (CR) rate was 83.3% (10/12) and stabilization of disease was 16.7% (2/12). The average number of cycles required to achieve CR was 1.9 (range 1-6). In three patients, mobilization of peripheral blood stem cells allowed a sufficient quantity of CD34+ cells to be harvested for future autotransplantation. The main adverse reactions included peripheral neuropathy (4/12), thrombocytopenia (3/12), electrocardiographic abnormalities (4/12), neutropenia (5/12), and liver function impairment (4/12), primarily grade I-II. Infection occurred in four patients with neutropenia, including one patient who developed sepsis. The estimated 1-year overall survival rate was 91.7 +/– 8.0%, and the estimated 1-year disease-free survival was 75.0 +/– 12.5%. BADT is a highly effective combined regimen, with acceptable toxicity, for the treatment of multiple myeloma.

The persisting challenge of selective and specific proteasome inhibition.

Groll M, Huber R, Moroder L.

J Pept Sci. 2008 Dec 24. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19109822?ordinalpos=19&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss new structural and biochemical insights, which place the proteasome as an important anti-cancer drug target, as revealed by bortezomib, which is currently used for treatment of myeloma. But serious side effects and partial cell resistance against bortezomib demand creation and discovery of new improved generations of more specific and potent proteasomal inhibitors.

Since the discovery of the proteasome and its structure elucidation intensive research programs in academic institutions and pharmaceutical industries led to identification of a wide spectrum of synthetic and natural small proteasomal inhibitors. Activity studies with these small molecules helped to deeply understand the complex biochemical organization and functioning of the proteasome. The new structural and biochemical insights placed the proteasome as an important anti-cancer drug target, as revealed by the dipeptide boronate proteasome inhibitor, bortezomib, which is currently used for treatment of multiple myeloma. Serious side effects and partial cell resistance against bortezomib demand creation and discovery of new improved generations of more specific and potent proteasomal inhibitors.

Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection.

Everly MJ, Everly JJ, Susskind B, Brailey P, Arend LJ, Alloway RR, Roy-Chaudhury P, Govil A, Mogilishetty G, Rike AH, Cardi M, Wadih G, Tevar A, Woodle ES.

Transplantation. 2008 Dec 27;86(12):1754-61.

http://www.ncbi.nlm.nih.gov/pubmed/19104417?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report the first clinical experience with plasma cell-targeted therapy (bortezomib) as an antirejection strategy, and find that bortezomib therapy represents the first effective antihumoral therapy with activity in humans that targets plasma cells.

BACKGROUND: Current antihumoral therapies in transplantation and autoimmune disease do not target the mature antibody-producing plasma cell. Bortezomib is a first in class proteosomal inhibitor, that is Food and Drug Administration approved, for the treatment of plasma cell-derived tumors that is multiple myeloma. We report the first clinical experience with plasma cell-targeted therapy (bortezomib) as an antirejection strategy. METHODS: Eight episodes of mixed antibody-mediated rejection (AMR) and acute cellular rejection (ACR) in six transplant recipients were treated with bortezomib at labeled dosing. Monitoring included serial donor-specific antihuman leukocyte antigen antibody (DSA) levels and repeated allograft biopsies. RESULTS: Six kidney transplant patients received bortezomib for AMR and concomitant ACR. In each case, bortezomib therapy provided (1) prompt rejection reversal, (2) marked and prolonged reductions in DSA levels, (3) improved renal allograft function, and (4) suppression of recurrent rejection for at least 5 months. Moreover, immunodominant DSA (iDSA) (i.e., the antidonor human leukocyte antigen antibody with the highest levels) levels were decreased by more than 50% within 14 days and remained substantially suppressed for up to 5 months. One or more additional DSA were present at lower concentrations (non-iDSA) in each patient and were also reduced to nondetectable levels. Bortezomib-related toxicities (gastrointestinal toxicity, thrombocytopenia, and paresthesias) were all transient. CONCLUSIONS: Bortezomib therapy: (1) provides effective treatment of AMR and ACR with minimal toxicity and (2) provides sustained reduction in iDSA and non-iDSA levels. Bortezomib represents the first effective antihumoral therapy with activity in humans that targets plasma cells.

Bone marrow microenvironment and the identification of new targets for myeloma therapy.

Podar K, Chauhan D, Anderson KC.

Leukemia. 2009 Jan;23(1):10-24. [Epub 2008 Oct 9.]

http://www.ncbi.nlm.nih.gov/pubmed/18843284?ordinalpos=123&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss new agents, including bortezomib, which mediate myeloma tumor cytotoxicity in the bone marrow milieu.

The development of multiple myeloma (MM) is a complex multi-step process involving both early and late genetic changes in the tumor cell as well as selective supportive conditions by the bone marrow (BM) microenvironment. Indeed, it is now well established that MM cell-induced

disruption of the BM homeostasis between the highly organized cellular and extracellular compartments supports MM cell proliferation, survival, migration and drug resistance through activation of various signaling (for example, PI3K/Akt, JAK/Stat-, Raf/MEK/MAPK-, NFkappaB- and Wnt-) pathways. Based on our enhanced understanding of the functional importance of the MM BM microenvironment and its inter-relation with the MM cell resulting in homing, seeding, proliferation and survival, new molecular targets have been identified and derived treatment regimens in MM have already changed fundamentally during recent years. These agents include thalidomide, its immunomodulatory derivative lenalidomide and the proteasome inhibitor bortezomib, which mediate tumor cytotoxicity in the BM milieu. Ongoing studies are further delineating MM pathogenesis in the BM to enhance cytotoxicity, avoid drug resistance and improve patient outcome.

Bortezomib in combination with epirubicin, dexamethasone and thalidomide is a highly effective regimen in the treatment of multiple myeloma: a single-center experience.

Lü S, Wang J, Xu X, Ni X, Huang C, Qiu H, Hu X, Yang J.

Int J Hematol. 2009 Jan;89(1):34-8. [Epub 2008 Dec 13.]

http://www.ncbi.nlm.nih.gov/pubmed/19082817?ordinalpos=118&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the effectiveness of bortezomib combined with epirubicin, dexamethasone, and thalidomide (BADT) for the treatment of myeloma and find it to be a highly effective combined regiment with acceptable toxicity.

The aim of the present study was to evaluate the effectiveness of bortezomib combined with epirubicin, dexamethasone, and thalidomide (BADT) for the treatment of multiple myeloma (MM). The BADT regimen consisted of a maximum of eight 4-week cycles of: intravenous bortezomib (1.0 mg/m(2)) and intravenous epirubicin (12 mg/m(2)) on days 1, 4, 8, and 11; dexamethasone (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12; and oral thalidomide (100 mg/m(2)) on days 1-28. Twelve patients with MM were included in the study, of whom four had not been previously treated and eight had been previously treated with at least one cycle of a systemic combined regimen. All the patients completed at least two cycles of treatment, with an average of five cycles; the complete response (CR) rate was 83.3% (10/12) and stabilization of disease was 16.7% (2/12). The average number of cycles required to achieve CR was 1.9 (range 1-6). In three patients, mobilization of peripheral blood stem cells allowed a sufficient quantity of CD34+ cells to be harvested for future autotransplantation. The main adverse reactions included peripheral neuropathy (4/12), thrombocytopenia (3/12), electrocardiographic abnormalities (4/12), neutropenia (5/12), and liver function impairment (4/12), primarily grade I-II. Infection occurred in four patients with neutropenia, including one patient who developed sepsis. The estimated 1-year overall survival rate was 91.7 +/– 8.0%, and the estimated 1-year disease-free survival was 75.0 +/– 12.5%. BADT is a highly effective combined regimen, with acceptable toxicity, for the treatment of multiple myeloma.

Bortezomib inhibits maturation and function of osteoclasts from PBMCs of patients with multiple myeloma by downregulating TRAF6.

Hongming H, Jian H.

Leuk Res. 2009 Jan;33(1):115-22. [Epub 2008 Sep 7.]

http://www.ncbi.nlm.nih.gov/pubmed/18778854?ordinalpos=122&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors observe the inhibitory effect of bortezomib on osteoclasts maturation and function from peripheral blood mononuclear cells of myeloma patients, in an attempt to clarify the upstream molecular mechanism of bortezomib on osteoclastogenesis. They conclude that bortezomib acts on osteoclastgenesis at low concentrations by interfering with TRAF6 production, which might prove to be a potential strategy for the treatment of myeloma bone disease.

Multiple myeloma (MM) is associated with increased activation of osteoclasts, causing enhanced bone degradation and formation of lytic bone lesions. In this study, we observed the inhibitory effect of bortezomib on osteoclasts maturation and function from peripheral blood mononuclear cells (PBMCs) of MM patients, in an attempt to clarify the upstream molecular mechanism of bortezomib on osteoclastogenesis. Osteoclast precursors from PBMCs of eight MM patients were cultured in the presence of receptor activator of NF-kappaB ligand (RANKL) and macrophage-colony stimulating factor (M-CSF). Administration of 2.5 and 5nM bortezomib resulted in the reduction of osteoclast differentiation by less formation of osteoclasts and the decreased activity level of TRAP. Osteoclast resorption capacity also decreased, suggesting that bortezomib was able to inhibit the function of osteoclasts. The results of Western-blot and RT-PCR assays suggested that bortezomib inhibited osteoclasts by decreasing TRAF6 production at both protein and mRNA levels. In conclusion, bortezomib acts on osteoclastgenesis at low concentrations by interfering with TRAF6 production, which might prove to be a potential strategy for the treatment of myeloma bone disease.

Effects of bortezomib on bone disease in multiple myeloma.

Drake MT, Rajkumar SV.

Am J Hematol. 2009 Jan;84(1):1-2.

http://www.ncbi.nlm.nih.gov/pubmed/19030185?ordinalpos=101&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: Am J Hematol. 2009 Jan;84(1):6-14.

High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: results of a global phase 3b expanded access program.

Mikhael JR, Belch AR, Prince HM, Lucio MN, Maiolino A, Corso A, Petrucci MT, Musto P, Komarnicki M, Stewart AK.

Br J Haematol. 2009 Jan;144(2):169-75. [Epub 2008 Nov 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19036114?ordinalpos=107&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In this study, the authors find that bortezomib, alone and combined with dexamethasone, is safe and effective in heavily pretreated patients with relapsed or refractory myeloma.

