



CITINGS

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VELCADE[®] (bortezomib) Issue

The INTERNATIONAL MYELOMA FOUNDATION (IMF) is pleased to present our fourth edition of CITINGS for 2007. 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 (2873) or www.myeloma.org

– Susie Novis, President, IMF

VELCADE (bortezomib) Publications 4th Quarter, 2007

Establishment and exploitation of hyperdiploid and non-hyperdiploid human myeloma cell lines.

Li X, Pennisi A, Zhan F, Sawyer JR, Shaughnessy JD, Yaccoby S.

Br J Haematol. 2007 Sep;138(6):802-11.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17760811&ordinalpos=50&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss their procedures for the establishment of clinically relevant human myeloma cell lines, including their development of bortezomib-sensitive and -resistant lines.

The establishment of clinically relevant human myeloma cell lines is central for our understanding of myeloma pathogenesis and development of novel therapies for the disease. Unfortunately, most available lines were generated from extramedullary sites, harbored multiple genetic abnormalities and categorized as non-hyperdiploid. In contrast, hyperdiploid myeloma cell lines, which represent more than 50% of patients, are rare. We established procedures for establishment of stroma-dependent myeloma lines by passaging primary myeloma cells, in severe combined immunodeficient-human (SCID-hu) or SCID-rab mice followed by maintenance in co-culture with stromal cells. We described the establishment and characterization of two hyperdiploid (LD and CF) and two non-hyperdiploid (JB and BN) cell lines. Using our animal models, we also established bortezomib-sensitive and -resistant BN lines. These cell lines were cellularly, phenotypically and molecularly characterized using flow cytometry immunophenotyping, DNA content, G-band and multicolor spectral karyotyping (SKY) and global gene expression profiling. All four cell lines were infected with lentiviral-expressing luciferase for detection of tumour cells at high sensitivity level and for monitoring myeloma growth in co-cultures and in vivo by live animal imaging. These myeloma cell lines and the procedures used for their establishment provide essential tools for studying myeloma biology and therapy.

 ***Ursolic acid inhibits STAT3 activation pathway leading to suppression of proliferation and chemosensitization of human multiple myeloma cells.***

Pathak AK, Bhutani M, Nair AS, Ahn KS, Chakraborty A, Kadara H, Guha S, Sethi G, Aggarwal BB.

Mol Cancer Res. 2007 Sep;5(9):943-55.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17855663&ordinalpos=66&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that ursolic acid significantly potentiates the apoptotic effects of thalidomide and bortezomib in multiple myeloma cells and that ursolic acid may have a potential in prevention and treatment of myeloma.

The activation of signal transducers and activators of transcription 3 (STAT3) has been linked with the proliferation of a variety of human cancer cells, including multiple myeloma. Agents that can suppress STAT3 activation have potential for prevention and treatment of cancer. In the present report, we tested an agent, ursolic acid, found in basil, apples, prunes, and cranberries, for its ability to suppress STAT3 activation. We found that ursolic acid, a pentacyclic triterpenoid, inhibited both constitutive and interleukin-6-inducible STAT3 activation in a dose- and time-dependent manner in multiple myeloma cells. The suppression was mediated through the inhibition of activation of upstream kinases c-Src, Janus-activated kinase 1, Janus-activated kinase 2, and extracellular signal-regulated kinase 1/2. Vanadate treatment reversed the ursolic acid-induced down-regulation of STAT3, suggesting the involvement of a tyrosine phosphatase. Indeed, we found that ursolic acid induced the expression of tyrosine phosphatase SHP-1 protein and mRNA. Moreover, knockdown of SHP-1 by small interfering RNA suppressed the induction of SHP-1 and reversed the inhibition of STAT3 activation, thereby indicating the critical role of SHP-1 in the action of this triterpene. Ursolic acid down-regulated the expression of STAT3-regulated gene products such as cyclin D1, Bcl-2, Bcl-xL, survivin, Mcl-1, and vascular endothelial growth factor. Finally, ursolic acid inhibited proliferation and induced apoptosis and the accumulation of cells in G1-G0 phase of cell cycle. This triterpenoid also significantly potentiated the apoptotic effects of thalidomide and bortezomib in multiple myeloma cells. Overall, these results suggest that ursolic acid is a novel blocker of STAT3 activation that may have a potential in prevention and treatment of multiple myeloma and other cancers.

 ***Use of bortezomib in the management of chronic graft-versus-host disease among multiple myeloma patients relapsing after allogeneic transplantation.***

Mateos-Mazon J, Pérez-Simón JA, Lopez O, Hernández E, Etxebarria J, San Miguel JF.

Haematologica. 2007 Sep;92(9):1295-6.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17768136&ordinalpos=58&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report on the use of bortezomib for the management of chronic graft versus host disease (cGVHD) and file the first report showing that bortezomib may be useful in the management of cGVHD and related ocular involvement.

