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VELCADE[®] (bortezomib) Issue

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

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

– Susie Novis, President, IMF

VELCADE (bortezomib) Publications 1st Quarter, 2008

Bortezomib inhibits osteoclast activity in patients with multiple myeloma.

Uy GL, Trivedi R, Peles S, Fisher NM, Zhang QJ, Tomasson MH, DiPersio JF, Vij R.

Clin Lymphoma Myeloma. 2007 Nov;7(9):587-9.



http://www.ncbi.nlm.nih.gov/pubmed/18186967?ordinalpos=114&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors examine parameters of bone turnover prospectively in patients with multiple myeloma treated with bortezomib before and after autologous transplantation. They find that the effects on osteoclasts occur in the absence of bisphosphonate treatment and independently of changes in monoclonal protein levels, suggesting that further studies exploring the role of bortezomib as a bone protective agent could be warranted.

BACKGROUND: The antimyeloma agent bortezomib functions as an inhibitor of nuclear factor (NF)-kappaB. Although NF-kappaB inhibition is predicted to affect osteoclast function, preclinical and clinical studies have primarily reported an effect on osteoblasts. **PATIENTS AND METHODS:** We examined parameters of bone turnover prospectively in patients with multiple myeloma treated with bortezomib before and after autologous transplantation. Thirty-nine patients received 2 cycles of bortezomib on days 1, 4, 8, and 11 of a 21-day cycle. After high-dose melphalan with autologous stem cell transplantation, bortezomib 1.3 mg/m² on days 1, 8, 15, and 22 of a 5-week cycle was administered as maintenance therapy. **RESULTS:** During posttransplantation bortezomib, decreases in the urinary excretion of collagen N-telopeptide indicated that bortezomib suppresses osteoclast function. **CONCLUSION:** The effects on osteoclasts occurred in the absence of bisphosphonate treatment and independently of changes in monoclonal protein levels. Further studies exploring the role of bortezomib as a bone protective agent could be warranted.

 ***Liposomal doxorubicin in combination with bortezomib for relapsed or refractory multiple myeloma.***

Ning YM, He K, Dagher R, Sridhara R, Farrell AT, Justice R, Pazdur R.

Oncology (Williston Park). 2007 Nov;21(12):1503-8; discussion 1511, 1513, 1516 passim.

 http://www.ncbi.nlm.nih.gov/pubmed/18077994?ordinalpos=119&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors summarize the FDA review of the data that support the approval of liposomal doxorubicin use in combination with bortezomib in patients with myeloma.

PURPOSE: On May 17, 2007, doxorubicin HCl liposome injection (Doxil) in combination with bortezomib (Velcade) received approval from the US Food and Drug Administration (FDA) for the treatment of relapsed or refractory multiple myeloma after at least one prior therapy that has not included bortezomib. Liposomal doxorubicin's efficacy and safety were demonstrated in a phase III, randomized, multicenter, international trial comparing the combination of this agent plus bortezomib vs bortezomib alone in multiple myeloma patients who had not previously received bortezomib and had received at least one prior therapy. Here we summarize the FDA review of the data that support this approval. **EXPERIMENTAL DESIGN AND RESULTS:** An interim analysis of time to disease progression (TTP), the primary endpoint, was conducted after 249 TTP events in this study that randomized 324 patients to liposomal doxorubicin plus bortezomib treatment and 322 patients to bortezomib monotherapy. Time to progression was significantly prolonged in the combination arm (median TTP = 9.3 months) compared with bortezomib monotherapy (median TTP = 6.5 months), $P < .0001$ (log-rank test); hazard ratio = 0.55 (95% confidence interval = 0.43-0.71). The response rates were similar between the two arms and not statistically different; however, among responding patients, the median duration of response was longer with the combination--10.2 months compared to 7.0 months in the monotherapy arm. Adverse reactions occurred more frequently with the combination therapy. As compared to the monotherapy, frequent grade 3/4 adverse reactions with the combination were neutropenia and thrombocytopenia. **CONCLUSIONS:** Liposomal doxorubicin received FDA approval for use in combination with bortezomib in patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

 ***Pharmacological and clinical profile of Bortezomib (Velcade). [Article in Japanese]***

Fujii H, Kotobuki Y, Nomura S, Harada Y.

Nippon Yakurigaku Zasshi. 2007 Nov;130(5):421-9.

 http://www.ncbi.nlm.nih.gov/pubmed/18000359?ordinalpos=118&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

 ***The Arkansas approach to therapy of patients with multiple myeloma.***

Barlogie B, Anaissie E, van Rhee F, Pineda-Roman M, Zangari M, Shaughnessy J, Epstein J, Crowley J.

Best Pract Res Clin Haematol. 2007 Dec;20(4):761-81.

 http://www.ncbi.nlm.nih.gov/pubmed/18070718?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This article gives an account of the experience of the Arkansas myeloma program since 1989 with transplant-supported high-dose melphalan, novel agents, and prognostic factors as they relate to standard laboratory features, gene expression profiling, and magnetic resonance imaging (MRI).

This chapter gives an account of the experience of the Arkansas myeloma program since 1989 with transplant-supported high-dose melphalan, novel agents, and prognostic factors as they relate to standard laboratory features, gene expression profiling, and magnetic resonance imaging (MRI). Incorporation of novel agents and new concepts, such as post-tandem transplant consolidation therapy, has improved the rate and duration of complete response and prolonged event-free and overall survival rates. With Total Therapy 2, median survival exceeds 8 years, while Total Therapy 3 with added bortezomib has sustained complete remissions in more than 90% of patients at 2 years which, when used as a survival surrogate in Total Therapy 2, assured a high 6-year survival rate of 75%. Gene expression profiling identified 15% of patients with very short survival. MRI-defined focal lesions are associated with poor outcome, while their resolution - although slower than the time course of attaining clinical complete remission - conferred superior survival. Representing a frequent source of recurrence, with genetic profiles (in both plasma and stromal cells) distinct from those in random bone-marrow samples, therapeutic efforts are directed at hastening onset and increasing frequency of focal lesion resolution.

Autologous stem cell transplantation in the elderly including pre- and post-treatment options.

Kumar SK, Hayman SR, Kyle RA.

Bone Marrow Transplant. 2007 Dec;40(12):1115-21. [Epub 2007 Aug 6.]

 http://www.ncbi.nlm.nih.gov/pubmed/17680019?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss how the introduction of novel agents, including bortezomib, has changed the paradigm for treatment of myeloma.

Multiple myeloma (MM) is a disease of the elderly with a median age at diagnosis of 67 years in a referral population. High-dose chemotherapy (HDT) and autologous stem cell transplantation has been shown to improve survival in patients with MM in randomized trials and remains the preferred option for eligible patients. However, the randomized clinical trials demonstrating an advantage for HDT included only patients younger than 65 years and evidence supporting its role for the elderly patients has been based on retrospective reviews. The introduction of thalidomide, lenalidomide and bortezomib has changed the paradigm for treatment of myeloma and improved the outcome for these patients. Several ongoing clinical trials are evaluating the role of these novel agents in this population, specifically comparing these to HDT-based approaches. Other trials are examining the role of maintenance therapy post-HDT with these novel drugs with or without steroids. The role of HDT will be further redefined in the coming years with improvements in other therapies.

Bortezomib in combination with conventional chemotherapeutic agents for multiple myeloma compared with bortezomib alone.

Min CK, Lee MJ, Eom KS, Lee S, Lee JW, Min WS, Kim CC, Kim M, Lim J, Kim Y, Han K.

Jpn J Clin Oncol. 2007 Dec;37(12):961-8. [Epub 2007 Dec 21.]

 http://www.ncbi.nlm.nih.gov/pubmed/18156171?ordinalpos=85&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study examines whether or not the speed of the response, progression and safety from a combination treatment of bortezomib with common chemotherapeutic drugs is superior to bortezomib monotherapy. The authors find that bortezomib in combination with common chemotherapeutic agents is more active in the treatment of relapsed, refractory myeloma than with bortezomib alone.

BACKGROUND: Recent studies have demonstrated synergy between bortezomib and a number of conventional cytotoxic agents. This study examined whether or not the speed of the response, progression and safety from a combination treatment of bortezomib with common chemotherapeutic drugs is superior to bortezomib monotherapy. **METHODS:** Fifty-seven patients with relapsed, refractory multiple myeloma (MM) who had received at least two cycles of treatment including bortezomib were enrolled in this study. The median age was 56 (35-79) years and 49.1% were male. Thirty-two patients were treated with bortezomib alone and 25 were treated with chemotherapeutic agents that were given in combination with bortezomib. The monoclonal immunoglobulin (mIg) or free light chain (FLC) concentrations were determined in the sera before and after two cycles of bortezomib treatment. The adverse events were assessed and graded according to the NCI Common Toxicity Criteria (version 2.0). **RESULTS:** Thirty-one of the 57 patients (54.4%) attained an early objective response (EOR) after the second bortezomib treatment, defined as a $\geq 50\%$ decrease in the serum mIg or FLC concentration. Improvements in the response were observed when common chemotherapeutic agents were added to bortezomib monotherapy. In patients who received bortezomib combined with chemotherapeutic agents, 19 out of 25 patients (76%) showed an EOR, whereas 12 out of 32 patients (37.5%) given bortezomib monotherapy achieved an EOR after the second cycle of bortezomib treatment ($P = 0.004$); the median decrease from the baseline in the paraprotein level was 74.6 ± 5.9 and $39.7 \pm 4.2\%$, respectively ($P = 0.003$). A statistically significant elevation of serum lactic dehydrogenase ($P = 0.007$) and alkaline phosphatase ($P = 0.027$) from baseline within two cycles of bortezomib treatment was observed in responding patients. With the combination treatment, peripheral neuropathy of \geq Grade II occurred in 12 out of 25 patients (48%) compared with 12 of 32 (37.5%) in those given bortezomib alone ($P = 0.589$). The median time to progression of disease was similar in the two groups (359 ± 43.5 versus 365 ± 103.5 , $P = 0.688$). The multivariate Cox regression model showed that a high serum albumin and low beta2-microglobulin are favorable factors for the progression-free survival following bortezomib treatment. **CONCLUSIONS:** Bortezomib in combination with common chemotherapeutic agents is more active in the treatment of relapsed, refractory MM than with bortezomib alone. However, more effective post-bortezomib treatment is needed to reduce the rate of disease progression particularly in patients with high tumor burden.

Bortezomib in multiple myeloma.

Mateos MV, San Miguel JF.

Best Pract Res Clin Haematol. 2007 Dec;20(4):701-15.

 http://www.ncbi.nlm.nih.gov/pubmed/18070714?ordinalpos=64&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss myeloma treatment uses for bortezomib, as well as practical management of its side effects.