Phase 2 trials have demonstrated that bortezomib +/– dexamethasone is safe and effective in relapsed multiple myeloma (MM). In this multicentre, open-label, phase 3b trial, 638 patients with relapsed or refractory MM (median 3 prior therapies) received bortezomib 1.3 mg/m2 on days 1, 4, 8, and 11 of a maximum of eight 3-week cycles (median 5 cycles). Dexamethasone 20 mg/d was added the day of and day after each bortezomib dose for progressive disease after > or =2 cycles or for stable disease after > or =4 cycles. Responses were assessed based on M-protein changes. Overall response rate was 67%, including 11% complete (100% M-protein reduction), 22% very good partial (75-99% reduction), 18% partial (50-74% reduction), and 16% minimal response (25-49% reduction). Dexamethasone was added in 208 patients (33%), of whom 70 (34%) showed improved response. Median time to best response of minimal response or better was 84 d. Most common grade 3/4 adverse events were thrombocytopenia (39%), neutropenia (16%), anaemia (12%), diarrhoea (7%), and peripheral neuropathy (6%). Neuropathy (any grade) was seen in 25% of the patients and led to discontinuation in 5%. Bortezomib, alone and combined with dexamethasone, is safe and effective in heavily pretreated patients with relapsed or refractory MM.

In pursuit of the allo-immune response in multiple myeloma: where do we go from here?

Cook G, Bird JM, Marks DI.

Bone Marrow Transplant. 2009 Jan;43(2):91-9. [Epub 2008 Dec 15.]

http://www.ncbi.nlm.nih.gov/pubmed/19079310?ordinalpos=106&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors examine concepts for improving the outcomes of AlloSCT and propose a potential direction of clinical investigation to maximize the effect of AlloSCT in multiple myeloma—keeping in mind the need to consider the whole patient management pathway both preceding (depth of response to novel agents, including bortezomib) and post-AlloSCT, to minimize the toxicity while harnessing the adoptive immunotherapy effect.

AlloSCT is a potentially curative procedure for haematological malignancies and marrow failure syndromes. However, unlike leukaemia and lymphoproliferative disorders, AlloSCT has yet to find its place in the clinical management of patients with multiple myeloma. AlloSCT in multiple myeloma is associated with a high procedure-related mortality (TRM up to 35%) when full-intensity conditioning is used and only up to 36% of cases show long-term disease-free survival. The introduction of reduced intensity conditioning AlloSCT, more recently following an autologous SCT, has reduced the TRM to <20%, but there is an associated increased relapse risk. The use of donor lymphocyte infusions and novel biological agents (thalidomide, bortezomib), alone or together, can be effective in relapsed and even persistent disease post-AlloSCT. Thus, in pursuit of the putative graft-versus-myeloma effect, we need to consider the whole patient management pathway both preceding (depth of response to novel agents) and post-AlloSCT, to minimize the toxicity while harnessing the adoptive immunotherapy effect. This review sets out what we have learned to date from the clinical research studies in this area, examines concepts for improving the outcomes of AlloSCT and proposes a potential direction of clinical investigation to maximize the effect of AlloSCT in multiple myeloma.

New generation pharmacotherapy in elderly multiple myeloma patients.

Ataergin SA, Kindwall-Keller T, Berger NA, Lazarus HM.

Expert Opin Pharmacother. 2009 Jan;10(1):81-98.

http://www.ncbi.nlm.nih.gov/pubmed/19236183?ordinalpos=115&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors review recent clinical trials that include new generation agents, such as thalidomide and lenalidomide, and autologous stem cell transplantation in older multiple myeloma patients. They conclude that implementation of new therapies results in significant benefits in the advanced-age population.

BACKGROUND: Observational databases have demonstrated that the overall prognosis of multiple myeloma patients has markedly improved over the past decade, yet the greatest strides have been attained in younger rather than older patients. OBJECTIVE: To review recent clinical trials that include new generation agents (thalidomide, lenalidomide and bortezomib) and autologous stem cell transplantation in older multiple myeloma patients. RESULTS: Conventional regimens such as melphalan plus prednisone can be improved with the addition of thalidomide or bortezomib: more patients attain complete and near-complete remission, and progression-free survival rates are nearly doubled. In addition, autologous hematopoietic stem cell transplantation studies show that this treatment approach can be used successfully in selected older myeloma patients in whom the toxicity profile of autotransplant and resulting overall survival may be similar to that obtained in the younger patient group. CONCLUSIONS: In the advanced-age population, implementation of new therapies results in significant benefits in older as well as younger patients.

The proteasome inhibitor, bortezomib suppresses primary myeloma and stimulates bone formation in myelomatous and nonmyelomatous bones in vivo.

Pennisi A, Li X, Ling W, Khan S, Zangari M, Yaccoby S.

Am J Hematol. 2009 Jan;84(1):6-14.

http://www.ncbi.nlm.nih.gov/pubmed/18980173?ordinalpos=102&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors conclude that bortezomib promotes bone formation in myelomatous and nonmyelomatous bones by simultaneously inhibiting osteoclastogenesis and stimulating osteoblastogenesis, with results that suggest and that bortezomib's effects on bone remodeling contribute to the antimyeloma efficacy of this drug.

Multiple myeloma (MM), a hematologic malignancy of terminally differentiated plasma cells is closely associated with induction of osteolytic bone disease, induced by stimulation of osteoclastogenesis and suppression of osteoblastogenesis. The ubiquitin-proteasome pathway regulates differentiation of bone cells and MM cell growth. The proteasome inhibitor, bortezomib, is a clinical potent antimyeloma agent. The main goal of this study was to investigate the effect of bortezomib on myeloma-induced bone resorption and tumor growth in SCID-rab mice engrafted with MM cells from 16 patients. Antimyeloma response of bortezomib, which was evident in >50% of 16 experiments and resembled clinical response, was associated with significant increased bone mineral density (BMD) and osteoblast numbers, and reduced osteoclast numbers in myelomatous bones. This bone anabolic effect, which was also visualized on X-ray radiographs and confirmed by static and dynamic histomorphometric analyses, was unique to bortezomib and was not observed in hosts responding to melphalan, a chemotherapeutic drug widely used to treat MM. Bortezomib also increased BMD and osteoblasts number and reduced osteoclasts number in nonmyelomatous implanted bones. In vitro bortezomib directly suppressed human osteoclast formation and promoted maturation of osteoblasts. We conclude that bortezomib promotes bone formation in myelomatous and nonmyelomatous bones by simultaneously inhibiting osteoclastogenesis and stimulating osteoblastogenesis. As clinical and experimental studies indicate that bone disease is both a consequence and necessity of MM progression our results suggest and that bortezomib's effects on bone remodeling contribute to the antimyeloma efficacy of this drug.

Serum concentrations of DKK-1 decrease in patients with multiple myeloma responding to anti-myeloma treatment.

Heider U, Kaiser M, Mieth M, Lamottke B, Rademacher J, Jakob C, Braendle E, Stover D, Sezer O.

Eur J Haematol. 2009 Jan;82(1):31-8. [Epub 2008 Nov 10.]

http://www.ncbi.nlm.nih.gov/pubmed/19067746?ordinalpos=89&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In this study, the effect of different treatment regimens for myeloma on serum DKK-1 is evaluated and correlated with the response to treatment in 101 myeloma patients receiving bortezomib, thalidomide, lenalidomide, adriamycin and dexamethasone or high-dose chemotherapy followed by autologous stem cell transplantation. The authors find, for the first time, that serum DKK-1 levels

decrease in myeloma patients responding to treatment, irrespective of the regimen chosen— data which suggests that myeloma cells are the main source of circulating DKK-1 protein, providing a framework for clinical trials on anti-DKK-1 treatment in myeloma.

Lytic bone destruction is a hallmark of multiple myeloma (MM) and is because of an uncoupling of bone remodeling. Secretion of Dickkopf (DKK)-1 by myeloma cells is a major factor which causes inhibition of osteoblast precursors. In this study, the effect of different treatment regimens for MM on serum DKK-1 was evaluated and correlated with the response to treatment in 101 myeloma patients receiving bortezomib, thalidomide, lenalidomide, adriamycin and dexamethasone (AD) or high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT). At baseline, myeloma patients had increased serum DKK-1 as compared with patients with MGUS (mean 3786 pg/mL vs. 1993 pg/mL). There was no difference between previously untreated MM patients and patients at relapse. A significant decrease of DKK-1 after therapy was seen in the following groups: Bortezomib (4059 pg/mL vs. 1862 pg/mL, P = 0.016), lenalidomide (11837 pg/mL vs. 4374 pg/mL, P = 0.039), AD (1668 pg/mL vs. 1241 pg/mL, P = 0.016), and AD + HDCT + ASCT (2446 pg/mL vs. 1082 pg/mL, P = 0.001). Thalidomide led to a non-significant decrease in DKK-1 (1705 pg/mL vs. 1269 pg/mL, P = 0.081). Within all groups, a significant decrease of DKK-1 was only seen in responders (i.e. patients achieving complete remission or partial remission), but not in non-responders. We show for the first time that serum DKK-1 levels decrease in myeloma patients responding to treatment, irrespective of the regimen chosen. These data suggest that myeloma cells are the main source of circulating DKK-1 protein and provide a framework for clinical trials on anti-DKK-1 treatment in MM.

Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy.

Vickrey E, Allen S, Mehta J, Singhal S.

Cancer. 2009 Jan 1;115(1):229-32.

http://www.ncbi.nlm.nih.gov/pubmed/19090004?ordinalpos=108&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that daily acyclovir (or a suitable alternative) appears to be effective at preventing herpes zoster virus in patients with myeloma who are receiving bortezomib, with or without corticosteroids.

BACKGROUND: Humoral-mediated as well as cell-mediated immunity is compromised in myeloma patients receiving treatment. Immunocompromised patients are at risk of developing herpes zoster. There is evidence from clinical trials that bortezomib therapy is associated with a significant risk of herpes zoster. It is the authors' clinical policy to administer long-term acyclovir prophylactically to all symptomatic myeloma patients. METHODS: A retrospective review of the records of 125 myeloma patients who were treated with bortezomib and who also received routine acyclovir prophylaxis at the dose of 400 mg daily in >80% of patients was undertaken. Alternatives, used in <20% of patients, were 200 mg of acyclovir, 250/500 mg of valacyclovir, or 500 mg of famciclovir administered daily. This was accompanied by patient education regarding the importance of compliance with these prophylactic medications. RESULTS: The duration of bortezomib therapy was 1 to 164 weeks (median, 16 weeks). The total duration of exposure to bortezomib was 4150 weeks (80 patient-years). Except for the occasional missed dose, the self-reported compliance with antiviral prophylaxis was 100%. Not a single episode of herpes zoster was reported during this period. No adverse effects were noted that could be definitely attributed to acyclovir, valacyclovir, or famciclovir. CONCLUSIONS: Daily acyclovir (or a suitable alternative) appears to be effective at preventing herpes zoster virus in patients with myeloma who are receiving bortezomib, with or without corticosteroids.

Preclinical activity of P276-00, a novel small-molecule cyclin-dependent kinase inhibitor in the therapy of multiple myeloma.

