CITINGS

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Novel Therapies Issue

The International Myeloma Foundation *(IMF) presents this edition of Citings, our premiere publication featuring the most up-to-date information on myeloma treatment, focused on the novel therapies currently under study and in use. This edition corresponds with articles published in September 2011.*

As part of our ongoing efforts to make information about myeloma more accessible, we have implemented a new format for CITINGS, providing these citations on a monthly basis and organizing them by topic. We welcome your comments.

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

– Susie Novis, President, IMF

NOVEL THERAPIES PUBLICATIONS – SEPTEMBER 2011

Genetics

Pharmacogenomics of bortezomib test-dosing identifies hyperexpression of proteasome genes, especially PSMD4, as novel high-risk feature in myeloma treated with Total Therapy 3.

Shaughnessy JD Jr, Qu P, Usmani S, Heuck CJ, Zhang Q, Zhou Y, Tian E, Hanamura I, van Rhee F, Anaissie E, Epstein J, Nair B, Stephens O, Williams R, Waheed S, Alsayed Y, Crowley J, Barlogie B.

Blood. 2011 Sep 29;118(13):3512-24. [Epub 2011 May 31.]

http://www.ncbi.nlm.nih.gov/pubmed/21628408

The authors add bortezomib in Total Therapy 3 (TT3). After 48 hours after bortezomib, gene expression profiling analysis identified 80 highly survival-discriminatory genes in a training set of 142 TT3A patients, validated in 128 patients receiving TT3B.

Gene expression profiling (GEP) of purified plasma cells 48 hours after thalidomide and dexamethasone test doses showed these agents' mechanisms of action and provided prognostic information for untreated myeloma patients on Total Therapy 2 (TT2). Bortezomib was added in Total Therapy 3 (TT3), and 48 hours after bortezomib GEP analysis identified 80 highly survival-discriminatory genes in a training set of 142 TT3A patients that were validated in 128 patients receiving TT3B. The 80-gene GEP model (GEP80) also distinguished outcomes when applied at baseline in both TT3 and TT2 protocols. In context of our validated 70-gene model (GEP70), the GEP80 model identified 9% of patients with a grave prognosis among those with GEP70-defined low-risk disease and 41% of patients with favorable prognosis among those with GEP70-defined high-risk disease. PMSD4 was 1 of 3 genes common to both models. Residing on chromosome 1q21, PSMD4 expression is highly sensitive to copy number. Both higher PSMD4 expression levels and higher 1q21 copy numbers affected clinical outcome adversely. GEP80 baseline-defined high risk, high lactate dehydrogenase, and low albumin were the only independent adverse variables surviving multivariate survival model. We are investigating whether second-generation proteasome inhibitors (eg, carfilzomib) can overcome resistance associated with high PSMD4 levels.

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

Genomic stratification of multiple myeloma treated with novel agents.

Jiang A, Reece D, Chang H.

Leuk Lymphoma. 2011 Sep 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21823830

The authors review recent studies that analyze the impact of specific genomic aberrations on the outcome of myeloma treated with bortezomib and/or lenalidomide.

Abstract Cytogenetic testing is now routinely performed for the prognostic work-up of multiple myeloma (MM). The abnormalities del(17p), t(4;14) and del(13q) have been established as predictors of poor outcome in patients with MM treated with conventional chemotherapy or stem cell transplant; chromosome 1q gains and 1p losses have also been identified as novel prognostic factors. In recent years, bortezomib and lenalidomide have emerged as effective treatments for both relapsed/refractory and newly diagnosed MM. However, the effect of cytogenetic abnormalities is unclear among patients with MM treated with these novel agents. Here we review recent studies that analyze the impact of specific genomic aberrations on the outcome of MM treated with bortezomib and/or lenalidomide.

Upregulated expression of the PSMB5 gene may contribute to drug resistance in patient with multiple myeloma when treated with bortezomib-based regimen.

Lü S, Yang J, Huang C, Hui C, Wang J.

Exp Hematol. 2011 Sep 12. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21920470

No abstract available.

Impact of high-risk classification by FISH: an Eastern Cooperative Oncology Group (ECOG) study E4A03.

Jacobus SJ, Kumar S, Uno H, Van Wier SA, Ahmann GJ, Henderson KJ, Callander NS, Williams ME, Siegel DS, Greipp PR, Rajkumar SV, Fonseca R.

Br J Haematol. 2011 Sep 9. doi: 10.1111/j.1365-2141.2011.08849.x. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21902684

In the context of the Phase III clinical trial E4A03 (lenalidomide plus dexamethasone in low or high doses), the authors query whether a fluorescence in situ hybridization (FISH)-based genetic classification into high risk and standard risk myeloma would remain clinically significant. The authors find that FISH-based risk classification retains prognostic significance in patients receiving lenalidomide-based induction.

Lenalidomide with dexamethasone is a standard induction treatment regimen for newly diagnosed myeloma (although a Federal Drug Administration indication is still absent). In the context of the Phase 3 clinical trial E4A03 (lenalidomide plus dexamethasone in low or high doses), we queried whether a fluorescence in situ hybridization (FISH)-based genetic classification into high risk (HR) and standard risk (SR) multiple myeloma (MM) would remain clinically significant. Of 445 E4A03 patients, 126 had FISH analysis; 21 were classified HR with t(4;14), t(14;16), or 17p13 deletions. Median survival follow-up approached 3 years. Patients with FISH data tended to be younger and healthier compared to the rest of the study population and, consequently, had superior overall survival (OS) results. Within the FISH cohort, shorter OS in the HR versus SR group (P = 0·004) corresponded to a hazard ratio of 3·48 [95% confidence interval: (1·42-8·53)], an effect also observed in multivariate analysis. Two-year OS rates were 91% for SR MM and 76% for HR MM. There was also evidence of interaction between risk status and treatment (P = 0·026). HR patients were less likely to attain good partial response (SR 46% and HR 30%, Odds Ratio = 2·0 [0·7-5·6]), but overall response rates were not different. FISH-based risk classification retained prognostic significance in patients receiving lenalidomide-based induction.

Impact on response and survival of DNA repair single nucleotide polymorphisms in relapsed or refractory multiple myeloma patients treated with thalidomide.

Cibeira MT, Fernández de Larrea C, Navarro A, Díaz T, Fuster D, Tovar N, Rosiñol L, Monzó M, Bladé J.