Multiple myeloma (MM) remains an incurable disease, and novel agents are therefore needed to improve outcome. Bortezomib is the first proteasome inhibitor to be approved by the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the treatment of refractory/relapsed MM. Bortezomib has demonstrated significant anti-myeloma activity as a single agent in refractory/relapsed MM. When used in combination with other agents, responses have suggested the possibility of chemosensitization and synergy. All these facts have been the rationale for the use of bortezomib-based regimens as upfront treatment in young and elderly newly diagnosed MM patients. Furthermore, bortezomib does not appear to have an adverse effect on subsequent stem-cell collection. Bortezomib is well tolerated; most side-effects are only mild to moderate and manageable. Practical management of these side-effects is given so that they can be recognized and minimized by dose modification or concomitant therapy.

Chemotherapy for multiple myeloma. [Article in Japanese]

Ishida T.

Nippon Rinsho. 2007 Dec;65(12):2280-4.

 http://www.ncbi.nlm.nih.gov/pubmed/18069273?ordinalpos=92&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses induction therapy prior to chemotherapy, including the use of bortezomib.

The combination of the melphalan and prednisolone (MP) can induce objective responses in about 50% of patients with multiple myeloma (MM) since its introduction in 1960. Since then many combination chemotherapy regimens have been used, but a large metaanalysis showed that the combination of oral MP is as effective as combination regimens including intravenous drugs. In recent years, many novel agents (including bortezomib, thalidomide, and liposomal doxorubicin) have been developed for the MM treatment. More recently, MP has been used in combination with these novel agents. The combination treatment of MP and thalidomide, overall survival was significantly better than seen in the MP treatment. In the near future, primary induction therapy will be changed.

Clinical updates and nursing considerations for patients with multiple myeloma.

Faiman B.

Clin J Oncol Nurs. 2007 Dec;11(6):831-40.

 http://www.ncbi.nlm.nih.gov/pubmed/18063542?ordinalpos=73&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses the oncology nurse's role in optimizing myeloma's new therapeutic options, including bortezomib.

Multiple myeloma accounts for approximately 1% of all new cancers and is characterized by abnormal plasma cell proliferation in the bone marrow. As a result, many patients develop bone lesions, hypercalcemia, anemia, and renal impairment. Although no cure exists for multiple myeloma, current treatments, such as oral melphalan and prednisone, can slow disease progression and prolong overall survival. Several new therapeutic options show promise: lenalidomide, thalidomide, liposomal doxorubicin, and bortezomib. Clinical research presented at the 2006 meeting of the American Society of Hematology, the 2007 meeting of the American Society of Clinical Oncology, and the 11th International Myeloma Workshop showed that newer therapeutic combinations were well tolerated and effective in patients with multiple myeloma. Oncology nurses, with their specialized knowledge of treatment administration and monitoring and their expertise in patient education, have an important role in the management of patients with multiple myeloma to help improve overall survival and quality of life. As newer regimens become available, oncology nurses must be aware of factors that optimize outcomes to help patients understand the benefits of treatment, how to manage side effects, and the importance of treatment adherence.

 ***Diagnosis and management guideline of multiple myeloma.*** [Article in Japanese]

Murakami H, Handa H, Saitoh T.

Nippon Rinsho. 2007 Dec;65(12):2167-76.

 http://www.ncbi.nlm.nih.gov/pubmed/18069257?ordinalpos=94&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

With the recent development of novel therapies, including bortezomib, the authors propose diagnosis and management guidelines for Japanese myeloma patients.

The prognosis of patients with multiple myeloma has been improved in the last decade due to the induction of autologous stem cell transplantation and novel drugs including thalidomide, lenalidomide, and bortezomib into the treatment. Recently, the UK Myeloma Forum and International Myeloma Foundation have successively proposed myeloma management guidelines. Because many novel drugs are not available in Japanese patients, we can not use the same treatment strategy in U.S.A. and Europe. In this chapter, the diagnosis and management guideline is proposed for Japanese patients with myeloma. For convenience, the recommendations are divided into: 1. Diagnostic criteria 2. Indications for starting therapy 3. Treatment(initial therapy, maintenance therapy, and therapy for refractory/relapsed patients) 4. Response criteria 5. Supportive care and management of specific complications.

 ***Escalation therapy with bortezomib, dexamethasone and bendamustine for patients with relapsed or refractory multiple myeloma.***

Fenk R, Michael M, Zohren F, Graef T, Czibere A, Bruns I, Neumann F, Fenk B, Haas R, Kobbe G.

Leuk Lymphoma. 2007 Dec;48(12):2345-51.

 http://www.ncbi.nlm.nih.gov/pubmed/18067009?ordinalpos=86&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In order to improve remission rates without causing undue toxicity, the authors treat 50 patients with relapsed/refractory multiple myeloma according to an institutional sequential treatment algorithm including bortezomib monotherapy.

In order to improve remission rates without causing undue toxicity, we treated 50 patients with relapsed/refractory multiple myeloma according to an institutional sequential treatment algorithm. Bortezomib was given as monotherapy (1.3 mg/m²) on day 1 + 4 + 8 + 11) followed by the addition of dexamethasone in a first (40 mg on day 1 + 4 + 8 + 11) and bendamustine (50 - 100 mg/m²) on day 1 + 8) in a second escalation step for patients with less than a minor response. Bortezomib monotherapy was sufficient in 23 (46%) patients, treatment escalation with dexamethasone was necessary in 20 (40%) patients and 7 (14%) patients needed triple combination therapy. Overall response rate was 84% while toxicity was manageable. Median time to progression and overall survival were 8 and 20 months, respectively. In conclusion, this treatment algorithm resulted in responses in the majority of heavily pre-treated patients while at the same time restricting the toxicity of triple combination therapy to only 14% of non-responding patients.

 ***The evolving background for high-dose treatment for myeloma.***

Sirohi B, Powles R, Harousseau JL, Anderson KC.

Bone Marrow Transplant. 2007 Dec;40(12):1097-100. [Epub 2007 Oct 1.]

 http://www.ncbi.nlm.nih.gov/pubmed/17906702?ordinalpos=66&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors address the challenge to optimize the use of stem cell transplantation into the emergence of the development, availability and regulatory approval of newer targeted therapies, such as bortezomib.

In the constantly evolving field of myeloma, this special issue is slanted towards how the newer targeted treatments fit in with various transplantation strategies. High-dose treatment for myeloma with autologous stem cell transplantation started 25 years ago, with the consequence of producing complete remissions and a doubling of survival. Since then, its role has been refined and it has been accepted as standard treatment. The current challenge is to optimize its use into a background of the development, availability and regulatory approval of newer targeted therapies such as Thalidomide, Revlimid (Lenalidomide) and Velcade (Bortezomib). This special issue addresses these problems, and gives particular emphasis on the attainment of very long-term survival, with normal quality of life for patients with myeloma who do not necessarily need to be cured of their molecular disease, that is, they are 'operationally cured.' It is hoped that the reader will find the information in this issue useful in the day-to-day management of patients and we hope that this will also inspire new research directions designed to improve the outcome of patients with myeloma.

High-dose chemotherapy and autologous hematopoietic stem cell transplantation in myeloma patients under the age of 65 years.

Mehta J, Singhal S.

Bone Marrow Transplant. 2007 Dec;40(12):1101-14. [Epub 2007 Aug 6.]

 http://www.ncbi.nlm.nih.gov/pubmed/17680020?ordinalpos=68&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the uses of novel agents, such as bortezomib, with respect to high-dose chemotherapy and stem cell transplantation for myeloma patients under 65 years of age.

One or two cycles of high-dose chemotherapy with autologous hematopoietic stem cell transplantation have been shown to improve response rates and survival in myeloma. While this observation has largely been made in patients under the age of 65 years, there is evidence to suggest that the conclusions can be extrapolated to older individuals as well. In contrast to other hematologic malignancies treated with high-dose therapy, autografted myeloma patients continue to relapse several years after transplantation, and few patients are cured with this modality. However, up to a third of patients may be alive beyond a decade; some with excellent quality of life giving rise to the concept of 'operational cure'. Relapsing disease can be treated with novel agents or repeat high-dose chemotherapy and transplantation. The pressing questions to which answers are not obvious at the moment are whether tandem transplantation should be offered to all patients, and whether novel agents should be used before transplantation or reserved for relapse. Despite their excellent activity, there is no evidence so far that novel agents such as thalidomide, bortezomib and lenalidomide can replace high-dose chemotherapy and stem cell transplantation.

The malignant clone and the bone-marrow environment.

Podar K, Richardson PG, Hideshima T, Chauhan D, Anderson KC.

Best Pract Res Clin Haematol. 2007 Dec;20(4):597-612.

 http://www.ncbi.nlm.nih.gov/pubmed/18070708?ordinalpos=65&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors review current knowledge of the multiple myeloma (MM) cell clone, as well as the impact of the bone marrow microenvironment on tumor-cell growth, survival, migration and drug resistance because, although novel agents such as bortezomib are now FDA-approved to treat MM, patients inevitably relapse and further improvements remain urgently needed.

Multiple myeloma (MM) is characterized by the clonal expansion of monoclonal immunoglobulin-secreting plasma cells within the bone marrow (BM). It has become clear that the intimate reciprocal relationship between the tumor cell clone and the niches of the BM microenvironment plays a pivotal pathophysiologic role in MM. We and others have identified several new molecular targets and derived novel therapies which induce cytotoxicity against MM cells in the BM milieu, including thalidomide, bortezomib, and lenalidomide. Importantly, these agents induce tumor-cell death, as well as inhibit MM-cell-BM-stromal-cell (BMSC) adhesion and related tumor-cell growth, survival, and migration. Moreover, they block both constitutive and MM-cell binding-induced growth factor and cytokine secretion in BMSCs. Further, they also block tumor angiogenesis and can augment anti-MM immunity. Although all three of these agents are now FDA-approved to treat MM, patients inevitably relapse, and further improvements remain urgently needed. Here we review our current knowledge of the MM cell clone, as well as the impact of the BM microenvironment on tumor-cell growth, survival, migration and drug resistance. Delineating the mechanisms and sequelae of the reciprocal relationship between the MM cell clone, distinct BM extracellular matrix proteins, and accessory cell compartments may provide the basis for new effective therapeutic strategies to re-establish BM homeostasis and thereby improve MM patient outcome.

The molecular pathogenesis of myeloma for the therapeutic targets. [Article in Japanese]

Hanamura I.

Nippon Rinsho. 2007 Dec;65(12):2202-8.

 http://www.ncbi.nlm.nih.gov/pubmed/18069261?ordinalpos=93&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author reviews the molecular pathogenesis of myeloma, especially the new findings related with NF-kappaB activation.