We report on the use of bortezomib for the management of chronic graft versus host disease (cGVHD) among 8 multiple myeloma (MM) patients who relapsed after reduced-intensity conditioning (RIC) allogeneic transplantation. Five patients (62%) responded to bortezomib demonstrating anti-myeloma effect. Four patients had active cGVHD, including 3 patients with severe punctate keratopathy, at the time of bortezomib administration. All showed an improvement in their condition. This is the first report showing that bortezomib may be useful in the management of cGVHD and related ocular involvement.

 ***Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature.***

Badros A, Goloubeva O, Dalal JS, Can I, Thompson J, Rapoport AP, Heyman M, Akpek G, Fenton RG.

Cancer. 2007 Sep 1;110(5):1042-9.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17654660&ordinalpos=53&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors retrospectively review the incidence, severity, and risk factors for peripheral neuropathy (PN) in 78 patients who received bortezomib and conclude that the bortezomib-related PN was greater in patients who had PN and diabetes mellitus at baseline.

BACKGROUND: Bortezomib is active in heavily pretreated multiple myeloma patients; the dose-limiting toxicity is peripheral neuropathy (PN). METHODS: The authors retrospectively reviewed the incidence, severity, and risk factors for PN in 78 patients who received bortezomib. The median age was 57 years (range, 33-80 years), 62% of patients were men, and 37% of patients were African Americans. Seventeen patients (22%) had diabetes mellitus (DM), and 66 patients (85%) had received thalidomide. Before bortezomib treatment, 37%

of the patients reported subjective, grade 1 or 2 PN. Patients received bortezomib alone (n = 10 patients) plus dexamethasone (n = 36 patients) and thalidomide (n = 20 patients) or chemotherapy (n = 12 patients). PN affected 52% of patients, including grade 3 and 4 PN in 15% and 7%, respectively. RESULTS: Twelve patients stopped bortezomib because of side effects that included PN (n = 9 patients), diarrhea (n = 2 patients) and cytomegalovirus pneumonia (n = 1 patient); 11 patients had dose reductions because of PN. Grade 4 PN affected 6 patients (sensory, n = 4 patients; motor/sensory, n = 2 patients). The onset of grade 4 PN was sudden rather than cumulative. Factors that were predictive of PN grade were baseline PN (P = .002), prior thalidomide use (P = .03), and the presence of DM (P = .03). Multiple myeloma responses included complete, near complete, and partial responses in 5% of patients, 10% of patients, and 27% of patients, respectively. Responses were independent of PN and of whether bortezomib was combined with chemotherapy or thalidomide. Patients remained on therapy longer for a median of 5 cycles (range, 2-36 cycles) when they received bortezomib plus thalidomide versus 3 cycles (range, 1-19 cycles) for the other combinations. PN therapy was mostly supportive. It was noteworthy that 6 of 9 patients with PN who received lenalidomide as salvage therapy after bortezomib had significant improvement in their symptoms. CONCLUSIONS: The risk of bortezomib-related PN was greater in patients who had PN and DM at baseline. The authors concluded that an unexpected, symptomatic improvement of PN on lenalidomide is worth further investigation.

Reversal of acute renal failure by bortezomib-based chemotherapy in patients with multiple myeloma.

Ludwig H, Drach J, Graf H, Lang A, Meran JG.

Haematologica. 2007 Sep 1; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17768111&ordinalpos=59&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

By means of bortezomib-based therapy, the authors show reversal of acute paraprotein-induced renal failure in myeloma patients.

Paraprotein induced renal failure is a frequent complication of multiple myeloma and is associated with poor survival. Previously, reversal of renal function has been hampered by the lack of fast acting and highly effective myeloma therapy and most patients remained or became dependent on hemodialysis. Here we show reversal of acute paraprotein-induced renal failure by bortezomib-based therapy in 5 out of 8 patients. Improvement of renal function was preceded by a significant reduction in paraprotein concentration in all patients, with improvement in renal function.

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

Raab MS, Breitzkreutz I, Anderson KC.

Bone Marrow Transplant. 2007 Sep 3; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17768392&ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the role of bortezomib in both induction therapy and maintenance treatment, as well as their potential roles in redefining the role of stem cell transplantation in first-line myeloma treatment.

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.

Gene mutation revelation points to new target for myeloma treatment, studies say.

Garber K.

J Natl Cancer Inst. 2007 Sep 19;99(18):1362-4. Epub 2007 Sep 11.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17848662&ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

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

Brenner H, Gondas A, Pulte D.

Blood. 2007 Sep 27; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17901246&ordinalpos=36&itool=EntrezSysstem2.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 bortezomib, and their dissemination in clinical practice.