Leuk Res. 2011 Sep;35(9):1178-83. [Epub 2011 Mar 23.]

http://www.ncbi.nlm.nih.gov/pubmed/21435719

The authors examine SNPs in 12 genes of 28 patients with relapsed/refractory myeloma treated with single agent thalidomide, correlating the results with response, toxicity and overall survival.

Single nucleotide polymorphisms (SNPs) in 12 genes involving multidrug resistance, drug metabolic pathways, DNA repair systems and cytokines were examined in 28 patients with relapsed/refractory multiple myeloma (MM) treated with single agent thalidomide and the results were correlated with response, toxicity and overall survival (OS). The response rate was higher in

patients with SNPs in ERCC1 (rs735482) (p=0.006), ERCC5 (rs17655) (p=0.04) or XRCC5 (rs1051685) (p=0.013). Longer OS was associated with the SNP in ERCC1 (rs735482) (p=0.005) and XRCC5 (rs1051685) (p=0.02). Finally, polymorphism in GSTT1 (rs4630) was associated with a lower frequency of thalidomide-induced peripheral neuropathy (p=0.04).

New Combinations

Preclinical evaluation of a novel SIRT1 modulator SRT1720 in multiple myeloma cells.

Chauhan D, Bandi M, Singh AV, Ray A, Raje N, Richardson P, Anderson KC.

Br J Haematol. 2011 Sep 26. doi: 10.1111/j.1365-2141.2011.08888.x. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21950728

The authors examine the anti-myeloma activity of a novel oral agent, SRT1720, which targets SIRT1. They find that this agent enhances the cytotoxic activity of bortezomib and dexamethasone, with preclinical studies providing the rationale for novel therapeutics targeting SIRT1 in myeloma.

SIRT1 belongs to the silent information regulator 2 (Sir2) protein family of enzymes and functions as a NAD(+) -dependent class III histone deacetylase. Here, we examined the anti-multiple myeloma (MM) activity of a novel oral agent, SRT1720, which targets SIRT1. Treatment of MM cells with SRT1720 inhibited growth and induced apoptosis in MM cells resistant to conventional and bortezomib therapies without significantly affecting the viability of normal cells. Mechanistic studies showed that anti-MM activity of SRT1720 is associated with: (i) activation of caspase-8, caspase-9, caspase-3, poly(ADP) ribose polymerase; (ii) increase in reactive oxygen species; (iii) induction of phosphorylated ataxia telangiectasia mutated/checkpoint kinase 2 signaling; (iv) decrease in vascular endothelial growth factor-induced migration of MM cells and associated angiogenesis; and (v) inhibition of nuclear factor-κB. Blockade of ATM attenuated SRT1720-induced MM cell death. In animal tumour model studies, SRT1720 inhibited MM tumour growth. Finally, SRT1720 enhanced the cytotoxic activity of bortezomib or dexamethasone. Our preclinical studies provide the rationale for novel therapeutics targeting SIRT1 in MM.

Bortezomib induced BRCAness sensitizes multiple myeloma cells to PARP inhibitors.

Neri P, Ren L, Gratton K, Stebner E, Johnson J, Klimowicz A, Duggan P, Tassone P, Mansoor A, Stewart DA, Lonial S, Boise LH, Bahlis NJ.

Blood. 2011 Sep 13. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21917757

The authors show that proteasome inhibition induces a BRCAness state in myeloma cells with depletion of their nuclear pool of ubiquitin and abrogation of H2AX polyubiquitylation, an essential step for the recruitment of BRCA1 and RAD51 to the sites of DNA double-stranded breaks and initiation of homology-mediated (HR) DNA repair. The heightened cytotoxicity of ABT-888 in combination with bortezomib compared to either drug alone was also confirmed in myeloma xenografts in scid mice. These studies indicate that bortezomib impairs HR in myeloma and results in a contextual synthetic lethality when combined with poly-ADP-ribose-polymerase inhibitors.

Chromosomal instability is a defining feature of clonal myeloma plasma cells resulting in the perpetual accumulation of genomic aberrations. In addition to its role in protein homeostasis the ubiquitin-proteasome system is also involved in the regulation of DNA damage repair proteins. Here we show that proteasome inhibition induces a BRCAness state in myeloma cells (MM) with depletion of their nuclear pool of ubiquitin and abrogation of H2AX polyubiquitylation, an essential step for the recruitment of BRCA1 and RAD51 to the sites of DNA double-stranded breaks (DSBs) and initiation of homology-mediated (HR) DNA repair. Inhibition of poly-ADP-ribose-polymerase (PARP) 1-2 with ABT-888 induced transient DNA-DSBs that were rapidly resolved and hence had no effect on MM cells viability. In contrast, co-treatment of MM cell lines and primary CD138+ cells with bortezomib and ABT-888 resulted in the sustained accumulation of unrepaired DNA-DSBs with persistence of unubiquitylated γH2AX foci, lack of recruitment of BRCA1 and RAD51 and ensuing MM cell death. The heightened cytotoxicity of ABT-888 in combination with bortezomib compared to either drug alone was also confirmed in MM xenografts in scid mice. Our studies indicate that bortezomib impairs HR in MM and results in a contextual synthetic lethality when combined with PARP inhibitors.

Safety and efficacy of bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in untreated multiple myeloma patients with renal impairment.

Morabito F, Gentile M, Mazzone C, Rossi D, Di Raimondo F, Bringhen S, Ria R, Offidani M, Patriarca F, Nozzoli C, Petrucci MT, Benevolo G, Vincelli I, Guglielmelli T, Grasso M, Marasca R, Baldini L, Montefusco V, Musto P, Cascavilla N, Majolino I, Musolino C, Cavo M, Boccadoro M, Palumbo A.

Blood. 2011 Sep 27. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21951682

The authors assess the efficacy, safety and renal impairment (RI) reversal in untreated myeloma patients treated with bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide (VMPT-VT) maintenance versus bortezomib-melphalan-prednisone (VMP). They find that VMPT-VT is superior to VMP for cases with normal renal function and moderate RI, while VMPT-VT failed to outperform VMP in patients with severe RI (although the relatively low number of cases due to protocol inclusion criteria preclude drawing definitive conclusions). The VMPT-VT had no advantage in terms of RI reversal over VMP.

