CITINGS

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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 publications from the third quarter of 2009 on bortezomib from both national and international medical journals and publications.

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® Publications – 3rd Quarter, 2009

Clinical challenges associated with bortezomib therapy in multiple myeloma and Waldenströms Macroglobulinemia.

Laubach JP, Mitsiades CS, Roccaro AM, Ghobrial IM, Anderson KC, Richardson PG.

Leuk Lymphoma. 2009 May;50(5):694-702.

http://www.ncbi.nlm.nih.gov/pubmed/19452315?ordinalpos=76&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This review highlights the rationale for bortezomib therapy in patients with multiple myeloma, mechanisms of bortezomib resistance, important therapy-related side effects, and new directions for the use of proteasome inhibitors in myeloma.

Rapid development of the small molecule proteasome inhibitor bortezomib has yielded important clinical benefit for patients with multiple myeloma. Early phase clinical trials suggest the agent has similar efficacy in Waldenströms Macroglobulinemia. Optimization of bortezomib-based therapy, though, requires an understanding of the various challenges associated with use of the drug. This review highlights the rationale for bortezomib therapy in patients with multiple myeloma and Waldenströms Macroglobulinemia, mechanisms of bortezomib resistance, important therapy-related side effects, and new directions for the use of proteasome inhibitors in these disorders.

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. 2009 May;43(10):793-800. [Epub 2008 Nov 24.]

http://www.ncbi.nlm.nih.gov/pubmed/19029964?ordinalpos=66&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

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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.

Bortezomib in combination with pegylated liposomal doxorubicin and thalidomide is an effective steroid independent salvage regimen for patients with relapsed or refractory multiple myeloma: results of a phase II clinical trial.

Chanan-Khan A, Miller KC, Musial L, Padmanabhan S, Yu J, Ailawadhi S, Sher T, Mohr A, Bernstein ZP, Barcos M, Patel M, Iancu D, Lee K, Czuczman MS.

Leuk Lymphoma. 2009 May 22:1-6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19479618?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This phase II trial investigates the efficacy of a steroid-free combination including bortezomib, pegylated liposomal doxorubicin and thalidomide (VDT regimen) and observes that VDT is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Novel agents have demonstrated enhanced efficacy when combined with other antimyeloma agents especially dexamethasone. The steroid doses employed in myeloma regimens are often poorly tolerated. Therefore, in a phase II clinical trial we investigated the efficacy of a steroid-free combination including bortezomib, pegylated liposomal doxorubicin and thalidomide (VDT regimen). Twenty-three patients with relapsed or refractory myeloma or other plasma cell cancers were treated with the VDT regimen. Patient had a median of five prior therapies and 65.2% were refractory to their last regimen. The overall response rates were 55.5% and 22%, respectively. The median progression free survival was 10.9 months (95% CI: 7.3-15.8) and the median overall survival was 15.7 months (95% CI: 9.1-not reached). Fatigue and sensory neuropathy were the most common side effects noted. We observe that VDT is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Activity of bortezomib administered once every 3 weeks for treatment of relapsed multiple myeloma.

Sadek I, Dispenzieri A, Gertz MA, Kumar S.

Leuk Lymphoma. 2009 Jun;50(6):1033-5.

http://www.ncbi.nlm.nih.gov/pubmed/19455462?ordinalpos=53&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

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 Jun;82(6):433-9. [Epub 2009 Feb 17.]

http://www.ncbi.nlm.nih.gov/pubmed/19226361?ordinalpos=47&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.

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-d 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 wk until progression. RESULTS: Among 35 patients enrolled (median age 70 yr), responses occurred in 23/31 evaluable patients (74%) including five (16%) complete, three (10%) very good partial, six (19%) partial and nine (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 and 4 adverse events occurred in 17 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 Jun;23(6):1098-105. [Epub 2009 Feb 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19225532?ordinalpos=56&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.

Dysregulation of unfolded protein response partially underlies proapoptotic activity of bortezomib in multiple myeloma cells.

Dong H, Chen L, Chen X, Gu H, Gao G, Gao Y, Dong B.

Leuk Lymphoma. 2009 Jun;50(6):974-84.

http://www.ncbi.nlm.nih.gov/pubmed/19391038?ordinalpos=54&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This data strongly suggest that dysregulated or disruptive unfolded protein response may, at least partly, underlie the antimyeloma activity of bortezomib.

The 26S proteasome inhibitor, bortezomib, has shown remarkable therapeutic efficacy in multiple myeloma (MM), however, the mechanism by which this compound acts remains unknown. Here, we have demonstrated that bortezomib targets the prototypical expression of unfolded protein response (UPR) genes BiP, CHOP and XBP-1 at the mRNA and protein levels, resulting in induction of proapoptotic UPR outputs and suppression of cytoprotective UPR components, leading to caspase-dependent apoptosis in human MM H929 and 8226/S cell lines. Moreover, knockdown of XPB-1s, via lentivirus-mediated RNA interference approach, sensitises MM cells to apoptosis induction by bortezomib. Together, these data strongly suggest that dysregulated or disruptive UPR may, at least partly, underlie the antimyeloma activity of bortezomib.

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 Jun;23(6):1152-7. [Epub 2009 Feb 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19225533?ordinalpos=55&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 $<$ or $=70$ 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, $P=0.001$).

Prophylaxis with acyclovir for herpes zoster infection during bortezomib-dexamethasone combination therapy.

Hasegawa Y, Kawahara F, Nagai H, Hirose T, Imai Y, Ishiguro T, Chou T.

Rinsho Ketsueki. 2009 Jun;50(6):488-94.

http://www.ncbi.nlm.nih.gov/pubmed/19571509?ordinalpos=58&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors conduct a retrospective survey on herpes zoster (HZ) infection (profile) after bortezomib therapy and find that HZ developed when acyclovir was not administrated to all six cases.

A novel molecular targeting drug, a proteasome inhibitor, bortezomib (Bor), has been reported to be highly effective for relapsed/refractory, as well as for newly diagnosed multiple myeloma, but is also associated with a high frequency of herpes zoster (HZ) infection (13%). We conducted a retrospective survey on HZ infection (profile) after Bor therapy in our hospital. Six of 30 patients developed HZ infection during bortezomib-dexamethasone treatment (BD therapy). Age, performance status, and stem cell transplantation were not related risk factors for HZ infection. HZ developed when acyclovir (ACV) was not administrated to all six cases. Continuous administration of ACV decreased the incidence of HZ infection. Based on these results, we started an anti- HZ prophylaxis program using ACV for all patients receiving BD therapy. Further study is warranted to establish the optimal dose and duration of ACV for appropriate prophylaxis of HZ infection.

Natural polyphenols antagonize the antimyeloma activity of proteasome inhibitor bortezomib by direct chemical interaction.

Kim TY, Park J, Oh B, Min HJ, Jeong TS, Lee JH, Suh C, Cheong JW, Kim HJ, Yoon SS, Park SB, Lee DS; the Korean Multiple Myeloma Working Party (KMMWP).

Br J Haematol. 2009 Jun 3. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19500098?ordinalpos=42&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the anticancer activity of bortezomib is blocked by polyphenols, suggesting that myeloma patients should consider restricting the intake of natural polyphenols in foods or vitamin supplements during bortezomib treatment.

Bortezomib is a therapeutic proteasome inhibitor with antimyeloma activity and polyphenols are well known compounds that exert antiproliferative effects against tumuors. We attempted to co-treat myeloma cells with bortezomib and polyphenols, anticipating a synergistic effect. However, the anticancer activity of bortezomib was blocked by the polyphenols. The structural features of the polyphenols correlated strikingly with their antagonistic effect; in particular, the presence or absence of a vicinal diol moiety was the key element for effective blockage of the anticancer function of bortezomib. We speculated that the vicinal diols in the polyphenols interact with the boronic acid of bortezomib and convert the active triangular boronic acid of bortezomib to an inactive tetrahedral boronate, thus abolishing the antimyeloma activity of bortezomib. We confirmed this hypothesis by (11)B nuclear magnetic resonance spectroscopy and an in vitro assay on multiple myeloma (MM) cell lines and primary myeloma cells from patients. Based on these findings, restriction of the intake of natural polyphenols in foods or vitamin supplements during bortezomib treatment in MM patients should be considered.

Bortezomib and EGCG: no green tea for you?

Shah JJ, Kuhn DJ, Orlowski RZ.

Blood. 2009 Jun 4;113(23):5695-6.

http://www.ncbi.nlm.nih.gov/pubmed/19498025?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: Blood. 2009 Jun 4;113(23):5927-37.

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, Schönthal AH.

Blood. 2009 Jun 4;113(23):5927-37. [Epub 2009 Feb 3.]

http://www.ncbi.nlm.nih.gov/pubmed/19190249?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' 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.

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 (BZM) 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 BZM in vitro and in vivo. This pronounced antagonistic function of EGCG was evident only with boronic acid-based proteasome inhibitors (BZM, MG-262, PS-IX), but not with several non-boronic acid proteasome inhibitors (MG-132, PS-I, nelfinavir). EGCG directly reacted with BZM and blocked its proteasome inhibitory function; as a consequence, BZM 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 BZM and suggest that consumption of green tea products may be contraindicated during cancer therapy with BZM.

Weekly and twice-weekly bortezomib in patients with systemic AL-amyloidosis: results of a phase 1 dose-escalation study.

Reece DE, Sanchorawala V, Hegenbart U, Merlini G, Palladini G, Fermand JP, Vescio RA, Liu X, Elsayed YA, Cakana A, Comenzo RL.

Blood. 2009 Jun 4. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19498019?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that once-weekly and twice-weekly bortezomib appear generally well tolerated in relapsed AL-amyloidosis, with promising hematologic responses.

New treatment options are required for primary systemic AL-amyloidosis (AL), a protein conformational disorder associated with a clonal plasma cell dyscrasia. This phase 1 dose-escalation component of a phase 1/2 study in relapsed AL aimed to determine the maximum tolerated dose (MTD) of bortezomib once-weekly (0.7-1.6 mg/m(2); days 1, 8, 15, 22; 35-day cycles) and twice-weekly (0.7-1.3 mg/m(2); days 1, 4, 8, 11; 21-day cycles) and assess preliminary hematologic responses. Thirty one patients with relapsed AL were enrolled across seven cohorts. Dose-limiting toxicity included grade 3 congestive heart failure in two patients (one at once-weekly, 1.6 mg/m(2), and one at twice-weekly, 1.0 mg/m(2)). MTD was not defined for either schedule; the maximum doses of 1.6 mg/m(2) (once-weekly) and 1.3 mg/m(2) (twice-weekly) are being used in phase 2 evaluation. Most commonly reported toxicities on both schedules included gastrointestinal events, fatigue, and nervous system disorders. Discontinuations and dose reductions for toxicity were reported in 12 and 4 patients, respectively. No treatment-related deaths occurred. Hematologic responses occurred in 15/30 (50%) evaluable patients, including 6 (20%) complete responses. Median time to first response was 1.2 months. Once-weekly and twice-weekly bortezomib appear generally well tolerated in relapsed AL, with promising hematologic responses.

Effect of autophagy on multiple myeloma cell viability.

Hoang B, Benavides A, Shi Y, Frost P, Lichtenstein A.

Mol Cancer Ther. 2009 Jun 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19509276?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that autophagy inhibitors have therapeutic potential in myeloma but caution against combining such drugs with bortezomib because their attempt to synergize the two led to antagonistic response.

Because accumulation of potentially toxic malfolded protein may be extensive in immunoglobulin-producing multiple myeloma (MM) cells, we investigated the phenomenon of autophagy in myeloma, a physiologic process that can protect against malfolded protein under some circumstances. Autophagy in MM cell lines that express and secrete immunoglobulin and primary specimens was significantly increased by treatment with the endoplasmic reticulum stress-inducing agent thapsigargin, the mammalian target of rapamycin inhibitor rapamycin, and the proteasome inhibitor bortezomib. Inhibition of basal autophagy in these cell lines and primary cells by use of the inhibitors 3-methyladenine and chloroquine resulted in a cytotoxic effect that was associated with enhanced apoptosis. Use of small interfering RNA to knock down expression of beclin-1, a key protein required for autophagy, also inhibited viable recovery of MM cells. Because the data suggested that autophagy protected MM cell viability, we predicted that autophagy inhibitors would synergize with bortezomib for enhanced antimyeloma effects. However, the combination of these drugs resulted in an antagonistic response. In contrast, the autophagy inhibitor 3-methyladenine did synergize with thapsigargin for an enhanced cytotoxic response. These data suggest that autophagy inhibitors have therapeutic potential in myeloma but caution against combining such drugs with bortezomib.