In the past, most patients with multiple myeloma (MM) died within 5-10 years following diagnosis. Within the past decade, several new therapeutic interventions have been introduced, including autologous stem cell transplant, thalidomide, lenalidomide, and bortezomib. We estimated trends in age specific 5- and 10-year relative survival of MM patients 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 employed to disclose most recent developments. Overall, 5-year relative survival increased from 28.8% to 34.7% ($p < 0.0001$), and 10-year relative survival increased from 11.1% to 17.4% ($p < 0.0001$) between 1990-92 and 2002-04. Much stronger increases were seen in age group < 50 , leading to 5- and 10-year relative survival of 56.7% and 41.3% in 2002-04, and in age group 50-59, 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 age group 60-69, 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 impact of recent advances in therapy and their dissemination in clinical practice.

High-dose treatment with autologous stem cell transplantation in multiple myeloma: past, present, and future.

Björkstrand B, Gahrton G.

Semin Hematol. 2007 Oct;44(4):227-33.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17961721&ordinalpos=36&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the historical results of autologous stem cell transplantation in myeloma, along with its future role with the introduction of novel drugs, such as bortezomib.

High-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) has been used in the treatment of multiple myeloma since the early 1980s. Its present position as the backbone of first-line treatment in patients up to 60 to 65 years of age is the result of several controlled randomized trials, where its superiority over standard chemotherapy has been demonstrated. However, the method is not considered to have curative potential, with the possible exception of a small proportion of about 5% to 10% of patients with very long-standing complete remissions (CRs) of more than 8 years. Over the years, there have been several attempts to improve the technique, where, for example, tandem transplants and post-transplant maintenance treatment have been successful, at least in certain subgroups of patients, while others, such as graft purging, have been of no value. Treatment results need further improvement, particularly in poor-prognosis disease-based on abnormal karyotype and high beta(2)-microglobulin-and the future will show if the introduction of novel drugs like bortezomib, thalidomide, and lenalidomide will lead to longer survival and prolongation of disease control in multiple myeloma.

New treatment of multiple myeloma. [Article in French]

Hulin C.

Rev Med Interne. 2007 Oct;28(10):682-688. Epub 2007 May 24.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17559982&ordinalpos=35&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses the new novel therapies, including bortezomib, which can be used successively or in combination in the effective treatment of myeloma.

PURPOSE: After decades of minimal progress, two new classes of drugs with novel mechanisms of action: immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib) have shown great activity for the treatment of multiple myeloma. **CURRENT KNOWLEDGE AND KEY POINTS:** Thalidomide acts by a variety of mechanisms; its efficacy is well known in disease relapse especially associated with dexamethasone. Recent results prove that combination of thalidomide with melphalan and prednisone should be considered as the first line standard of care in elderly patient. The main side effects are peripheral neuropathy and deep-vein thrombosis. Bortezomib is the first proteasome inhibitor. It is approved for the treatment in first disease relapse. The combination with glucocorticoids

is synergistic. This combination in induction treatment before autologous stem cell transplantation is promising, as well as the combination with melphalan and prednisone in elderly patient. The main toxicities are fatigue and peripheral neuropathy. Lenalidomide is a structural analogue of thalidomide. Its efficacy in combination with dexamethasone has been proved in relapsing patients. The main toxicity is hematologic. Utilization as first line treatment is also promising.

FUTURE PROSPECTS AND PROJECTS: These three drugs have toxicities predictable and manageable and can be used successively or in combination for greater effectiveness. They have an impact on the multiple myeloma treatment strategies and on the disease course itself.

Proteasome inhibitor, bortezomib, for myeloma and lymphoma.

Tobinai K.

J Clin Oncol. 2007 Oct;12(5):318-26. Epub 2007 Oct 22.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17929113&ordinalpos=26&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author reviews the results of clinical trials of bortezomib for multiple myeloma, including a Japanese phase I/II and pharmacokinetic/pharmacodynamic study.

Bortezomib, a boronic acid, is a potent and selective proteasome inhibitor. The 20S proteasome is an enzyme complex present in cells, and it degrades many cell-cycle control factors, signal transduction factors, transcription factors, and oncogene and anti-oncogene products, thus controlling cell proliferation, differentiation, and apoptosis. Bortezomib is a novel molecular targeting agent which was designed to exhibit an antitumor effect by selectively inhibiting the 20S proteasome. Multiple myeloma is one of the incurable B-cell malignancies that continues to relapse with current treatment modalities, and the duration to progression becomes shorter in patients who repeatedly receive chemotherapy. There are no available treatment options in which durable efficacy can be expected after relapse; therefore, an effective therapy with a novel mechanism of action has been desired. In this review article, the results of clinical trials of bortezomib for multiple myeloma, including a Japanese phase I/II and pharmacokinetic/pharmacodynamic study, and those for non-Hodgkin lymphoma, especially for mantle cell lymphoma, are summarized. In the Japanese phase I/II study of bortezomib for relapsed multiple myeloma, this agent showed remarkable efficacy, with acceptable toxicities and unique pharmacokinetic/pharmacodynamic profiles, warranting further investigations, including more relevant administration schedules.