Multiple myeloma (MM) is a neoplasia of plasma cells in bone marrow. High dose chemotherapy followed by stem cell transplantation and new drugs such as thalidomide and bortezomib have improved the survival in MM. However, most of patients with myeloma are incurable so there is a need for the new therapeutic approaches that have been developed against molecular targets and pathway. It has been reported that activation of NF-kappaB pathway was required to survival of myeloma cells and this pathway was the potential target for anti-MM therapy. Recently we reported diverse genetic aberrations that activated NF-kappaB signaling in MM. In this section, the molecular pathogenesis of myeloma, especially the new findings related with NF-kappaB activation, will be reviewed in Japanese.

 **Molecular targeting therapy for multiple myeloma.** [Article in Japanese]

Takatoku M.

Nippon Rinsho. 2007 Dec;65(12):2345-50.

 http://www.ncbi.nlm.nih.gov/pubmed/18069281?ordinalpos=89&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses recent clinical data regarding bortezomib for both newly diagnosed and relapsed/refractory myeloma.

Molecular target therapy is the most progressive and promising anticancer therapy in last decade. Multiple myeloma is also one of the major therapeutic targets for using molecular based technology. The recent availability of clinical data regarding thalidomide-, lenalidomide-, and bortezomib-based regimens has provided new, effective treatment options for patients with both newly diagnosed and relapsed/refractory multiple myeloma. We are expecting that future clinical trials can be designed to achieve a high likelihood of success based on molecular studies, cell-signaling, and correlative science studies. Studies with these agents also provide new insight into the cancer biology underlying multiple myeloma in humans.

 **Role of autologous stem-cell transplantation in multiple myeloma.**

Attal M, Harousseau JL.

Best Pract Res Clin Haematol. 2007 Dec;20(4):747-59.

 http://www.ncbi.nlm.nih.gov/pubmed/18070717?ordinalpos=62&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the current results of autologous stem-cell transplantation and the introduction of novel agents, such as bortezomib.

Multiple myeloma (MM) is one of the diseases in which the impact of dose intensity has been demonstrated. Consequently, in 2005 MM was the first disease for which autologous stem-cell transplantation (ASCT) was indicated in Europe and the US. However, ASCT is not curative, and most patients relapse in a median of 3 years. The introduction of novel agents such as thalidomide, bortezomib (Velcade((R))) or lenalidomide (Revlimid((R))) was logical to try to improve the high-dose strategy, and promising results have been reported. This article will focus on the current results of ASCT and will discuss the main research area to try to improve this strategy.

 **The role of bortezomib in the treatment of multiple myeloma.** [Article in Japanese]

Gotoh A, Ohyashiki K.

Nippon Rinsho. 2007 Dec;65(12):2309-14.

 http://www.ncbi.nlm.nih.gov/pubmed/18069278?ordinalpos=91&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the growing body of clinical evidence showing bortezomib's effectiveness alone and in combination not only in relapsed/refractory cases but also in the front line setting.

The proteasome inhibitor bortezomib is approved for the treatment of patients with relapsed/refractory multiple myeloma. Bortezomib represents a new generation of treatments for multiple myeloma that affects both specific intracellular signaling pathways and the tumor microenvironment. There is a growing body of clinical evidence showing its effectiveness alone and in combination not only in relapsed/refractory cases but also in the front line setting. Regimens incorporating bortezomib and other novel agents such as immunomodulatory derivatives of thalidomide together with commonly used conventional drugs show considerable high response rates including complete response that resulting in improving survival, with or without following stem cell transplantation. Thus these approaches represent a promising future direction in myeloma treatment.

 ***The role of stem cell transplantation for multiple myeloma.*** [Article in Japanese]

Shimazaki C.

Nippon Rinsho. 2007 Dec;65(12):2338-44.

 http://www.ncbi.nlm.nih.gov/pubmed/18069280?ordinalpos=90&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (SCT) for newly diagnosed myeloma patients under 65 years of age, including how recently developed drugs, including bortezomib, in combination with SCT might improve survival.

The role of stem cell transplantation in the treatment of multiple myeloma (MM) is described. High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (SCT) is routinely recommended for most patients with newly diagnosed MM under 65 years of age. However, recently published meta-analysis of randomized controlled trials indicated PFS benefit but not OS benefit for HDT with autologous SCT performed early in MM. Tandem autologous SCT is superior to single transplantation in terms of event-free survival. Survival in recipients of autologous SCT followed by reduced-intensity conditioning allogeneic transplantation is superior to that in recipients of tandem autologous SCT. Recently developed new drugs including thalidomide, lenalidomide or bortezomib in combination with SCT might improve survival of myeloma patients.

 ***Targeted treatments to improve stem cell outcome: old and new drugs.***

Raab MS, Breitkreutz I, Anderson KC.

Bone Marrow Transplant. 2007 Dec;40(12):1129-37. [Epub 2007 Sep 3.]

 http://www.ncbi.nlm.nih.gov/pubmed/17768392?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the increasingly integrated role of bortezomib in therapeutic regimens for newly diagnosed myeloma patients.

Thalidomide, lenalidomide and bortezomib have been approved for the treatment of relapsed or refractory multiple myeloma in the recent years. These agents are now being increasingly integrated into therapeutic regimens for newly diagnosed patients. First data are available on the promising activity of these novel agents in induction therapy, as well as maintenance treatment to improve outcome after stem cell transplantation. Whether these early results will lead to prolonged overall survival and thereby ultimately redefine the role of stem cell transplantation in first-line treatment of multiple myeloma will be one of the most important questions to be answered in the coming years.

 ***Targeting apoptosis in solid tumors: the role of bortezomib from preclinical to clinical evidence.***

Russo A, Fratto ME, Bazan V, Schiró V, Agnese V, Cicero G, Vincenzi B, Tonini G, Santini D.

Expert Opin Ther Targets. 2007 Dec;11(12):1571-86.

 http://www.ncbi.nlm.nih.gov/pubmed/18020979?ordinalpos=75&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This review focuses on the use of bortezomib both in its therapeutic and its biologic role and also discusses the most recent applications of the drug in solid tumors, both at a preclinical and clinical level.

The ubiquitin-proteasome pathway is the main proteolytic system present in the nucleus and cytoplasm of all eukaryotic cells. Apoptosis activation induced by ubiquitin-proteasome pathway inhibition makes the proteasome a new target of anticancer therapy. Bortezomib is the first proteasome inhibitor to be approved by the US FDA; in 2003 as a third line and in 2005 as a second line therapy for the treatment of multiple myeloma only. This review focuses on the use of bortezomib, not only in its therapeutic role but also, more specifically, in its biologic role and discusses the most recent applications of the drug in solid tumors, both at a preclinical and clinical level.

 **Therapy of multiple myeloma: indications and options.** [Article in German]

Peest D, Ganser A.

Internist (Berl). 2007 Dec;48(12):1343-1348.

 http://www.ncbi.nlm.nih.gov/pubmed/17960351?ordinalpos=81&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss approaches to the treatment of myeloma, including use of bortezomib.

The multiple myeloma (MM) has an incidence of 3-4/100,000 in the Caucasian population. MM has to be distinguished from smouldering MM and monoclonal gammopathy of uncertain significance (MGUS). In younger patients (<65 years) a good long-term remission is the aim of therapy, while in the elderly patients with comorbidities the aim is a good partial remission with good quality of life. In the elderly this can be achieved with a combination of melphalan and prednisone. High-dose chemotherapy, often as a tandem transplantation, is part of standard therapy of MM patients <65 years. However, allogeneic stem cell transplantation is the only curative approach. New substances approved for treatment of relapsed MM include bortezomib, thalidomide, and lenalidomide.

 **Bortezomib in combination with celecoxib in patients with advanced solid tumors: a phase I trial.**

Hayslip J, Chaudhary U, Green M, Meyer M, Dunder S, Sherman C, Salzer S, Kraft A, Montero AJ.

BMC Cancer. 2007 Dec 3;7(1):221. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18053191?ordinalpos=57&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors seek to determine the maximum tolerated dose and dose-limiting toxicities of bortezomib in combination with celecoxib in patients with advanced solid tumors and find that the combination of bortezomib and celecoxib was well tolerated, without dose limiting toxicities observed throughout the dosing ranges tested.

ABSTRACT: BACKGROUND: COX-2 inhibitors, such as celecoxib, and ubiquitin-proteasome pathway inhibitors, such as bortezomib, can down-regulate NF-kappaB, a transcription factor implicated in tumor growth. The objective of this study was to determine the maximum tolerated dose and dose-limiting toxicities of bortezomib in combination with celecoxib in patients with advanced solid tumors. METHODS: Patients received escalating doses of bortezomib either on a weekly schedule (days 1, 8, 15, 22, and 29 repeated every 42 days) or on a twice-weekly administration schedule (days 1, 4, 8, and 11 repeated every 21 days), in combination with escalating doses of celecoxib twice daily throughout the study period from 200 mg to 400 mg twice daily. RESULTS: No dose-limiting toxicity was observed during the study period. Two patients had stable disease lasting for four and five months each, and sixteen patients developed progressive disease. CONCLUSIONS: The combination of bortezomib and celecoxib was well tolerated, without dose limiting toxicities observed throughout the dosing ranges tested, and will be studied further at the highest dose levels investigated.

 **Alkylating agents induce activation of NFkappaB in multiple myeloma cells.**

Baumann P, Mandl-Weber S, Oduncu F, Schmidmaier R.

Leuk Res. 2007 Dec 14. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18083229?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors' data suggest that the drug-sensitizing effect of bortezomib on myeloma cells is due to inhibition of melphalan- and doxorubicin-induced activation of NFkappaB activity.

Multiple myeloma is still not curable and drug combination strategies are currently being evaluated in order to achieve high remission rates with tolerable toxicity. Bortezomib has been shown to exert inhibitory effects on NFkappaB activity. NFkappaB in turn is known to be activated by cytokines, growth factors and by cellular adhesion to bone marrow stromal cells and represents an important mediator of primary and secondary drug resistance in multiple myeloma that confers to proliferation and survival. In this study we confirm that bortezomib sensitized MM cells to the DNA-damaging drugs melphalan and doxorubicin. Further, we demonstrate that the sole incubation of MM cells with melphalan or doxorubicin leads to a vast activation of NFkappaB activity. Additionally, we show that the co-incubation of bortezomib with melphalan or doxorubicin reduces activation of NFkappaB. These data suggest that the drug-sensitizing effect of bortezomib on MM cells is due to inhibition of melphalan- and doxorubicin-induced activation of NFkappaB activity. This study, therefore, supports the idea of combining a NFkappaB inhibitor with alkylating drugs in the therapy of multiple myeloma.

Bortezomib blocks Bax degradation in malignant B-cells during treatment with TRAIL.

Liu FT, Agrawal SG, Gribben JG, Ye H, Du MQ, Newland AC, Jia L.

Blood. 2007 Dec 26. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18160669?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study reveals that Bax instability confers resistance to TRAIL, which can be reversed by Bax stabilization with a proteasome inhibitor such as bortezomib.