Raje N, Hideshima T, Mukherjee S, Raab M, Vallet S, Chhetri S, Cirstea D, Pozzi S, Mitsiades C, Rooney M, Kiziltepe T, Podar K, Okawa Y, Ikeda H, Carrasco R, Richardson PG, Chauhan D, Munshi NC, Sharma S, Parikh H, Chabner B, Scadden D, Anderson KC.

Leukemia. 2009 Jan 8. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19151776?ordinalpos=100&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to identify the effects of targeting cyclin D in myeloma and find that because the cyclins are substrates of proteasome degradation, combination studies with bortezomib resulted in synergism.

Cyclin D dysregulation and overexpression is noted in the majority of multiple myeloma (MM) patients, suggesting its critical role in MM pathogenesis. Here, we sought to identify the effects of targeting cyclin D in MM. We first confirmed cyclin D mRNA overexpression in 42 of 64 (65%) patient plasma cells. Silencing cyclin D1 resulted in >50% apoptotic cell death suggesting its validity as a potential therapeutic target. We next evaluated P276-00, a clinical-grade small-molecule cyclin-dependent kinase inhibitor as a way to target the cyclins. P276-00 resulted in dose-dependent cytotoxicity in MM cells. Cell-cycle analysis confirmed either growth arrest or caspase-dependent apoptosis; this was preceded by inhibition of Rb-1 phosphorylation with associated downregulation of a range of cyclins suggesting a regulatory role of P276-00 in cell-cycle progression through broad activity. Proliferative stimuli such as interleukin-6, insulin-like growth factor-1 and bone-marrow stromal

cell adherence induced cyclins; P276-00 overcame these growth, survival and drug resistance signals. Because the cyclins are substrates of proteasome degradation, combination studies with bortezomib resulted in synergism. Finally, in vivo efficacy of P276-00 was confirmed in an MM xenograft model. These studies form the basis of an ongoing phase I study in the treatment of relapsed/refractory MM.

Bortezomib, dexamethasone, and fibroblast growth factor receptor 3-specific tyrosine kinase inhibitor in t(4;14) myeloma.

Bisping G, Wenning D, Kropff M, Gustavus D, Müller-Tidow C, Stelljes M, Munzert G, Hilberg F, Roth GJ, Stefanic M, Volpert S, Mesters RM, Berdel WE, Kienast J.

Clin Cancer Res. 2009 Jan 15;15(2):520-31.

http://www.ncbi.nlm.nih.gov/pubmed/19147757?ordinalpos=94&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Using combinations of novel drugs, the authors investigate potential enhancement of single-agent activities within the tumor cells, targeting of the marrow micromilieu, or circumvention of drug resistance in t(4;14)+myeloma and conclude that combining novel drugs in poor-prognosis t(4;14)+myeloma should take into account at least bortezomib sensitivity and probably Ras mutational status.

PURPOSE: Novel drugs including targeted approaches have changed treatment paradigms for multiple myeloma (MM) and may also have therapeutic potential in the poor-prognosis t(4;14) subset; t(4;14) results in overexpressed and activated fibroblast growth factor receptor 3 (FGFR3). Blocking this receptor tyrosine kinase (RTK) induces apoptosis in t(4;14)+ MM cells and decreases adhesion to bone marrow stromal cells (BMSC). Using combinations of novel drugs, we investigated potential enhancement of single-agent activities within the tumor cells, targeting of the marrow micromilieu, or circumvention of drug resistance in t(4;14)+ MM. EXPERIMENTAL DESIGN: We tested effects on apoptosis and related signaling pathways in the t(4;14)+ MM subset, applying drug combinations including a FGFR3 tyrosine kinase inhibitor (RTKI), the proteasome inhibitor bortezomib, and dexamethasone. RESULTS: RTKI, bortezomib, and dexamethasone were active as single agents in t(4;14)+ MM. RTK inhibition triggered complementary proapoptotic pathways (e.g., decrease of Mcl-1, down-regulation of p44/42 mitogen-activated protein kinase, and activation of proapoptotic stress-activated protein/c-Jun NH(2)-terminal kinases). Synergistic or additive effects were found by combinations of RTKI with dexamethasone or bortezomib. In selected cases of t(4;14)+ MM, triple combinations were superior to dual combinations tested. Prevention from MM cell apoptosis by BMSC or exogenous interleukin-6 was circumvented by drug combinations. In t(4;14)+, N-ras-mutated NCI-H929 cells, resistance to RTKI was overcome by addition of dexamethasone. Notably, the combination of RTKI and dexamethasone showed additive proapoptotic effects in bortezomib-insensitive t(4;14)+ MM. CONCLUSIONS: Combining novel drugs in poor-prognosis t(4;14)+ MM should take into account at least bortezomib sensitivity and probably Ras mutational status.

Bortezomib overcomes cell adhesion-mediated drug resistance through downregulation of VLA-4 expression in multiple myeloma.

Noborio-Hatano K, Kikuchi J, Takatoku M, Shimizu R, Wada T, Ueda M, Nobuyoshi M, Oh I, Sato K, Suzuki T, Ozaki K, Mori M, Nagai T, Muroi K, Kano Y, Furukawa Y, Ozawa K.

Oncogene. 2009 Jan 15;28(2):231-42. [Epub 2008 Oct 13.]

http://www.ncbi.nlm.nih.gov/pubmed/18850009?ordinalpos=96&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors perform functional screening using short hairpin RNA (shRNA) to define the molecule(s) responsible for CAM-DR of myeloma. They find that bortezomib is relatively resistant to CAM-DR because of its ability to specifically downregulate CD49d expression and that the combination of bortezomib with conventional anti-myeloma drugs may be effective in overcoming CAM-DR of myeloma.

Multiple myeloma (MM) is incurable, mainly because of cell adhesion-mediated drug resistance (CAM-DR). In this study, we performed functional screening using short hairpin RNA (shRNA) to define the molecule(s) responsible for CAM-DR of MM. Using four bona fide myeloma cell lines (KHM-1B, KMS12-BM, RPMI8226 and U266) and primary myeloma cells, we identified CD29 (beta1-integrin), CD44, CD49d (alpha4-integrin, a subunit of VLA-4), CD54 (intercellular adhesion molecule-1 (ICAM-1)), CD138 (syndecan-1) and CD184 (CXC chemokine receptor-4 (CXCR4)) as major adhesion molecules expressed on MM. shRNA-mediated knockdown of CD49d but not CD44, CD54, CD138 and CD184 significantly reversed CAM-DR of myeloma cells to bortezomib, vincristine, doxorubicin and dexamethasone. Experiments using blocking antibodies yielded almost identical results. Bortezomib was relatively resistant to CAM-DR because of its ability to specifically downregulate CD49d expression. This property was unique to bortezomib and was not observed in other anti-myeloma drugs. Pretreatment with bortezomib was able to ameliorate CAM-DR of myeloma cells to vincristine and dexamethasone. These results suggest that VLA-4 plays a critical role in CAM-DR of MM cells. The combination of bortezomib with conventional anti-myeloma drugs may be effective in overcoming CAM-DR of MM.

Clinical and immunohistochemical features associated with a response to bortezomib in patients with multiple myeloma.

Dawson MA, Opat SS, Taouk Y, Donovan M, Zammit M, Monaghan K, Horvath N, Roberts AW, Prince HM, Hertzberg M, McLean CA, Spencer A.

Clin Cancer Res. 2009 Jan 15;15(2):714-22.

http://www.ncbi.nlm.nih.gov/pubmed/19147779?ordinalpos=91&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors aim to identify the patients most likely to respond to bortezomib salvage therapy. They find that baseline clinical variables and selective immunohistochemical markers expressed by patients may be used effectively to identify patients that are most likely to achieve a meaning ful clinical response to bortezomib salvage therapy.

PURPOSE: Multiple myeloma is an incurable disease with heterogeneous clinical behavior. Bortezomib has offered some patients with relapsed and refractory disease an opportunity for prolonged survival. However, there remains a paucity of data in patients treated with bortezomib that accurately delineates and identifies such patients. This information is crucial to guide management. EXPERIMENTAL DESIGN: In this study, we aimed to identify the patients most likely to respond to bortezomib salvage therapy. We analyzed the baseline clinical variables and profiled the baseline expression of a broad range of immunohistochemical markers of cell cycle activity, apoptosis, and angiogenesis in a large cohort of multiply relapsed myeloma patients recruited to one of two prospective multicentre trials assessing the efficacy of bortezomib salvage therapy. RESULTS: Using the European Group for Bone Marrow Transplantation criteria, response (complete or partial) to bortezomib salvage therapy was associated with a previous history of complete response to alternative antimyeloma treatment. Patients who expressed cyclin D1 were more likely to achieve a response. In contrast, patients who expressed p16(INK4A), cytoplasmic p53, and the highest intensity of Bcl-2 staining had a poor response. Patients who achieved a response to bortezomib and those patients who expressed cyclin D1 at baseline showed a significant survival advantage. Patients who expressed FGFR3, a poor prognostic marker, responded equally well and had similar outcomes with bortezomib compared with FGFR3-negative patients. CONCLUSIONS: Baseline clinical variables and selective immunohistochemical markers expressed by patients may be used effectively to identify patients that are most likely to achieve a meaningful clinical response to bortezomib salvage therapy.

Novel agents in myeloma: an exciting saga.

Mark T, Niesvizky R, Coleman M.

Cancer. 2009 Jan 15;115(2):236-42.

http://www.ncbi.nlm.nih.gov/pubmed/19025986?ordinalpos=90&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

A humanised anti-IGF-1R monoclonal antibody (AVE1642) enhances Bortezomib-induced apoptosis in myeloma cells lacking CD45.

Descamps G, Gomez-Bougie P, Venot C, Moreau P, Bataille R, Amiot M.

Br J Cancer. 2009 Jan 27;100(2):366-9.

http://www.ncbi.nlm.nih.gov/pubmed/19165200?ordinalpos=87&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' results support the therapeutic use of anti-IGF-1R/bortezomib in CD45(neg) myeloma patients, particularly those with the most aggressive form, t(4,14).

The humanised form of an antagonistic anti-IGF-1R mAb (AVE1642) selectively inhibits the growth of CD45(neg) myeloma cells. AVE1642 strongly increased bortezomib-induced apoptosis, correlated with an increase of Noxa expression. These results support the therapeutic use of anti-IGF-1R/bortezomib in CD45(neg) Myeloma patients, particularly those with the most aggressive form, t(4,14).