Use of bortezomib as induction therapy prior to stem cell transplantation in frontline treatment of multiple myeloma: Impact on stem cell harvesting and engraftment.

Oakervee H, Popat R, Cavenagh JD.

Leuk Lymphoma. 2007 Oct;48(10):1910-21.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17917960&ordinalpos=30&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss bortezomib's potential role as front-line therapy for the treatment of myeloma and the ongoing phase 3 studies for this use.

High-dose melphalan therapy with peripheral blood stem cell (PBSC) transplantation is a standard treatment for younger patients with untreated multiple myeloma that results in high overall and complete response (CR) rates, and improved event-free and overall survival compared with standard chemotherapy alone. Induction therapy serves to reduce tumor burden prior to stem cell mobilization and thus must not adversely impact stem cell mobilization and harvesting, or engraftment following high dose therapy plus autologous stem cell transplantation. Bortezomib, an approved agent for the treatment of multiple myeloma patients who have received at least one prior therapy, is also being investigated in the frontline setting. Preclinical studies have demonstrated that bortezomib has no toxic effects on stem cells, megakaryocytes or neutrophil precursors, and causes only transient and reversible thrombocytopenia and neutropenia. Clinical studies with bortezomib-based induction regimens have demonstrated no adverse impact on PBSC harvest numbers nor on their quality as defined by engraftment times. These regimens appear to be well tolerated and highly active as induction therapy, with high response rates and consistently high CR rates. Randomized phase 3 studies comparing bortezomib-based regimens with current standard induction therapies are ongoing.

The evolving background for high-dose treatment for myeloma.

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

Bone Marrow Transplant. 2007 Oct 1; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17906702&ordinalpos=21&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.

Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: efficacy and clinical implications of tumor response kinetics.

Rosiñol L, Oriol A, Mateos MV, Sureda A, García-Sánchez P, Gutiérrez N, Alegre A, Lahuerta JJ, de la Rubia J, Herrero C, Liu X, Van de Velde H, San Miguel J, Bladé J.

J Clin Oncol. 2007 Oct 1;25(28):4452-8. Epub 2007 Sep 4.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17785704&ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this first study in which bortezomib and dexamethasone were administered on an alternating basis as up-front therapy in multiple myeloma, the authors conclude that bortezomib alternating with dexamethasone is a highly effective induction regimen with low toxicity.

PURPOSE: This is the first study in which bortezomib and dexamethasone were administered on an alternating basis as up-front therapy in multiple myeloma (MM). We investigated the efficacy and kinetics of response to each drug and safety.

PATIENTS AND METHODS: Patients with newly diagnosed MM who were less than 66 years old were treated with bortezomib at 1.3 mg/m² on days 1, 4, 8, and 11 (cycles 1, 3, and 5) and dexamethasone 40 mg orally on days 1 through 4, 9 to 12, and 17 to 20 (cycles 2, 4, and 6), followed by autologous stem-cell transplantation (ASCT). Responses were evaluated by modified European Bone Marrow Transplantation criteria. Random effects models were used to analyze the tumor response kinetics.

RESULTS: Forty patients were enrolled. Partial response (PR) or greater was 65% (12.5% complete response [CR], 10% very good PR [VGPR], and 42.5% PR) plus 17.5% minor response. Time to response was rapid, with 82% serum M-protein reduction achieved within the first two cycles. The M-protein decrease was similar with dexamethasone and with bortezomib (P = .48). Chromosome 13 deletion, t(4;14), and t(14;16) did not have a negative impact on response. Toxicity was low, with no grade 3 to 4 peripheral neuropathy and no grade 2 to 4 thrombocytopenia. The response rate after ASCT was 88%, with 33% CR (negative immunofixation) plus 22% VGPR.

CONCLUSION: Bortezomib alternating with dexamethasone is a highly effective induction regimen with low toxicity. The kinetic study has shown a high degree of heterogeneity in response and rapid effect from both agents, supporting the use of a short induction regimen before ASCT in MM.

 ***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. 2007 Oct 18; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17947507&ordinalpos=11&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that bortezomib significantly enhances the sensitivity of patient myeloma to allogeneic and autologous natural killer cell-mediated lysis.

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. Down-regulation 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.

 ***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. 2007 Oct 23; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17955241&ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

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

Peeß D, Ganser A.

Internist (Berl). 2007 Oct 26; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17960351&ordinalpos=9&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors provide an overview of treatment options, including 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.

 ***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. 2007 Oct 29; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17970782&ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors conduct a phase I and II study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of bortezomib in Japanese patients with relapsed or refractory multiple myeloma and find it to be an effective treatment option.

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.

 ***The histone deacetylase inhibitor, PXD101, potentiates bortezomib-induced anti-multiple myeloma effect by induction of oxidative stress and DNA damage.***

Feng R, Oton A, Mapara MY, Anderson G, Belani C, Lentzsch S.