Bortezomib plus dexamethasone is highly effective in relapsed and refractory myeloma patients but responses are short-lived.

Corso A, Varettoni M, Mangiacavalli S, Zappasodi P, Pica GM, Algarotti A, Pascutto C, Lazzarino M.

Eur J Haematol. 2009 Jun 10. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19519727?ordinalpos=36&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the efficacy and toxicity of bortezomib in combination with dexamethasone in a cohort of myeloma relapsed/refractory patients treated in a single center and conclude that bortezomib in combination with dexamethasone is highly effective in relapsed/refractory myeloma, producing an impressive rate of complete response/very good partial response, but that responses are short-lived.

Bortezomib has proven to be effective as single agent in myeloma patients. Aim of this study was to evaluate the efficacy and toxicity of bortezomib in combination with dexamethasone in a cohort of MM relapsed/refractory patients treated in a single centre. Patients and Methods In this single center study 70 patients were treated with bortezomib alone (9) or in combination with dexamethasone (61). Results Forty-one patients (59%) achieved at least a partial response (PR), including 7% complete response (CR), 36% very good partial response (VGPR) reaching the best response within 4 cycles. The duration of response (DOR) was significantly longer for patients achieving CR/VGPR than for those achieving PR (7.3 versus 3.8 months, p=0.03). Likewise, time to progression (TTP), time to alternative treatment (TTAT), and treatment free interval (TFI) were significantly better for patients obtaining CR/VGPR (6.8, 9.4, 6.5 months respectively) as compared to PR (4.9, 6.3, 2 months respectively). The only dose-limiting toxicity was peripheral neuropathy (PN), which occurred in 38/70 patients (55%) and was of grade 3-4 in 12 (17%). PN led to a dose reduction or treatment discontinuation in 17 (24%) patients. Complete resolution or improvement of PN occurred in 29/38 (76%) after a median time of 100 days (range: 17-202). Conclusions Bortezomib in combination to dexamethasone is highly effective in relapsed/refractory MM producing an impressive rate of CR/VGPR, but responses are short-lived.

Bortezomib treatment and regulatory T-cell depletion enhance the antitumor effects of adoptively infused NK cells.

Lundqvist A, Yokoyama H, Smith A, Berg M, Childs R.

Blood. 2009 Jun 11;113(24):6120-7. [Epub 2009 Feb 6.]

http://www.ncbi.nlm.nih.gov/pubmed/19202127?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' findings suggest that depletion of Treg cells followed by bortezomib-induced tumor sensitization to autologous natural killer cells could be used as a novel strategy to treat cancer.

Ligation of inhibitory receptors renders natural killer (NK) cells inactive against autologous tumors. Recently, the proteasome inhibitor bortezomib was shown to sensitize tumors to autologous NK-cell cytotoxicity in vitro. Here, we show bortezomib augments the antitumor effects of syngeneic NK-cell infusions in tumor-bearing animals; this effect is further enhanced in regulatory T cell (Treg cell)-depleted hosts. In vitro, bortezomib-treated tumors had higher tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and perforin/granzyme-mediated caspase-8 activity, which enhanced their susceptibility to NK-cell lysis. Bioluminescence imaging of mice with established tumors showed treatment with bortezomib and syngeneic NK cells reduced tumor growth and prolonged survival compared with controls receiving bortezomib or NK cells alone. In contrast, tumor progression was not delayed when animals received bortezomib and perforin-deficient NK cells, showing drug-induced augmentation in NK-cell cytotoxicity was mediated through perforin/granzyme. Furthermore, tumor growth was slower in bortezomib-treated recipients when host Treg cells were eradicated with anti-CD25 antibody before infusing NK cells compared with mice without Treg-cell ablation (tumor doubling time, 16.7 vs 4.9 days, respectively; P = .02). These findings suggest that depletion of Treg cells followed by bortezomib-induced tumor sensitization to autologous NK cells could be used as a novel strategy to treat cancer.

Single-Agent Bortezomib in Previously Untreated Multiple Myeloma: Efficacy, Characterization of Peripheral Neuropathy, and Molecular Correlations With Response and Neuropathy.

Richardson PG, Xie W, Mitsiades C, Chanan-Khan AA, Lonial S, Hassoun H, Avigan DE, Oaklander AL, Kuter DJ, Wen PY, Kesari S, Briemberg HR, Schlossman RL, Munshi NC, Thompson Heffner L, Doss D, Esseltine DL, Weller E, Anderson KC, Amato AA.

J Clin Oncol. 2009 Jun 15. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19528374?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that single-agent bortezomib is effective in previously untreated myeloma, but that baseline myeloma-associated neuropathy seems more common than previously reported (though reversible for most patients).

PURPOSE: To assess efficacy and safety of single-agent bortezomib in previously untreated patients with multiple myeloma, investigate prevalence of baseline and treatment-emergent polyneuropathy, and identify molecular markers associated with response and neuropathy.

PATIENTS AND METHODS: Patients received bortezomib 1.3 mg/m(2) on days 1, 4, 8, and 11, for up to eight 21-day cycles. A subset of patients underwent neurophysiologic evaluation pre- and post-treatment. Bone marrow aspirates were performed at baseline for exploratory whole-genome analyses. RESULTS: Among 64 patients, 41% had partial response or better, including 9% complete/near-complete responses; median duration of response was 8.4 months. Response rates did not differ in the presence or absence of adverse cytogenetics. After median follow-up of 29 months, median time to progression was 17.3 months. Median overall survival had not been reached; estimated 1-year survival was 92%. Thirty-two patients successfully underwent optional stem-cell transplantation. Bortezomib treatment was generally well tolerated. At baseline, 20% of patients had sensory polyneuropathy. Sensory polyneuropathy developed during treatment in 64% of patients (grade 3 in 3%), but proved manageable and resolved in 85% within a median of 98 days. Neurologic examination, neurophysiologic testing, and measurements of epidermal nerve fiber densities in 35 patients confirmed pretreatment sensory neuropathy in 20% and new or worsening neuropathy in 63%. Pharmacogenomic analyses identified molecular markers of response and treatment-emergent neuropathy, which will require future study. CONCLUSION: Single-agent bortezomib is effective in previously untreated myeloma. Baseline myeloma-associated neuropathy seems more common than previously reported, and bortezomib-associated neuropathy, although a common toxicity, is reversible in most patients.

Multiple myeloma.

Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC.

Lancet. 2009 Jun 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19541364?ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss the characteristics of myeloma and how bortezomib targets both myeloma cells and the bone marrow microenvironment—creating a treatment framework that promises improved outcomes not only for myeloma patients but also those with other hematological malignancies and solid tumors.

Multiple myeloma is characterised by clonal proliferation of malignant plasma cells, and mounting evidence indicates that the bone marrow microenvironment of tumour cells has a pivotal role in myeloma pathogenesis. This knowledge has already expanded treatment options for patients with multiple myeloma. Prototypic drugs thalidomide, bortezomib, and lenalidomide have each been approved for the treatment of this disease by targeting both multiple myeloma cells and the bone marrow microenvironment. Although benefit was first shown in relapsed and refractory disease, improved overall response, duration of response, and progression-free and overall survival can be achieved when these drugs are part of first-line regimens. This treatment framework promises to improve outcome not only for patients with multiple myeloma, but also with other haematological malignancies and solid tumours.

Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide, lenalidomide or bortezomib- containing regimens.

Kumar S, Giralt S, Stadtmauer EA, Harousseau JL, Palumbo A, Bensinger W, Comenzo RL, Lentzsch S, Munshi N, Niesvizky R, San Miguel J, Ludwig H, Bergsagel L, Blade J, Lonial S, Anderson KC, Tosi P, Sonneveld P, Sezer O, Vesole D, Cavo M, Einsele H, Richardson PG, Durie BG, Rajkumar SV.

Blood. 2009 Jun 26. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19561323?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

With increasing use of the novel agents (such as bortezomib) in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. The authors recommend early mobilization of stem cells, preferable with in the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

The past decade has witnessed a paradigm shift in the initial treatment of multiple myeloma with the introduction of novel agents such as thalidomide, lenalidomide and bortezomib, leading to improved outcomes. High dose therapy and autologous stem cell transplantation remains an important therapeutic option for patients with multiple myeloma eligible for the procedure. Prior to the advent of the novel agents, patients underwent stem cell collection prior to significant alkylating agent exposure, given their potential deleterious effect on stem cell collection. With increasing use of the novel agents in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. An expert panel of the International Myeloma Working Group was convened to examine the implications of these therapies on stem collection in patients with myeloma and to develop recommendations for addressing these issues. Here we summarize the currently available data and present our perspective on the problem and potential options to overcome this problem. Specifically, we recommend early mobilization of stem cells, preferable with in the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

Bortezomib in combination with pegylated liposomal doxorubicin and thalidomide is an effective steroid independent salvage regimen for patients with relapsed or refractory multiple myeloma: results of a phase II clinical trial.

Chanan-Khan A, Miller KC, Musial L, Padmanabhan S, Yu J, Ailawadhi S, Sher T, Mohr A, Bernstein ZP, Barcos M, Patel M, Iancu D, Lee K, Czuczman MS.

Leuk Lymphoma. 2009 Jul;50(7):1096-101.

http://www.ncbi.nlm.nih.gov/pubmed/19479618?ordinalpos=68&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In this phase II trail, the authors observe that bortezomib-dexamethasone-thalidomide is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Novel agents have demonstrated enhanced efficacy when combined with other antimyeloma agents especially dexamethasone. The steroid doses employed in myeloma regimens are often poorly tolerated. Therefore, in a phase II clinical trial we investigated the efficacy of a steroid-free combination including bortezomib, pegylated liposomal doxorubicin and thalidomide (VDT regimen). Twenty-three patients with relapsed or refractory myeloma or other plasma cell cancers were treated with the VDT regimen. Patient had a median of five prior therapies and 65.2% were refractory to their last regimen. The overall response rates were 55.5% and 22%, respectively. The median progression free survival was 10.9 months (95% CI: 7.3-15.8) and the median overall survival was 15.7 months (95% CI: 9.1-not reached). Fatigue and sensory neuropathy were the most common side effects noted. We observe that VDT is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Clinical development of novel proteasome inhibitors for cancer treatment.

Yang H, Zonder JA, Dou QP.

Expert Opin Investig Drugs. 2009 Jul;18(7):957-71.

http://www.ncbi.nlm.nih.gov/pubmed/19505187?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This summary of clinical trials concludes that bortezomib as a single agent and in combination with glucocorticoids, cytotoxic agents, immunomodulatory drugs and radiation as treatment for myeloma has led to some impressive results, but that there is less evidence of bortezomib's efficacy in solid tumors.

BACKGROUND: Emerging evidence demonstrates that targeting the tumor proteasome is a promising strategy for cancer therapy. OBJECTIVE: This review summarizes recent results from cancer clinical trials using specific proteasome inhibitors or some natural compounds that have proteasome-inhibitory effects. METHODS: A literature search was carried out using PubMed. Results about the clinical application of specific proteasome inhibitors and natural products with proteasome-inhibitory activity for cancer prevention or therapy were reviewed. RESULTS/CONCLUSION: Bortezomib, the reversible proteasome inhibitor that first entered clinical trials, has been studied extensively as a single agent and in combination with glucocorticoids, cytotoxic agents, immunomodulatory drugs and radiation as treatment for multiple myeloma and other hematological malignancies. The results in some cases have been impressive. There is less evidence of bortezomib's efficacy in solid tumors. Novel irreversible proteasome inhibitors, NPI-0052 and carfilzomib, have also been developed and clinical trials are underway. Natural products with proteasome-inhibitory effects, such as green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG), soy isoflavone genistein, and the spice turmeric compound curcumin, have been studied alone and in combination with traditional chemotherapy and radiotherapy against various cancers. There is also interest in developing these natural compounds as potential chemopreventive agents.