Pro-apoptotic Bcl-2 family member Bax is a crucial protein in the induction of apoptosis and its activation is required for this process. Here we report that Bax is a short-lived protein in malignant B-cells and Bax protein levels decreased rapidly when protein synthesis was blocked. Malignant B-cells were relatively resistant to TNF-related apoptosis inducing ligand (TRAIL)-induced apoptosis and this correlated with low basal Bax protein levels. Furthermore, during treatment with TRAIL, the resistant cell lines showed prominent Bax degradation activity. This degradation activity was localized to mitochondrial Bax and could be prevented by truncated Bid (tBid), a BH3-only protein; in contrast, cytosolic Bax was relatively stable. The proteasome inhibitor Bortezomib is a potent drug in inducing apoptosis in vitro in malignant B-cell lines and primary chronic B-lymphocytic leukemic (CLL) cells. In CLL cells, Bortezomib induced Bax accumulation, translocation to mitochondria, conformational change, and oligomerization. Accumulation and stabilization of Bax protein by Bortezomib sensitized malignant B-cells to TRAIL-induced apoptosis. This study reveals that Bax instability confers resistance to TRAIL, which can be reversed by Bax stabilization with a proteasome inhibitor.

Bortezomib-induced skin eruption.

Sanchez-Politta S, Favet L, Kerl K, Dietrich PY, Piguat V.

Dermatology. 2008;216(2):156-8. [Epub 2008 Jan 23.]

 http://www.ncbi.nlm.nih.gov/pubmed/18216478?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors describe the case of a patient who developed erythematous and edematous plaques after treatment with bortezomib.

Bortezomib (Velcade) is a proteasome inhibitor recently developed and mainly used for the treatment of multiple myeloma. Bortezomib represents a novel class of drugs functioning as proteasome inhibitors. Skin complications of bortezomib treatment are very frequent but poorly characterized. We describe the case of a patient who developed erythematous and edematous plaques after treatment with bortezomib. This case illustrates one of the potential reactions associated with bortezomib administration and underlines the need to recognize and report cutaneous side effects of this new drug.

Phase I and II pharmacokinetic and pharmacodynamic study of the proteasome inhibitor bortezomib in Japanese patients with relapsed or refractory multiple myeloma.

Ogawa Y, Tobinai K, Ogura M, Ando K, Tsuchiya T, Kobayashi Y, Watanabe T, Maruyama D, Morishima Y, Kagami Y, Taji H, Minami H, Itoh K, Nakata M, Hotta T.

Cancer Sci. 2008 Jan;99(1):140-4. [Epub 2007 Oct 27.]

 http://www.ncbi.nlm.nih.gov/pubmed/17970782?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This phase I and II study evaluates the safety, pharmacokinetics, pharmacodynamics, and efficacy of bortezomib in Japanese patients with relapsed or refractory multiple myeloma and finds bortezomib to be effective in Japanese patients.

The purpose of this phase I and II study was to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of bortezomib in Japanese patients with relapsed or refractory multiple myeloma. This was a dose-escalation study designed to determine the recommended dose for Japanese patients (phase I) and to investigate the antitumor activity and safety (phase II) of bortezomib administered on days 1, 4, 8, and 11 every 21 days. Thirty-four patients were enrolled. A dose-limiting toxicity was febrile neutropenia, which occurred in one of six patients in the highest-dose cohort in phase I and led to the selection of 1.3 mg/m² as the recommended dose. Adverse events \geq grade 3 were rare except for hematological toxicities, although there was one fatal case of interstitial lung disease. The overall response rate was 30% (95% confidence interval, 16-49%). Pharmacokinetic evaluation showed a biexponential decline, characterized by a rapid distribution followed by a longer elimination, after dose administration, whereas the area under the concentration-time curve increased proportionately with the dose. Bortezomib was effective in Japanese patients with relapsed or refractory multiple myeloma. A favorable tolerability profile was also seen, although the potential for pulmonary toxicity should be monitored closely. The pharmacokinetic and pharmacodynamic profiles of bortezomib in the present study warrant further investigations, including more relevant administration schedules.

An update on drug combinations for treatment of myeloma.

Srikanth M, Davies FE, Morgan GJ.

Expert Opin Investig Drugs. 2008 Jan;17(1):1-12.

 http://www.ncbi.nlm.nih.gov/pubmed/18095914?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the enormous potential of using novel therapies in combination, such as bortezomib, as challenges for both drug development and clinical trial evaluation.

Multiple myeloma is the second most common haematological malignancy. It is becoming increasingly manageable with conventional and high-dose chemotherapy but there remains a critical need to develop both new drugs and combinations to improve long-term outcomes. Novel biological therapies that specifically target myeloma cells and/or their microenvironmental interactions are being developed that are highly effective, both as single agents and as combinations. Chief among these new agents are the proteasome inhibitor, bortezomib, and the immunomodulatory agents, thalidomide and lenalidomide. These drugs show improved single agent activity that is enhanced in combination. However, many drugs that are being developed in this setting may only have limited single agent activity, but combination use with these and other agents represents a very exciting way of targeting important pathogenic pathways crucial in myeloma development. This represents a challenge for both drug development and clinical trial evaluation, which has the potential to revolutionise the clinical management of myeloma and a paradigm for drug development in other diseases.

Bone marrow angiogenesis and angiogenic factors in multiple myeloma treated with novel agents.

Cibeira MT, Rozman M, Segarra M, Lozano E, Rosiñol L, Cid MC, Filella X, Bladé J.

Cytokine. 2008 Jan 3. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18178097?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors study bone marrow angiogenesis in multiple myeloma treated with novel agents, including bortezomib. They find that there is no relationship between microvessel density estimation and baseline serum levels of angiogenic cytokines.

Introduction. An increased bone marrow (BM) angiogenesis is associated with poor outcome in multiple myeloma (MM). Objective. Angiogenesis study in MM treated with novel antimyeloma agents: thalidomide, lenalidomide, bortezomib, and with dexamethasone. Patients and methods. Forty-four patients with MM (14 newly diagnosed, 30 refractory/relapsed) were treated with novel agents at our institution. A BM biopsy was obtained before the initiation of therapy in 19. Angiogenesis was assessed by microvessel density (MVD) estimation in BM biopsies stained with the monoclonal anti-CD34 antibody, and by serum levels of angiogenic factors (VEGF, bFGF, and HGF) and cytokines (IL-6 and TNF-alpha). Results. A positive correlation was found between BM plasma cell involvement and MVD estimation ($p=0.01$). However, MVD was not significantly correlated with either disease phase ($p=0.065$) or response to therapy ($p=0.79$). Neither baseline serum levels of angiogenic cytokines correlated to response to treatment. No significant correlation was found between BM MVD and serum levels of angiogenic cytokines. Serum levels of angiogenic cytokines before and after therapy showed a significant increase of bFGF ($p=0.008$). Conclusion. There is no relationship between MVD estimation and baseline serum levels of angiogenic cytokines, neither between each of them and response to therapy.

Bortezomib inhibits tumor adaptation to hypoxia by stimulating the FIH-mediated repression of hypoxia-inducible factor-1.

Shin DH, Chun YS, Lee DS, Huang LE, Park JW.

Blood. 2008 Jan 3. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18174379?ordinalpos=42&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors demonstrate that bortezomib attenuates the hypoxic induction of erythropoietin and vascular endothelial growth factor at sub-nanomolar concentrations in multiple myeloma and liver cancer cell-lines, regardless of cytotoxic concentrations of bortezomib.

Bortezomib (Velcade or PS-341), a proteasome inhibitor, has been examined clinically for the treatment of multiple myeloma and several solid tumors. Bortezomib directly induces tumor cell death and has also been reported to inhibit tumor adaptation to hypoxia by functionally inhibiting HIF-1alpha. However, the mechanism underlying HIF-1-inhibition by bortezomib remains obscure. In the present study, we demonstrated that bortezomib attenuated the hypoxic induction of erythropoietin and vascular endothelial growth factor at sub-nanomolar concentrations in multiple myeloma and liver cancer cell-lines, regardless of cytotoxic concentrations of bortezomib. Bortezomib repressed HIF-1alpha activity by inhibiting the recruitment of p300 co-activator. Specifically, bortezomib targeted HIF-1alpha C-terminal

transactivation domain (CAD) but not the CAD lacking Asn803, which is a hydroxylation site by FIH. Accordingly, this effect of bortezomib on CAD was augmented by FIH expression and abolished by FIH knock-down. Furthermore, bortezomib stimulated the interaction between CAD and FIH under hypoxic conditions, and FIH inhibition reversed the suppressions of erythropoietin and vascular endothelial growth factor by bortezomib. We propose that the mechanism underlying the inhibitory effects of bortezomib on tumor angiogenesis and hypoxic adaptation involves the repression of HIF-1 α transcriptional activity by reinforcing the FIH-mediated inhibition of p300 recruitment.

Eye ***Pure antiestrogen-induced G1-arrest in myeloma cells results from the reduced kinase activity of cyclin D3/CDK6 complexes whereas apoptosis is mediated by endoplasmic reticulum-dependent caspases.***

Gauduchon J, Seguin A, Marsaud V, Clay D, Renoir JM, Sola B.

Int J Cancer. 2008 Jan 8. [Epub ahead of print.]



http://www.ncbi.nlm.nih.gov/pubmed/18183592?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that RU 58668 mediates the inhibition of survival, the activation of apoptosis and potentiates anticancer drugs, such as bortezomib. Those combinatory effects provide a basis for the potential use of pure antiestrogens in myeloma treatment.

Multiple myeloma (MM) is a malignancy characterized by the accumulation of tumoral plasma cells in bone marrow. This disease remains incurable and the development of new therapeutic strategies is urgently required. We have studied the effects of 2 selective estrogen receptor disrupters (SERDs), RU 58668 (RU) and ICI 182,780 (ICI) or pure antiestrogens (AEs) on MM cell lines. Both compounds have antimyeloma activity through either cell cycle arrest or induction of apoptosis. To analyze the molecular mechanisms of SERD action, we choose 2 differently responding cell lines as models. In LP-1 cells, RU blocked cell cycle at the G1 phase. RU treatment induced a rapid decrease of c-Myc, an upregulation of p27(Kip1), and the subsequent decreased activity of cyclin-dependent kinase, CDK6 and associated cyclin D3, impairing the inactivation of the retinoblastoma protein (pRb). In RPMI 8226 cells, RU induced apoptosis by recruiting endoplasmic reticulum- as well as mitochondria-associated caspases. Moreover, RU interfered with the NF-kappaB survival pathway, often deregulated in MM malignancy. Antimyeloma activities were observed in dexamethasone (Dex)- and RU-resistant cells when RU was combined with bortezomib; Dex and bortezomib being frequently used in MM therapy. RU induced the death of CD138+ cells purified from MM patients but not CD19+ normal cells obtained from tonsils. Therefore, RU mediates the inhibition of survival, the activation of apoptosis and finally potentiates anticancer drug. Those combinatory effects provide a basis for the potential use of pure AEs in MM treatment.