We assessed efficacy, safety and renal impairment (RI) reversal in untreated multiple myeloma patients treated with bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide (VMPT-VT) maintenance versus bortezomib-melphalan-prednisone (VMP). Exclusion criteria included serum creatinine ≥2.5mg/dL. In the VMPT-VT/VMP arms, severe RI [estimated glomerular filtration rate (eGFR)≤30mL/min], moderate (eGFR=31-50mL/min) and normal renal function (eGFR>50mL/min), were respectively 6%/7.9%, 24.1%/24.9% and 69.8%/67.2%. Statistically significant improvements in overall response rates (ORRs) and progression-free survival (PFS) were observed in VMPT-VT versus VMP arms across renal cohorts, except in severe RI patients. In the VMPT group, severe RI reduced OS. RI was reversed in 16/63 (25.4%) patients receiving VMPT-VT versus 31/77 (40.3%) receiving VMP. Multivariate analysis showed male sex (P=.022) and moderate RI (P=.003) significantly predicted RI recovery. VMP patients achieving renal response showed longer OS. In both arms, higher rates of severe hematologic adverse events (AEs) were associated with RI (eGFR<50mL/min), however therapy discontinuation rates were unaffected. VMPT-VT was superior to VMP for cases with normal renal function and moderate RI, while VMPT-VT failed to outperform VMP in patients with severe RI, although the relatively low number of cases due to protocol inclusion criteria preclude drawing definitive conclusions. The VMPT-VT had no advantage in terms of RI reversal over VMP. This study was registered at www.clinicaltrials.gov as #NCT01063179.

A modified regimen of pegylated liposomal doxorubicin, bortezomib and dexamethasone (DVD) is effective and well tolerated for previously untreated multiple myeloma patients.

Berenson JR, Yellin O, Chen CS, Patel R, Bessudo A, Boccia RV, Yang HH, Vescio R, Yung E, Mapes R, Eades B, Hilger JD, Wirtschafter E, Hilger J, Nassir Y, Swift RA.

Br J Haematol. 2011 Sep 26. doi: 10.1111/j.1365-2141.2011.08884.x. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21950583

The authors evaluate the combination of pegylated liposomal doxorubicin (PLD), bortezomib and dexamethasone in the frontline setting in a prospective multi-center phase II trial. They find that this combination shows improved tolerability and safety while maintaining a high response rate when compared to standard treatment with these agents in the frontline setting.

The combination of pegylated liposomal doxorubicin (PLD), bortezomib and dexamethasone has shown efficacy in the treatment of multiple myeloma (MM) patients. Our earlier retrospective study suggested that modification of the doses, schedules and route of administration of these drugs appears to reduce toxicity without compromising anti-MM activity. As a result, we evaluated this modified drug combination in the frontline setting in a prospective multicentre phase II trial. Thirty-five previously untreated MM patients were enrolled. Dexamethasone IV 40 mg, bortezomib 1mg/m^2 and PLD 5mg/m^2 were administered on days 1, 4, 8 and 11 of a 4-week cycle. Patients were treated to their maximum response plus two additional cycles. The treatment regimen was discontinued after a maximum of eight cycles. Our modified schedule and dosing regimen achieved a high overall response rate of 86%, while showing a marked decrease in the incidence and severity of peripheral neuropathy, palmar-plantar erythrodysesthesia and myelosuppression compared to the standard dosing on a 3-week cycle using these drugs. This modified regimen of dexamethasone, bortezomib and PLD shows improved tolerability and safety while maintaining a high response rate when compared to standard treatment with these agents in the frontline setting.

Bortezomib for previously untreated multiple myeloma.

Delforge M.

Expert Opin Pharmacother. 2011 Sep 23. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21942881

The author discusses the most recent data on the frontline use of bortezomib and bortezomib-based combinations in myeloma.

Introduction: The paradigm of antimyeloma treatment has rapidly changed since the introduction of the first-in-class proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide. Areas covered: This manuscript discusses the most recent data on the frontline use of bortezomib and bortezomib-based combinations in multiple myeloma. Preclinical data, pharmacokinetics and pharmacodynamics of bortezomib are summarized, as well as published clinical trials of its use as a first-line treatment for transplant-eligible and elderly myeloma patients. Additionally, the use of bortezomib in particular myeloma subgroups, including patients with high-risk cytogenetics and renal insufficiency, is discussed. Finally, the prevention and management of bortezomib-induced side effects, including the latest data on weekly dosing for untreated elderly patients, is focused on. Expert opinion: Bortezomib has become an important backbone of frontline myeloma treatment. Nevertheless, continued efforts to implement newer dosing regimens and to identify new partner drugs for bortezomib remain an important challenge.

Bortezomib, liposomal doxorubicin and dexamethasone followed by thalidomide and dexamethasone is an effective treatment for patients with newly diagnosed multiple myeloma with Internatinal Staging System stage II or III, or extramedullary disease.

Landau H, Pandit-Taskar N, Hassoun H, Cohen A, Lesokhin A, Lendvai N, Drullinsky P, Schulman P, Jhanwar S, Hoover E, Bello C, Riedel E, Nimer SD, Comenzo RL.

Leuk Lymphoma. 2011 Sep 23. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21824051

The authors evaluate sequential bortezomib, liposomal doxorubicin and dexamethasone (BDD) followed by thalidomide and dexamethasone (TD) or bortezomib and TD in untreated patients with myeloma with International Staging System stage II/III or extramedullary disease. They find that BDD followed by TD or BTD is effective initial therapy for this higher-risk myeloma population, and results in rapid disease control and a high response rate.

Abstract We evaluated sequential bortezomib, liposomal doxorubicin and dexamethasone (BDD) followed by thalidomide and dexamethasone (TD) if ≥ partial response (PR) or bortezomib and TD (BTD) if < PR in untreated patients with multiple myeloma with International Staging System stage II/III or extramedullary disease. Of the 42 patients enrolled, two-thirds had cytogenetic abnormalities including high-risk findings [del(13q) by karyotype, t(4;14), loss of p53 or gain 1q] in one-third. After the planned three cycles of BDD, the overall response rate (ORR) was 81% with 40% ≥ very good partial response (VGPR), including 26% near complete and complete responses (nCR/CR). After the additional two cycles of TD or BTD, ORR was 83% with 60% ≥ VGPR including 43% nCR/CR, indicating deeper responses following sequential therapy (p = 0.008). Two-thirds of patients who presented with significant renal impairment had improved renal function. All patients undergoing stem cell harvest had a successful collection. BDD followed by TD or BTD is effective initial therapy for this population with higher-risk myeloma and results in rapid disease control and a high response rate.

Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation.

Zamagni E, Patriarca F, Nanni C, Zannetti B, Englaro E, Pezzi A, Tacchetti P, Buttignol S, Perrone G, Brioli A, Pantani L, Terragna C, Carobolante F, Baccarani M, Fanin R, Fanti S, Cavo M.