Combination regimens using doxorubicin and pegylated liposomal doxorubicin prior to autologous transplantation in multiple myeloma.

Moreau P.

Expert Rev Anticancer Ther. 2009 Jul;9(7):885-90.

http://www.ncbi.nlm.nih.gov/pubmed/19589027?ordinalpos=62&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The author summarizes the more recent data available on the efficacy of doxorubicin and pegylated liposomal doxorubicin in combinations, including with bortezomib.

Doxorubicin and pegylated liposomal doxorubicin are key compounds of several induction regimens used prior to autologous stem cell transplantation in patients with de novo multiple myeloma, such as vincristine, doxorubicin, dexamethasone (VAD), vincristine, pegylated liposomal doxorubicin/Doxil, dexamethasone (DVd) or PS-341/bortezomib, doxorubicin, dexamethasone (PAD). The aim of this article is to summarize the more recent data available on the efficacy of these combinations and to discuss their role as part of initial therapy.

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 Jul;23(7):1337-41. [Epub 2009 Feb 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19225538?ordinalpos=69&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 (>or= partial response) was 88%, with 61% of very good partial response or better (>or=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 >or=VGPR in 74%. In conclusion, CyBorD produces a rapid and profound response in patients with newly diagnosed MM with manageable toxicity.

Effect of autophagy on multiple myeloma cell viability.

Hoang B, Benavides A, Shi Y, Frost P, Lichtenstein A.

Mol Cancer Ther. 2009 Jul;8(7):1974-84. [Epub 2009 Jun 9.]

http://www.ncbi.nlm.nih.gov/pubmed/19509276?ordinalpos=72&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' data suggest that autophag y inhibitors have therapeutic potential in myeloma but caution against combining such drugs with bortezomib because of the found antagonistic response.

Because accumulation of potentially toxic malfolded protein may be extensive in immunoglobulin-producing multiple myeloma (MM) cells, we investigated the phenomenon of autophagy in myeloma, a physiologic process that can protect against malfolded protein under some circumstances. Autophagy in MM cell lines that express and secrete immunoglobulin and primary specimens was significantly increased by treatment with the endoplasmic reticulum stress-inducing agent thapsigargin, the mammalian target of rapamycin inhibitor rapamycin, and the proteasome inhibitor bortezomib. Inhibition of basal autophagy in these cell lines and primary cells by use of the inhibitors 3-methyladenine and chloroquine resulted in a cytotoxic effect that was associated with enhanced apoptosis. Use of small interfering RNA to knock down expression of beclin-1, a key protein required for autophagy, also inhibited viable recovery of MM cells. Because the data suggested that autophagy protected MM cell viability, we predicted that autophagy inhibitors would synergize with bortezomib for enhanced antimyeloma effects. However, the combination of these drugs resulted in an antagonistic response. In contrast, the autophagy inhibitor 3-methyladenine did synergize with thapsigargin for an enhanced cytotoxic response. These data suggest that autophagy inhibitors have therapeutic potential in myeloma but caution against combining such drugs with bortezomib.

Post-transplant immunotherapy with donor-lymphocyte infusion and novel agents to upgrade partial into complete and molecular remission in allografted patients with multiple myeloma.

Kröger N, Badbaran A, Lioznov M, Schwarz S, Zeschke S, Hildebrand Y, Ayuk F, Atanackovic D, Schilling G, Zabelina T, Bacher U, Klyuchnikov E, Shimoni A, Nagler A, Corradini P, Fehse B, Zander A.

Exp Hematol. 2009 Jul;37(7):791-8. [Epub 2009 May 31.]

http://www.ncbi.nlm.nih.gov/pubmed/19487069?ordinalpos=59&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to investigate post-transplant immunotherapy with escalating donor-lymphocyte infusions and novel agents (including bortezomib) to target complete remission. Their findings demonstrate the clinical relevance of posttransplantation therapies to upgrade remission, and of remission's depth for long-term survival in myeloma patients.

OBJECTIVE: To investigate post-transplant immunotherapy with escalating donor-lymphocyte infusions (DLI) and novel agents (thalidomide, bortezomib, and lenalidomide) to target complete remission (CR). MATERIALS AND METHODS: Thirty-two patients with multiple myeloma who achieved only partial remission after allogeneic stem cell transplantation were treated with DLI. If no CR was achieved, one of the novel agents was added to target CR. RESULTS: CR defined either by European Group for Blood and Marrow Transplantation criteria, flow cytometry, or molecular methods as assessed by patient-specific immunoglobulin H-polymerase chain reaction or plasma cell chimerism polymerase chain reaction was

accomplished in 59%, 63%, and 50% of patients, respectively. Achievement of CR resulted in improved 5-year progressive-free and overall survival, according to European Group for Blood and Marrow Transplantation criteria (53% vs 35%; p=0.03 and 90% vs 62%; p=0.06), flow cytometry (74% vs 15%; p=0.001 and 100% vs 52%; p=0.1), or molecular methods (84% vs 38%; p=0.001 and 100% vs 71%; p=0.03). CONCLUSIONS: Our finding demonstrates the clinical relevance of posttransplantation therapies to upgrade remission, and of remission's depth for long-term survival in myeloma patients.

Retrospective comparison of bortezomib-containing regimens with vincristine-doxorubicin-dexamethasone (VAD) as induction treatment prior to autologous stem cell transplantation for multiple myeloma.

Eom HS, Min CK, Cho BS, Lee S, Lee JW, Min WS, Kim CC, Kim M, Kim Y.

Jpn J Clin Oncol. 2009 Jul;39(7):449-55. [Epub 2009 Jun 1.]

http://www.ncbi.nlm.nih.gov/pubmed/19487425?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The results of this retrospective comparison of bortezomib-containing regimens with vincristine, doxorubicin and dexamethasone as induction treatment prior to by autologous stem cell transplantation for myeloma provide a demonstration of the superiority of bortezomib therapy in terms of achieving a high-quality response.

OBJECTIVE: Patients with multiple myeloma (MM) achieving high-quality responses, defined as a complete response (CR) and a very good partial response (VGPR) after transplant, benefit from high-dose therapy followed by autologous stem cell transplantation (ASCT). Induction pre-transplantation treatment with vincristine, doxorubicin and dexamethasone (VAD) is currently being replaced by new targeted agents with high anti-myeloma activity. The use of these novel agents may increase the CR + VGPR rate before ASCT, which may improve post-transplantation responses and survival. METHODS: We performed a retrospective analysis of 69 patients with MM who received bortezomib-containing regimens (n = 30) or VAD (n = 39) before collection of peripheral blood stem cells and ASCT. RESULTS: Objective response rate (at least a partial response) prior to ASCT was documented in 27 (90%) of 30 and 31 (81.6%) of evaluable 38 patients with bortezomib-containing regimens and VAD, respectively. The difference between the two groups was not significant (P = 0.494). However, the high-quality response rate with VGPR or more in the bortezomib group was significantly higher compared with the VAD group (66.7% vs. 34.2%, respectively, P = 0.006). The superiority of bortezomib-containing regimens in the high-quality response rate remained significant for only the newly diagnosed patients (n = 16, P = 0.008). The engraftment data as well as stem cell harvesting were comparable between the two groups. The major bortezomib-related toxicities were thrombocytopenias and peripheral neuropathies; toxicities of VAD were hematologic and infectious. After ASCT, the difference between the two groups did not reach the level of statistical significance with respect to progression-free survival and overall survival (P = 0.498 and 0.835, respectively). CONCLUSIONS: The results of this retrospective comparison of bortezomib-containing regimens with the VAD as induction treatment prior to ASCT for MM provided a demonstration of the superiority of bortezomib therapy in terms of achieving a high-quality response. However, survivals following ASCT did not differ according to the induction regimens.

Successful mobilization of peripheral blood stem cells with bortezomib + high-dose cyclophosphamide + G-CSF in a light chain myeloma patient after failure with Total Therapy 2.

Giglio G, Romito S, Carrozza F, Musacchio M, Antuzzi G, Gigli R, Magri M, Bavaro P, Di Bartolomeo P, Dell'Isola M, Accorsi P.

Int J Hematol. 2009 Jul;90(1):81-6. [Epub 2009 Jun 16.]

http://www.ncbi.nlm.nih.gov/pubmed/19529980?ordinalpos=64&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors describe the case of a myeloma patient in which a successful mobilization of peripheral stem cells was obtained with bortezomib, cyclophosphamide and G-CSF after two failed attempts in the framework of Total Therapy 2.

Autologous stem cell transplantation is considered the best post-induction therapy for multiple myeloma (MM). Therefore, therapy for myeloma should be chosen not only on the basis of efficacy, but also taking into account their impact on the hematopoietic stem cell compartment. We describe the case of a MM patient in which a successful mobilization of peripheral stem cells was obtained with bortezomib, cyclophosphamide and G-CSF, after two failed attempts in the framework of Total Therapy 2. The patient underwent an autologous transplantation, showing a rapid and complete post-transplant hematological recovery. Our experience suggests that bortezomib is an effective anti-myeloma agent without negative impact on stem cell mobilization, even in patients with a previous history of failed harvest.

Treatment with bortezomib of human CD4+ T cells preserves natural regulatory T cells and allows the emergence of a distinct suppressor T-cell population.

Blanco B, Pérez-Simón JA, Sánchez-Abarca LI, Caballero-Velazquez T, Gutierrez-Cossío S, Hernández-Campo P, Díez-Campelo M, Herrero-Sanchez C, Rodriguez-Serrano C, Santamaría C, Sánchez-Guijo FM, Del Cañizo C, San Miguel JF.

Haematologica. 2009 Jul;94(7):975-83. [Epub 2009 Jun 8.]

http://www.ncbi.nlm.nih.gov/pubmed/19508976?ordinalpos=63&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' results reinforce the proposal of using bortezomib in the prevention of graft versus host disease and, moreover, in the generation of regulatory T-cell populations that could be used in the treatment of multiple T-cell mediated diseases.

BACKGROUND: In vitro depletion of alloreactive T cells using the proteasome inhibitor bortezomib is a promising approach to prevent graft-versus-host disease after allogeneic stem cell transplantation. We have previously described the ability of bortezomib to selectively eliminate alloreactive T cells in a mixed leukocyte culture, preserving non-activated T cells. Due to the role of regulatory T cells in the control of graft versus host disease, in the current manuscript we have analyzed the effect of bortezomib in regulatory T cells. DESIGN AND METHODS: Conventional or regulatory CD4(+) T cells were isolated with immunomagnetic microbeads based on the expression of CD4 and CD25. The effect of bortezomib on T-cell viability was analyzed by flow cytometry using 7-amino-actinomycin D staining. To investigate the possibility of obtaining an enriched regulatory T-cell population in vitro with the use of bortezomib, CD4(+) T cells were cultured during four weeks in the presence of anti-CD3 and anti-CD28 antibodies, IL-2 and bortezomib. The phenotype of these long-term cultured cells was studied, analyzing the expression of CD25, CD127 and FOXP3 by flow cytometry, and mRNA levels were determined by RT-PCR. Their suppressive capacity was assessed in co-culture experiments, analyzing proliferation and IFN-gamma and CD40L expression of stimulated responder T cells by flow cytometry. RESULTS: We observed that naturally occurring CD4(+)CD25(+) regulatory T cells are resistant to the pro-apoptotic effect of bortezomib. Furthermore, we found that long-term culture of CD4(+) T cells in the presence of bortezomib promotes the emergence of a regulatory T-cell population that significantly inhibits proliferation, IFN-gamma production and CD40L expression among stimulated effector T cells. CONCLUSIONS: These results reinforce the proposal of using bortezomib in the prevention of graft versus host disease and, moreover, in the generation of regulatory T-cell populations, that could be used in the treatment of multiple T-cell mediated diseases.

Bortezomib alone or in combination with the histone deacetylase inhibitor JNJ-26481585: effect on myeloma bone disease in the 5T2MM murine model of myeloma.

Deleu S, Lemaire M, Arts J, Menu E, Van Valckenborgh E, Vande Broek I, De Raeve H, Coulton L, Van Camp B, Croucher P, Vanderkerken K.