Eye ***High-risk myeloma: a gene expression based risk-stratification model for newly diagnosed multiple myeloma treated with high-dose therapy is predictive of outcome in relapsed disease treated with single-agent bortezomib or high-dose dexamethasone.***

Zhan F, Barlogie B, Mulligan G, Shaughnessy JD Jr, Bryant B.

Blood. 2008 Jan 15;111(2):968-9.



http://www.ncbi.nlm.nih.gov/pubmed/18182586?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Eye ***Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study.***

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

Leukemia. 2008 Jan 17. [Epub ahead of print.]



http://www.ncbi.nlm.nih.gov/pubmed/18200040?ordinalpos=31&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that bortezomib is active and well tolerated in patients with relapsed myeloma with varying degrees of renal insufficiency.

Renal impairment is associated with poor prognosis in multiple myeloma (MM). This subgroup analysis of the phase 3 Assessment of Proteasome Inhibition for Extending Remissions (APEX) study of bortezomib vs high-dose dexamethasone assessed efficacy and safety in patients with relapsed MM with varying degrees of renal impairment (creatinine clearance (CrCl) <30, 30-50, 51-80 and >80 ml min⁻¹). Time to progression (TTP), overall survival (OS) and safety were compared between subgroups with CrCl \leq 50 ml min⁻¹ (severe-to-moderate) and >50 ml min⁻¹ (no/mild impairment). Response rates with bortezomib were similar (36-47%) and time to response rapid (0.7-1.6 months) across subgroups. Although the trend was toward shorter TTP/OS in bortezomib patients with severe-to-moderate vs no/mild impairment, differences were not significant. OS was significantly shorter in dexamethasone patients with CrCl \leq 50 vs >50

ml min⁻¹ (P=0.003), indicating that bortezomib is more effective than dexamethasone in overcoming the detrimental effect of renal impairment. Safety profile of bortezomib was comparable between subgroups. With dexamethasone, grade 3/4 adverse events (AEs), serious AEs and discontinuations for AEs were significantly elevated in patients with CrCl \leq 50 vs $>$ 50 ml min⁻¹. These results indicate that bortezomib is active and well tolerated in patients with relapsed MM with varying degrees of renal insufficiency. Efficacy/safety were not substantially affected by severe-to-moderate vs no/mild impairment.

Stem-cell transplantation for multiple myeloma in the era of novel drugs.

Bensinger W.

J Clin Oncol. 2008 Jan 20;26(3):480-92. [Epub 2007 Dec 3.]

 http://www.ncbi.nlm.nih.gov/pubmed/18056678?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses how the substantial activity of new drug affects the role of stem-cell transplantation as myeloma treatment.

The treatment of multiple myeloma (MM) is changing rapidly. During the last 10 years, higher rates of complete response (CR) and prolonged progression-free and overall survival have been seen with high-dose chemotherapy plus autologous stem-cell transplantation (HDT-ASCT). Achievement of CR and good partial response have been shown to be key prognostic factors for prolonged survival, with eradication of minimal residual disease seeming crucial to long-term disease-free survival. Until recently, high rates of CR and other major responses were primarily seen with HDT-ASCT, but insights into the biology of MM have led to the development and approval of new drugs with significant activity, and new induction regimens based on these novel agents are offering improved responses. Thalidomide, bortezomib, and lenalidomide have been combined with corticosteroids, alkylators, and anthracyclines in front-line MM treatment. Phase II studies have indicated that high rates of response and CR may be achieved. The substantial activity seen with these new drug combinations has prompted a re-examination of the role of SCT in MM treatment. Will achievement of major responses with these new regimens translate into improved survival after consolidation with transplantation? Will these improved induction regimens reduce the need for tandem transplantation, or does achievement of CR obviate the need for front-line transplantation altogether? To help address these questions, randomized trials are needed, as well as tests with improved sensitivity to better define depth of remission.

Prospective evaluation of coagulopathy in multiple myeloma patients before, during and after various chemotherapeutic regimens.

van Marion AM, Auwerda JJ, Lisman T, Sonneveld P, de Maat MP, Lokhorst HM, Leebeek FW.

Leuk Res. 2008 Jan 30. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18241919?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors perform a prospective study in 138 multiple myeloma patients in whom coagulation factor levels are evaluated longitudinally before, during induction and after intensification. During induction treatment several changes in coagulation factor levels are observed, which they find may result in a prothrombotic state. Larger studies are required to establish whether the changes in these coagulation factors during induction treatment contribute to the increased risk of venous thromboembolism in multiple myeloma patients.

BACKGROUND: Venous thromboembolism (VTE) occurs frequently in multiple myeloma patients, especially during induction treatment with thalidomide in combination with anthracyclines and/or dexamethasone. Several coagulation abnormalities have been described in untreated myeloma patients, but these have not been prospectively evaluated during and after treatment. **PATIENTS AND METHODS:** We performed a prospective study in 138 multiple myeloma patients in whom coagulation factor levels were evaluated longitudinally before, during induction and after intensification. Patients were randomized to induction treatment consisting of adriamycin and dexamethasone, in combination with either vincristin (VAD), thalidomide (TAD), or bortezomib (PAD) followed by high-dose melphalan (HDM) and autologous stem cell transplant (ASCT). **RESULTS:** Factor VIII:C (FVIII:C) and von Willebrand factor (VWF) were significantly elevated before treatment (median FVIII:C 2.26U/ml, VWF:Ag 1.95U/ml). Irrespective of the type of induction regimen, these variables increased strongly during induction therapy (FVIII:C 2.55U/ml and VWF:Ag 2.96U/ml). Fibrinogen also showed a significant increase after induction therapy (3.5g/l pre-treatment and 4.0g/l after treatment, respectively, P<0.001). This was significantly higher in TAD than VAD treated patients. Three to six month after ASCT levels of VWF and FVIII:C had decreased to values lower than observed before treatment (1.71 and 1.67U/ml respectively). There was no correlation between the increased levels at start and the response of multiple myeloma to treatment. High levels of VWF, fibrinogen and FVIII:C before start of treatment were significantly associated with mortality. Fourteen patients (10%) developed a venous thrombotic event (VTE). The coagulation factor abnormalities before and during treatment were not associated with the development of VTE. **CONCLUSION:** During induction treatment several changes in coagulation factor levels are observed, which may result in a prothrombotic state. Larger studies are required to establish whether the changes in these coagulation factors during induction treatment contribute to the increased risk of venous thromboembolism in multiple myeloma patients.

Bone building with bortezomib.

Roodman GD.

J Clin Invest. 2008 Feb;118(2):462-4.

 http://www.ncbi.nlm.nih.gov/pubmed/18219395?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses several myeloma treatments, including bortezomib, which block the activity of bone-resorbing osteoclasts.

In this issue of the JCI, Mukherjee et al. report that bortezomib, a clinically available proteasome inhibitor active against myeloma, induces the differentiation of mesenchymal stem/progenitor cells (MSCs)--rather than mature osteoprogenitor cells--into osteoblasts, resulting in new bone formation (see the related article beginning on page 491). These results were observed when MSCs were implanted subcutaneously in mice or were used to treat a mouse model of postmenopausal bone loss. Others have reported that immunomodulatory drugs (e.g., thalidomide and lenalidomide), which are active against myeloma, also block the activity of bone-resorbing osteoclasts. These results reflect the utility of targeting endogenous MSCs for the purpose of tissue repair and suggest that combining different classes of agents that are antineoplastic and also inhibit bone destruction and increase bone formation should be very beneficial for myeloma patients suffering from severe bone disease.

Concurrent radiation therapy and bortezomib in myeloma patient.

Berges O, Decaudin D, Servois V, Kirova YM.

Radiother Oncol. 2008 Feb;86(2):291-2. [Epub 2008 Jan 15.]

 http://www.ncbi.nlm.nih.gov/pubmed/18199515?ordinalpos=62&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease.

Wechalekar AD, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD.

Haematologica. 2008 Feb;93(2):295-8.

 http://www.ncbi.nlm.nih.gov/pubmed/18245653?ordinalpos=54&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report preliminary observations on the efficacy of bortezomib in 20 patients with AL amyloidosis whose clonal disease was active despite treatment with a median of 3 lines of prior chemotherapy, and find that bortezomib shows promise in the treatment of systemic AL amyloidosis.

We report preliminary observations on the efficacy of bortezomib in 20 patients with AL amyloidosis whose clonal disease was active despite treatment with a median of 3 lines of prior chemotherapy, including a thalidomide combination in all cases. Patients received a median of 3 (range 1-6) cycles of bortezomib and 9 (45%) patients received concurrent dexamethasone. Three (15%) patients achieved complete hematologic responses, and a further 13 (65%) achieved partial responses. Fifteen (75%) patients experienced some degree of toxicity, which in 8 (40%) cases resulted in discontinuation of bortezomib. Bortezomib shows promise in the treatment of systemic AL amyloidosis.

Position statement on the use of bortezomib in multiple myeloma.

Morgan GJ, Davies FE, Cavenagh JD, Jackson GH; United Kingdom Myeloma Forum (UKMF); Haematology Oncology Task Force of the British Committee for Standards in Haematology.

Int J Lab Hematol. 2008 Feb;30(1):1-10.

 http://www.ncbi.nlm.nih.gov/pubmed/18190461?ordinalpos=55&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Given the strength of discussed data, the UK Myeloma Forum and British Committee for Standards in Haematology believe that bortezomib should be available for prescription by UK hematologists according to its licensed indication in patients with relapsed myeloma.

Bortezomib (Velcade) is a boron containing molecule which reversibly inhibits the proteasome, an intracellular organelle which is central to the breakdown of ubiquitinated proteins and consequently crucial for normal cellular homeostasis. Phase II clinical trials demonstrate it is effective for the treatment of relapsed refractory myeloma, and a phase III trial comparing bortezomib to dexamethasone in second/third line treatment showed superiority in progression free and overall survival. It is administered intravenously in the outpatient setting on days 1, 4, 8 and 11 of a 21-day cycle and regular monitoring for side effects is essential. It is currently approved for the treatment of multiple

myeloma patients who have received at least one prior therapy and who have already undergone or are unsuitable for transplantation. Given the strength of this data the UK Myeloma Forum and British Committee for Standards in Haematology believe that bortezomib should be available for prescription by UK haematologists according to its licensed indication in patients with relapsed myeloma.

Unusual discordant responses in two multiple myeloma patients during bortezomib treatment.

Pirrotta MT, Gozzetti A, Cerase A, Bucalossi A, Bocchia M, Defina M, Lauria F.

Onkologie. 2008 Feb;31(1-2):45-7. [Epub 2008 Jan 22.]



http://www.ncbi.nlm.nih.gov/pubmed/18268398?ordinalpos=54&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss pharmacokinetics of bortezomib and physiopathology in the case of patients with extramedullary myeloma localizations that developed during bortezomib treatment with a concomitant serum monoclonal protein reduction.