Blood. 2011 Sep 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21900189

The authors prospectively analyze the prognostic relevance of PET/CT at diagnosis, after thalidomide-dexamethasone induction therapy and double autotransplantation (ASCT) in 192 newly diagnosed myeloma patients. They find that PET/CT involvement at diagnosis, after novel agent-based induction and subsequent ASCT, is a reliable predictor of prognosis in myeloma patients.

We prospectively analyzed the prognostic relevance of PET/CT at diagnosis, after thalidomide-dexamethasone (TD) induction therapy and double autotransplantation (ASCT) in 192 newly diagnosed multiple myeloma (MM) patients. Presence at baseline of at least 3 focal lesions (FLs, 44% of cases), a SUV > 4.2 (46%) and extramedullary disease (EMD, 6%) adversely affected 4-year estimates of PFS (≥ 3 FLs: 50%; SUV > 4.2: 43%; presence of EMD: 28%). SUV > 4.2 and EMD were also correlated with shorter OS (4-year rates: 77% and 66%, respectively). Persistence of SUV > 4.2 after TD induction was an early predictor

for shorter PFS. Three months after ASCT, PET/CT was negative in 65% of patients, whose 4-year rates of PFS and OS were superior to those of PET-positive patients (PFS: 66% and OS: 89%). In a multivariate analysis, both EMD and SUV > 4.2 at baseline and persistence of FDG uptake after ASCT were independent variables adversely affecting PFS (EMD, HR: 9.35; SUV > 4.2, HR: 2.13; FDG uptake after ASCT, HR: 1.93) and OS (EMD, HR: 6.99; post ASCT FDG uptake, HR: 3.57). PET/CT involvement at diagnosis, after novel agent-based induction and subsequent ASCT is a reliable predictor of prognosis in MM patients. This study is registered at www.clinicaltrials.gov as NTC01341262.

An overview of the VISTA trial: newly diagnosed, untreated patients with multiple myeloma ineligible for stem cell transplantation.

Spicka I, Mateos M, Redman K, Dimopoulos M, Richardson P.

Immunotherapy. 2011 Sep;3(9):1033-40.

http://www.ncbi.nlm.nih.gov/pubmed/21913826

The VISTA study evaluates the effect of melphalan and prednisone (MP) with or without the bortezomib in newly diagnosed myeloma patients who are not candidates for autologous stem cell transplantation. The authors' results confirm the superiority of MP plus bortezomib combination over MP therapy in treatment-naive patients of this population.

Multiple myeloma, a plasma cell neoplasm, is the second most common hematologic malignancy after non-Hodgkins lymphoma and is responsible for 2% of cancer deaths. Melphalan and prednisone (MP) has been the standard treatment in elderly patients for many decades. The VISTA study evaluated the effect of this combination with or without the first-in-class proteasome inhibitor bortezomib in newly diagnosed myeloma patients who were not candidates for autologous stem cell transplantation. Altogether 682 patients were enrolled and prospectively randomized in this trial. All patients received nine 6-week cycles of oral melphalan (9 mg/m^2) and prednisone (60 mg/m^2) on days 1-4, either alone or with bortezomib administered intravenously (1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29 and 32 during the first four cycles and on days 1, 8, 22, 29 during remaining course of therapy). Median time to progression (the primary end point of the trial) was 24 months in the bortezomib-containing group compared with 16.6 months in the control group ($p < 0.001$). Response was evaluated in 337 patients receiving bortezomib compared with 331 patients in the control group who received MP alone; the percentages of partial response or better was 71 vs 35% ($p < 0.001$), with complete response seen in 30 vs 4%, respectively ($p < 0.001$). Median response duration in both groups was 19.9 versus 13.1 months, respectively. Median overall survival has not been reached in VMP group compared with 43 months in the MP group ($p < 0.001$), and this benefit is maintained after long term follow-up and subsequent antimyeloma therapies. Hematological adverse events (AEs) were similar in both groups, although patients in the bortezomib group experienced more frequent peripheral sensory neuropathy (including 13% grade 3, with less than 1% grade 4). Overall, the occurrence of grade 3 AEs was higher in patients receiving bortezomib (53 vs 44%, $p = 0.02$), but the risk of grade 4 AEs was identical (28 vs 27%). These results confirm the superiority of MP plus bortezomib combination over MP therapy in treatment-naive patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation.

Bendamustine, thalidomide and dexamethasone is an effective salvage regimen for advanced stage multiple myeloma – response to Grey-Davies et al.

Ramasamy K, Schey S.

Br J Haematol. 2011 Sep 27. doi: 10.1111/j.1365-2141.2011.08886.x. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21950635

No abstract available.

Bendamustine, Thalidomide and Dexamethasone is an effective salvage regimen for advanced stage multiple myeloma.

Grey-Davies E, Bosworth JL, Boyd KD, Ebdon C, Saso R, Chitnavis D, Mercieca JE, Morgan GJ, Davies FE.

Br J Haematol. 2011 Sep 26. doi: 10.1111/j.1365-2141.2011.08887.x. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21950692

No abstract available.

A high rate of durable responses with romidepsin, bortezomib, and dexamethasone in relapsed or refractory multiple myeloma.

Harrison SJ, Quach H, Link E, Seymour JF, Ritchie DS, Ruell S, Dean J, Januszewicz H, Johnstone R, Neeson P, Dickinson M, Nichols J, Prince HM.

Blood. 2011 Sep 12. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21911830

The authors report results from a study exploring the combination of romidepsin, bortezomib, and dexamethasone for the treatment of patients with myeloma previously treated with more than one prior therapy. They find that this regimen shows activity with manageable toxicity, warranting further evaluation.

We report results from a study exploring the combination of romidepsin, bortezomib, and dexamethasone for the treatment of patients with multiple myeloma (MM) previously treated with >1 prior therapy. The primary objective was to determine the maximum tolerated dose (MTD) of the combination using a novel accelerated dose-escalation schedule in patients with relapsed or refractory MM. The secondary objective was to determine overall response (OR), time to progression (TTP) and overall survival (OS). The MTD identified was bortezomib 1.3mg/m^2 (D1,4,8 and 11), dexamethasone 20mg (D1,2,4,5,8,9,11 and 12) and romidepsin 10mg/m^2 (day 1,8 and 15) every 28 days. Thrombocytopenia (64%) was the most common grade ≥3 hematological toxicity. Peripheral neuropathy occurred in 76% (n = 19) (grade ≥ 3, 8% [95% confidence interval (CI) [1% - 26%]). Maintenance romidepsin 10mg/m^2 (D1 and 8 of a 28-day cycle) proved feasible, with 12 patients receiving a median of 7.5 (range: 1- 29) cycles. An OR (M-protein) of >MR was seen in 18/25 patients (72%); 2 (8%) CR, 13 (52%) PR including 7 (28%) VGPR. Median TTP was 7.2 (95% CI 5.5 - 19.6) months and median OS was over 36 months. This regimen shows activity with manageable toxicity and warrants further evaluation. This trial was registered at www.clinicaltrials.gov (NCT00431990).