Cancer Res. 2009 Jul 1;69(13):5307-11. [Epub 2009 Jun 16.]

http://www.ncbi.nlm.nih.gov/pubmed/19531653?ordinalpos=57&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' data suggest that bortezomib has bone-remodeling properties that can be improved in combination with low dose JNJ-26481585, indicating that this combination therapy could be a useful strategy for the treatment of myeloma patients, especially in those patients with skeletal complications.

The proteasome inhibitor bortezomib (Velcade) is currently approved as second-line treatment of multiple myeloma (MM). MM-related bone disease is one of the most debilitating complications of MM. Besides supportive care with biphosphonates, which have proven efficacy in reducing and delaying skeletal-related events, there is no specific treatment of lytic bone lesions. The present study investigated the effect of bortezomib alone or in combination with a hydroxamate-based histone deacetylase inhibitor, JNJ-26481585 on tumor burden, and MM bone disease in the 5T2MM model. Injection of 5T2MM cells into C57Bl/KaLwRij mice resulted in MM bone disease, characterized by an increase in the percentage osteoclasts, a decrease in osteoblasts, trabecular bone volume, trabecular number, and the development of bone lesions. Treatment of 5T2MM-bearing mice with bortezomib significantly reduced tumor burden, angiogenesis, and MM bone disease. More importantly, the combination of bortezomib with JNJ-26481585 resulted in a more pronounced reduction of osteoclasts and increase of osteoblasts, trabecular bone volume, and trabecular number compared with bortezomib as single agent. These data suggest that bortezomib has bone remodeling properties that can be improved in combination with low dose JNJ-26481585. The study indicates that this combination therapy could be a useful strategy for the treatment of MM patients, especially in those patients with skeletal complications.

Re: Tandem vs single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis.

Giralt S, Vesole DH, Somlo G, Krishnan A, Stadtmauer E, Mccarthy P, Pasquini MC; Blood and Marrow Transplant Clinical Trials Network Multiple Myeloma Working Group.

J Natl Cancer Inst. 2009 Jul 1;101(13):964; author reply 966-7. [Epub 2009 Jun 17.]

http://www.ncbi.nlm.nih.gov/pubmed/19535777?ordinalpos=56&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: *J Natl Cancer Inst.* 2009 Jan 21;101(2):100-6.

Multiple myeloma: management of adverse events.

Gay F, Palumbo A.

Med Oncol. 2009 Jul 7. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19582597?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

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

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

Cutaneous myeloma and bortezomib.

Gozzetti A, Defina M, Bocchia M.

Ann Hematol. 2009 Jul 14. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19597817?ordinalpos=46&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Enhanced antimyeloma cytotoxicity by the combination of arsenic trioxide and bortezomib is further potentiated by p38 MAPK inhibition.

Wen J, Feng Y, Huang W, Chen H, Liao B, Rice L, Preti HA, Kamble RT, Zu Y, Ballon DJ, Chang CC.

Leuk Res. 2009 Jul 14. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19608275?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors study the cytotoxicity of bortezomib, ATO, and ATO+bortezomib with or without inhibiting p38 MAPK, along with associated molecular changes in myeloma cells. Their results suggest the opportunity for using p38 MAPK inhibition to enhance the efficacy of ATO+bortezomib in myeloma.

The combination of ATO and bortezomib (ATO+bortezomib) has been recently shown to enhance antimyeloma activity; nevertheless, the mechanisms remained unclear in these studies. However, both bortezomib and ATO have been shown to activate the p38 MAPK pathway, which may counteract the enhancement induced by this combination. We studied the cytotoxicity of bortezomib, ATO, and ATO+bortezomib with or without inhibiting p38 MAPK, along with associated molecular changes in myeloma cells. The treatment of myeloma cells with ATO+bortezomib induced higher cytotoxicity than either agent alone. This increased cytotoxicity was further synergistically enhanced by inhibiting p38 MAPK. This effect was preserved in the presence of marrow stromal cells designed to simulate the tumor micro-environment and in the CD138+ neoplastic plasma cells directly isolated from myeloma patients. The enhanced cytotoxicity of ATO+bortezomib was associated with augmented STAT3 inhibition and JNK activation, up-regulation of Bim, p21, p27, p53 as well as down-regulation of Bcl-2. Furthermore, the synergistically potentiated apoptosis by p38 MAPK inhibition was associated with the attenuation of ATO+bortezomib-mediated activation of Hsp27 as well as the enhancement of ATO+bortezomib-mediated JNK activation, p53 up-regulation, and Bcl-2 down-regulation. The results suggest the opportunity for using p38 MAPK inhibition to enhance the efficacy of ATO+bortezomib in myeloma.

Prognostic significance of apoptotic index in multiple myeloma patients treated by conventional therapy and novel agents, thalidomide and bortezomib.

Jiri M, Vlastimil S, Jaroslav B, Marketa Z, Tomas P, Marta O, Katerina L.

Eur J Haematol. 2009 Jul 18. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19624720?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to assess the outcome of the measurement of apoptotic index in myeloma patients treated by conventional chemotherapy and novel drugs (including bortezomib). Their results suggest the use of apoptotic index by flow cytometry measurement as a fast and accessible method for prognostic stratification of myeloma patients in routine practice.

ABSTRACT Objective: To assess the outcome of the measurement of apoptotic index in myeloma patients treated by conventional chemotherapy and novel drugs with biological mechanism of action, thalidomide and bortezomib. Patients and methods: In a cohort of 189 patients with newly diagnosed multiple myeloma (MM) from November 1997 through February 2008, we assessed the prognostic significance of plasma cell apoptotic index (PC-AI) using annexin-V. The whole group was subsequently divided according to treatment approach (conventional chemotherapy only vs inclusion of novel drugs, thalidomide and bortezomib), and curves of overall survival were constructed. Results: In the whole group (n = 189), low levels of PC-AI < 4.5% significantly separated patients with unfavorable prognosis (median OS 16 vs 38 months, p = 0.004). In patients treated with conventional chemotherapy only (n = 139) the results were similar (median OS 10 vs 25 months, p = 0.02), and the apoptotic index maintained its significance even within the group of 50 patients treated also with novel drugs (median OS 30 vs 54 months, p = 0.027). PC-AI was found to be independent both on Durie-Salmon staging system (D-S) and the International Prognostic Index (IPI). Conclusion: Presented results suggest the use of apoptotic index by flow cytometry measurement as a fast and accessible method for prognostic stratification of myeloma patients in routine practice.

Single-agent bortezomib in previously untreated multiple myeloma: efficacy, characterization of peripheral neuropathy, and molecular correlations with response and neuropathy.

Richardson PG, Xie W, Mitsiades C, Chanan-Khan AA, Lonial S, Hassoun H, Avigan DE, Oaklander AL, Kuter DJ, Wen PY, Kesari S, Briemberg HR, Schlossman RL, Munshi NC, Heffner LT, Doss D, Esseltine DL, Weller E, Anderson KC, Amato AA.

J Clin Oncol. 2009 Jul 20;27(21):3518-25. [Epub 2009 Jun 15.]

http://www.ncbi.nlm.nih.gov/pubmed/19528374?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find single-agent bortezomib to be effective in previously untreated myeloma. Though baseline myeloma-associated neuropathy seems more common than previously reported, it is reversible in most patients.

PURPOSE To assess efficacy and safety of single-agent bortezomib in previously untreated patients with multiple myeloma, investigate prevalence of baseline and treatment-emergent polyneuropathy, and identify molecular markers associated with response and neuropathy. PATIENTS AND METHODS Patients received bortezomib 1.3 mg/m(2) on days 1, 4, 8, and 11, for up to eight 21-day cycles. A subset of patients underwent neurophysiologic evaluation pre- and post-treatment. Bone marrow aspirates were performed at baseline for exploratory whole-genome analyses. Results Among 64 patients, 41% had partial response or better, including 9% complete/near-complete responses; median duration of response was 8.4 months. Response rates did not differ in the presence or absence of adverse cytogenetics. After median follow-up of 29 months, median time to progression was 17.3 months. Median overall survival had not been reached; estimated 1-year survival was 92%. Thirty-two patients successfully underwent optional stem-cell transplantation. Bortezomib treatment was generally well tolerated. At baseline, 20% of patients had sensory polyneuropathy. Sensory polyneuropathy developed during treatment in 64% of patients (grade 3 in 3%), but proved manageable and resolved in 85% within a median of 98 days. Neurologic examination, neurophysiologic testing, and measurements of epidermal nerve fiber densities in 35 patients confirmed pretreatment sensory neuropathy in 20% and new or worsening neuropathy in 63%. Pharmacogenomic analyses identified molecular markers of response and treatment-emergent neuropathy, which will require future study. CONCLUSION Single-agent bortezomib is effective in previously untreated myeloma. Baseline myeloma-associated neuropathy seems more common than previously reported, and bortezomib-associated neuropathy, although a common toxicity, is reversible in most patients.

High levels of tRNA abundance and alteration of tRNA charging by bortezomib in multiple myeloma.

Zhou Y, Goodenbour JM, Godley LA, Wickrema A, Pan T.

Biochem Biophys Res Commun. 2009 Jul 24;385(2):160-4. [Epub 2009 May 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19450555?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors demonstrate that tRNA levels are significantly elevated in myeloma cell lines compared to normal bone marrow cells, and that the addition of bortezomib results in decreased charging levels of tRNAs, in particular those coding for hydrophobic amino acids.

In multiple myeloma (MM), malignant plasma cells produce large amounts of antibodies and have highly active protein translational machinery. It is not known whether regulation of the abundance and aminoacylation (charging) of transfer RNA (tRNA) takes place in myeloma cells to accommodate

for the increased amount of protein translation. Using tRNA-specific microarrays, we demonstrate that tRNA levels are significantly elevated in MM cell lines compared to normal bone marrow cells. We furthermore show that the addition of the proteasome inhibitor, bortezomib (Velcade, PS-341) results in decreased charging levels of tRNAs, in particular those coding for hydrophobic amino acids. These results suggest that tRNA properties are altered in MM to accommodate for its increased need for protein translation, and that proteasome inhibition directly impacts protein synthesis in MM through effects on tRNA charging.

Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients.

Varettoni M, Corso A, Pica G, Mangiacavalli S, Pascutto C, Lazzarino M.

Ann Oncol. 2009 Jul 24. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19633044?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors investigate the incidence of extramedullary (EM) disease, its relationship with prior exposure to high-dose therapy (HDT) or novel agents (including bortezomib), and its prognostic impact on myeloma patients. They find HDT and novel agents seem not to increase the risk of EM disease.

BACKGROUND: There are few data on the incidence and prognosis of extramedullary (EM) multiple myeloma (MM). There are concerns about a possible increase of EM relapses with the expanding use of high-dose therapy (HDT) and biological agents. PATIENTS AND METHODS: The incidence of EM disease, its relationship with prior exposure to HDT or novel agents, and its prognostic impact were analyzed in 1003 MM patients. Based on the different therapies available, three periods were considered: 1971-1993, conventional-dose chemotherapy; 1994-1999, HDT for younger patients; and 2000-2007, introduction of novel agents. RESULTS: Overall, 13% of patients had EM disease, 7% at diagnosis and 6% later. In the 2000-2007 period, there was a significant increase of EM involvement, at diagnosis ($P = 0.02$) and during follow-up ($P = 0.03$). The risk of EM spread was not significantly increased after HDT [hazard ratio (HR 0.6)], bortezomib (HR 1.62), or thalidomide/lenalidomide (HR 1.07). EM disease was associated with shorter overall (HR 3.26, $P < 0.0001$) and progression-free (HR 1.46, $P = 0.04$) survival. CONCLUSIONS: The incidence of EM disease has increased, probably due to the availability of more sensitive imaging techniques and the prolongation of patients' survival. HDT or novel agents seem not to increase the risk of EM disease. EM involvement confers a poor prognosis.

Multiple myeloma.

Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC.

Lancet. 2009 Jul 25;374(9686):324-39. [Epub 2009 Jun 21.]

http://www.ncbi.nlm.nih.gov/pubmed/19541364?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss the nature of myeloma and treatment drugs, including bortezomib, as a framework that promises to improve outcome not only for myeloma patients but also those with other hematological malignancies and solid tumors.