BACKGROUND: Cases of discordant responses in multiple myeloma (MM) patients after thalidomide therapy have been sometimes reported, in which extramedullary masses progress or present de novo with a simultaneous serum monoclonal protein reduction. PATIENTS AND METHODS: We hereby report, for the first time, on two cases of MM patients with extramedullary myeloma localizations that developed during Velcade (bortezomib, PS341) treatment with a concomitant serum monoclonal protein reduction. RESULTS: We observed in both patients a very good response in the serum monoclonal protein level, while extramedullary lesions appeared in the central nervous system and subcutaneously. CONCLUSIONS: We discuss pharmacokinetics of bortezomib and physiopathology of this unusual event and review the literature.

Bortezomib down-regulates the cell-surface expression of HLA class I and enhances natural killer cell-mediated lysis of myeloma.

Shi J, Tricot GJ, Garg TK, Malaviarachchi PA, Szmania SM, Kellum RE, Storrie B, Mulder A, Shaughnessy JD Jr, Barlogie B, van Rhee F.

Blood. 2008 Feb 1;111(3):1309-17. [Epub 2007 Oct 18.]



http://www.ncbi.nlm.nih.gov/pubmed/17947507?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report that bortezomib down-regulates class I in a time- and dose-dependent fashion on all myeloma cell lines and patient myeloma cells tested.

Human leukocyte antigen class I molecules expressed by tumor cells play a central role in the regulation of natural killer (NK) cell-mediated immune responses. The proteasome inhibitor bortezomib has demonstrated significant activity in multiple myeloma (MM). We hypothesized that treatment of MM with bortezomib results in the reduction of cell-surface expression of class I and thereby sensitizes MM to NK cell-mediated lysis. Here we report that bortezomib down-regulates class I in a time- and dose-dependent fashion on all MM cell lines and patient MM cells tested. Downregulation of class I can also be induced in vivo after a single dose of 1.0 mg/m² bortezomib. Bortezomib significantly enhances the sensitivity of patient myeloma to allogeneic and autologous NK cell-mediated lysis. Further, the level of decrease in class I expression correlates with increased susceptibility to lysis by NK cells. Clinically relevant bortezomib concentrations do not affect NK-cell function. Our findings have clear therapeutic implications for MM and other NK cell-sensitive malignancies in the context of both allogeneic and autologous adoptively transferred NK cells.

Combination of proteasome inhibitors bortezomib and NPI-0052 trigger in vivo synergistic cytotoxicity in multiple myeloma.

Chauhan D, Singh A, Brahmandam M, Podar K, Hideshima T, Richardson P, Munshi N, Palladino MA, Anderson KC.

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The authors demonstrate that combining NPI-0052 and bortezomib induces synergistic anti-myeloma activity both in vitro using myeloma cell lines or patient CD138(+) myeloma cells and in vivo in a human plasmacytoma xenograft mouse model, providing the preclinical rationale for clinical protocols evaluating bortezomib together with NPI-0052 to improve patient outcome in myeloma.

Our recent study demonstrated that a novel proteasome inhibitor NPI-0052 triggers apoptosis in multiple myeloma (MM) cells, and importantly, that is distinct from bortezomib (Velcade) in its chemical structure, effects on proteasome activities, and mechanisms of action. Here, we demonstrate that combining NPI-0052 and bortezomib induces synergistic anti-MM activity both in vitro using MM cell lines or

patient CD138(+) MM cells and in vivo in a human plasmacytoma xenograft mouse model. NPI-0052 plus bortezomib-induced synergistic apoptosis is associated with: (1) activation of caspase-8, caspase-9, caspase-3, and PARP; (2) induction of endoplasmic reticulum (ER) stress response and JNK; (3) inhibition of migration of MM cells and angiogenesis; (4) suppression of chymotrypsin-like (CT-L), caspase-like (C-L), and trypsin-like (T-L) proteolytic activities; and (5) blockade of NF-kappaB signaling. Studies in a xenograft model show that low dose combination of NPI-0052 and bortezomib is well tolerated and triggers synergistic inhibition of tumor growth and CT-L, C-L, and T-L proteasome activities in tumor cells. Immunostaining of MM tumors from NPI-0052 plus bortezomib-treated mice showed growth inhibition, apoptosis, and a decrease in associated angiogenesis. Taken together, our study provides the preclinical rationale for clinical protocols evaluating bortezomib together with NPI-0052 to improve patient outcome in MM.

Bisphosphonate-induced osteonecrosis of the jaws: Prospective study of 80 patients with multiple myeloma and other malignancies.

Boonyapakorn T, Schirmer I, Reichart PA, Sturm I, Massenkeil G.

Oral Oncol. 2008 Feb 15. [Epub ahead of print.]



http://www.ncbi.nlm.nih.gov/pubmed/18282788?ordinalpos=44&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This prospective study is performed in 80 patients receiving bisphosphonates in order to determine frequency of occurrence, risk factors, clinical presentation, radiology, pathology and proper treatment of osteonecrosis of the jaw (ONJ). The authors find no association of ONJ with bortezomib.

A prospective study was performed in 80 patients receiving bisphosphonates in order to determine frequency of occurrence, risk factors, clinical presentation, radiology, pathology and proper treatment of osteonecrosis of the jaw (ONJ). Of 80 patients, 22 (28%) developed ONJ. There were 11 male and 11 female patients. Median age was 65 years. Ten patients (46%) had multiple myeloma (MM), 5 (23%) had breast cancer and 7 (32%) had other malignancies. Of 22 patients with ONJ, 14 patients (64%) received zoledronate, 3 (14%) received pamidronate, 4 (18%) received pamidronate later followed by zoledronate and 1 patient received ibandronate later followed by zoledronate. The median time of exposure in ONJ group was 32 months compared with 27 months in patients without ONJ. The mean induction time until bone exposure was 26 months for patients who received zoledronate, 54 months for pamidronate and 48 months for pamidronate followed by zoledronate. Thirteen patients (59%) had ONJ with bone exposure of mandible, 6 (27%) of maxilla and 3 (14%) of both jaws. ONJ occurred spontaneously in 5 patients (23%) and in 17 patients (77%) occurred after tooth extractions and surgical tooth removals ($P < 0.001$). Nine patients (41%) had previous extractions of molars, 6 (27%) of premolars and 2 (9%) of front teeth. The cumulative hazard is significantly higher in zoledronate group ($P = 0.015$). It was 3.48 times higher than the other group (pamidronate alone; pamidronate followed by zoledronate; ibandronate alone; etidronate alone; ibandronate followed by pamidronate; ibandronate followed by zoledronate; ibandronate followed by pamidronate and zoledronate). There was no association of ONJ with age, sex, use of high-dose or conventional chemotherapy or the use of corticosteroids, thalidomide or bortezomib ($P > 0.05$). Patients diagnosed with multiple myeloma and breast cancer were found significantly associated with ONJ ($P = 0.001$ and $P = 0.014$, respectively). Long-term use of bisphosphonates (> 2.5 years) increases the risk for development of ONJ. Intravenous application of zoledronate and previous dental extractions or surgical tooth removals are important risk factors of ONJ. Neither treatment with high-dose chemotherapy with autologous stem cell transplantation nor treatment with corticosteroids, thalidomide or bortezomib is a risk factor in this study.

BCL-2 family regulation by the 20S proteasome inhibitor bortezomib.

Fennell DA, Chacko A, Mutti L.

Oncogene. 2008 Feb 21;27(9):1189-97. [Epub 2007 Sep 10.]



http://www.ncbi.nlm.nih.gov/pubmed/17828309?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This article reviews the mechanisms of bortezomib and the implications for favorable novel drug interactions.

Bortezomib (Velcade, PS341) was licensed in 2003 as a first-in-class 20S proteasome inhibitor indicated for treatment of multiple myeloma, and is currently being evaluated clinically in a range of solid tumours. The mechanisms underlying its cancer cell toxicity are complex. A growing body of evidence suggests proteasome inhibition-dependent regulation of the BCL-2 family is a critical requirement. In particular, the stabilization of BH3-only proteins BIK, NOXA and BIM, appear to be essential for effecting BAX- and BAK-dependent cell death. These mechanisms are reviewed and the implications for favourable novel drug interactions are highlighted.

 ***Combined pegylated liposomal doxorubicin and bortezomib is highly effective in patients with recurrent or refractory multiple myeloma who received prior thalidomidelenalidomide therapy.***

Sonneveld P, Hajek R, Nagler A, Spencer A, Bladé J, Robak T, Zhuang SH, Harousseau JL, Orłowski RZ; for the DOXIL-MMY-3001.

Cancer. 2008 Feb 25. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18300257?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors observe a significantly prolonged time to progression with combined pegylated liposomal doxorubicin plus bortezomib combination therapy compared with bortezomib alone despite prior immunomodulatory drug exposure.

BACKGROUND: Recently, the authors reported improved time to disease progression (TTP) with a combination of pegylated liposomal doxorubicin (PLD) and bortezomib compared with bortezomib alone in a phase 3 randomized trial in patients with recurrent/refractory multiple myeloma (MM). In the current analysis, they determined 1) the efficacy of PLD plus bortezomib versus bortezomib alone in patients with MM who had failed on prior thalidomide/lenalidomide (immunomodulatory drug [IMiD]) treatment and 2) the efficacy and safety profile of PLD plus bortezomib in IMiD-exposed and IMiD-naïve patients. **METHODS:** This prespecified analysis included 646 patients who were randomized to receive either PLD with bortezomib (n = 324; 194 IMiD-naïve patients and 130 IMiD-exposed patients) or bortezomib alone (n = 322; 184 IMiD-naïve patients and 138 IMiD-exposed patients). The primary efficacy endpoint was TTP, and secondary endpoints included overall survival, response rate, and safety. **RESULTS:** The median TTP was significantly longer with PLD plus bortezomib compared with bortezomib alone in IMiD-exposed patients (270 days vs 205 days). No statistical difference was noted with respect to TTP between IMiD-naïve (295 days) versus IMiD-exposed (270 days) subgroups who received PLD plus bortezomib. A sustained trend favoring combination therapy was observed in analyses of overall survival. In patients who achieved a response, the response duration was comparable for IMiD-naïve patients and IMiD-exposed patients in the combination treatment group and lasted a median of 310 days and 319 days, respectively. The incidence of grade 3/4 adverse events was similar with PLD plus bortezomib regardless of prior IMiD exposure. **CONCLUSIONS:** A significantly prolonged TTP was observed with combined PLD plus bortezomib combination therapy compared with bortezomib alone despite prior IMiD exposure. For the combination treatment arm in the IMiD-naïve and IMiD-exposed subgroups, TTP was comparable. Similarly, the safety profile of the PLD plus bortezomib combination was unaltered by prior IMiD exposure.