Br J Haematol. 2007 Nov;139(3):385-97.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17910628&ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors examine the activity of bortezomib combined with PXD101, a histone deacetylase inhibitor, against multiple myeloma and osteoclastogenesis. They find that their combination induces cell death in myeloma cells via reactive oxygen species-mediated DNA damage and also inhibits osteoclastogenesis, providing the rationale for clinical evaluation of this combination.

Clinical trials have shown the high anti-myeloma activity of the proteasome inhibitor bortezomib. The present study examined the activity of bortezomib combined with PXD101, a histone deacetylase inhibitor, against multiple myeloma (MM) and osteoclastogenesis. Treatment of myeloma cell lines with combinations of bortezomib and PXD101 led to synergistic inhibition of proliferation and induction of cell death. The combination significantly decreased the viability of primary human CD138(+) myeloma cells but not of bone marrow mononuclear cells. Further studies showed a dose-dependent activation of caspases-3, -8 and -9 and nuclear fragmentation in myeloma cells. Bortezomib/PXD101 treatment markedly triggered reactive oxygen species (ROS) generation that was accompanied by p53, H2A.X and p38-mitogen-activated protein kinase phosphorylation. ROS generation could be blocked by the free radical scavenger N-acetyl-L-cysteine. The combination of bortezomib and PXD101 also resulted in synergistic inhibition of osteoclast formation. In conclusion, bortezomib and PXD101 have different molecular targets. The combination induces cell death in myeloma cells via ROS-mediated DNA damage and also inhibits osteoclastogenesis. Therefore, this study provides the rationale for the clinical evaluation of bortezomib combined with PXD101 in patients with MM.

Management of multiple myeloma: The changing landscape.

Reece DE.

Blood Rev. 2007 Nov;21(6):301-14. Epub 2007 Aug 29.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17761373&ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author highlights some of the key recent findings in multiple myeloma and describes areas for future research, including the role of bortezomib.

Many changes have been incorporated into the approach to multiple myeloma over the last few years, due to improvements in our understanding of the disease biology. New diagnostic and prognostic criteria from the International Myeloma Working Group have clarified the initial clinical approach to this disease. The prognostic impact of chromosomal abnormalities is now recognized, and the detection of specific abnormal cytogenetics is beginning to influence therapeutic decisions. The introduction of the novel agents thalidomide, bortezomib and lenalidomide has expanded treatment options at different points in the disease course; these agents are being evaluated in conjunction with conventional chemotherapy and stem cell transplantation. This report highlights some of the key recent findings in multiple myeloma, and describes areas for future research.

Novel therapies in myeloma.

Hayden PJ, Mitsiades CS, Anderson KC, Richardson PG.

Curr Opin Hematol. 2007 Nov;14(6):609-15.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17898564&ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors summarize some of the trials leading to the approval of proteasome inhibitor bortezomib, and the current evidence for its clinical use.

PURPOSE OF REVIEW: Several novel therapies have been licensed for the treatment of myeloma in recent years. We summarize some of the trials leading to their approval and the current evidence for their clinical use. A number of promising agents undergoing phase I/II trial evaluation are also discussed.

RECENT FINDINGS: The immunomodulatory drugs, thalidomide and lenalidomide, and the proteasome inhibitor, bortezomib, have been shown to be effective agents, both alone and as part of combination regimens, for the treatment of myeloma. Studies are now focusing on the optimal sequencing of these drugs throughout the disease course, with a view to maximizing antitumor efficacy and minimizing overlapping toxicities. New protocols are increasingly based on preclinical evidence of synergy. The incorporation of these agents into transplant-based treatment protocols has improved outcomes. Other examples of novel agents undergoing assessment at present include arsenic trioxide, hsp90 inhibitors and histone deacetylase inhibitors. Future developments are likely to include individualized treatment plans based on patient-specific parameters including cytogenetic analysis and gene expression profiling.

SUMMARY: Thalidomide, lenalidomide and bortezomib can now be considered as standard options both as first-line agents and beyond for the treatment of myeloma, with respective combinations also emerging as valid choices for all stages of the disease.

Stimulation of new bone formation by the proteasome inhibitor, bortezomib: implications for myeloma bone disease.

Oyajobi BO, Garrett IR, Gupta A, Flores A, Esparza J, Muñoz S, Zhao M, Mundy GR.

Br J Haematol. 2007 Nov;139(3):434-8.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17910634&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study suggests a novel mechanism by which bortezomib exerts its effects in bone. Clinical trials in patients with myeloma bone disease are needed to validate this study's results.