Multiple myeloma is characterised by clonal proliferation of malignant plasma cells, and mounting evidence indicates that the bone marrow microenvironment of tumour cells has a pivotal role in myeloma pathogenesis. This knowledge has already expanded treatment options for patients with multiple myeloma. Prototypic drugs thalidomide, bortezomib, and lenalidomide have each been approved for the treatment of this disease by targeting both multiple myeloma cells and the bone marrow microenvironment. Although benefit was first shown in relapsed and refractory disease, improved overall response, duration of response, and progression-free and overall survival can be achieved when these drugs are part of first-line regimens. This treatment framework promises to improve outcome not only for patients with multiple myeloma, but also with other haematological malignancies and solid tumours.

Bortezomib induces canonical nuclear factor-kappaB activation in multiple myeloma cells.

Hideshima T, Ikeda H, Chauhan D, Okawa Y, Raje N, Podar K, Mitsiades C, Munshi NC, Richardson PG, Carrasco RD, Anderson KC.

Blood. 2009 Jul 30;114(5):1046-52. [Epub 2009 May 12.]

http://www.ncbi.nlm.nih.gov/pubmed/19436050?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study demonstrates that bortezomib significantly down-regulates IkappaBalpha expression and triggers NF-kappaB activation in myeloma cell lines and primary tumor cells from myeloma patients, suggesting that bortezomib-induced cytotoxicity cannot be fully attributed to inhibition of canonical NF-kappaB activity in myeloma cells.

Bortezomib is a proteasome inhibitor with remarkable preclinical and clinical antitumor activity in multiple myeloma (MM) patients. The initial rationale for its use in MM was inhibition of nuclear factor (NF)-kappaB activity by blocking proteasomal degradation of inhibitor of kappaBalpha (IkappaBalpha). Bortezomib inhibits inducible NF-kappaB activity; however, its impact on constitutive NF-kappaB activity in MM cells has not yet been defined. In this study, we demonstrate that bortezomib significantly down-regulated IkappaBalpha expression and triggered NF-kappaB activation in MM cell lines and primary tumor cells from MM patients. Importantly, no inhibition of p65 (RelA) nuclear translocation was recognized after bortezomib treatment in a murine xenograft model bearing human MM cells. Bortezomib-induced NF-kappaB activation was mediated via the canonical pathway.

Moreover, other classes of proteasome inhibitors also induced IkappaBalpha down-regulation associated with NF-kappaB activation. Molecular mechanisms whereby bortezomib induced IkappaBalpha down-regulation were further examined. Bortezomib triggered phosphorylation of IkappaB kinase (IKKbeta) and its upstream receptor-interacting protein 2, whereas IKKbeta inhibitor MLN120B blocked bortezomib-induced IkappaBalpha down-regulation and NF-kappaB activation, indicating receptor-interacting protein 2/IKKbeta signaling plays crucial role in bortezomib-induced NF-kappaB activation. Moreover, IKKbeta inhibitors enhanced bortezomib-induced cytotoxicity. Our studies therefore suggest that bortezomib-induced cytotoxicity cannot be fully attributed to inhibition of canonical NF-kappaB activity in MM cells.

Bortezomib paradigm shift in myeloma.

McConkey DJ.

Blood. 2009 Jul 30;114(5):931-2.

http://www.ncbi.nlm.nih.gov/pubmed/19643992?ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Adenovirus-associated hemorrhagic cystitis in a patient with plasma cell myeloma treated with bortezomib.

Yokose N, Hirakawa T, Inokuchi K.

Leuk Res. 2009 Aug;33(8):e106. [Epub 2009 Mar 13.]

http://www.ncbi.nlm.nih.gov/pubmed/19285724?ordinalpos=63&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: *Blood.* 2009 Jul 30;114(5):1046-52.

Very good partial response and long time to progression by short-term bortezomib plus dexamethasone therapy for a patient with relapsed and refractory multiple myeloma-a case report. [Article in Japanese]

Fukushima T, Iwao H, Nakajima A, Miki M, Sakai T, Sawaki T, Tanaka M, Masaki Y, Hirose Y, Umehara H.

Gan To Kagaku Ryoho. 2009 Aug;36(8):1387-9.

http://www.ncbi.nlm.nih.gov/pubmed/19692786?ordinalpos=59&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report on a 63-year-old female with relapsed and refractory myeloma treated with bortezomib and dexamethasone. Their findings suggest that the therapeutic efficacy of bortezomib may persist over a long period regardless of the duration of chemotherapy.

A 63-year-old female with relapsed and refractory multiple myeloma, in whom the duration of disease and history of chemotherapy were 15 years and 9 years, respectively, was treated with bortezomib and dexamethasone. A very good partial response and about 500 days to progression were obtained at a total dose of 10.2 mg bortezomib, until the day 4 injection of the second course. Bone pain has completely disappeared. These findings suggested that the therapeutic efficacy of bortezomib may persist over a long period regardless of the duration of chemotherapy. When a favorable response is obtained, but continuous therapy with bortezomib is difficult for reasons such as adverse events (other than refractory to bortezomib), careful observation may be one of the important options.

Treatment of multiple myeloma: a comprehensive review.

Kyle RA, Rajkumar SV.

Clin Lymphoma Myeloma. 2009 Aug;9(4):278-88.

http://www.ncbi.nlm.nih.gov/pubmed/19717377?ordinalpos=56&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This comprehensive review of myeloma treatment strategies includes use of novel therapies, including bortezomib.

Multiple myeloma (MM) is a neoplastic plasma cell disorder that results in end-organ damage (hypercalcemia, renal insufficiency, anemia, or skeletal lesions). Patients should not be treated unless they have symptomatic (end-organ damage) MM. They should be classified as having high-risk or standard-risk disease. Patients are classified as high risk in the presence of hypodiploidy or deletion of chromosome 13 (del[13]) with conventional cytogenetics, the presence of t(4:14), t(14;16), t(14;20) translocations or del(17p) with fluorescence in situ hybridization. High-risk disease accounts for about 25% of patients with symptomatic MM. If the patient is deemed eligible for an autologous stem cell transplantation (ASCT), 3 or 4 cycles of lenalidomide and low-dose dexamethasone, or bortezomib and dexamethasone, or thalidomide and dexamethasone are reasonable choices. Stem cells should then be collected and one may proceed with an ASCT. If the patient has a complete response or a very good partial response (VGPR), the patient may be followed without maintenance therapy. If the patient has a less than VGPR, a second ASCT is encouraged. If the patient is in the high-risk group, a bortezomib-containing regimen to maximum response followed by 2 additional cycles of therapy is a reasonable approach. Lenalidomide and low-dose dexamethasone is another option for maintenance until progression. If the patient is considered ineligible for an ASCT, then melphalan, prednisone, and thalidomide is suggested for the standard-risk patient, and melphalan, prednisone, and bortezomib (MPV) for the high-risk patient. Treatment of relapsed or refractory MM is covered. The novel therapies-thalidomide, bortezomib, and lenalidomide-have resulted in improved survival

rates. The complications of MM are also described. Multiple myeloma is a plasma cell neoplasm that is characterized by a single clone of plasma cells producing a monoclonal protein (M-protein). The malignant proliferation of plasma cells produces skeletal destruction that leads to bone pain and pathologic fractures. The M-protein might lead to renal failure, hyperviscosity syndrome, or through the suppression of uninvolved immunoglobulins, recurrent infections. Anemia and hypercalcemia are common complications.

Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors.

Dimopoulos MA, Roussou M, Gavriatopoulou M, Zagouri F, Migkou M, Matsouka C, Barbarousi D, Christoulas D, Primenou E, Grapsa I, Terpos E, Kastritis E.

Clin Lymphoma Myeloma. 2009 Aug;9(4):302-6.

http://www.ncbi.nlm.nih.gov/pubmed/19717380?ordinalpos=55&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors analyze 46 consecutive patients who presented with renal impairment in order to evaluate the impact of bortezomib on the improvement of renal function and to identify predictive factors associated with renal response. They conclude that bortezomib-based regimens may improve renal function in the majority of myeloma patients with renal impairment.

PURPOSE: Renal impairment is a frequent complication of multiple myeloma (MM) and is associated with significant morbidity and increased early death rate. Bortezomib is active and well tolerated in patients with MM who present or develop renal impairment. PATIENTS AND METHODS: We analyzed 46 consecutive patients who presented with renal impairment in order to evaluate the impact of bortezomib on the improvement of renal function and to identify predictive factors associated with renal response. All patients received bortezomib with dexamethasone with or without other agents. RESULTS: Renal response was documented in 59% of patients within a median of 11 days (range, 8-41 days). Two of 9 patients who required dialysis became dialysis independent. A complete renal response (CRrenal) was documented in 30% of patients. Toxicities were similar to those seen in myeloma patients without renal failure who were treated with bortezomib-based regimens. Patients with light chain-only myeloma had a higher probability of achieving a renal response, and previously untreated patients had a higher probability for complete resolution of renal impairment, while light chain-only myeloma was independently associated with a shorter time to renal response. The degree of renal impairment was not predictive of the probability for renal response or CRrenal; however, in a subset of patients for whom cystatin C was available, a baseline cystatin C > 2 mg/L or cystatin C calculated estimated glomerular filtration rate < 30 mL/min were associated with a lower probability of CRrenal. CONCLUSION: We conclude that bortezomib-based regimens may improve renal function in the majority of myeloma patients with renal impairment.

Natural polyphenols antagonize the antimyeloma activity of proteasome inhibitor bortezomib by direct chemical interaction.

Kim TY, Park J, Oh B, Min HJ, Jeong TS, Lee JH, Suh C, Cheong JW, Kim HJ, Yoon SS, Park SB, Lee DS; Korean Multiple Myeloma Working Party (KMMWP).

Br J Haematol. 2009 Aug;146(3):270-81. [Epub 2009 Jun 3.]

http://www.ncbi.nlm.nih.gov/pubmed/19500098?ordinalpos=53&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors attempt to co-treat myeloma cells with bortezomib and polyphenols, anticipating a synergistic effect, but find that the anticancer activity of bortezomib is blocked by the polyphenols. Based on these findings, restriction of the intake of natural polyphenols in foods or vitamin supplements during bortezomib treatment in myeloma patients should be considered.

Bortezomib is a therapeutic proteasome inhibitor with antimyeloma activity and polyphenols are well known compounds that exert antiproliferative effects against tumuors. We attempted to co-treat myeloma cells with bortezomib and polyphenols, anticipating a synergistic effect. However, the anticancer activity of bortezomib was blocked by the polyphenols. The structural features of the polyphenols correlated strikingly with their antagonistic effect; in particular, the presence or absence of a vicinal diol moiety was the key element for effective blockage of the anticancer function of bortezomib. We speculated that the vicinal diols in the polyphenols interact with the boronic acid of bortezomib and convert the active triangular boronic acid of bortezomib to an inactive tetrahedral boronate, thus abolishing the antimyeloma activity of bortezomib. We confirmed this hypothesis by (11)B nuclear magnetic resonance spectroscopy and an in vitro assay on multiple myeloma (MM) cell lines and primary myeloma cells from patients. Based on these findings, restriction of the intake of natural polyphenols in foods or vitamin supplements during bortezomib treatment in MM patients should be considered.

Constitutive down-regulation of Osterix in osteoblasts from myeloma patients: In vitro effect of Bortezomib and Lenalidomide.

De Matteo M, Brunetti AE, Maiorano E, Cafforio P, Dammacco F, Silvestris F.

Leuk Res. 2009 Aug 3. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19656567?ordinalpos=50&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' findings provide additional evidence suggesting that, at least in vitro, bortezomib promotes osteoblast maturation.

Bortezomib and Lenalidomide have been shown to be effective in the control of multiple myeloma (MM) progression. We have investigated their role in the in vitro expression of Osterix by primary osteoblast cultures from MM patients and found that Osterix RNA was constitutively down-regulated in these cells. Treatment of osteoblasts with Bortezomib resulted in an increase of Osterix RNA and in enhanced activity of both BMP-2 and Runx2. Instead, Lenalidomide was unable to modify Osterix transcription. These findings provide additional evidence suggesting that, at least in vitro, Bortezomib promotes the osteoblast maturation whereas Lenalidomide is ineffective.

Successful Bortezomib-Based Treatment in POEMS Syndrome.