Long-term results of thalidomide and dexamethasone (thal-dex) as therapy of first relapse in multiple myeloma.

Zamagni E, Petrucci A, Tosi P, Tacchetti P, Perrone G, Brioli A, Pantani L, Zannetti B, Terragna C, Baccarani M, Cavo M.

Ann Hematol. 2011 Sep 8. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21901342

The authors evaluate thalidomide-dexamethasone as salvage treatment of myeloma patients at first relapse. They find that this combination is an effective salvage treatment at first relapse, as demonstrated by durable disease control and prolonged overall survival. Thalidomide-dexamethasone is also well tolerated, as reflected by the long stay on treatment without disease progression (median 25 months) and a low discontinuation rate due to toxicity (8%).

Thal-dex (TD) is an effective therapy for advanced MM. We evaluated TD as salvage treatment of MM patients at first relapse. Thal was given at a daily dose of 100 or 200 mg until progression. Dex was administered 160 mg/month. One hundred patients were enrolled. First line therapy included ASCT (72%) and conventional CHT (28%). Fifty-nine percent received a fixed thal dose of 100 mg/day. The most frequent adverse events were constipation (42%), peripheral neuropathy (58%, 5% grade 3), bradycardia (20%), skin rash (11%), and VTE (7%). Discontinuation of thal due to adverse events was recorded in eight patients.

On ITT, 46% of patients achieved at least a PR. Median DOR was 28 months, median time to next therapy was 15.5 months. Median OS, TTP, and PFS were 43, 22, and 21 months, respectively. TTP and PFS were significantly longer for patients with at least PR to TD. TD was an effective salvage treatment for MM patients at first relapse, as demonstrated by durable disease control and prolonged OS. TD was well tolerated, as reflected by the long stay on treatment without disease progression (median 25 months) and a low discontinuation rate due to toxicity (8%).

Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib.

Möller J, Nicklasson L, Murthy A.

J Med Econ. 2011 Sep 5. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21892856

The authors seek to estimate the cost-effectiveness (cost per additional life-year [LY] and quality-adjusted life-year [QALY] gained) of lenalidomide plus dexamethasone compared with bortezomib for the treatment of relapsed-refractory myeloma in Norway. Their simulation model shows that treatment with lenalidomide/ dexamethasone leads to greater LYs and QALYs when compared to bortezomib in the treatment of this patient group; the incremental cost-effectiveness ratio indicates treatment with lenalidomide to be cost-effective and is the basis of the reimbursement approval of this treatment combination in Norway.

Abstract Objective: To estimate the cost-effectiveness (cost per additional life-year [LY] and quality-adjusted life-year [QALY] gained) of lenalidomide plus dexamethasone (LEN/DEX) compared with bortezomib for the treatment of relapsed-refractory multiple myeloma (rrMM) in Norway. Methods: A discrete-event simulation model was developed to predict patients' disease course using patient data, best response, and efficacy levels obtained from LEN/DEX MM-009/-010 trials and the bortezomib (APEX) published clinical trial. Predictive equations for time-to-progression (TTP) and post-progression survival (PPS) were developed by identifying the best fitting parametric survival distributions and selecting the most significant predictors. Disease and adverse event management was obtained via survey from Norwegian experts. Costs, derived from official Norwegian pricing data bases, included drug, administration, monitoring, and adverse event management costs. Results: Complete or partial responders were 65% for LEN/DEX compared to 43% for bortezomib. Derived median TTP was 11.45 months for LEN/DEX compared to 5.15 months for bortezomib. LYs and QALYs were higher for LEN/DEX (4.06 and 2.95, respectively) than for bortezomib (3.11 and 2.19, respectively). The incremental costs per QALY and LY gained from LEN/DEX were NOK 247,978 and NOK 198,714, respectively, compared to bortezomib. Multiple sensitivity analyses indicated the findings were stable. The parameters with the greatest impact were 4-year time horizon (NOK 441,457/QALY) and higher bound confidence intervals for PPS (NOK 118,392). Limitations: The model analyzed two therapies not compared in head-to-head trials, and predicted results using an equation incorporating patient-level characteristics. It is a limited estimation of the costs and outcomes in a Norwegian setting. Conclusions: The simulation model showed that treatment with LEN/DEX leads to greater LYs and QALYs when compared to bortezomib in the treatment of rrMM patients. The incremental cost-effectiveness ratio indicated treatment with LEN/DEX to be cost-effective and was the basis of the reimbursement approval of LEN/DEX in Norway.

Phase I Trial of Lenalidomide and CCI-779 in Patients With Relapsed Multiple Myeloma: Evidence for Lenalidomide-CCI-779 Interaction via P-Glycoprotein.

Hofmeister CC, Yang X, Pichiorri F, Chen P, Rozewski DM, Johnson AJ, Lee S, Liu Z, Garr CL, Hade EM, Ji J, Schaaf LJ, Benson DM Jr, Kraut EH, Hicks WJ, Chan KK, Chen CS, Farag SS, Grever MR, Byrd JC, Phelps MA.

J Clin Oncol. 2011 Sep 1;29(25):3427-34. [Epub 2011 Aug 8.]

http://www.ncbi.nlm.nih.gov/pubmed/21825263

In this phase I trial, patients with relapsed myeloma are administered oral lenalidomide on days 1 to 21 and CCI-779 intravenously once per week during a 28-day cycle. The authors pinpoint a maximum tolerated dose for this regimen, as well as identifying toxicities of fatigue, neutropenia, and electrolyte wasting. Pharmacokinetic and clinical interactions between lenalidomide and CCI-779 seem to occur, with in vitro data indicating lenalidomide is an ABCB1 (P-gp) substrate; to the authors' knowledge, this is the first report of a clinically significant P-gp-based drug-drug interaction with lenalidomide.