Bortezomib combined with other drugs for treating 60 cases of multiple myeloma. [Article in Chinese]

Zhong YP, Chen SL, Li X, Hu Y, Zhang JJ.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2009 Feb;17(1):214-7.

http://www.ncbi.nlm.nih.gov/pubmed/19236782?ordinalpos=85&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors investigate the efficacy and safety of bortezomib-combined with dexamethasone, methyl prednisolone and other drugs in the treatment of patients with multiple myeloma (MM) and conclude that bortezomib combined with other drugs is a very effective regimen, with side effects that are predictable and manageable.

The aim of this study was to investigate the efficacy and safety of bortezomib-combined with dexamethasone, methyl prednisolone and other drugs in the treatment of patients with multiple myeloma (MM). 60 MM patients including 19 de novo patients, out of them 14 patients received the treatment using regimen of bortezomib in combination with thalidomide (BT), 5 patients received bortezomib-methyl prednisolone regimen (BMP). Out of 41 patients with refractory or relapsed myeloma 26 cases of MM received the treatment using regimen of bortezomib combined with methyl prednisolone (BMP), 6 cases received the treatment using regimen of bortezomib combined with cyclophosphamide, predisone and thalidomide (BCPT), 5 cases received the treatment using regimen of bortezomib combined with cis-diaminodichloroplatimm, etoposide, cydophosphomide and dexamethasone (BDECD), 4 cases received the treatment using regimen of bortezomib combined with dexamethasone (BD). Each patient received treatment of 2-8 courses at least. Response was assessed according to the criteria of the Bladè. Adverse events were graded according to the common Toxicity Criteria, version 3.0 (NCI CTCAE, USA). The median follow-up from the start of bortezomib treatment was 9 months. The results showed that out of 19 newly diagnosed patients, 6 cares achieved CR, 6 cases achieved nearly CR, 5 cases achieved PR, 1 case acheived MR, resulting in an ORR of 94.7%. Out of 41 refractory or relapsed patients, 5 cases achieved CR, 10 cases got nearly CR, 14 cases were PR and 5 cases were MR, resulting in an ORR of 82.92%. The main toxicities were fatigue, gastrointestinal disorders, peripheral neuropathy, thrombocytopenia, herpes zoster, skin rash. All adverse events were diminished by using routine ways. In conclusion, bortezomib combined with other drugs is a very effective regimen, its side effects are predictable and manageable.

Bortezomib-induced BiP Expression and Apoptosis in Multiple Myeloma Cells. [Article in Chinese]

Dong HJ, Chen XQ, Gao GX, Gu HT, Pan YZ, Gao Y, Zhu HF.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2009 Feb;17(1):107-10.

http://www.ncbi.nlm.nih.gov/pubmed/19236758?ordinalpos=86&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors explore the effect of bortezomib on the apoptosis and expression of the molecular chaperon BiP in human multiple myeloma cell line NCI-H929 (H929) and conclude that bortezomib-induced apoptosis in H929 cells correlates closely with endoplasmic reticulum stress.

This study was aimed to explore the effect of bortezomib on the apoptosis and expression of the molecular chaperon BiP in human multiple myeloma cell line NCI-H929 (H929). After treatment of H929 cells with different concentrations of bortezomib for 24 hours, cell apoptosis was assayed by flow cytometry with Annexin V-FITC/PI staining, and the expression levels of BiP mRNA and protein were detected by RT-PCR and Western blotting analysis. The results showed that bortezomib of different concentrations (20, 40 and 80 nmol/L) induced apoptosis of H929 cells in dose-dependent manner, with apoptotic rates (15.73 +/– 0.67)%, (27.83 +/– 1.26)% and (44.17 +/– 2.25)% respectively, which were significantly higher than that in control (1.21 +/– 0.07%) ($p < 0.05$). Bortezomib-induced up-regulation of BiP mRNA levels was almost on a parallel with BiP protein when compared with control. Under the similar apoptosis-stimulating conditions with apoptotic rates varying from 40% to 50%, expression levels of BiP mRNA and BiP protein induced by the classical endoplasmic reticulum stressor Brefeldin A (500 ng/ml, 24 h) were almost consistent with those by bortezomib (80 nmol/L, 24 h). It is concluded that bortezomib-induced apoptosis in H929 cells correlates closely with endoplasmic reticulum stress.

Considerations in the treatment of multiple myeloma: a consensus statement from Italian experts.

Patriarca F, Petrucci MT, Bringhen S, Baldini L, Caravita T, Corradini P, Corso A, Di Raimondo F, Falcone A, Ferrara F, Morabito F, Musto P, Offidani M, Petrini M, Rizzi R, Semenzato G, Tosi P, Vacca A, Cavo M, Boccadoro M, Palumbo A.

Eur J Haematol. 2009 Feb;82(2):93-105. [Epub 2008 Nov 6.]

http://www.ncbi.nlm.nih.gov/pubmed/19018865?ordinalpos=74&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The panel discusses: 1) evidence that maintenance with thalidomide after autologous stem cell transplantation in young patients failing to reach at least very good partial response could prolong survival; 2) in elderly patients, the combination of an alkylating drug with a novel agent should be considered as standard approach; 3) salvage regimens should include corticosteroids plus bortezomib, thalidomide or lenalidomide.

PURPOSE AND BASIC PROCEDURE OF THE STUDY: The availability of new targeted therapies has revolutionised the treatment of multiple myeloma (MM), for both the newly diagnosed and the relapsed and refractory settings. A panel of Italian experts provided guidelines for optimal clinical practice in the treatment of MM. MAIN FINDINGS AND CONCLUSIONS: The panel recommended that treatment should only be initiated in symptomatic patients. Autologous stem cell transplantation (ASCT) with melphalan is the treatment of choice in patients younger than 65 yr, and induction therapy including new drugs seems the most suitable preparatory regimen before ASCT. In patients who fail to achieve at least a very good partial response (VGPR) after transplant, a consolidation with a second transplant is of clinical benefit. Also, there is evidence that maintenance with thalidomide after ASCT in young patients failing to reach at least VGPR could prolong survival. In elderly patients, the combination of an alkylating drug with a novel agent should be considered as standard approach. Relapsed MM should be retreated after the reappearance of symptoms and signs of organ and tissue damage. Salvage regimens should include corticosteroids plus bortezomib, thalidomide or lenalidomide.

Development of an extramedullary plasmacytoma despite disappearing M protein in multiple myeloma by bortezomib treatment.

Koiso H, Tahara K, Osaki Y, Mawatari M, Sekigami T, Yokohama A, Saitoh T, Uchiumi H, Handa H, Tsukamoto N, Karasawa M, Nojima Y, Murakami H.

Rinsho Ketsueki. 2009 Feb;50(2):78-82.

http://www.ncbi.nlm.nih.gov/pubmed/19265298?ordinalpos=84&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors document a case of extramedullary plasmacytoma development during successful bortezomib therapy.

A 65-year-old male with IgG-kappa multiple myeloma was treated with melphalan-prednisolone (MP) and obtained a minimal response. Five months after the initiation of MP, he developed back pain, renal failure, hypercalcemia and increased plasma cells in the bone marrow. He was treated with bortezomib. After 2 cycles, he developed a peripheral neuropathy, and the dose of bortezomib was decreased to 1.0 mg/m(2). After 5 cycles, serum monoclonal protein was not detected by immunofixation, and the percentage of bone marrow plasma cells decreased to less than 5%. In March 2007, he developed lumbago again, and MRI of the lumbar vertebrae showed a tumor at the para pediculus arcus vertebrae. Immunohistochemistry of the biopsied tumor demonstrated monoclonal plasma cell infiltration. The patient was treated with local radiation therapy. Bortezomib is a new and effective agent for refractory/relapsed multiple myeloma. It has also been reported that bortezomib is effective for solitary extramedullary plasmacytoma (EMP). However, in the patient reported here, although bortezomib induced a complete response with regard to the serum monoclonal protein and the percentage of bone marrow plasma cells, EMP developed in the parapediculus arcus vertebrae. Herein, we document a case of EMP development during successful bortezomib therapy.

Generalized cutis laxa and fibrillar glomerulopathy resulting from IgG Deposition in IgG-lambda Monoclonal Gammopathy: pulmonary hemorrhage during stem cell mobilization and complete hematological response with bortezomib and dexamethasone therapy.

Fernández de Larrea C, Rovira M, Mascaró JM Jr, Torras A, Solé M, Lloreta J, Serra N, Cibeira MT, Bladé J.

Eur J Haematol. 2009 Feb;82(2):154-8. [Epub 2008 Nov 5.]

http://www.ncbi.nlm.nih.gov/pubmed/19018863?ordinalpos=75&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The case of a 52-years-old man with generalized acquired cutis laxa associated with IgG-lambda monoclonal gammopathy and nephrotic syndrome with renal failure (due to fibrillar glomerulopathy resulting from IgG deposition) is reported. Treatment with bortezomib and dexamethasome was subsequently started, and a complete hematological response was achieved.

The case of a 52-years-old man with generalized acquired cutis laxa associated with IgG-lambda monoclonal gammopathy and nephrotic syndrome with renal failure (due to fibrillar glomerulopathy resulting from IgG deposition) is reported. A peripheral blood autologous stem cell transplant was planned, but the procedure was complicated by severe pulmonary hemorrhage during stem cells mobilization with granulocyte colony-stimulating factor (G-CSF). Treatment with bortezomib and dexamethasome was subsequently started and a complete hematological response was achieved. Finally, the complete hematological response with the disappearance of the toxic M-protein allows the possibility of a long-term benefit with a kidney transplant followed by an autologous bone marrow transplant.

A phase I study of bortezomib, etoposide and carboplatin in patients with advanced solid tumors refractory to standard therapy.

Lieu C, Chow L, Pierson AS, Eckhardt SG, O'Bryant CL, Morrow M, Tran ZV, Wright JJ, Gore L.

Invest New Drugs. 2009 Feb;27(1):53-62. [Epub 2008 Jul 11.]

http://www.ncbi.nlm.nih.gov/pubmed/18618082?ordinalpos=78&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the toxicity, pharmacological, and biological properties of the combination of bortezomib, etoposide, and carboplatin in adults with advanced solid malignancies. They find that no objective responses were observed, and stable disease was noted for greater or equal to four cycles in nine highly refractory patients.

Purpose: To evaluate the toxicity, pharmacological, and biological properties of the combination of bortezomib, etoposide, and carboplatin in adults with advanced solid malignancies. Patients and methods: Patients received escalating doses of bortezomib, etoposide, and carboplatin every 21 days. Surrogate markers of angiogenesis were evaluated. Results: Twenty-four patients received 64 courses of therapy. The most common treatment-related adverse events were myelosuppression. Dose-limiting grade 3 and 4 neutropenia and thrombocytopenia were observed when bortezomib was given on days 1, 4, 8, 11. With revised dosing, the maximum tolerated dose (MTD) of bortezomib 0.75 mg/m(2) (days 1, 8), etoposide 75 mg/m(2) (days 1-3), and carboplatin AUC 5 (day 1) was well tolerated, and are the recommended doses for further studies with this combination. No objective responses were observed, however stable disease was noted for greater or equal to four cycles in nine highly refractory patients.