Tang X, Shi X, Sun A, Qiu H, Gu B, Zhou H, Xue S, Liu Y, Ruan C, Wu D.

Eur J Haematol. 2009 Aug 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19674063?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Bortezomib-induced peripheral neuropathy in multiple myeloma: A comparison between previously treated and untreated patients.

Corso A, Mangiacavalli S, Varettoni M, Pascutto C, Zappasodi P, Lazzarino M.

Leuk Res. 2009 Aug 10. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19674790?ordinalpos=45&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors compare the incidence, risk factors, severity and outcome of peripheral neuropathy (PN) and neuropathic pain in patients treated with bortezomib up-front or at relapse. They find that severity and outcome of bortezomib-related PN are similar in untreated and pre-treated myeloma patients, except for neuropathic pain, which has lower incidence and shorter duration in untreated patients with less frequent need for bortezomib discontinuation.

Peripheral neuropathy (PN), with neuropathic pain as main symptom, represents the dose-limiting toxicity of the proteasome inhibitor bortezomib. Aim of this study was to compare the incidence, risk factors, severity and outcome of PN and neuropathic pain in patient treated with bortezomib up-front or at relapse. We studied 55 patients with multiple myeloma (MM) who received bortezomib as first line therapy and 70 pre-treated patients who received bortezomib in relapse or progression. Regarding PN, no differences were found among untreated and pre-treated patients in the incidence (55% vs 52%, p=0.43), severity (NCI grade 3-4 9% vs 14%, p=0.27), and outcome (improved/resolved 90% vs 91%, p=0.58). Concerning neuropathic pain, the incidence was lower (50% vs 81%, p=0.008) and solved earlier (35 days vs 91 days, p=0.02) in untreated compared with pre-treated patients. Untreated patients needed dose modification less frequently (36% vs 73%, p=0.012). No correlation was found between development of PN and prior exposure to potentially neurotoxic drugs such as thalidomide, vincristine, and cysplatin. Age represented the main risk factor for PN (p=0.036) with an increase in risk of PN amounting to 6% per year of age. In conclusion, incidence, severity and outcome of bortezomib-related PN are similar in untreated and pre-treated MM patients except for neuropathic pain which has lower incidence and shorter duration in untreated patients with less frequent need for bortezomib discontinuation. Age emerges as the most relevant risk factor for peripheral neuropathy, with a risk increase for PN of 6% per year of age.

Synergistic interaction of proteasome and topoisomerase II inhibition in multiple myeloma.

von Metzler I, Heider U, Mieth M, Lamottke B, Kaiser M, Jakob C, Sezer O.

Exp Cell Res. 2009 Aug 15;315(14):2471-8. [Epub 2009 May 3.]

http://www.ncbi.nlm.nih.gov/pubmed/19410573?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors examine the effects of co-treatment with proteasome-inhibitor bortezomib and topoisomerase II inhibitor etoposide in multiple myeloma cells lines OPM-2, RPMI-S and NCI-H929. Their data that suggest that combining etoposide with bortezomib might be useful for cancer treatment, as bortezomib potentially inhibits counter-regulatory mechanisms of tumor cells, which are induced by topoisomerase II inhibition and which may contribute to acquired chemoresistance.

Multiple myeloma is a malignancy of terminally differentiated plasma cells and is incurable in the majority of the patients. Thus, novel effective treatment regimens are urgently needed. In this study, we examined the effects of co-treatment with proteasome-inhibitor bortezomib and

topoisomerase II inhibitor etoposide in multiple myeloma cells lines OPM-2, RPMI-S and NCI-H929. Using the median effect method of Chou and Talalay, we evaluated the combination indices (CI) for simultaneous and sequential treatment schedules. In the sequential treatment schedule, we found strong synergistic effects in all three cell lines, even at low single-agent cytotoxicity levels. When cells were treated simultaneously with both drugs, the synergy was present but less pronounced than in the sequential treatment schedule. The synergistic effects observed in the co-treatment schedules were accompanied by an inhibition of anti-apoptotic effects that were induced by etoposide alone. Namely, bortezomib abrogated both etoposide-induced NF-kappaB activation and etoposide-induced bcl-2 up-regulation. Our data suggest that combining etoposide with bortezomib might be useful for cancer treatment, as bortezomib potentially inhibits counter-regulatory mechanisms of tumor cells, which are induced by topoisomerase II inhibition and which may contribute to acquired chemoresistance.

Phase I study of vorinostat in combination with bortezomib for relapsed and refractory multiple myeloma.

Badros A, Burger AM, Philip S, Niesvizky R, Kolla SS, Goloubeva O, Harris C, Zwiebel J, Wright JJ, Espinoza-Delgado I, Baer MR, Holleran JL, Egorin MJ, Grant S.

Clin Cancer Res. 2009 Aug 15;15(16):5250-7. [Epub 2009 Aug 11.]

http://www.ncbi.nlm.nih.gov/pubmed/19671864?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the combination of vorinostat and bortezomib shows promising antimyeloma activity of the regimen in refractory patients and merits further evaluation.

PURPOSE: Vorinostat, a histone deacetylase inhibitor, enhances cell death by the proteasome inhibitor bortezomib in vitro. We sought to test the combination clinically. EXPERIMENTAL DESIGN: A phase I trial evaluated sequential dose escalation of bortezomib at 1 to 1.3 mg/m2 i.v. on days 1, 4, 8, and 11 and vorinostat at 100 to 500 mg orally daily for 8 days of each 21-day cycle in relapsed/refractory multiple myeloma patients. Vorinostat pharmacokinetics and dynamics were assessed. RESULTS: Twenty-three patients were treated. Patients had received a median of 7 prior regimens (range, 3-13), including autologous transplantation in 20, thalidomide in all 23, lenalidomide in 17, and bortezomib in 19, 9 of whom were bortezomib-refractory. Two patients receiving 500 mg vorinostat had prolonged QT interval and fatigue as dose-limiting toxicities. The most common grade >3 toxicities were myelo-suppression (n = 13), fatigue (n = 11), and diarrhea (n = 5). There were no drug-related deaths. Overall response rate was 42%, including three partial responses among nine bortezomib refractory patients. Vorinostat pharmacokinetics were nonlinear. Serum Cmax reached a plateau above 400 mg. Pharmacodynamic changes in CD-138+ bone marrow cells before and on day 11 showed no correlation between protein levels of NF-kappaB, IkappaB, acetylated tubulin, and p21CIP1 and clinical response. CONCLUSIONS: The maximum tolerated dose of vorinostat in our study was 400 mg daily for 8 days every 21 days, with bortezomib administered at a dose of 1.3 mg/m2 on days 1, 4, 8, and 11. The promising antimyeloma activity of the regimen in refractory patients merits further evaluation.

Bortezomib-induced painful neuropathy in rats: A behavioral, neurophysiological and pathological study in rats.

Meregalli C, Canta A, Carozzi VA, Chiorazzi A, Oggioni N, Gilardini A, Ceresa C, Avezza F, Crippa L, Marmiroli P, Cavaletti G.

Eur J Pain. 2009 Aug 18. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19695912?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In order to obtain a pre-clinical model to reproduce the characteristic pain symptoms in bortezomib-treated patients, the authors develop an animal model of bortezomib-induced nociceptive sensory neuropathy.

Bortezomib is a proteasome inhibitor showing strong antitumor activity against many tumors, primarily multiple myeloma. Bortezomib-induced neuropathic pain is the main side effect and the dose-limiting factor of the drug in clinical practice. In order to obtain a pre-clinical model to reproduce the characteristic pain symptoms in bortezomib-treated patients, we developed an animal model of bortezomib-induced nociceptive sensory neuropathy. In this study, bortezomib (0.15 or 0.20mg/kg) was administered to Wistar rats three times/week for 8 weeks, followed by a 4 week follow-up period. At the end of the treatment period a significant decrease in weight gain was observed in the treated groups vs. controls, and hematological and histopathological parameters were evaluated. After the treatment period, both doses of bortezomib induced a severe reduction in nerve conduction velocity and demonstrated a dose-cumulative effect of the drug. The sensory behavioral assessment showed the onset of mechanical allodynia, while no effect on thermal perception was observed. Sciatic nerves and dorsal root ganglia (DRG) were collected at the end of the 8-week treatment and at the end of the follow-up period. The pathological examination revealed a dose-dependent axonopathy of the unmyelinated fibers in nerves of treated animals. No pathological alteration in most of DRG satellite cells and neurons was observed. Therefore, this animal model may be useful for studying the neurotoxicity and pain onset mechanisms related to bortezomib treatment.

Activation of SHIP via a Small Molecule Agonist Kills Multiple Myeloma Cells.

Kennah M, Yau TY, Nodwell M, Krystal G, Andersen RJ, Ong CJ, Mui AL.

Exp Hematol. 2009 Aug 21. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19703514?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the small molecule agonist AQX-MN100 augments the effects of the bortezomib.

OBJECTIVES: Multiple myeloma (MM) is a B-lymphocyte neoplasia that is presentlly incurable because the tumor cells become resistant to currently available drugs. The growth and survival signals resulting from interactions between the malignant clones and the bone marrow microenvironment are mediated chiefly through the phosphoinositide 3'-kinase/Akt kinase (PI3 K/Akt) signaling pathway. Thus agents that can abrogate this pathway have great potential as targeted therapies. A novel approach in this regard is through activation of the Src homology 2-containing inositol 5'-phosphatase (SHIP), using the small molecule agonist, AQX-MN100. METHODS: The SHIP agonist AQX-MN100 was tested in vitro for its ability to inhibit DNA synthesis, induce apoptosis in MM cell lines, as well as inhibit phosphorylation of the kinases in the PI3 K/Akt cascade. The ability of AQX-MN100 to enhance the cytotoxicity of the current MM therapeutic drugs dexamethasone and bortezomib was also examined. RESULTS: We demonstrate herein that activation of SHIP using AQX-MN100 is sufficient to prevent growth and induce cytotoxicity of MM cell lines, while having no significant effects on non-hematopoietic cells lacking SHIP. AQX-MN100 also augments the effects of the established agents dexamethasone and bortezomib. CONCLUSION: These results provide the basis for the further study of small molecule SHIP activators to improve MM patient outcome.

Neurological adverse effects caused by cytotoxic and targeted therapies.

Schiff D, Wen PY, van den Bent MJ.

Nat Rev Clin Oncol. 2009 Aug 25. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19707193?ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors review the prevalence, prevention, and management of important and unusual neurotoxicities related to chemotherapy and targeted agents approved by the FDA since January 1999, including bortezomib.

Historically, body tissues with a high rate of cell turnover, such as the bone marrow, have been most susceptible to chemotherapy-induced damage. The widespread use of hematopoietic colony-stimulating factors, as well as the development of new agents, has led to improved outcomes in many types of cancer. As a consequence, neurotoxicity has become increasingly important as a cause of dose-limiting chemotherapy toxicity. An understanding of the neurologic complications of these new agents is crucial in order to prevent irreversible neurologic injury. Moreover, chemotherapy complications that require discontinuation of a potentially effective drug need to be distinguished from other causes of neurotoxicity including the tumor itself, paraneoplasia, radiation and surgery, which may require a different therapeutic strategy. We review the prevalence, prevention, and management of important and unusual neurotoxicities related to chemotherapy and targeted agents approved by the FDA since January 1999. These agents include DNA-damaging agents such as oxaliplatin and temozolomide, microtubule poisons like ixabepilone, proteasome inhibitors (bortezomib), and signal transduction inhibitors such as imatinib, sunitinib and bevacizumab.

Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens.

Kumar S, Giralt S, Stadtmauer EA, Harousseau JL, Palumbo A, Bensinger W, Comenzo RL, Lentzsch S, Munshi N, Niesvizky R, San Miguel J, Ludwig H, Bergsagel L, Blade J, Lonial S, Anderson KC, Tosi P, Sonneveld P, Sezer O, Vesole D, Cavo M, Einsele H, Richardson PG, Durie BG, Rajkumar SV; International Myeloma Working Group.

Blood. 2009 Aug 27;114(9):1729-35. [Epub 2009 Jun 26.]

http://www.ncbi.nlm.nih.gov/pubmed/19561323?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

An expert panel examines the implications of therapies (bortezomib) on stem collection in patients with myeloma and to develops recommendations for addressing their impact on the ability to collect stem cells, ultimately recommending early mobilization of stem cells, preferably within the first four cycles of initial therapy.