PURPOSE Multiple myeloma (MM) is an incurable plasma-cell neoplasm for which most treatments involve a therapeutic agent combined with dexamethasone. The preclinical combination of lenalidomide with the mTOR inhibitor CCI-779 has displayed synergy in vitro and represents a novel combination in MM. PATIENTS AND METHODS A phase I clinical trial was initiated for patients with relapsed myeloma with administration of oral lenalidomide on days 1 to 21 and CCI-779 intravenously once per week during a 28-day cycle. Pharmacokinetic data for both agents were obtained, and in vitro transport and uptake studies were conducted to evaluate potential drug-drug interactions. Results Twenty-one patients were treated with 15 to 25 mg lenalidomide and 15 to 20 mg CCI-779. The maximum-tolerated dose (MTD) was determined to be 25 mg lenalidomide

with 15 mg CCI-779. Pharmacokinetic analysis indicated increased doses of CCI-779 resulted in statistically significant changes in clearance, maximum concentrations, and areas under the concentration-time curves, with constant doses of lenalidomide. Similar and significant changes for CCI-779 pharmacokinetics were also observed with increased lenalidomide doses. Detailed mechanistic interrogation of this pharmacokinetic interaction demonstrated that lenalidomide was an ABCB1 (P-glycoprotein [P-gp]) substrate. CONCLUSION The MTD of this combination regimen was 25 mg lenalidomide with 15 mg CCI-779, with toxicities of fatigue, neutropenia, and electrolyte wasting. Pharmacokinetic and clinical interactions between lenalidomide and CCI-779 seemed to occur, with in vitro data indicating lenalidomide was an ABCB1 (P-gp) substrate. To our knowledge, this is the first report of a clinically significant P-gp-based drug-drug interaction with lenalidomide.

Lenalidomide is effective for extramedullary disease in relapsed or refractory multiple myeloma.

Calvo-Villas JM, Alegre A, Calle C, Hernández MT, García-Sánchez R, Ramírez G; GEM-PETHEMA/Spanish Myeloma Group, Spain.

Eur J Haematol. 2011 Sep;87(3):281-4. doi: 10.1111/j.1600-0609.2011.01644.x. [Epub 2011 Jul 26.]

http://www.ncbi.nlm.nih.gov/pubmed/21557775

No abstract available.

Supportive Care

Activation of coagulation by a thalidomide-based regimen.

Hoshi A, Matsumoto A, Chung J, Isozumi Y, Koyama T.

Blood Coagul Fibrinolysis. 2011 Sep;22(6):532-40.

http://www.ncbi.nlm.nih.gov/pubmed/21670663

The authors investigated the procoagulant effects of thalidomide when combined with chemotherapeutic agents in vitro, focusing on tissue factor (TF) and phosphatidylserine. They find that when thalidomide is given in combination with chemotherapies or dexamethasone, endothelial cell and monocyte procoagulant activity may be induced through phosphatidylserine exposure or TF expression; induction may be protracted by thalidomide, which has an antiangiogenic activity. Therefore, prophylactic anticoagulant strategies should be considered in thalidomide-based combination regimens.

Combining thalidomide (Thal) with chemotherapeutic agents or steroid preparations led to improved response rates in the treatment of multiple myeloma. However, deep vein thrombosis (DVT) is one of the most serious side-effects noted with this regimen, and how a Thal-based regimen causes DVT is unclear. We investigated the procoagulant effects of Thal when combined with chemotherapeutic agents in vitro, focusing on tissue factor (TF) and phosphatidylserine. We examined the effects of the chemotherapeutic doxorubicin hydrochloride (Dox) and the steroid dexamethasone (Dex), with or without Thal. Our study used the human vascular endothelial, monocytic, and myeloma cell lines, EAhy926, THP-1, and RPMI8226, respectively. In EAhy926 and THP-1, Dex treatment increased expression of TF, which may induce procoagulant activity (PCA). Upregulation of TF mRNA correlated with activation of the Egr-1 pathway. In Thal and Dex treatments, the increase of PCA induction from phosphatidylserine exposure was modest. In contrast, Dox and Thal-Dox increased phosphatidylserine exposure in both cell types. In THP-1 cells, cell surface phosphatidylserine exposure correlated with increased PCA by Dox. Thal alone showed a modest increase in phosphatidylserine exposure in endothelial cells and monocytes. When Thal is given in combination with chemotherapies or Dex, endothelial cell and monocyte PCA may be induced through phosphatidylserine exposure, or TF expression. Induction may be protracted by Thal, which has an antiangiogenic activity. Therefore, prophylactic anticoagulant strategies should be considered in Thal-based combination regimens.

Successful bone reconstruction after bortezomib therapy in a myeloma patient.

Tanaka T, Yamasaki R, Omura H, Hino N.

Int J Hematol. 2011 Sep;94(3):221. [Epub 2011 Aug 23.]

http://www.ncbi.nlm.nih.gov/pubmed/21861100

No abstract available.

Toxicities & Adverse Effects

Chemotherapy-induced peripheral neurotoxicity (CIPN): An update.

Argyriou AA, Bruna J, Marmiroli P, Cavaletti G.

Crit Rev Oncol Hematol. 2011 Sep 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21908200

The authors review the features of chemotherapy-induced peripheral neurotoxicity (such as from thalidomide and bortezomib), with a focus on new classes of promising antineoplastic agents, such as epothilones and proteasome inhibitors.

The peripheral nervous system can be vulnerable to the toxic action of several drugs since it is not protected as effectively as the central nervous system from noxious exogenous agents. Drug-induced neurotoxicity can affect the nerve fibers or the neuronal bodies (generally the dorsal root ganglia of the primary sensory neurons). Among the neurotoxic drugs antineoplastic agents represent a major clinical problem, given their widespread use and the potential severity of their toxicity. In fact, the peripheral neurotoxicity of antineoplastic agents frequently represents one of their dose-limiting side effects. Moreover, even when antineoplastic agents' peripheral neurotoxicity is not dose-limiting, its onset may severely affect the quality of life of cancer patients and cause chronic discomfort. Among the anticancer chemotherapy drugs, platinum derivates, antitubulins, thalidomide and bortezomib can induce the most severe effects on the peripheral nervous system of the treated patients. Therefore, we will review the features of chemotherapy-induced peripheral neurotoxicity (CIPN) resulting from the administration of these drugs with a focus on new classes of promising antineoplastic agents, such as epothilones and proteasome inhibitors.

Thrombotic complications in multiple myeloma: a report of three cases and review of the literature.

Ipek Y, Fehmi H, Sevgi BK, Deniz S.