Treatment of light chain deposition disease with bortezomib and dexamethasone.

Kastritis E, Migkou M, Gavriatopoulou M, Zirogiannis P, Hadjikonstantinou V, Dimopoulos MA.

Haematologica. 2009 Feb;94(2):300-2. [Epub 2008 Dec 9.]

http://www.ncbi.nlm.nih.gov/pubmed/19066331?ordinalpos=77&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

A phase I study of samarium lexidronam/bortezomib combination therapy for the treatment of relapsed or refractory multiple myeloma.

Berenson JR, Yellin O, Patel R, Duvivier H, Nassir Y, Mapes R, Abaya CD, Swift RA.

Clin Cancer Res. 2009 Feb 1;15(3):1069-75.

http://www.ncbi.nlm.nih.gov/pubmed/19188182?ordinalpos=71&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that bortezomib combined with 153Sm-lexidronam appears to be a well-tolerated regimen, which showed clinical activity in this phase I trial for patients with relapsed or refractory myeloma.

PURPOSE: This open-label, phase I dose-escalation study assessed the safety, tolerability, and initial efficacy of Samariam 153 (153Sm)-lexidronam/bortezomib combination therapy for patients with relapsed/refractory multiple myeloma. EXPERIMENTAL DESIGN: Patients were enrolled in six cohorts and given bortezomib (1.0 or 1.3 mg/m2) on days 1, 4, 8, and 11 and 153Sm-lexidronam (0.25, 0.5, or 1.0 mCi/kg) on day 3 of a 56-day cycle (maximum of four cycles). The primary endpoints were safety and tolerability of the 153Sm-lexidronam/bortezomib regimen. RESULTS: Twenty-four patients were enrolled. Median values for age, time since diagnosis, and number of prior treatments were 63 years, 29 months, and three regimens, respectively. The most common toxicities were hematologic; during the first cycle, median neutrophil and platelet nadirs were 1,000/mm3 and 98,500/mm3, respectively, and observed generally 3 to 4 weeks post-treatment. The incidences of grade 4 neutropenia and thrombocytopenia were 12.5% and 8.3%, respectively, during treatment cycle 1. Dose-limiting toxicity, reached in cohort 6 as a result of hematologic toxicity, defined the maximum tolerated dose as 0.5 mCi/kg 153Sm-lexidronam in combination with 1.3 mg/m2 bortezomib. The maximum tolerated dose for 153Sm-lexidronam in combination with the 1.0 mg/m2 bortezomib was not reached. No nonhematologic dose-limiting toxicities were observed; both the incidence and the severity of peripheral neuropathy were low. Responses occurred in 5 (21%) patients, including 3 (12.5%) complete and 2 (8.3%) minimal responses. CONCLUSIONS: Bortezomib combined with 153Sm-lexidronam appears to be a well-tolerated regimen, which showed clinical activity in this phase I trial for patients with relapsed or refractory multiple myeloma.

Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors.

Golden EB, Lam PY, Kardosh A, Gaffney KJ, Cadenas E, Louie SG, Petasis NA, Chen TC, Schonthal AH.

Blood. 2009 Feb 3. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19190249?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study indicates that green tea polyphenols may have the potential to negate the therapeutic efficacy of bortezomib. The authors suggest that consumption of green tea products may be contraindicated during cancer therapy with bortezomib.

The anticancer potency of green tea and its individual components is being intensely investigated, and some cancer patients already self-medicate with this 'miracle herb' in hopes of augmenting the anticancer outcome of their chemotherapy. Bortezomib (Velcade((R))) is a proteasome inhibitor in clinical use for multiple myeloma. Here, we investigated whether the combination of these compounds would yield increased antitumor efficacy in multiple myeloma and glioblastoma cell lines in vitro and in vivo. Unexpectedly, we discovered that various green tea constituents, in particular (-)-epigallocatechin gallate (EGCG) and other polyphenols with 1,2-benzenediol moieties, effectively prevented tumor cell death induced by bortezomib in vitro and in vivo. This pronounced antagonistic function of EGCG was only evident with boronic acid-based proteasome inhibitors (bortezomib, MG-262, PS-IX), but not with several non-boronic acid proteasome inhibitors (MG-132, PS-I, nelfinavir). EGCG directly reacted with bortezomib and blocked its proteasome inhibitory function; as a consequence, bortezomib could not trigger endoplasmic reticulum stress or caspase-7 activation, and did not induce tumor cell death. Taken together, our results indicate that green tea polyphenols may have the potential to negate the therapeutic efficacy of bortezomib and suggest that consumption of green tea products may be contraindicated during cancer therapy with bortezomib.

Treatment of Multiple Myeloma in the Targeted Therapy Era (February)(CE).

Saad AA, Sharma M, Higa GM.

Ann Pharmacother. 2009 Feb 3. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19193585?ordinalpos=66&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors review the clinical trials that have impacted treatment standards of myeloma and conclude that thalidomide, lenalidomide, or bortezomib in combination with dexamethasone have replaced traditional chemotherapy as initial therapy of myeloma patients who are eligible for stem-cell transplantation. Furthermore, these novel drugs can be incorporated into regimens used to treat transplant-ineligible patients or those with relapsing disease.

OBJECTIVE: To review the clinical trials that have impacted treatment standards of multiple myeloma (MM). DATA SOURCE: A PubMed search (1980-June 2008) restricted to English-language publications was conducted using the key words multiple myeloma, clinical trials, targeted therapy, thalidomide, lenalidomide, bortezomib, dexamethasone, melphalan, autologous stem-cell transplantation, and tumor biology. Abstracts emanating from the meetings of the American Society of Clinical Oncology and American Society of Hematology from June 2002 to June 2008 were also reviewed. DATA SYNTHESIS: Although hematopoietic stem-cell transplantation has improved the response rate and duration of overall survival, MM remains an incurable disease. However, focused research aimed at the molecular basis of the disease has led to a number of new treatment strategies. Evidence from clinical trials indicates that each of the 3 novel agents, thalidomide, lenalidomide, and bortezomib, is remarkably effective as first-line therapy. The data also suggest that clinicians may need to reevaluate the role of stem-cell transplantation in the disease. CONCLUSIONS: Thalidomide, lenalidomide, or bortezomib in combination with dexamethasone have replaced traditional chemotherapy such as melphalan, doxorubicin, and vincristine as initial therapy of patients with MM who are eligible for stem-cell transplantation. Furthermore, these novel drugs can be incorporated into regimens used to treat transplant-ineligible patients or those with relapsing disease.

Myeloma cells exhibit an increase in proteasome activity and an enhanced response to proteasome inhibition in the bone marrow microenvironment in vivo.

Edwards CM, Lwin ST, Fowler JA, Oyajobi BO, Zhuang J, Bates AL, Mundy GR.

Am J Hematol. 2009 Feb 11. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19296472?ordinalpos=59&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors demonstrate that myeloma cells exhibit an increase in proteasome activity and an enhanced response to bortezomib treatment when located within the bone marrow microenvironment in vivo.

The proteasome inhibitor bortezomib has a striking clinical benefit in patients with multiple myeloma. It is unknown whether the bone marrow microenvironment directly contributes to the dramatic response of myeloma cells to proteasome inhibition in vivo. We have used the

well-characterized 5TGM1 murine model of myeloma to investigate myeloma growth within bone and response to the proteasome inhibitor bortezomib in vivo. Myeloma cells freshly isolated from the bone marrow of myeloma-bearing mice were found to have an increase in proteasome activity and an enhanced response to in vitro proteasome inhibition, as compared with pre-inoculation myeloma cells. Treatment of myeloma-bearing mice with bortezomib resulted in a greater reduction in tumor burden when the myeloma cells were located within the bone marrow when compared with extra-osseous sites. Our results demonstrate that myeloma cells exhibit an increase in proteasome activity and an enhanced response to bortezomib treatment when located within the bone marrow microenvironment in vivo.

Inhibition of eIF2alpha dephosphorylation maximizes bortezomib efficiency and eliminates quiescent multiple myeloma cells surviving proteasome inhibitor therapy.

Schewe DM, Aguirre-Ghiso JA.

Cancer Res. 2009 Feb 15;69(4):1545-52. [Epub 2009 Feb 3.]

http://www.ncbi.nlm.nih.gov/pubmed/19190324?ordinalpos=54&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This data indicates that bortezomib can induce growth arrest in therapy-surviving myeloma cells and that attenuation of eIF2alpha phosphorylation contributes to this survival. Most importantly, this survival mechanism can be blocked by inhibiting eIF2alpha dephosphorylation. Thus, strategies that maintain eIF2alpha in a hyperphosphorylated state may be a novel therapeutic approach to maximize bortezomib-induced apoptosis and reduce residual disease and recurrences in this type of cancer.

The proteasome inhibitor bortezomib (Velcade) effectively eradicates multiple myeloma (MM) cells, partly by activating endoplasmic reticulum (ER) stress apoptotic signaling. However, MM recurrences in bortezomib-treated patients are invariable. We have shown that ER stress signaling can also induce growth arrest and survival in cancer cells. Thus, we hypothesized that bortezomib therapy could induce quiescence and survival of residual MM cells, contributing to disease recurrence. Here, we report that in MM cells, proteasome inhibition with MG-132 or bortezomib results in a surviving cell fraction that enters a prolonged quiescent state (G(0)-G(1) arrest). Mechanism analysis revealed that bortezomib-surviving quiescent cells attenuate eIF2alpha phosphorylation and induction of the ER stress proapoptotic gene GADD153. This occurs independently of the eIF2alpha upstream kinases PERK, GCN2, and PKR. In contrast, the prosurvival ER-chaperone BiP/Grp78 was persistently induced. The bortezomib-surviving quiescent fraction could be eradicated by a simultaneous or sequential combination therapy with salubrinal, an inhibitor of GADD34-PP1C phosphatase complex, and, in consequence, eIF2alpha dephosphorylation. This effect was mimicked by expression of a phosphorylated mimetic eIF2alpha-S51D mutant. Our data indicate that bortezomib can induce growth arrest in therapy-surviving MM cells and that attenuation of eIF2alpha phosphorylation contributes to this survival. Most importantly, this survival mechanism can be blocked by inhibiting eIF2alpha dephosphorylation. Thus, strategies that maintain eIF2alpha in a hyperphosphorylated state may be a novel therapeutic approach to maximize bortezomib-induced apoptosis and reduce residual disease and recurrences in this type of cancer.