The past decade has witnessed a paradigm shift in the initial treatment of multiple myeloma with the introduction of novel agents such as thalidomide, lenalidomide, and bortezomib, leading to improved outcomes. High-dose therapy and autologous stem cell transplantation remains an important therapeutic option for patients with multiple myeloma eligible for the procedure. Before the advent of the novel agents, patients underwent stem cell collection prior to significant alkylating agent exposure, given its potential deleterious effect on stem cell collection. With increasing use of the novel agents in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. An expert panel of the International Myeloma Working Group (IMWG) was convened to examine the implications of these therapies on stem collection in patients with myeloma and to develop recommendations for addressing these issues. Here we summarize the currently available data and present our perspective on the problem and potential options to overcome this problem. Specifically, we recommend early mobilization of stem cells, preferably within the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

Bortezomib, tacrolimus and methotrexate for prophylaxis of graft-versus-host-disease after reduced-intensity conditioning allogeneic stem cell transplantation from HLA-mismatched unrelated donors.

Koreth J, Stevenson KE, Kim HT, Garcia M, Ho VT, Armand P, Cutler C, Ritz J, Antin JH, Soiffer RJ, Alyea EP 3rd.

Blood. 2009 Aug 27. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19713456?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors undertake a phase-I trial of bortezomib, tacrolimus and methotrexate for graft-versus-host-disease GVHD prophylaxis after reduced-intensity conditioning alloSCT and find that bortezomib is a promising novel immunomodulatory agent in allogeneic transplantation.

Graft-versus-host-disease (GVHD) is a significant complication of allogeneic stem cell transplantation (alloSCT). The proteasome-inhibitor bortezomib has immunomodulatory properties of potential benefit for GVHD control. We undertook a phase-I trial of bortezomib, tacrolimus and methotrexate for GVHD prophylaxis after reduced-intensity conditioning alloSCT using HLA-mismatched unrelated donors. Twenty-three patients were enrolled. Bortezomib dose-levels of 1, 1.3 and 1.5 mg/m(2) were evaluated with 5, 3, and 5 patients respectively. Ten additional patients were accrued at the 1.3 mg/m(2) bortezomib dose-level. Bortezomib-related toxicity was minimal. With a 12-month median follow-up, grade II-IV acute GVHD occurred in 3 patients, a 180-day cumulative incidence of 13%. Chronic GVHD occurred in 9 patients, a 1-year cumulative incidence of 41%. At 1-year the non-relapse mortality was zero, cumulative incidence of relapse/progression was 29%, and overall, progression-free, and event-free survival was 75%, 64%, and 59% respectively. Bortezomib is a promising novel immunomodulatory agent in allogeneic transplantation.

GRP-78 secreted by tumor cells blocks the anti-angiogenic activity of bortezomib.

Kern J, Untergasser G, Zenzmaier C, Sarg B, Gastl G, Gunsilius E, Steurer M.

Blood. 2009 Aug 27. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19713465?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

From their data, the authors conclude that distinct solid tumor cells are able to secrete GRP-78 into the tumor microenvironment, thus demonstrating a hitherto unknown mechanism of resistance to bortezomib.

Anti-angiogenic effects of the proteasome inhibitor bortezomib were analyzed on tumor xenografts in vivo. Bortezomib strongly inhibited angiogenesis and vascularization in the chicken chorioallantoic membrane (CAM). Bortezomib's inhibitory effects on CAM vascularization were abrogated in the presence of distinct tumor xenografts thanks to a soluble factor secreted by tumor cells. Through size-exclusion and ion-exchange chromatography as well as mass spectroscopy we identified GRP-78, a chaperone protein of the unfolded protein response, as being responsible for bortezomib resistance. In fact, a variety of bortezomib-resistant solid tumor cell lines (PC-3, HRT-18), but not myeloma cell lines (U266, OPM-2), were able to secrete high amounts of GRP-78. Recombinant GRP-78 conferred bortezomib resistance to endothelial cells and OPM-2 myeloma cells. Knockdown of GRP78 gene expression in tumor cells and immunodepletion of GRP78 protein from tumor cell supernatants restored bortezomib sensitivity. GRP-78 did not bind or complex bortezomib, but induced prosurvival signals by phosphorylation of ERK and inhibited p53-mediated expression of pro-apoptotic Bok and Noxa proteins in endothelial cells. From our data we conclude that distinct solid tumor cells are able to secrete GRP-78 into the tumor microenvironment, thus demonstrating a hitherto unknown mechanism of resistance to bortezomib.

Cord blood transplantation with a reduced-intensity conditioning regimen for patients with relapsed aggressive multiple myeloma after cytoreduction with bortezomib.

Kasahara I, Nishio M, Yamamoto S, Endo T, Fujimoto K, Yamaguchi K, Takeda Y, Goto H, Sato N, Koike T.

Int J Hematol. 2009 Aug 29. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19728021?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study of two myeloma patients suggests that the timing of cord blood transplantation (CBT) with a reduced-intensity conditioning regimen may be very important, and cytoreduction with not only ASCT but also bortezomib could give a promising chance for a successful CBT.

Two multiple myeloma patients relapsed after autologous stem cell transplantation (ASCT). Conventional chemotherapy, including thalidomide, showed very little effect, but both patients responded well to a standard dose of bortezomib. One patient was treated with two additional cycles of bortezomib, but his clinical course suddenly deteriorated. Unrelated cord blood transplantation (CBT) with reduced-intensity conditioning regimen (RIC) was performed in refractory disease. After CBT, the clinical course was aggravated by tumor lysis syndrome and other conditions, thus resulting in patient death on day 34. Thereafter, we administered CBT with RIC on the second patient after just one course of bortezomib therapy since she was in partial remission. The second patient developed acute and chronic GVHD, and both responded to the steroid therapy. She has been in complete remission for more than 48 months after CBT. These results suggested that the timing of CBT with RIC may be very important, and cytoreduction with not only ASCT but also bortezomib could give a promising chance for a successful CBT.

Bortezomib and Liposomal Doxorubicin Are Highly Effective in Obtaining the Best Possible Response before Autologous Transplant for Multiple Myeloma.

Buda G, Orciuolo E, Galimberti S, Cecconi N, Petrini M.

Acta Haematol. 2009 Aug 29;122(1):39-41. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19729887?ordinalpos=18&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Ascorbic acid inhibits antitumor activity of bortezomib in vivo.

Perrone G, Hideshima T, Ikeda H, Okawa Y, Calabrese E, Gorgun G, Santo L, Cirstea D, Raje N, Chauhan D, Baccarani M, Cavo M, Anderson KC.

Leukemia. 2009 Sep;23(9):1679-86. [Epub 2009 Apr 16.]

http://www.ncbi.nlm.nih.gov/pubmed/19369963?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study shows for the first time show that vitamin C can significantly reduce the activity of bortezomib treatment in vivo, suggesting that patients receiving treatment with bortezomib should avoid taking vitamin C dietary supplements.

Earlier studies have shown that ascorbic acid (vitamin C) inhibits bortezomib-induced cytotoxicity against cancer cells in vitro. However, the clinical significance of vitamin C on bortezomib treatment is unclear. In this study, we examined whether daily oral intake of vitamin C inhibits antimultiple myeloma (MM) activities of bortezomib. Vitamin C, at orally achievable concentrations, inhibited in vitro MM cell cytotoxicity of bortezomib and blocked its inhibitory effect on 20S proteasome activity. Specifically, plasma collected from healthy volunteers taking 1 g/day vitamin C reduced bortezomib-induced MM cell death in vitro. This antagonistic effect of vitamin C against proteasome inhibitors is limited to the boronate class of inhibitors (bortezomib and MG262). In vivo activity of this combination treatment was then evaluated using our xenograft model of human MM in SCID (severe combined immune-deficient) mice. Bortezomib (0.1 mg/kg twice a week for 4 weeks) significantly inhibits in vivo MM cell growth, which was blocked by oral vitamin C (40 mg/kg/day). Therefore, our results for the first time show that vitamin C can significantly reduce the activity of bortezomib treatment in vivo; and importantly, suggest that patients receiving treatment with bortezomib should avoid taking vitamin C dietary supplements.

Extended follow-up of a phase 2 trial of bortezomib alone and in combination with dexamethasone for the frontline treatment of multiple myeloma.

Jagannath S, Durie BG, Wolf JL, Camacho ES, Irwin D, Lutzky J, McKinley M, Potts P, Gabayan AE, Mazumder A, Crowley J, Vescio R.

Br J Haematol. 2009 Sep;146(6):619-26. [Epub 2009 Jul 20.]

http://www.ncbi.nlm.nih.gov/pubmed/19622094?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report on the extended follow-up of a phase II study in frontline myeloma of bortezomib alone and in combination with dexamethasone, finding that bortezomib +/- dexamethasone is an effective and well-tolerated induction regimen for the frontline treatment of myeloma.

High-quality response to multiple myeloma (MM) therapy can be predictive for improved outcomes. Novel agents may improve the depth of responses and therefore prolong survival. We report on the extended follow-up of a phase II study in frontline MM of bortezomib alone and in combination with dexamethasone. Forty-nine previously untreated, symptomatic MM patients received bortezomib 1.3 mg/m(2), days 1, 4, 8, 11, for up to six 3-week cycles. High-dose dexamethasone was added for patients not reaching either a partial response after cycle 2 or a complete response (CR) after cycle 4. The overall response rate in 48 evaluable patients was 90%, with 42% achieving at least a very good partial response, of which 19% were CR/near CR. Thirty-six patients received high-dose dexamethasone with 28 (77%) showing improved response. Twenty-seven patients have undergone successful stem-cell transplantation (SCT). After median follow-up of 49 months, 15 patients have died; median overall survival has still not been reached, with an estimated survival at 4 years of 67%. Overall survival with and without SCT was not different (P = 0.54). Grade 3/4 adverse events included neutropenia (10%), sensory neuropathy (6% grade 3), neuropathic pain (4% grade 3), and diarrhoea (4% grade 3). Bortezomib +/- dexamethasone is an effective and well-tolerated induction regimen for the frontline treatment of MM.

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 Sep;15(3):131-41. [Epub 2009 Mar 10.]

http://www.ncbi.nlm.nih.gov/pubmed/19276138?ordinalpos=27&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.

Combinatorial efficacy of anti-CS1 monoclonal antibody elotuzumab (HuLuc63) and bortezomib against multiple myeloma.

van Rhee F, Szmania SM, Dillon M, van Abbema AM, Li X, Stone MK, Garg TK, Shi J, Moreno-Bost AM, Yun R, Balasa B, Ganguly B, Chao D, Rice AG, Zhan F, Shaughnessy JD Jr, Barlogie B, Yaccoby S, Afar DE.

Mol Cancer Ther. 2009 Sep 1. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19723891?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' findings provide the rationale for a clinical trial combining elotuzumab and bortezomib, which will test the hypothesis that combining both drugs would result in enhanced immune lysis of myeloma by elotuzumab and direct targeting of myeloma by bortezomib.

Monoclonal antibody (mAb) therapy for multiple myeloma, a malignancy of plasma cells, has not been clinically efficacious in part due to a lack of appropriate targets. We recently reported that the cell surface glycoprotein CS1 (CD2 subset 1, CRACC, SLAMF7, CD319) was highly and universally expressed on myeloma cells while having restricted expression in normal tissues. Elotuzumab (formerly known as HuLuc63), a humanized mAb targeting CS1, is currently in a phase I clinical trial in relapsed/refractory myeloma. In this report we investigated whether the activity of elotuzumab could be enhanced by bortezomib, a reversible proteasome inhibitor with significant activity in myeloma. We first showed that elotuzumab could induce patient-derived myeloma cell killing within the bone marrow microenvironment using a SCID-hu mouse model. We next showed that CS1 gene and cell surface protein expression persisted on myeloma patient-derived plasma cells collected after bortezomib administration. In vitro bortezomib pretreatment of myeloma targets significantly enhanced elotuzumab-mediated antibody-dependent cell-mediated cytotoxicity, both for OPM2 myeloma cells using natural killer or peripheral blood mononuclear cells from healthy donors and for primary myeloma cells using autologous natural killer effector cells. In an OPM2 myeloma xenograft model, elotuzumab in combination with bortezomib exhibited significantly enhanced in vivo antitumor activity. These findings provide the rationale for a clinical trial combining elotuzumab and bortezomib, which will test the hypothesis that combining both drugs would result in enhanced immune lysis of myeloma by elotuzumab and direct targeting of myeloma by bortezomib.