 ***Bone marrow angiogenesis and angiogenic factors in multiple myeloma treated with novel agents.***

Cibeira MT, Rozman M, Segarra M, Lozano E, Rosiñol L, Cid MC, Filella X, Bladé J.

Cytokine. 2008 Mar;41(3):244-53. [Epub 2008 Jan 4.]

 http://www.ncbi.nlm.nih.gov/pubmed/18178097?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors perform an angiogenesis study in myeloma treated with thalidomide, lenalidomide, bortezomib, and with dexamethasone.

INTRODUCTION: An increased bone marrow (BM) angiogenesis is associated with poor outcome in multiple myeloma (MM). **OBJECTIVE:** Angiogenesis study in MM treated with novel antimyeloma agents: thalidomide, lenalidomide, bortezomib, and with dexamethasone. **PATIENTS AND METHODS:** Forty-four patients with MM (14 newly diagnosed, 30 refractory/relapsed) were treated with novel agents at our institution. A BM biopsy was obtained before the initiation of therapy in 19. Angiogenesis was assessed by microvessel density (MVD) estimation in BM biopsies stained with the monoclonal anti-CD34 antibody, and by serum levels of angiogenic factors (VEGF, bFGF, and HGF) and cytokines (IL-6 and TNF-alpha). **RESULTS:** A positive correlation was found between BM plasma cell involvement and MVD estimation (p=0.01). However, MVD was not significantly correlated with either disease phase (p=0.065) or response to therapy (p=0.79). Neither baseline serum levels of angiogenic cytokines correlated to response to treatment. No significant correlation was found between BM MVD and serum levels of angiogenic cytokines. Serum levels of angiogenic cytokines before and after therapy showed a significant increase of bFGF (p=0.008). **CONCLUSION:** There is no relationship between MVD estimation and baseline serum levels of angiogenic cytokines, neither between each of them and response to therapy.

 ***Bortezomib in combination with thalidomide and dexamethasone – a successful treatment regimen in refractory extramedullary multiple myeloma.***

Dytfeld D, Matuszak M, Lewandowski K, Komarnicki M.

Ann Hematol. 2008 Mar;87(3):253-4. [Epub 2007 Oct 23.]

 http://www.ncbi.nlm.nih.gov/pubmed/17955241?ordinalpos=31&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

 ***High response rate and improved graft-versus-host disease following bortezomib as salvage therapy after reduced intensity conditioning allogeneic stem cell transplantation for multiple myeloma.***

El-Cheikh J, Michallet M, Nagler A, de Lavallade H, Nicolini FE, Shimoni A, Faucher C, Sobh M, Revesz D, Hardan I, Fürst S, Blaise D, Mohty M.

Haematologica. 2008 Mar;93(3):455-8. [Epub 2008 Feb 20.]

 http://www.ncbi.nlm.nih.gov/pubmed/18287132?ordinalpos=44&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors describe the results of 37 myeloma patients who received bortezomib following reduced intensity allogeneic stem cell transplantation (RIC-*allo*-SCT), results that suggest that bortezomib is a safe and efficient option for myeloma patients after RIC-*allo*-SCT.

We describe the results of 37 myeloma patients who received bortezomib following reduced intensity allogeneic stem cell transplantation (RIC-*allo*-SCT). Grade 1-2 peripheral neuropathy (35%), mild thrombocytopenia (24%) and fatigue (19%) were the most frequent adverse events, while there was no worsening of graft-vs-host disease symptoms. Twenty-seven patients (73%; 95% CI, 59-87%) achieved an objective response. With a median follow-up of 9 months from bortezomib initiation, the estimate of overall survival was 65% at 18 months while this was significantly higher ($p=0.002$) in the 27 patients achieving an objective response, suggesting that bortezomib is a safe and efficient option for myeloma patients after RIC-*allo*-SCT.

 ***Normalization of the serum angiopoietin-1 to angiopoietin-2 ratio reflects response in refractory/resistant multiple myeloma patients treated with bortezomib.***

Anargyrou K, Terpos E, Vassilakopoulos TP, Pouli A, Sachanas S, Tzenou T, Masouridis S, Christoulas D, Angelopoulou MK, Dimitriadou EM, Kalpadakis C, Tsionos K, Panayiotidis P, Dimopoulos MA, Pangalis GA, Kyrtsonis MC; Greek Myeloma Study Group.

Haematologica. 2008 Mar;93(3):451-4. [Epub 2008 Feb 20.]

 http://www.ncbi.nlm.nih.gov/pubmed/18287135?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors determine serum levels of angiopoietin-1 and angiopoietin-2 with ELISA pre- and post-bortezomib administration in 35 patients with relapsed/refractory multiple myeloma and conclude that angiopoietin-1/angiopoietin-2 ratio normalization reflected response to bortezomib.

Neoangiogenesis is involved in the pathophysiology of multiple myeloma and angiopoietins possibly contribute to myeloma-induced neovascularization. Bortezomib's antineoplastic potential includes an anti-angiogenic effect. We determined serum levels of angiopoietin-1 and angiopoietin-2 with ELISA pre- and post-bortezomib administration in 35 patients with relapsed/refractory multiple myeloma. Pre-bortezomib, serum angiopoietin-1 levels did not differ in patients and in healthy individuals, while serum angiopoietin-2 levels were elevated. Corresponding serum angiopoietin-1/angiopoietin-2 ratio was reduced in patients compared with controls. After treatment, serum angiopoietin-1 levels increased, while serum angiopoietin-2 levels decreased, therefore the angiopoietin-1/angiopoietin-2 ratio increased and normalized. This increase was significant in patients who responded to treatment. In conclusion, angiopoietin-1/angiopoietin-2 ratio normalization reflected response to bortezomib.

Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2.

Pineda-Roman M, Zangari M, Haessler J, Anaissie E, Tricot G, van Rhee F, Crowley J, Shaughnessy JD Jr, Barlogie B.

Br J Haematol. 2008 Mar;140(6):625-34.



http://www.ncbi.nlm.nih.gov/pubmed/18302711?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this study, the authors' data strongly suggest that the addition of bortezomib in total therapy 3 (TT3) is accountable for its superior performance rather than greater compliance with protocol completion as a result of greater dose-density in TT3 vs. total therapy 2.

Total therapy 3 (TT3), incorporating bortezomib up-front into a tandem transplant regimen for newly diagnosed multiple myeloma (MM), effected 2-year complete response (CR) estimates >90%, which appeared superior to results reported for total therapy 2 (TT2). With median follow-up times of 2 years with TT3 and 5 years with TT2, the clinical outcomes of 303 patients in the former and 668 in the latter trial were compared, including the subset of 607 patients with gene expression profiling (GEP) data. With similar baseline prognostic factors, event-free survival (EFS) ($P = 0.0002$) and CR duration ($P = 0.003$) were superior with TT3 vs. TT2 with a strong trend noted also for improved overall survival (OS) ($P = 0.16$). In the GEP-defined FGFR3 subgroup, TT3 imparted significantly superior OS, EFS and CR duration vis-à-vis TT2. Matching 300 patients each by standard prognostic factors, TT3 yielded superior EFS and CR duration and borderline superior OS. The advantage of TT3 still pertained when the comparison was limited to patients who completed TT2 consolidation rapidly within 24 months. Our data strongly suggest that the addition of bortezomib in TT3 was accountable for its superior performance rather than greater compliance with protocol completion as a result of greater dose-density in TT3 vs. TT2.

Improved survival in multiple myeloma and the impact of novel therapies.

Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, Dingli D, Russell SJ, Lust JA, Greipp PR, Kyle RA, Gertz MA.

Blood. 2008 Mar 1;111(5):2516-20. [Epub 2007 Nov 1.]



http://www.ncbi.nlm.nih.gov/pubmed/17975015?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors demonstrate the improved outcome of patients using novel therapies, including thalidomide and lenalidomide, both in the relapsed setting as well as at diagnosis.

Treatments for myeloma have expanded in the last decade, but it is not clear if the introduction of novel therapies and the increased use of high-dose therapy have translated into better outcome for patients with myeloma. We examined the outcome of 2 groups of patients seen at a single institution, one from time of diagnosis and the other from the time of relapse, to examine the survival trends over time. Among 387 patients relapsing after stem-cell transplantation, a clear improvement in overall survival from the time of relapse was seen, with those relapsing after 2000 having a median overall survival of 23.9 versus 11.8 months ($P < .001$) for those who relapsed prior to this date. This improvement was independent of other prognostic factors. Patients treated with one or more of the newer drugs (thalidomide, lenalidomide, bortezomib) had longer survival from relapse (30.9 vs 14.8 months; $P < .001$). In a larger group of 2981 patients with newly diagnosed myeloma, those diagnosed in the last decade had a 50% improvement in overall survival (44.8 vs 29.9 months; $P < .001$). In this study, we demonstrate improved outcome of patients with myeloma in recent years, both in the relapsed setting as well as at diagnosis.

Recent major improvement in long-term survival of younger patients with multiple myeloma.

Brenner H, Gondos A, Pulte D.

Blood. 2008 Mar 1;111(5):2521-6. [Epub 2007 Sep 27.]



http://www.ncbi.nlm.nih.gov/pubmed/17901246?ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find a major increase in long-term survival of younger myeloma patients in recent years, which most likely reflects the impact of recent advances in therapy, including thalidomide and lenalidomide, and their dissemination in clinical practice.

In the past, most patients with multiple myeloma (MM) died within 5 to 10 years after diagnosis. Within the past decade, several new therapeutic interventions have been introduced, including autologous stem-cell transplantation, thalidomide, lenalidomide, and bortezomib. We estimated trends in age-specific 5- and 10-year relative survival of patients with MM in the United States from 1990-1992 to 2002-2004 from the 1973-2004 database of the Surveillance, Epidemiology, and End Results (SEER) Program. Techniques of period analysis were used to show most recent developments. Overall, 5-year relative survival increased from 28.8% to 34.7% ($P < .001$), and 10-year relative

survival increased from 11.1% to 17.4% ($P < .001$) between 1990-1992 and 2002-2004. Much stronger increases were seen in the age group younger than 50 years, leading to 5- and 10-year relative survival of 56.7% and 41.3% in 2002-2004, and in the age group 50 to 59 years, leading to 5- and 10-year relative survival of 48.2% and 28.6% in 2002-2004. By contrast, only moderate improvement was seen in the age group 60 to 69 years, and essentially no improvement was achieved among older patients. Our period analysis discloses a major increase in long-term survival of younger patients with MM in recent years, which most likely reflects the effect of recent advances in therapy and their dissemination in clinical practice.

Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression.

Mateos MV, Hernández JM, Hernández MT, Gutiérrez NC, Palomera L, Fuertes M, García-Sánchez P, Lahuerta JJ, de la Rubia J, Terol MJ, Sureda A, Bargay J, Ribas P, Alegre A, de Arriba F, Oriol A, Carrera D, García-Laraña J, García-Sanz R, Bladé J, Prósper F, Mateo G, Esseltine DL, van de Velde H, San Miguel JF.