Preclinical studies in support of defibrotide for the treatment of multiple myeloma and other neoplasias.

Mitsiades CS, Rouleau C, Echart C, Menon K, Teicher B, Distaso M, Palumbo A, Boccadoro M, Anderson KC, Iacobelli M, Richardson PG.

Clin Cancer Res. 2009 Feb 15;15(4):1210-21.

http://www.ncbi.nlm.nih.gov/pubmed/19228727?ordinalpos=55&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate whether defibrotide modulates the protection conferred to myeloma cells by bone marrow stromal cells and conclude that defibrotide in combination with conventional and novel therapies (including bortezomib) could potentially improve patient outcome in myeloma and other malignancies.

PURPOSE OF THE STUDY: Defibrotide, an orally bioavailable polydisperse oligonucleotide, has promising activity in hepatic veno-occlusive disease, a stem cell transplantation-related toxicity characterized by microangiopathy. The antithrombotic properties of defibrotide and its minimal hemorrhagic risk could serve for treatment of cancer-associated thrombotic complications. Given its cytoprotective effect on endothelium, we investigated whether defibrotide protects tumor cells from cytotoxic antitumor agents. Further, given its antiadhesive properties, we evaluated whether defibrotide modulates the protection conferred to multiple myeloma cells by bone marrow stromal cells. METHODS-RESULTS: Defibrotide lacks significant single-agent in vitro cytotoxicity on multiple myeloma or solid tumor cells and does not attenuate their in vitro response to dexamethasone, bortezomib, immunomodulatory thalidomide derivatives, and conventional chemotherapeutics, including melphalan and cyclophosphamide. Importantly, defibrotide enhances in vivo chemosensitivity of multiple myeloma and mammary carcinoma xenografts in animal models. In cocultures of multiple myeloma cells with bone marrow stromal cells in vitro, defibrotide enhances the multiple myeloma cell sensitivity to melphalan and dexamethasone, and decreases multiple myeloma-bone marrow stromal cell adhesion and its sequelae, including nuclear factor-kappaB activation in multiple myeloma and bone marrow stromal cells, and associated cytokine production. Moreover, defibrotide inhibits expression and/or function of key mediators of multiple myeloma interaction with bone marrow stromal cell and endothelium, including heparanase, angiogenic cytokines, and adhesion molecules. CONCLUSION: Defibrotide's in vivo chemosensitizing properties and lack of direct in vitro activity against tumor cells suggest that it favorably modulates antitumor interactions between bone marrow stromal cells and endothelia

in the tumor microenvironment. These data support clinical studies of defibrotide in combination with conventional and novel therapies to potentially improve patient outcome in multiple myeloma and other malignancies.

Bortezomib, ascorbic acid and melphalan (BAM) therapy for patients with newly diagnosed multiple myeloma: an effective and well-tolerated frontline regimen.

Berenson JR, Yellin O, Woytowitz D, Flam MS, Cartmell A, Patel R, Duvivier H, Nassir Y, Eades B, Abaya CD, Hilger J, Swift RA.

Eur J Haematol. 2009 Feb 17. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19226361?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that bortezomib, ascorbic acid and melphalan is an efficacious, well-tolerated and steroid- and immunomodulatory drug-free frontline treatment regimen for myeloma patients.

Abstract BACKGROUND: We conducted a single-arm, multicentre phase 2 study to evaluate bortezomib, ascorbic acid and melphalan (BAM) for patients with newly diagnosed multiple myeloma (MM). METHODS: Induction consisted of up to eight 28-day cycles of bortezomib 1.0 mg/m(2) on days 1, 4, 8 and 11, plus oral ascorbic acid 1 g and oral melphalan 0.1 mg/kg on days 1-4, followed by maintenance bortezomib 1.3 mg/m(2) every 2 weeks until progression. RESULTS: Among 35 patients enrolled (median age 70 years), responses occurred in 23/31 evaluable patients (74%) including 5 (16%) complete, 3 (10%) very good partial, 6 (19%) partial and 9 (29%) minimal responses. Six patients (19%) had stable disease. Thus, disease control was achieved in 29 (94%) patients. Median times to first and best responses were 2 and 3 months (ranges 1-5 and 1-7), respectively. Median time to progression was 19 months and median overall survival has not been reached (range 2-23+ months). Grade 3 or 4 adverse events occurred in 25 and 5 patients, respectively; the most common were neutropenia, neuropathy and thrombocytopenia. CONCLUSIONS: BAM is an efficacious, well-tolerated and steroid- and immunomodulatory drug (IMiD)-free frontline treatment regimen for MM patients.

Characterization of the ubiquitin-proteasome system in bortezomib-adapted cells.

Rückrich T, Kraus M, Gogel J, Beck A, Ovaa H, Verdoes M, Overkleeft HS, Kalbacher H, Driessen C.

Leukemia. 2009 Feb 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19225532?ordinalpos=50&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors conclude that different types of bortezomib-adapted cell lines, including myeloma, show similar patterns of changes in the proteasomal machinery which result in residual proteasome activity in the presence of bortezomib and a quantitative balance between protein biosynthesis and destruction.

Resistance towards the proteasome inhibitor bortezomib is poorly understood. We adapted the HL-60, ARH-77 and AMO-1 cell lines (myeloid leukemia, plasmocytoid lymphoma, myeloma) to bortezomib exceeding therapeutic plasma levels, and compared characteristics of the ubiquitin-proteasome system, alternative proteases and the unfolded protein response (UPR) between adapted cells and parental lines. Adapted cells showed increased transcription rates, activities and polypeptide levels of the bortezomib-sensitive beta5, but also of the beta2 proteasome subunit and consistently retained elevated levels of active beta1/beta5-type proteasome subunits in the presence of therapeutic levels of bortezomib. Bortezomib-adapted HL-60 cells showed increased expression and proteasome association of the 11S proteasome activator, and did not accumulate poly-ubiquitinated protein, activate the UPR or UPR-mediated apoptosis in response to bortezomib. The rate of protein biosynthesis was reduced, and the transcription of chaperone genes downmodulated. We did not observe major changes in the activities of TPPII, cathepsins or deubiquitinating proteases. We conclude that different types of bortezomib-adapted cell lines, including myeloma, show similar patterns of changes in the proteasomal machinery which result in residual proteasome activity in the presence of bortezomib and a quantitative balance between protein biosynthesis and destruction.

Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial.

Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J, Noble B, Pirooz NA, Spong JE, Piza JG, Zepeda VH, Mikhael JR, Leis JF, Bergsagel PL, Fonseca R, Stewart AK.

Leukemia. 2009 Feb 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19225538?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that with cyclophosphamide, bortezomib and dexamethasone produces a rapid and profound response in patients with newly diagnosed myeloma with manageable toxicity.

We have studied a three-drug combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) on a 28-day cycle in the treatment of newly diagnosed multiple myeloma (MM) patients to assess response and toxicity. The primary endpoint of response was evaluated

after four cycles. Thirty-three newly diagnosed, symptomatic patients with MM received bortezomib 1.3 mg/m(2) intravenously on days 1, 4, 8 and 11, cyclophosphamide 300 mg/m(2) orally on days 1, 8, 15 and 22 and dexamethasone 40 mg orally on days 1-4, 9-12 and 17-20 on a 28-day cycle for four cycles. Responses were rapid with a mean 80% decline in the sentinel monoclonal protein at the end of two cycles. The overall intent to treat response rate (>/= partial response) was 88%, with 61% of very good partial response or better (>/=VGPR) and 39% of complete/near complete response (CR/nCR). For the 28 patients who completed all four cycles of therapy, the CR/nCR rate was 46% and VGPR rate was 71%. All patients undergoing stem cell harvest had a successful collection. Twenty-three patients underwent stem cell transplantation (SCT) and are evaluable through day 100 with CR/nCR documented in 70% and >/=VGPR in 74%. In conclusion, CyBorD produces a rapid and profound response in patients with newly diagnosed MM with manageable toxicity.

Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG).

Kastritis E, Zervas K, Symeonidis A, Terpos E, Delimbassi S, Anagnostopoulos N, Michali E, Zomas A, Katodritou E, Gika D, Pouli A, Christoulas D, Roussou M, Kartasis Z, Economopoulos T, Dimopoulos MA.

Leukemia. 2009 Feb 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19225533?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors compare the outcome of 1,376 unselected patients with symptomatic myeloma, who started treatment before or after the introduction of thalidomide. The median overall survival in patients who started treatment after the introduction of novel agents increased by 12 months.

When the novel agents thalidomide, bortezomib and lenalidomide are administered to patients with myeloma in the context of clinical trials, they are associated with a significant improvement in response, progression-free survival and in some studies, overall survival (OS); however, their effect on the outcome of unselected myeloma patients has not been fully assessed. We compared the outcome of 1376 unselected patients with symptomatic myeloma, who started treatment before or after the introduction of thalidomide. The median OS in patients who started treatment after the introduction of novel agents increased by 12 months (48 vs 36 months, P<0.001). This improvement was more pronounced in patients </=70 years (from 39 to 74 months, P<0.001), but less evident in patients >70 years (from 26 to 33 months, P=0.27). In patients treated after the introduction of novel agents, the international staging system (ISS) could discriminate three groups with significantly different outcomes (5-year survival for ISS stage I, II and III was 66, 45 and 18%, respectively, P<0.001). ISS was also valid in patients who actually received upfront treatment with novel drugs (4-year survival rate was 85, 61 and 26% for ISS stage I, II and III patients, P=0.001).

Bortezomib, low-dose intravenous melphalan, and dexamethasone for patients with relapsed multiple myeloma.

Popat R, Oakervee H, Williams C, Cook M, Craddock C, Basu S, Singer C, Harding S, Foot N, Hallam S, Odeh L, Joel S, Cavenagh J.

Br J Haematol. 2009 Mar;144(6):887-94. [Epub 2009 Jan 12.]

http://www.ncbi.nlm.nih.gov/pubmed/19183191?ordinalpos=25&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This phase I/II study shows bortezomib and low-dose IV melphalan combination therapy is a safe and highly effective regimen for patients with relapsed myeloma. These data suggest further investigation of this combination is warranted.