Impact of prior therapies on the relative efficacy of bortezomib compared with dexamethasone in patients with relapsed/refractory multiple myeloma.

Vogl DT, Stadtmauer EA, Richardson PG, Sonneveld P, Schuster MW, Irwin D, Facon T, Harousseau JL, Boral A, Neuwirth R, Anderson KC.

Br J Haematol. 2009 Sep 1. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19725827?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This phase III trial examines whether prior exposure to specific therapies affects the relative efficacy of bortezomib versus dexamethasone in relapsed/refractory myeloma, with results that confirm the superiority of bortezomib, regardless of prior exposure to specific therapies.

Summary This subgroup analysis of the phase III APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial examined whether prior exposure to specific therapies affected the relative efficacy of bortezomib versus dexamethasone in relapsed/refractory myeloma. Time to progression and overall survival were superior with bortezomib in all subgroups, with no evidence of interaction between any prior therapies and assignment to study therapy. Patients with prior thalidomide exposure had worse outcomes overall, but neither prior thalidomide nor prior autologous stem cell transplantation affected the relative efficacy of bortezomib versus dexamethasone. These results confirm the superiority of bortezomib over dexamethasone, regardless of prior exposure to specific therapies (clinicaltrials.gov: NCT00048230).

"Short Course" Bortezomib plus Melphalan and Prednisone as Induction Prior to Transplant or as Frontline Therapy for Non-Transplant Candidates in Patients with Previously Untreated Multiple Myeloma.

Gasparetto C, Gockerman JP, Diehl LF, de Castro CM, Moore JO, Long GD, Horwitz ME, Keogh G, Chute JP, Sullivan KM, Neuwirth R, Davis PH, Sutton LM, Anderson RD, Chao NJ, Rizzieri D.

Biol Blood Marrow Transplant. 2009 Sep 2. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19733251?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that short-course course bortezomib, melphalan, prednisone (VMP) is highly effective and generally well tolerated, both as initial treatment in non-ASCT patients and induction prior to ASCT, and that VMP does not negatively affect stem cell collection.

PURPOSE: Evaluate the efficacy and safety of short-course bortezomib, melphalan, prednisone (VMP) in previously untreated multiple myeloma as frontline therapy for transplant-ineligible patients and induction prior to autologous stem cell transplantation (ASCT). METHODS: Patients received up to six 28-day cycles of bortezomib 1.3 mg/m(2), days 1, 4, 8, and 11, plus melphalan 6 mg/m(2) and prednisone 60 mg/m(2), days 1-7. After 2-6 cycles, eligible and consenting patients could proceed to ASCT. Responses were assessed by International Uniform Response Criteria. The primary end point was complete response (CR) rate with VMP. RESULTS: Forty five patients were enrolled. Among 44 evaluable patients, response rate was 95%, including 18% >/=CR (9% stringent CR), 27% very good partial responses (VGPR), and 50% partial responses (PR). Twenty patients proceeded to ASCT. Stem cell collection was successful in all; median yield was 5.6x10(6) CD34(+) cells/kg. Post-transplant response rates were 30% >/=CR (10% stringent CR), 65% VGPR, and 5% PR. After median follow-up of 14.0/14.6 months, median time to progression and progression-free survival were both 19.8/27.9 months in non-ASCT/ASCT patients. Seven patients have died; 1-year survival rates were 82%/95% in non-ASCT/ASCT patients. The most common grade 3/4 toxicities were thrombocytopenia (20%), neutropenia (28%), and infection (9%). Peripheral neuropathy grade 2-4 was the most common non-hematopoietic side effect occurring 17 patients (38%), though it was typically reversible and only 5 patients (11%) discontinued therapy as a result of it. CONCLUSION: Short-course VMP is highly effective and generally well tolerated, both as initial treatment in non-ASCT patients and induction prior to ASCT. VMP did not negatively affect stem cell collection. Longer follow-up and prospective phase III trials are required to validate these initial observations.

In vitro anti-myeloma activity of the Aurora kinase inhibitor VE-465.

Negri JM, McMillin DW, Delmore J, Mitsiades N, Hayden P, Klippel S, Hideshima T, Chauhan D, Munshi NC, Buser CA, Pollard J, Richardson PG, Anderson KC, Mitsiades CS.

Br J Haematol. 2009 Sep 8. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19751238?ordinalpos=15&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study characterizes the preclinical anti-myeloma activity of VE465 and finds that combination with bortezomib finds no antagonism.

Summary This study characterized the preclinical anti-myeloma activity of VE465, a low molecular weight pan-Aurora kinase inhibitor. After 96-h drug exposure, several multiple myeloma (MM) cell lines were more sensitive to VE465 compared to non-malignant cells. The anti-MM activity of VE465 was maintained in the presence of interleukin-6 and, interestingly, enhanced by co-culture with stromal cells. However, primary MM cells were less responsive than cell lines. Combinations with dexamethasone (Dex), doxorubicin (Doxo) and bortezomib showed no antagonism. Our study highlights the potential role of the tumour microenvironment in modulating the activity of this drug class.

Phase II Trial of Combination Therapy With Bortezomib, Pegylated Liposomal Doxorubicin, and Dexamethasone in Patients With Newly Diagnosed Myeloma.

Jakubowiak AJ, Kendall T, Al-Zoubi A, Khaled Y, Mineishi S, Ahmed A, Campagnaro E, Brozo C, Braun T, Talpaz M, Kaminski MS.

J Clin Oncol. 2009 Sep 8. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19738129?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the bortezomib, pegylated liposomal doxorubicin and dexamethasone combination regimen is highly effective for initial treatment of myeloma followed by SCT in appropriate patients, and it has a reasonable safety profile.

PURPOSE: This single-center, open-label, phase II trial evaluated the bortezomib, pegylated liposomal doxorubicin (PLD), and dexamethasone combination regimen (VDD) as initial treatment for patients with newly diagnosed multiple myeloma (MM). PATIENTS AND METHODS: Enrolled patients (N = 40) received up to six 3-week cycles of treatment with bortezomib 1.3 mg/m(2) intravenously (IV) on days 1, 4, 8, and 11; PLD 30 mg/m(2) IV on day 4; and dexamethasone 20 to 40 mg daily as specified in the study design. The primary end point was the complete/near-complete response (CR/nCR) rate after six cycles. Secondary end points included overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). The impact of VDD on stem-cell mobilization and collection also was evaluated. RESULTS: After six cycles, the ORR was 85.0% (CR/nCR, 37.5%; very good partial response [VGPR] or better, 57.5%). Patients who underwent stem-cell transplantation (SCT) after VDD (n = 30) experienced increased rates of VGPR or better (53.3% to 76.6% after SCT). Overall, 1-year PFS and OS rates were 92.5% and 97.5%, respectively. Those who achieved VGPR or better after treatment with VDD showed a significantly greater 1-year PFS versus those who achieved less than VGPR (100% v 82%, respectively; P = .03). Similar results were observed in patients who underwent SCT. Grades 3 or 4 hematologic toxicities occurred in </= 10% of

patients; grade 2 painful neuropathy occurred in 7.5%; and grade 3 palmar-plantar erythrodysesthesia occurred in 2.5%. CONCLUSION: VDD is highly effective for initial treatment of MM followed by SCT in appropriate patients, and it has a reasonable safety profile. Achievement of VGPR or better with this initial therapy predicted longer PFS, regardless of the consolidation therapy given.

Involvement of mitochondria and recruitment of Fas/CD95 signaling in lipid rafts in resveratrol-mediated antimyeloma and antileukemia actions.

Reis-Sobreiro M, Gajate C, Mollinedo F.

Oncogene. 2009 Sep 10;28(36):3221-34. [Epub 2009 Jun 29.]

http://www.ncbi.nlm.nih.gov/pubmed/19561642?ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the combination of resveratrol with perifosine or bortezomib potentiated the apoptotic response induced by each single drug.

We have found that resveratrol (trans-3,4',5-trihydroxystilbene) induced apoptosis in multiple myeloma (MM) and T-cell leukemia cells through coclustering of Fas/CD95 death receptor and lipid rafts, whereas normal lymphocytes were spared. Tumor necrosis factor-related apoptosis-inducing ligand receptors, Fas-associated death domain-containing protein (FADD), procaspase-8, procaspase-10, c-Jun amino-terminal kinase and Bid were also recruited into lipid rafts on resveratrol incubation with MM and T-cell leukemia cells. Raft disruption inhibited resveratrol-induced apoptosis. Bcl-XL overexpression prevented resveratrol-induced disruption of mitochondrial transmembrane potential (DeltaPsi(m)) and apoptosis. A FADD dominant-negative mutant, that blocked Fas/CD95 downstream signaling, precluded resveratrol-induced DeltaPsi(m) loss and apoptosis, indicating a sequence of Fas/CD95 signaling-->mitochondrion in the apoptotic response triggered by resveratrol. Cells deficient in Fas/CD95 did not undergo resveratrol-induced apoptosis. Pretreatment of MM cells with interferon-gamma upregulated Fas/CD95 and caspase-8, and potentiated resveratrol-induced apoptosis. Our data indicate that recruitment of Fas/CD95 death receptor and downstream signaling molecules into lipid rafts, followed by DeltaPsi(m) disruption, underlies the apoptotic action of resveratrol in MM and T-cell leukemic cells. Combination of resveratrol with perifosine or bortezomib potentiated the apoptotic response induced by each single drug. These results also highlight the role of recruitment of Fas/CD95 signaling in lipid rafts in antimyeloma and antileukemia chemotherapy.

Proteasome inhibitors in the treatment of multiple myeloma.

Shah JJ, Orlowski RZ.

Leukemia. 2009 Sep 10. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19741722?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors provide an overview of the current state of the art use of bortezomib against multiple myeloma, and highlight areas for future study that will further optimize our ability to benefit patients with this disease.

Targeting intracellular protein turnover by inhibiting the ubiquitin-proteasome pathway as a strategy for cancer therapy is a new addition to our chemotherapeutic armamentarium, and has seen its greatest successes against multiple myeloma. The first-in-class proteasome inhibitor, bortezomib, was initially approved for treatment of patients in the relapsed/refractory setting as a single agent, and was recently shown to induce even greater benefits as part of rationally designed combinations that overcome chemoresistance. Modulation of proteasome function is also a rational approach to achieve chemosensitization to other antimyeloma agents, and bortezomib has now been incorporated into the front-line setting. Bortezomib-based induction regimens are able to achieve higher overall response rates and response qualities than was the case with prior standards of care, and unlike these older approaches, maintain efficacy in patients with clinically and molecularly defined high-risk disease. Second-generation proteasome inhibitors with novel properties, such as NPI-0052 and carfilzomib, are entering the clinical arena, and showing evidence of antimyeloma activity. In this spotlight review, we provide an overview of the current state of the art use of bortezomib and other proteasome inhibitors against multiple myeloma, and highlight areas for future study that will further optimize our ability to benefit patients with this disease.

The use of novel agents in the treatment of relapsed and refractory multiple myeloma.

Laubach JP, Mahindra A, Mitsiades CS, Schlossman RL, Munshi NC, Ghobrial IM, Carreau N, Hideshima T, Anderson KC, Richardson PG.

Leukemia. 2009 Sep 10. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19741729?ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This review focuses on the role of thalidomide, lenalidomide, and bortezomib in relapsed and refractory myeloma.

Although outcomes for patients with multiple myeloma (MM) have improved over the past decade, the disease remains incurable and even patients who respond well to induction therapy ultimately relapse and require additional treatment. Conventional chemotherapy and high-dose therapy with stem cell transplantation (SCT) have historically been utilized in the management of relapsed MM, but in recent years the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib, have assumed a primary role in this setting. This review focuses on the role of thalidomide, lenalidomide and bortezomib in relapsed and refractory MM, with additional discussion dedicated to emerging drugs in relapsed MM that may prove beneficial to patients with this disease.

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