J Thromb Thrombolysis. 2011 Sep 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21904842

The authors report three cases of myeloma with venous thromboembolism (VTE) with a review of the literature that highlights the risk factors for VTE in myeloma as well as general, disease-specific, and treatment-related mechanisms for thrombosis.

The risk of venous thromboembolism (VTE) increases in the presence of plasma cell dyscrasias. Monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) share an intrinsic increased risk of VTE. Treatment with thalidomide and lenalidomide further increases the incidence of VTE in certain MM patient subsets. The pathogenesis remains unclear, but probably involves several factors such as activation of procoagulant factors, acquired activated protein C resistance, and inflammation. In addition to general risk factors for VTE, such as older age, immobility, surgery, and inherited thrombophilia, there are some MM-specific and treatment-related factors that contribute to the increased risk. The risk for VTE is high under treatment with thalidomide or lenalidomide in combination with dexamethasone or multi-agent chemotherapy. We report 3 cases of MM with VTE with review of the literature. This review highlights the risk factors for VTE in MM and general, disease-specific and treatment-related mechanisms for thrombosis.

Follow-up psychophysical studies in bortezomib-related chemoneuropathy patients.

Boyette-Davis JA, Cata JP, Zhang H, Driver LC, Wendelschafer-Crabb G, Kennedy WR, Dougherty PM.

J Pain. 2011 Sep;12(9):1017-24. [Epub 2011 Jun 24.]

http://www.ncbi.nlm.nih.gov/pubmed/21703938

This is the first article to address the persistence, and potential contributing factors, of bortezomib chemoneuropathy, and its results indicate a persistent, painful peripheral neuropathy in patients treated with bortezomib.

Many frontline chemotherapeutic agents produce robust neuropathy as a dose-limiting side effect; however, the persistence of chemotherapy-related sensory disturbances and pain are not well documented. We have previously investigated the qualities of bortezomib-induced pain, and now seek to determine the ongoing nature of this pain. Twenty-six control subjects and 11 patients who had previously been treated with bortezomib and who were experiencing ongoing pain consented to recurring quantitative sensory testing. A pilot immunohistochemistry study of skin innervation was also performed on patient-obtained biopsies. Psychophysical testing in patients revealed persistent changes including decreased skin temperature in the area of pain, diminished touch and sharpness detection, increased pegboard completion times, and decreased sensitivity to skin heating. Additionally, the intensity of pain, as captured by the use of a visual analog scale and pain descriptors, was reported by patients to be unchanged during the retest despite similar morphine equivalent daily doses. The patient skin biopsies displayed a marked decrease in the density of epidermal nerve fibers and Meissner's corpuscles. These results signify a persistent and severe impairment of Aβ, Aδ, and C fibers in patients with chronic bortezomib-induced chemoneuropathy. Further, this study reports

a loss of both epidermal nerve fibers and Meissner's corpuscles. PERSPECTIVE: The results of this article indicate a persistent, painful peripheral neuropathy in patients treated with bortezomib. Pilot data indicates a loss of nerve fibers innervating the area of pain. This is the first paper to address the persistence, and potential contributing factors, of bortezomib chemoneuropathy.

Transplantation & Induction Therapy

Induction treatment of light chain deposition disease with bortezomib - rapid hematological response with persistence of renal involvement.

Minarik J, Scudla V, Tichy T, Pika T, Bacovsky J, Lochman P, Zadrazil J.

Leuk Lymphoma. 2011 Sep 2. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21883030

No abstract available.

Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial.

Kneppers E, van der Holt B, Kersten MJ, Zweegman S, Meijer E, Huls G, Cornelissen JJ, Janssen JJ, Huisman C, Cornelisse PB, Bruijnen CP, Emmelot M, Sonneveld P, Lokhorst HM, Mutis T, Minnema MC.

Blood. 2011 Sep 1;118(9):2413-9. [Epub 2011 Jun 20.]

http://www.ncbi.nlm.nih.gov/pubmed/21690556

In order to improve the outcome of allogeneic stem cell transplantation (allo-SCT) in myeloma as part of first-line treatment, the authors prospectively investigate the feasibility and efficacy of lenalidomide maintenance. They find that for myeloma patients, lenalidomide maintenance 10 mg daily after nonmyeloablative allo-SCT with unmanipulated graft is not feasible, mainly because of the induction of acute graft versus host disease.

To improve the outcome of allogeneic stem cell transplantation (allo-SCT) in multiple myeloma as part of first-line treatment, we prospectively investigated the feasibility and efficacy of lenalidomide maintenance. Patients started maintenance 1 to 6 months after nonmyeloablative allo-SCT. Lenalidomide was dosed 10 mg on days 1 to 21 of a 28-day schedule for a total of 24 cycles. Peripheral blood samples were taken to evaluate immune modulating effects. Thirty-five eligible patients were enrolled, and 30 started with lenalidomide. After 2 cycles, 14 patients (47%) had to stop treatment, mainly because of the development of acute graft versus host disease (GVHD). In total, 13 patients (43%) stopped treatment because of development of GVHD, 5 patients (17%) because of other adverse events, and 5 patients (17%) because of progression. Responses improved in 37% of patients, and the estimated 1-year progression-free survival from start of maintenance was 69% (90% confidence interval, 53%-81%). Lenalidomide increased the frequency of human leukocyte antigen-DR(+) T cells and regulatory T cells, without correlation with clinical parameters. In conclusion, lenalidomide maintenance 10 mg daily after nonmyeloablative allo-SCT with unmanipulated graft in multiple myeloma patients is not feasible, mainly because of the induction of acute GVHD. This trial was registered at www.trialregister.nl as #NTR1645.

and More

Outcome according to cytogenetic abnormalities and DNA ploidy in myeloma patients receiving short induction with weekly bortezomib followed by maintenace.

Mateos MV, Gutiérrez NC, Martín-Ramos ML, Paiva B, Montalbán MA, Oriol A, Martínez-López J, Teruel AI, Bengoechea E, Martín A, Díaz-Mediavilla J, de Arriba F, Palomera L, Hernández JM, Sureda A, Bargay J, Peñalver FJ, Ribera JM, Martín-Mateos ML, Fernández M, García-Sanz R, Vidriales MB, Bladé J, Lahuerta JJ, San Miguel JF.

Blood. 2011 Sep 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21900193

The authors evaluate the influence of cytogenetic abnormalities (CAs) by FISH and DNA ploidy by flow cytometry on response and survival in 231 elderly newly diagnosed myeloma patients receiving an induction with weekly bortezomib, followed by maintenance therapy with bortezomib-based combinations. They find that this schema does not overcome the negative prognosis of high-risk CAs and non-hyperdiploidy.