This multicenter phase I/II study investigated the maximum tolerated dose (MTD), safety, and efficacy of low dose intravenous (IV) melphalan in combination with bortezomib for patients with relapsed multiple myeloma (MM). Patients received bortezomib 1.3 mg/m(2) on days 1, 4, 8, and 11 and escalating doses of IV melphalan (2.5-10.0 mg/m(2)) on day 2 of a 28-day cycle for a maximum of eight cycles. Dexamethasone 20 mg was added for progressive or stable disease. Fifty-three patients were enrolled. The MTD was defined at melphalan 7.5 mg/m(2) and bortezomib 1.3 mg/m(2). The overall response rate (ORR) was 68% (23% complete or near-complete responses [CR/nCR]) whilst at the MTD (n = 33) the ORR was 76% (34% CR/nCR). After median follow-up of 17 months, the median progression free survival was 10 months, rising to 12 months at the MTD (P < 0.05 vs. non-MTD regimens). The median overall survival was 28 months, but was not yet reached at the MTD. Grade 3/4 adverse events included thrombocytopenia (62%), neutropenia (57%), infection (21%), and neuropathy (15%). Bortezomib and low-dose IV melphalan combination therapy is a safe and highly effective regimen for patients with relapsed MM. These data suggest further investigation of this combination is warranted.

Cystatin-C is an independent prognostic factor for survival in multiple myeloma and is reduced by bortezomib administration.

Terpos E, Katodritou E, Tsiftsakis E, Kastritis E, Christoulas D, Pouli A, Michalis E, Verrou E, Anargyrou K, Tsionos K, Dimopoulos MA, Zervas K; Greek Myeloma Study Group.

Haematologica. 2009 Mar;94(3):372-9.

http://www.ncbi.nlm.nih.gov/pubmed/19252175?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that serum cystatin-C is not only a sensitive marker of renal impairment, but also reflects tumor burden and is of prognostic value in myeloma. Its reduction after treatment with bortezomib reflects bortezomib's anti-myeloma activity and possibly bortezomib's direct effect on renal function.

BACKGROUND: Renal impairment is a common complication of multiple myeloma. Cystatin-C is considered an accurate marker of glomerular filtration rate in several renal disorders. Microarray analysis has revealed that cystatin-C is one of the most highly up-regulated genes in multiple myeloma. The aim of this study was to evaluate the serum levels of cystatin-C in myeloma patients, explore possible correlations with clinical data, including survival, and assess the effect of bortezomib on cystatin-C in relapsed multiple myeloma. DESIGN AND METHODS: We measured serum cystatin-C in 157 newly diagnosed, previously untreated myeloma patients, in 28 patients with relapsed disease pre- and post-bortezomib therapy and in 52 healthy controls, using a latex particle-enhanced nephelometric immunoassay. RESULTS: In newly diagnosed patients, cystatin-C was elevated and showed strong correlations with advanced ISS stage, extensive bone disease, high beta(2)-microglobulin, high serum creatinine, and low creatinine clearance. Multivariate analysis revealed that only cystatin-C and lactate dehydrogenase had an independent prognostic impact on patients' survival. The combination of cystatin-C and lactate dehydrogenase revealed three prognostic groups of patients: a high-risk group (both elevated cystatin-C and lactate dehydrogenase) with a median survival of 24 months, an intermediate-risk group (elevated cystatin-C or elevated lactate dehydrogenase) with a median survival of 48 months and a low-risk group (both low cystatin-C and lactate dehydrogenase) in which median survival has not yet been reached ($p<0.001$). Cystatin-C could also identify a subset of ISS-II patients with worse outcome. Relapsed patients had higher cystatin-C levels even compared to newly diagnosed patients. Treatment with bortezomib produced a significant reduction of cystatin-C, mainly in responders. CONCLUSIONS: Serum cystatin-C is not only a sensitive marker of renal impairment but also reflects tumor burden and is of prognostic value in myeloma. Its reduction after treatment with bortezomib reflects bortezomib's anti-myeloma activity and possibly bortezomib's direct effect on renal function.

Emerging therapies for multiple myeloma.

Podar K, Tai YT, Hideshima T, Vallet S, Richardson PG, Anderson KC.

Expert Opin Emerg Drugs. 2009 Mar;14(1):99-127.

http://www.ncbi.nlm.nih.gov/pubmed/19249983?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This article reviews the scientific rationale of new therapy regimens (including the use of bortezomib) and newly identified therapeutic agents— small molecules as well as therapeutic antibodies— that hold promise to further improve outcome in myeloma.

Multiple myeloma (MM) is a clonal plasma cell malignancy clinically characterized by osteolytic lesions, immunodeficiency, and renal disease. There are an estimated 750,000 people diagnosed with MM worldwide, with a median overall survival of 3 - 5 years. Besides chromosomal aberrations, translocations, and mutations in essential growth and tumor-suppressor genes, accumulating data strongly highlight the pathophysiologic role of the bone marrow (BM) microenvironment in MM pathogenesis. Based on this knowledge, several novel agents have been identified, and treatment options in MM have fundamentally changed during the last decade. Thalidomide, bortezomib, and lenalidomide have been incorporated into conventional cytotoxic and transplantation regimens, first in relapsed and refractory and now also in newly diagnosed MM. Despite these significant advances, there remains an urgent need for more efficacious and tolerable drugs. Indeed, a plethora of preclinical agents awaits translation from the bench to the bedside. This article reviews the scientific rationale of new therapy regimens and newly identified therapeutic agents - small molecules as well as therapeutic antibodies - that hold promise to further improve outcome in MM.

Marked improvement of platelet transfusion refractoriness after bortezomib therapy in multiple myeloma.

Miki H, Ozaki S, Tanaka O, Lee E, Takimoto T, Watanabe H, Fujii S, Nakamura S, Kagawa K, Takeuchi K, Yata K, Abe M, Kagami S, Matsumoto T.

Int J Hematol. 2009 Mar;89(2):223-6. [Epub 2009 Feb 20.]

http://www.ncbi.nlm.nih.gov/pubmed/19225725?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report a patient with refractory myeloma who developed platelet transfusion refractoriness, a case that suggests bortezomib might be effective in different types of immune disease by inhibiting allo-reactive antibody.

We report a patient with refractory multiple myeloma (MM) who developed platelet transfusion refractoriness (PTR). A 61-year-old woman was diagnosed with MM in July 2003. She underwent high-dose chemotherapy followed by autologous stem cell transplantation, and achieved a very good partial response. However, she relapsed in June 2006, and was referred to our hospital in October of the same year. Laboratory examinations showed pancytopenia and increased plasma cells in the peripheral blood. Platelet transfusions from random donors became ineffective, and anti-HLA class I antibody (83.8% positive) was detected in the serum by flow cytometry assay (Flow PRA). Therefore, she was considered to have developed PTR due to anti-HLA class I antibody caused by the previous blood transfusions. She was transfused with HLA-matched platelets, and then treated with bortezomib plus dexamethasone (BD) for refractory MM. The serum IgG level decreased from 7,451 to 1,735 mg/dL, and HLA class I antibody was markedly decreased to 1.9%. In addition, platelet transfusion from random donors showed clinical effects after BD therapy. This case suggests that bortezomib might be effective in different types of immune disease by inhibiting allo-reactive antibody.

Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline.

Richardson PG, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, Bladé J, Boccadoro M, Cavenagh JD, Boral AL, Esseltine DL, Wen PY, Amato AA, Anderson KC, San Miguel J.

Br J Haematol. 2009 Mar;144(6):895-903. [Epub 2009 Jan 16.]

http://www.ncbi.nlm.nih.gov/pubmed/19170677?ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study finds that bortezomib-associated peripheral neuropathy is manageable and reversible in most patients with relapsed myeloma. Dose modification using a specific guideline improves peripheral neuropathy management without adversely affecting outcome.

The frequency, characteristics and reversibility of bortezomib-associated peripheral neuropathy were evaluated in the phase III APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial in patients with relapsed myeloma, and the impact of a dose-modification guideline on peripheral neuropathy severity and reversibility was assessed. Patients received bortezomib 1.3 mg/m(2) (days 1, 4, 8, 11, eight 21-d cycles, then days 1, 8, 15, 22, three 35-d cycles); bortezomib was held, dose-reduced or discontinued depending on peripheral neuropathy severity, according to a protocol-specified dose-modification guideline. Overall, 124/331 patients (37%) had treatment-emergent peripheral neuropathy, including 30 (9%) with grade >or=3; incidence and severity were not affected by age, number/type of prior therapies, baseline glycosylated haemoglobin level, or diabetes history. Grade >or=3 incidence appeared lower versus phase II trials (13%) that did not specifically provide dose-modification guidelines. Of patients with grade >or=2 peripheral neuropathy, 58/91 (64%) experienced improvement or resolution to baseline at a median of 110 d, including 49/72 (68%) who had dose modification versus 9/19 (47%) who did not. Efficacy did not appear adversely affected by dose modification for grade >or=2 peripheral neuropathy. Bortezomib-associated peripheral neuropathy is manageable and reversible in most patients with relapsed myeloma. Dose modification using a specific guideline improves peripheral neuropathy management without adversely affecting outcome.

Role of autologous and allogeneic stem cell transplantation in myeloma.

Bensinger WI.

Leukemia. 2009 Mar;23(3):442-8. [Epub 2009 Jan 29.]

http://www.ncbi.nlm.nih.gov/pubmed/19277049?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss autologous stem cell transplantation in light of the approval of immunomodulators and proteosome inhibitors, which have resulted in improved response rates and increased overall survivals, and how thalidomide and lenalidomide have been combined with corticosteroids, alkylators and anthracyclines in front-line myeloma treatment.

The treatment of multiple myeloma (MM), a largely incurable B-cell hematologic malignancy, is changing dramatically. Autologous stem cell transplantation (SCT) and the approval of two new classes of drugs, immunomodulators and proteosome inhibitors, have resulted in improved response rates and increased overall survivals. Thalidomide, bortezomib and lenalidomide have been combined with corticosteroids, alkylators and anthracyclines in front-line MM treatment. Phase 2 and preliminary phase 3 studies have reported very high response rates and complete

response rates formerly seen only with SCT. When patients with MM who have received these new drugs then proceed to transplant, major response rates are further increased. Owing to limited follow-up, it is unclear whether these higher response rates translate into increased survival. Despite these improvements, the disease remains incurable for all but a small fraction of patients. Allogeneic SCT is potentially curative, due in part to a graft-versus-myeloma effect but is limited by mortality. Mortality can be reduced through the use of lower intensity conditioning regimens but this comes at a cost of higher rates of disease progression and relapse. Strategies to improve outcomes of allogeneic transplants include more intensive, yet non-myeloablative conditioning regimens, tandem transplants, peripheral blood cells, graft engineering, post-transplant maintenance and targeted conditioning therapies.

Topical analgesic combinations for bortezomib neuropathy.

Prommer EE.

J Pain Symptom Manage. 2009 Mar;37(3):e3-5. [Epub 2009 Jan 25.]

http://www.ncbi.nlm.nih.gov/pubmed/19171460?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Treatment of newly diagnosed myeloma.

Palumbo A, Rajkumar SV.