Impaired bone formation contributes to the lack of bone healing in multiple myeloma and there is a need for agents with bone anabolic properties to reverse the bone deficit in patients. Bortezomib, a proteasome inhibitor with antitumour efficacy in myeloma patients, enhanced new bone formation in mouse calvarial cultures; this effect was blocked by dickkopf 1 (Dkk1), an antagonist of Wnt signalling implicated in myeloma bone disease. Bortezomib inhibited Dkk1 expression in calvariae and bone marrow-derived stromal cells, suggesting a novel mechanism by which bortezomib exerts its effects in bone. Clinical trials in patients with myeloma bone disease are needed to validate these results.

 ***Tissue distribution and depletion kinetics of bortezomib and bortezomib-related radioactivity in male rats after single and repeated intravenous injection of 14 C-bortezomib.***

Hemeryck A, Geerts R, Monbaliu J, Hassler S, Verhaeghe T, Diels L, Verluyten W, van Beijsterveldt L, Mamidi RN, Janssen C, De Coster R.

Cancer Chemother Pharmacol. 2007 Nov;60(6):777-87. Epub 2007 Feb 7.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17285316&ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors study the body distribution of total radioactivity (TR) and bortezomib in rats and find no undue tissue accumulation of TR or of bortezomib in the rats following a full clinical dosing cycle of bortezomib.

PURPOSE: The body distribution of total radioactivity (TR) and bortezomib was investigated in male Sprague-Dawley rats after single and repeated i.v. (bolus) administration with (14)C-labelled bortezomib (VELCADE) (0.2 mg/kg; 0.28 MBq/kg).

METHODS: Bortezomib was dosed on days 1, 4, 8, and 11 (i.e. a clinical dosing cycle) and the animals were sacrificed at selected time points following single and repeated dose administration for the quantification of TR in blood, plasma, and various tissues by liquid scintillation counting following organ dissection or by quantitative whole body autoradiography. In selected tissues, bortezomib levels were determined by LC-MS/MS.

RESULTS: In general, plasma TR levels were less than 10% of the corresponding blood concentrations. TR was rapidly and widely distributed to the tissues with only limited penetration into the central nervous system (CNS). In the tissues, highest levels of TR were measured in bortezomib-eliminating organs (liver and kidney), lymphoid tissues, and regions of rapidly dividing cells (e.g. the bone marrow, intestinal mucosa). Low TR concentrations were found in the CNS (tissue-to-blood ratio of approximately 0.05 after repeated dosing). With the exception of the liver, TR consisted almost exclusively of the parent drug. Tissue concentrations of TR and bortezomib increased up to about threefold from the first to the third dose administration, after which they remained constant.

CONCLUSION: No undue tissue accumulation of TR and of bortezomib was observed in rats following a full clinical dosing cycle of bortezomib.

 ***Use of intrapleural bortezomib in myelomatous pleural effusion.***

Iannitto E, Minardi V, Tripodo C.

Br J Haematol. 2007 Nov;139(4):621-2.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17979947&ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

 ***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. 2007 Nov 1; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17975015&ordinalpos=18&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors demonstrate the improved outcome of patients using novel therapies, including bortezomib, 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 two 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 transplant, 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 vs. 11.8 months ($P < 0.001$) 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; $P < 0.001$). 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; $P < 0.001$). In this study, we demonstrate improved outcome of patients with myeloma in recent years, both in the relapsed setting as well as at diagnosis.

 ***Inhibition of Interleukin-6 Signaling with CNTO 328 Enhances the Activity of Bortezomib in Preclinical Models of Multiple Myeloma.***

Voorhees PM, Chen Q, Kuhn DJ, Small GW, Hunsucker SA, Strader JS, Corringham RE, Zaki MH, Nemeth JA, Orlowski RZ.
Clin Cancer Res. 2007 Nov 1;13(21):6469-6478.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17975159&ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find a strong preclinical rationale for the clinical development of the bortezomib/CNTO 328 combination for patients with myeloma.

PURPOSE: Inhibition of the proteasome leads to the activation of survival pathways in addition to those that promote cell death. We hypothesized that down-regulation of interleukin-6 (IL-6) signaling using the monoclonal antibody CNTO 328 would enhance the antitumor activity of the proteasome inhibitor bortezomib in multiple myeloma by attenuating inducible chemoresistance.

EXPERIMENTAL DESIGN: The cytotoxicity of bortezomib, CNTO 328, and the combination, along with the associated molecular changes, was assessed in IL-6-dependent and IL-6-independent multiple myeloma cell lines, both in suspension and in the presence of bone marrow stromal cells and in patient-derived myeloma samples.

RESULTS: Treatment of IL-6-dependent and IL-6-independent multiple myeloma cell lines with CNTO 328 enhanced the cytotoxicity of bortezomib in a sequence-dependent fashion. This effect was additive to synergistic and was preserved in the presence of bone marrow stromal cells and in CD138(+) myeloma samples derived from patients with relative clinical resistance to bortezomib. CNTO 328 potentiated bortezomib-mediated activation of caspase-8 and caspase-9 and the common downstream effector caspase-3; attenuated bortezomib-mediated induction of antiapoptotic heat shock protein-70, which correlated with down-regulation of phosphorylated signal transducer and activator of transcription-1; and inhibited bortezomib-mediated accumulation of myeloid cell leukemia-1, an effect that was associated with down-regulation of phosphorylated signal transducer and activator of transcription-3.