Cytogenetic abnormalities (CAs), such as t(4;14), t(14;16) or del(17p) and non-hyperdiploidy, are associated with poor prognosis in Multiple Myeloma. We evaluate the influence of CAs by FISH and DNA ploidy by flow cytometry on response and survival in 231 elderly newly diagnosed myeloma patients receiving an induction with weekly bortezomib followed by maintenance therapy with bortezomib-based combinations. Response was similar in the high-risk and standard-risk CAs groups, both after induction

(21% vs. 27% CR) and maintenance (39% vs. 45% CR). However, high-risk patients showed shorter PFS than standard risk, both from first (24m vs. 33m, p=0.04) and second randomization (17m vs. 27m, p=0.01). This also translated into shorter OS for high-risk patients (3-y OS: 55% vs. 77%, p=0.001). This adverse prognosis applied to either t(4;14) or del(17p). Concerning DNA ploidy, hyperdiploid patients showed longer OS than non-hyperdiploid patients (77% vs. 63% at 3 y, p=0.04), and this was more evident in patients treated with bortezomib, thalidomide and prednisone (77% versus 53% at 3 y, p=0.02). The present schema doesn't overcome the negative prognosis of high-risk CAs and non-hyperdiploidy. The trial was registered with ClinicalTrials.gov, number NCT00443235.

Soft-Tissue Plasmacytomas in Multiple Myeloma: Incidence, Mechanisms of Extramedullary Spread, and Treatment Approach.

Bladé J, Fernández de Larrea C, Rosiñol L, Cibeira MT, Jiménez R, Powles R.

J Clin Oncol. 2011 Sep 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/21900099

The authors provide an overview on soft-tissue extramedullary plasmacytomas (EMPs) in myeloma, reviewing the incidence of EMPs in myeloma, myeloma bone marrow homing, possible mechanisms of extramedullary spread, and prognosis and response to therapy, including use of thalidomide and bortezomib.

We provide an overview on soft-tissue extramedullary plasmacytomas (EMPs) in multiple myeloma (MM). We reviewed the incidence of EMPs in MM, myeloma bone marrow homing, possible mechanisms of extramedullary spread, and prognosis and response to therapy. The incidence of EMPs is 7% to 18% at MM diagnosis and up to 20% at relapse. The current notion that EMPs are more frequent after treatment with novel agents remains to be proven, especially considering that different patterns of disease recurrence can emerge as patients live longer in the era of novel drugs. Bone marrow genetic abnormalities are not associated with extramedullary spread per se, which also suggests that microenvironmental interactions are key. Possible mechanisms of extramedullary spread include decreased adhesion molecule expression and downregulation of chemokine receptors. EMPs usually show plasmablastic morphology with negative CD56 expression. High-dose therapy with autologous stem-cell transplantation (ASCT) can overcome the negative prognostic impact of extramedullary disease in younger selected patients. EMPs do not typically respond to thalidomide alone, but in contrast, responses to bortezomib have been reported. The incidence of EMPs in patients with MM is high and is associated with poor outcome in patients treated conventionally. A potential first-line treatment option seems to be a bortezomib-containing regimen followed by ASCT, whenever possible. Experimental studies on the mechanisms of myeloma cell adhesion, myeloma growth at extramedullary sites, and drug sensitivity are priorities for this area of continuing therapeutic challenge.

Bone marrow stromal cells protect myeloma cells from bortezomib induced apoptosis by suppressing microRNA-15a expression.

Hao M, Zhang L, An G, Meng H, Han Y, Xie Z, Xu Y, Li C, Yu Z, Chang H, Qiu L.

Leuk Lymphoma. 2011 Sep;52(9):1787-94. [Epub 2011 May 3.]

http://www.ncbi.nlm.nih.gov/pubmed/21534877

This study aims to determine whether bone marrow stromal cells (BMSCs) have a role in the development of chemoresistance in myeloma. The authors' data suggest that via suppressing miRNA-15a expression, BMSCs provide survival support and protect myeloma cells from bortezomib induced apoptosis.

Despite unsurpassed anti-tumor activity of bortezomib for multiple myeloma (MM), drug resistance has emerged as a challenge, especially when MM cells adhere to the stroma. This study aimed to determine whether bone marrow stromal cells (BMSCs) have a role in the development of chemoresistance in MM. Our data demonstrate that the secretion of interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and cell-to-cell contact with microenvironment-derived stromal cells from patients with multiple myeloma (MM-BMSCs) significantly decreased the sensitivity of myeloma cells to bortezomib treatment. Mechanistically, we found that microRNA (miRNA)- 15a expression was up-regulated in U266 and NCI-H929 cells treated by bortezomib, which was inhibited by MM-BMSCs. miRNA-15a transfected myeloma cells were arrested in G1/S checkpoint and secreted less VEGF compared to control transfected cells, although no significant difference was found in VEGF mRNA levels. In conclusion, our data suggest that via suppressing miRNA-15a expression, BMSCs provide survival support and protect myeloma cells from bortezomib induced apoptosis.

Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant-ineligible patients with multiple myeloma: a meta-analysis.

Kapoor P, Rajkumar SV, Dispenzieri A, Gertz MA, Lacy MQ, Dingli D, Mikhael JR, Roy V, Kyle RA, Greipp PR, Kumar S, Mandrekar SJ.

Leukemia. 2011 Sep;25(9):1523-4. doi: 10.1038/leu.2011.164.

http://www.ncbi.nlm.nih.gov/pubmed/21897397

No abstract available.

Pegylated liposomal doxorubicin in combination with dexamethasone and bortezomib (VMD) or lenalidomide (RMD) in multiple myeloma pretreated patients.

Buda G, Orciuolo E, Galimberti S, Pelosini M, Petrini M.

Ann Hematol. 2011 Sep;90(9):1115-6. [Epub 2010 Dec 22.]

http://www.ncbi.nlm.nih.gov/pubmed/21181162

No abstract available.

Successful treatment with bortezomib and thalidomide for POEMS syndrome.

Ohguchi H, Ohba R, Onishi Y, Fukuhara N, Okitsu Y, Yamamoto J, Ishizawa K, Ichinohasama R, Harigae H.

Ann Hematol. 2011 Sep;90(9):1113-4. [Epub 2010 Dec 10.]

http://www.ncbi.nlm.nih.gov/pubmed/21153416

No abstract available.

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