Leukemia. 2009 Mar;23(3):449-56. [Epub 2008 Nov 13.]

http://www.ncbi.nlm.nih.gov/pubmed/19005483?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss how the introduction of thalidomide and lenalidomide have dramatically changed the treatment paradigm of myeloma, including in the induction regimens and maintenance therapies for autologous stem cell transplantation.

The introduction of thalidomide, bortezomib and lenalidomide has dramatically changed the treatment paradigm of multiple myeloma (MM). In patients eligible for autologous stem cell transplant (ASCT), combinations including thalidomide/dexamethasone (Thal/Dex) or bortezomib/dexamethasone (Bort/Dex) or lenalidomide/dexamethasone (Rev/Dex) have been introduced as induction regimens in patients eligible for ASCT. New induction regimens have significantly increased complete response rate before and after ASCT with a positive impact on progression-free survival. Maintenance therapy with thalidomide, under investigation with lenalidomide, may further prolong remission duration. In patients not eligible for ASCT, randomized studies have shown that melphalan, prednisone, thalidomide (MPT) and melphalan, prednisone and bortezomib (MPV) are both superior to melphalan and prednisone (MP), and are now considered standard of care. Ongoing trials will soon assess if MP plus lenalidomide may be considered an attractive option. More complex regimens combining thalidomide or bortezomib or lenalidomide with cyclophosphamide or doxorubicin have been also tested. In small cohorts of patients bortezomib or lenalidomide may overcome the poor prognosis induced by deletion 13 or translocation t(4;14) or deletion 17p13. If these data will be confirmed, a cytogenetically risk-adapted strategy might become the most appropriate strategy.

Cooperation between Apo2L/TRAIL and bortezomib in multiple myeloma apoptosis.

Balsas P, López-Royuela N, Galán-Malo P, Anel A, Marzo I, Naval J.

Biochem Pharmacol. 2009 Mar 1;77(5):804-12. [Epub 2008 Dec 3.]

http://www.ncbi.nlm.nih.gov/pubmed/19100720?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the possibility of improving bortezomib therapy with Apo2L/TRAIL, with results that indicate Apo2L/TRAIL can cooperate with bortezomib to induce apoptosis in myeloma cells and can be a useful adjunct for myeloma therapy.

The proteasome inhibitor bortezomib is currently an important drug for treatment of relapsed and refractory multiple myeloma (MM) and for elderly patients. However, cells from some patients show resistance to bortezomib. We have evaluated the possibility of improving bortezomib therapy with Apo2L/TRAIL, a death ligand that induces apoptosis in MM but not in normal cells. Results indicate that cotreatment with low doses of bortezomib significantly increased apoptosis of MM cells showing partial sensitivity to Apo2L/TRAIL. Bortezomib treatment did not significantly alter plasma membrane amount of DR4 and DR5 but increased Apo2L/TRAIL-induced caspase-8 and caspase-3 activation. Apo2L/TRAIL reverted bortezomib-induced up-regulation of beta-catenin, Mcl-1 and FLIP, associated with the enhanced cytotoxicity of combined treatment. More important, some cell lines displaying resistance to bortezomib were sensitive to Apo2L/TRAIL-induced apoptosis. A cell line made resistant by continuous culture of RPMI 8226 cells in the presence of bortezomib (8226/7B) was highly sensitive to Apo2L/TRAIL-induced apoptosis. Moreover, RPMI 8226 cells overexpressing Mcl-1 (8226/Mcl-1) or Bcl-x(L) (8226/Bcl-x(L)) also showed enhanced resistance to bortezomib, but co-treatment with Apo2L/TRAIL reverted this resistance. These results indicate that Apo2L/TRAIL can cooperate with bortezomib to induce apoptosis in myeloma cells and can be an useful adjunct for MM therapy.

Cutaneous involvement in multiple myeloma and bortezomib.

Siniscalchi A, Fratoni S, Santeusanio G, Del Poeta G, de Fabritiis P, Caravita T.

Ann Hematol. 2009 Mar 4. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19259673?ordinalpos=19&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

DSMM XI study: dose definition for intravenous cyclophosphamide in combination with bortezomib/dexamethasone for remission induction in patients with newly diagnosed myeloma.

Kropff M, Liebisch P, Knop S, Weisel K, Wand H, Gann CN, Berdel WE, Einsele H; on behalf of the Deutsche Studiengruppe Multiples Myelom, DSMM.

Ann Hematol. 2009 Mar 10. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19274460?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The results of this clinical trial suggest that bortezomib in combination with cyclophosphamide at 900 mg/m(2) and dexamethasone is an effective induction treatment for patients with newly diagnosed myeloma that warrants further investigation.

A clinical trial was initiated to evaluate the recommended dose of cyclophosphamide in combination with bortezomib and dexamethasone as induction treatment before stem cell transplantation for younger patients with newly diagnosed multiple myeloma (MM). Thirty patients were treated with three 21-day cycles of bortezomib 1.3 mg/m(2) on days 1, 4, 8, and 11 plus dexamethasone 40 mg on the day of bortezomib injection and the day after plus cyclophosphamide at 900, 1,200, or 1,500 mg/m(2) on day 1. The maximum tolerated dose of cyclophosphamide was defined as 900 mg/m(2). At this dose level, 92% of patients achieved at least a partial response. The overall response rate [complete response (CR) plus partial response (PR)] across all dose levels was 77%, with a 10% CR rate. No patient experienced progressive disease. The most frequent adverse events were hematological and gastrointestinal toxicities as well as neuropathy. The results suggest that bortezomib in combination with cyclophosphamide at 900 mg/m(2) and dexamethasone is an effective induction treatment for patients with newly diagnosed MM that warrants further investigation.

Initial therapy in multiple myeloma: investigating the new treatment paradigm.

Kettle JK, Finkbiner KL, Klenke SE, Baker RD, Henry DW, Williams CB.

J Oncol Pharm Pract. 2009 Mar 10. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19276138?ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss the development of three novel chemotherapeutic agents—thalidomide, lenalidomide, and bortezomib— that has resulted in a fundamental shift in the management of myeloma.

The development of three novel chemotherapeutic agents - thalidomide, lenalidomide, and bortezomib - has resulted in a fundamental shift in the management of multiple myeloma. Despite this tremendous advancement, the selection of initial treatment must still be made with a degree of uncertainty as a true standard therapy has yet to be established. Although challenging, the relative abundance of therapeutic options, when taken into consideration with unique patient characteristics, creates the potential for individualization of care.For patients eligible for autologous stem cell transplantation, various combinations of novel agents with dexamethasone or traditional chemotherapy have supplanted the previous standard regimen consisting of vincristine, doxorubicin, and dexamethasone. In elderly patients or others that are deemed ineligible for the transplant procedure, the addition of a novel agent to melphalan-prednisone has demonstrated significant improvements in response rates.Due to the immaturity of the available data, it is perhaps best to regard the era of novel agents with a degree of rational enthusiasm, as the ultimate impact on patient care remains undetermined. Although further research is clearly implicated, recent advancements have resulted in significant progress toward obtaining optimum outcomes in a historically challenging disease.

A retrospective analysis of bortezomib therapy for Japanese patients with relapsed or refractory multiple myeloma: beta2-microglobulin associated with time to progression.

Ohguchi H, Sugawara T, Ishikawa I, Okuda M, Tomiya Y, Yamamoto J, Onishi Y, Fujiwara Yamada M, Ishizawa K, Kameoka J, Harigae H.

Int J Hematol. 2009 Mar 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19296199?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors retrospectively analyze 40 patients with relapsed or refractory myeloma who have received bortezomib at three collaborating centers in Miyagi prefecture in Japan. They find bortezomib is well tolerated and effective for Japanese patients with relapsed or refractory myeloma, with results suggesting that serum beta2-microglobulin level may be a marker of prognosis on bortezomib therapy for patients with relapsed or refractory myeloma— though further studies are needed.

Bortezomib is approved for the treatment of patients with relapsed or refractory multiple myeloma (MM), but only a few clinical studies for Japanese patients who were treated with bortezomib have been reported. We retrospectively analyzed 40 patients with relapsed or refractory MM who have received bortezomib at three collaborating centers in Miyagi prefecture in Japan. All the patients have been received bortezomib in combination with dexamethasone. Responses were determined using International Myeloma Working Group uniform response criteria. The overall response was observed in 30 patients (75%), including very good partial response in 8 patients (20%), and partial response in 22 patients (55%). The median time to disease progression was 8.7 months, and the median overall survival has not been reached. The factors affecting time to disease progression were International Staging System stage, serum beta2-microglobulin level, and number of treatment cycles. The most common grade 3 and 4 adverse events were thrombocytopenia (50%), peripheral neuropathy (25%), leukopenia (25%), and herpes zoster infection (25%). Thus, bortezomib is well tolerated and effective for Japanese patients with relapsed or refractory MM. Our results suggest that serum beta2-microglobulin level may be a marker of prognosis on bortezomib therapy for patients with relapsed or refractory MM although further studies are needed.

Does Bortezomib Induce De Facto Varicella Zoster Virus Reactivation in Patients With Multiple Myeloma?

Dasanu CA, Alexandrescu DT.

J Clin Oncol. 2009 Mar 23. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19307496?ordinalpos=11&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Novel agents on the horizon for cancer therapy.

Ma WW, Adjei AA.

CA Cancer J Clin. 2009 Mar-Apr;59(2):111-37.

http://www.ncbi.nlm.nih.gov/pubmed/19278961?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This article discusses the success of a target-based cancer drug development approach, such as the use of bortezomib, and highlights the pipeline of rationally designed drugs in clinical development that have the potential to impact clinical care in the near future.

Although cancer remains a devastating diagnosis, several decades of preclinical progress in cancer biology and biotechnology have recently led to successful development of several biological agents that substantially improve survival and quality of life for some patients. There is now a rich pipeline of novel anticancer agents in early phase clinical trials. The specific tumor and stromal aberrancies targeted can be conceptualized as membrane-bound receptor kinases (HGF/c-Met, human epidermal growth factor receptor and insulin growth factor receptor pathways), intracellular signaling kinases (Src, PI3k/Akt/mTOR, and mitogen-activated protein kinase pathways), epigenetic abnormalities (DNA methyltransferase and histyone deacetylase), protein dynamics (heat shock protein 90, ubiquitin-proteasome system), and tumor vasculature and microenvironment (angiogenesis, HIF, endothelium, integrins). Several technologies are available to target these abnormalities. Of these, monoclonal antibodies and small-molecule inhibitors have been the more successful, and often complementary, approaches so far in clinical settings. The success of this target-based cancer drug development approach is discussed with examples of recently approved agents, such as bevacizumab, erlotinib, trastuzumab, sorafenib, and bortezomib. This review also highlights the pipeline of rationally designed drugs in clinical development that have the potential to impact clinical care in the near future.

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