CONCLUSIONS: Taken together, our results provide a strong preclinical rationale for the clinical development of the bortezomib/CNTO 328 combination for patients with myeloma.

 ***Efficacy of Bortezomib followed by local irradiation in two patients with extramedullary plasmacytomas.***

Varettoni M, Mangiacavalli S, Zappasodi P, Pica GM, Lazzarino M, Corso A.
Leuk Res. 2007 Nov 6; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17997154&ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report the efficacy of a combined therapeutic approach including 3 cycles of bortezomib as initial debulking, followed by adjuvant radiotherapy in two myeloma patients with an extramedullary plasmacytomas of the head.

The standard approach for the treatment of extramedullary plasmacytomas (EMPs) is radiotherapy, alone or combined with chemotherapy in case of multiple myeloma (MM) with extramedullary disease. Among novel agents recently adopted for the treatment of MM, Bortezomib seems to be very active on EMPs. We report the efficacy of a combined therapeutic approach including 3 cycles of Bortezomib as initial debulking, followed by adjuvant radiotherapy in two patients with an EMP of the head.

 ***Improvement of Zoledronic Acid-Induced Jaw Osteonecrosis with Bortezomib.***

Timuragaoglu A, Ozkaynak C, Tuzuner S, Bostan F, Undar L.
Acta Haematol. 2007 Nov 9;118(4):203-204 [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17992010&ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial.

Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, Miguel JS, Bladé J, Boccadoro M, Cavenagh J, Alsina M, Rajkumar SV, Lacy M, Jakubowiak A, Dalton W, Boral A, Esseltine DL, Schenkein D, Anderson KC.

Blood. 2007 Nov 15;110(10):3557-60. [Epub 2007 Aug 9.]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17690257&ordinalpos=11&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors' data confirm the activity of bortezomib and support extended treatment in relapsed multiple myeloma patients tolerating therapy.

Initial analysis of the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial of relapsed multiple myeloma patients showed significantly longer time to progression, higher response rate, and improved survival with single-agent bortezomib versus high-dose dexamethasone. In this updated analysis (median follow-up: 22 months), survival was assessed in both arms, and efficacy updated for the bortezomib arm. Median survival was 29.8 months for bortezomib versus 23.7 months for dexamethasone, a 6-month benefit, despite substantial crossover from dexamethasone to bortezomib. Overall and complete response rates with bortezomib were 43% and 9%, respectively; among responding patients, 56% improved response with longer therapy beyond initial response, leading to continued improvement in overall quality of response. Higher response quality (100% M-protein reduction) was associated with longer response duration; response duration was not associated with time to response. These data confirm the activity of bortezomib and support extended treatment in relapsed multiple myeloma patients tolerating therapy.

Access to expensive drugs in the NHS: myths and realities for cancer patients.

Mehta AB, Low E.

Int J Clin Pract. 2007 Dec;61(12):2126-9.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17997811&ordinalpos=9&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors conclude that the current funding arrangements for new drugs to treat myeloma in the UK, such as bortezomib, are inequitable and do not lend themselves to achieving the best possible outcome for patients.

Setting: Patient support organisation (Myeloma UK) and Hospital Myeloma Clinic. Type of study: Case review of two patients, one whose treatment is funded by a private insurance company in the UK, and the other who is funded by the National Health Service (NHS) and questionnaire survey of 51 haematologists from Myeloma UK database. Results: The treatment options available for private patients with myeloma in the UK are broader and more in line with national and international practice than are options available to UK NHS patients. 22/41 (54%) of respondents had received refusals to fund bortezomib by NHS funding agencies; all the rejections had been from Primary Care Trusts in England, which are governed by guidance issued from a different regulator than the other UK countries and subject to divergent local funding arrangements; 19/46 (41%) felt that it was currently (May 2007) more difficult to obtain funding approval for one treatment, bortezomib, than in September 2006, when it received a negative recommendation from the National Institute for health and Clinical Excellence and 15/17 doctors who prescribe on the NHS and privately felt it was easier to obtain bortezomib for a private patient than an NHS patient in the UK. Conclusion: The current funding arrangements for new drugs to treat myeloma in the UK are inequitable and do not lend themselves to achieve the best possible outcome for patients.

Management of newly diagnosed myeloma.

Rajkumar SV, Palumbo A.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1141-56.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996592&ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the dramatic changes in myeloma treatment over the last decade, including the introduction of bortezomib.