Haematologica. 2008 Mar 5. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18322252?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors combine melphalan and prednisone with novel agents and find that the regimen of bortezomib plus melphalan and prednisone is highly active and well tolerated in elderly patients with newly diagnosed myeloma.

Background New treatment options offering enhanced activity in elderly, newly diagnosed patients with multiple myeloma are required. One strategy is to combine melphalan and prednisone with novel agents. We previously reported an 89% response rate, including 32% complete responses and 11% near complete responses, in our phase 1/2 study of bortezomib plus melphalan and prednisone (VMP) in 60 newly diagnosed multiple myeloma patients with a median age of 75 years. Here, we report updated time-to-events data and the impact of poor prognosis factors on outcome. DESIGN AND METHODS: Updated analyses of time to biochemical progression and overall survival with VMP were conducted, and compared with those of historical controls treated with melphalan and prednisone. A univariate analysis was performed to evaluate the influence of known prognostic factors on the time to progression. RESULTS: After a median follow-up of 26 months, the median time to progression with VMP was 27.2 months, compared with 20.0 months with melphalan plus prednisone. The median overall survival with VMP was not reached versus 26 months with melphalan and prednisone; the survival rate at 38 months was 85% versus 38%, respectively. Time to progression was not significantly affected by elevated beta(2)-microglobulin or lactate dehydrogenase levels, advanced age, or cytogenetic abnormalities, but was shorter in patients with albumin < 3 g/dL, Karnofsky performance status $\leq 70\%$, bone marrow plasma cell infiltration $\geq 40\%$, and, particularly, high plasma cell proliferative activity ($\geq 2.5\%$ S-phase cells). Conclusions VMP is highly active and well tolerated in elderly patients with newly diagnosed multiple myeloma, with 85% of patients alive at 3 years. Moreover, VMP may overcome the poor prognostic impact of various factors, particularly cytogenetic abnormalities.

Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma.

Palumbo A, Gay F, Bringhen S, Falcone A, Pescosta N, Callea V, Caravita T, Morabito F, Magarotto V, Ruggeri M, Avonto I, Musto P, Cascavilla N, Bruno B, Boccadoro M.

Ann Oncol. 2008 Mar 6. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18326520?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that the combination of bortezomib, doxorubicin and low-dose dexamethasone is an active salvage therapy with manageable toxicity in patients with relapsed/refractory myeloma.

BACKGROUND: Bortezomib has shown significant activity in myeloma. In this multicenter trial, we assessed for the first time the combination of bortezomib, doxorubicin and low-dose dexamethasone (PAD) in the treatment of relapsed/refractory myeloma. PATIENTS AND METHODS: Sixty-four patients were treated for a median of four 28-day cycles (1-6). Bortezomib was given at 1.3 mg/m² (days 1, 4, 8, 11) and dexamethasone at 40 mg (days 1-4); 34 patients receive doxorubicin at 20 mg/m² (days 1, 4) while 30 patients pegylated liposomal doxorubicin at 30 mg/m² (day 1). RESULTS: Fifty-eight percent of patients had undergone prior autologous transplantation, 70% prior anthracycline and 27% prior bortezomib-based regimens. Forty-three patients (67%) achieved at least a partial response including 16 (25%) with at least a very good partial response. One-year event-free survival was 34% after PAD and 31% after the previous line of therapy (hazard ratio 1.20, 95% confidence interval 0.76-1.90, $P = 0.43$). One-year overall survival from the start of PAD was 66%. Grade 3-4 toxic effects included thrombocytopenia (48%), neutropenia (36%), infections (15%), anemia (13%), gastrointestinal disturbances (11%) and peripheral neuropathy (10%). Two patients had grade 3-4 cardiac heart failure. CONCLUSIONS: PAD is an active salvage therapy with manageable toxicity in patients with relapsed/refractory myeloma.

 ***A phase I pharmacodynamic trial of bortezomib in combination with doxorubicin in patients with advanced cancer.***

Loconte NK, Thomas JP, Alberti D, Heideman J, Binger K, Marnocha R, Utecht K, Geiger P, Eickhoff J, Wilding G, Kolesar J. *Cancer Chemother Pharmacol.* 2008 Mar 6. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18322686?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This phase I trial seeks to define the toxicity, maximally tolerated dose and pharmacodynamics of a combination of bortezomib and doxorubicin in patients with advanced malignancies and finds that the combination can be administered safely and determines a recommended phase II dose.

PURPOSE: This phase I trial sought to define the toxicity, maximally tolerated dose (MTD) and pharmacodynamics of a combination of bortezomib and doxorubicin in patients with advanced malignancies. **PATIENTS AND METHODS:** Twenty-six patients were treated with bortezomib intravenously on days 1, 4, 8 and 11, with doxorubicin also administered intravenously on days 1 and 8, both in a 21-day cycle. Dosing ranged from 1.0 mg/m² of bortezomib with 15 mg/m² of doxorubicin to 1.5 mg/m² of bortezomib with 20 mg/m² of doxorubicin. Pharmacodynamic studies performed included assessment of levels of 20S proteasome activity and ubiquitin-protein conjugates. **RESULTS:** The combination of bortezomib and doxorubicin was generally well tolerated. There were two dose limiting toxicities (DLT) at dose cohort 3 (1.3 mg/m² bortezomib, 20 mg/m² doxorubicin) and 2 DLT at dose cohort 3a (1.5 mg/m² bortezomib, 15 mg/m² doxorubicin). DLT seen included neutropenia, thrombocytopenia, and neuropathy. In addition, one patient developed grade 3 central nervous system toxicity in cycle 2 (not a DLT). One patient with hormone refractory prostate cancer had a partial response. Proteasome inhibition in whole blood was demonstrated and an increase in ubiquitin-protein conjugates was observed in peripheral blood mononuclear cells of most patients. **CONCLUSIONS:** Bortezomib and doxorubicin can be administered safely. The recommended phase II dose for this 21-day cycle is bortezomib 1.3 mg/m² intravenously on days 1, 4, 8 and 11, and doxorubicin 20 mg/m² intravenously on days 1 and 8. This combination may be of special interest in multiple myeloma, given the activity of both drugs in that disease.

 ***The insulin-like growth factor-I receptor inhibitor NVP-AEW541 provokes cell cycle arrest and apoptosis in multiple myeloma cells.***

Maiso P, Ocio EM, Garayoa M, Montero JC, Hofmann F, García-Echeverría C, Zimmermann J, Pandiella A, San Miguel JF. *Br J Haematol.* 2008 Mar 12. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18341634?ordinalpos=19&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that NVP-AEW541 potentiates the action of myeloma drugs, including bortezomib.

Multiple myeloma (MM) is a B-cell malignancy characterized by accumulation of monoclonal plasma cells in the bone marrow (BM). Despite recent advances in the treatment, MM represents an incurable disease for which development of new therapies is required. We report the antimyeloma effect of NVP-AEW541, a small molecule that belongs to the pyrrolo[2,3-d]pyrimidine class, identified as a selective inhibitor of the insulin-like growth factor-I receptor (IGF-IR) in vitro kinase activity. NVP-AEW541 had a potent cytotoxic effect on fresh cells and in a murine MM model. NVP-AEW541 partially abrogated the proliferative advantage conferred by the coculture with BM stromal cells and the presence of growth factors produced by the BM microenvironment. In addition, NVP-AEW541 potentiated the action of drugs, such as bortezomib, lenalidomide, dexamethasone or melphalan. Moreover the triple combination of NVP-AEW541, dexamethasone and bortezomib resulted in a significant increase in growth inhibition. Mechanistic studies indicated that NVP-AEW541 provoked a marked cell cycle blockade accompanied by pRb downregulation. Interestingly, NVP-AEW541 increased the levels of p27 associated with a reduction in the CDK2 activity. Finally, NVP-AEW541 induced cell death through caspase-dependent and -independent mechanisms. All these data, suggest the potential effect of IGF-IR kinase inhibitors as therapeutic agents for MM patients.

Redox homeostasis modulates the sensitivity of myeloma cells to bortezomib.

Nerini-Molteni S, Ferrarini M, Cozza S, Caligaris-Cappio F, Sitia R.

Br J Haematol. 2008 Mar 12. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18341633?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study analyzes the relationships between redox homeostasis and bortezomib treatment in myeloma cells with findings that demonstrate tight links between sensitivity to proteasome inhibition and redox homeostasis in myeloma cells that have potential implications for treatment.

The use of proteasome inhibitors have been a major advance in the treatment of multiple myeloma (MM), but their mechanisms of action remain largely unclear. A better understanding of the cellular events downstream of proteasome inhibition is essential to improve the response and identify new combination therapies for MM and other malignancies. This study analysed the relationships between redox homeostasis and bortezomib treatment in MM cells. Our data showed that decreasing intracellular glutathione through buthionine sulfoximine treatment strongly enhances bortezomib toxicity, whilst antioxidants protect MM cells from bortezomib-mediated cell death. Bortezomib treatment decreases intracellular glutathione both in MM cell lines and in malignant plasma cells obtained from MM patients. Glutamate-cysteine ligase (GCLM) and haem-oxygenase-1 (HMOX1), two genes involved in the Nrf-2-mediated antioxidant response, as well as two eIF2alpha-downstream transcription factors, activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP), are upregulated, indicating that redox-related adaptive responses are initiated in bortezomib-treated MM cells. These findings demonstrate tight links between sensitivity to proteasome inhibition and redox homeostasis in MM cells and have potential implications for treatment.

Proteasome inhibitors in cancer therapy: lessons from the first decade.

Orlowski RZ, Kuhn DJ.

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 http://www.ncbi.nlm.nih.gov/pubmed/18347166?ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss how lessons learned from bortezomib are now being applied to the development of a new generation of proteasome inhibitors.

The ubiquitin-proteasome pathway is involved in intracellular protein turnover, and its function is crucial to cellular homeostasis. First synthesized as probes of proteolytic processes, proteasome inhibitors began to be thought of as potential drug candidates when they were found to induce programmed cell death preferentially in transformed cells. They made their first leap into the clinic to be tested as therapeutic agents 10 years ago, and since then, great strides have been made in defining their mechanisms of action, their clinical efficacy and toxicity, and some of their limitations in the form of resistance pathways. Validation of the ubiquitin-proteasome pathway as a target for cancer therapy has come in the form of approvals of the first such inhibitor, bortezomib, for relapsed/refractory multiple myeloma and mantle cell lymphoma, for which this agent has become a standard of care. Lessons learned from this first-in-class agent are now being applied to the development of a new generation of proteasome inhibitors that hold the promise of efficacy in bortezomib-resistant disease and possibly in a broader spectrum of diseases. This saga provides a salient example of the promise of translational medicine and a paradigm by which other agents may be successfully brought from the bench to the bedside.



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