The treatment of multiple myeloma has changed dramatically in the last decade with the introduction of thalidomide, bortezomib, and lenalidomide. Patients eligible for autologous stem cell transplantation (ASCT) are treated with non-alkylating agent-containing regimens as initial therapy; typically thalidomide-dexamethasone or lenalidomide-dexamethasone. For patients not eligible for ASCT, the current standard of care is melphalan, prednisone, and thalidomide. Ongoing trials will soon assess if combinations including melphalan and prednisone plus bortezomib or MP plus lenalidomide may be considered an attractive option. Patients who have risk factors, such as deletion 13 or translocation t(4;14) or t(14;16), are candidates for novel, more aggressive treatments.

Management of relapsed and relapsed refractory myeloma.

Kastritis E, Mitsiades CS, Dimopoulos MA, Richardson PG.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1175-215.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996594&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the accumulating experience from ongoing trials of bortezomib/lenalidomide/dexamethasone combinations in patients who have relapsed/refractory or newly diagnosed myeloma.

Studies of bortezomib, thalidomide, and lenalidomide have shown promising clinical activity in relapsed/refractory multiple myeloma (MM). Bortezomib alone and in combination with other agents is associated with high response rates, consistently high rates of complete response, and a predictable and manageable profile of adverse events. Thalidomide-based regimens have also shown substantial clinical activity. The accumulating experience from ongoing trials of bortezomib/lenalidomide/dexamethasone combinations in patients who have relapsed/refractory or newly diagnosed MM will provide critical information that will determine the possible role of this combination as the basic backbone for combination regimens for management of advanced MM.

Neurologic complications of chemotherapy agents.

Kannarkat G, Lasher EE, Schiff D.

Curr Opin Neurol. 2007 Dec;20(6):719-725.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17992096&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors address the reversible peripheral neuropathy of bortezomib.

PURPOSE OF REVIEW: To review neurologic complications of common and recently developed chemotherapeutic agents, as well as recent research regarding 'chemobrain'.

RECENT FINDINGS: Bortezomib, a new anticancer agent, has a propensity toward causing a largely sensory and reversible peripheral neuropathy. Infusion of magnesium and calcium pre and post-oxaliplatin infusion reduces neuropathy but may interfere with clinical response to oxaliplatin. No other measures currently reduce the incidence or severity of neuropathy related to platinum compounds, taxanes, or thalidomide. Chemobrain, cognitive decline attributed to chemotherapy, has garnered research interest. Prevalence and epidemiology of chemobrain are poorly understood. Potential underlying mechanisms are under investigation in animal models and include effects on long-term potentiation and cerebral blood flow. Blood-brain barrier permeability, efficiency of cellular efflux pumps, DNA damage, telomere shortening, alteration of cytokine regulation, defects in neural repair, and oxidative stress may play roles in the effects of chemotherapy on central nervous system function.

SUMMARY: Data on prevention and treatment of chemotherapy-induced peripheral neuropathy are limited. Calcium and magnesium infusions for oxaliplatin administration have the most scientific support and are widely used in practice but may interfere with the clinical efficacy of oxaliplatin. Some novel agents, particularly bortezomib, have significant risk of chemotherapy-induced peripheral neuropathy. Animal models are beginning to reveal the mechanisms underlying the impact of individual chemotherapeutic drugs on cognition.

Preclinical studies of novel targeted therapies.

Hideshima T, Anderson KC.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1071-91.

The authors discuss how novel therapies, such as bortezomib, are usefully directed not only at myeloma cells but also at the bone marrow milieu.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996589&ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The bone marrow (BM) milieu confers drug resistance in multiple myeloma (MM) cells to conventional therapies. Novel biologically based therapies are therefore needed. Preclinical studies have identified and validated molecular targeted therapeutics in MM. In particular, recognition of the biologic significance of the BM microenvironment in MM pathogenesis and as a potential target for novel therapeutics has already derived several promising approaches. Thalidomide, lenalidomide (Revlimid), and bortezomib (Velcade) are directed not only at MM cells but also at the BM milieu and have moved rapidly from the bench to the bedside and United States Food and Drug Administration approval to treat MM.

Role of stem cell transplantation.

Harousseau JL.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1157-74.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996593&ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author concludes that the role of allogeneic stem cell transplantation remains controversial, even with reduced intensity conditionings, given the introduction of novel agents, such as bortezomib.

Hematopoietic stem cell transplantation (SCT) was introduced in the treatment of multiple myeloma in the 1980s. In the autologous setting, the use of peripheral blood stem cells instead of bone marrow has markedly improved feasibility. In fit patients who have normal renal function and are younger than 65 years of age, randomized studies have shown the superiority of autologous stem cell transplantation (ASCT) compared with conventional chemotherapy. ASCT is now considered the standard of care in this population of patients. It is currently challenged, however, by the introduction of novel agents, such as thalidomide, bortezomib, and lenalidomide. The role of allogeneic SCT remains controversial, even with reduced intensity conditionings. Prospective studies still are needed to evaluate the impact of both autologous and allogeneic SCT in this new era.



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