



CITINGS

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VELCADE® (bortezomib) Issue

Welcome to the International Myeloma Foundation's (IMF) special edition of CITINGS, our premiere publication featuring the most up-to-date information on myeloma treatment. This issue focuses on VELCADE (bortezomib), the first of a new class of drugs called proteasome inhibitors. In this issue, we provide a list of references to the latest publications from the third quarter of 2008 on bortezomib from both national and international medical journals and publications.

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

– Susie Novis, President, IMF

VELCADE® Publications – 3rd Quarter, 2008

Bortezomib in multiple myeloma.

Terpos E, Roussou M, Dimopoulos MA.

Expert Opin Drug Metab Toxicol. 2008 May;4(5):639-54.



http://www.ncbi.nlm.nih.gov/pubmed/18484921?ordinalpos=137&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This article summarizes the chemistry, pharmacokinetics and metabolism of bortezomib, and reviews its clinical efficacy and toxicity, including use in elderly patients, use in patients with renal impairment and/or a poor prognosis, and effects on bone metabolism.

Fatty acid synthase is a novel therapeutic target in multiple myeloma.

Okawa Y, Hideshima T, Ikeda H, Raje N, Vallet S, Kiziltepe T, Yasui H, Enatsu S, Pozzi S, Breitkreutz I, Cirstea D, Santo L, Richardson P, Anderson KC.

Br J Haematol. 2008 May;141(5):659-71. [Epub 2008 Apr 10.]



http://www.ncbi.nlm.nih.gov/pubmed/18410446?ordinalpos=125&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study investigates the biological significance of the inhibition of fatty acid synthase in multiple myeloma using the small molecule inhibitor Cerulenin and finds in part that Cerulenin shows synergistic cytotoxic effects with various agents, including bortezomib.

 **p38 mitogen-activated protein kinase inhibitor LY2228820 enhances bortezomib-induced cytotoxicity and inhibits osteoclastogenesis in multiple myeloma; therapeutic implications.**

Ishitsuka K, Hideshima T, Neri P, Vallet S, Shiraishi N, Okawa Y, Shen Z, Raje N, Kiziltepe T, Ocio EM, Chauhan D, Tassone P, Munshi N, Campbell RM, Dios AD, Shih C, Starling JJ, Tamura K, Anderson KC.

Br J Haematol. 2008 May;141(5):598-606. [Epub 2008 Apr 7.]

 http://www.ncbi.nlm.nih.gov/pubmed/18397345?ordinalpos=126&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors' findings suggest that inhibitor LY2228820 represents a promising novel targeted approach to improve myeloma patient outcome both by enhancing the effect of bortezomib and by reducing osteoskeletal events.

 **New therapeutic strategies for multiple myeloma. Efficacy and cost-effectiveness analyses.** [Article in Spanish]

García Querglas E, Azanza Perea JR, Lecumberri Villamediana R.

Med Clin (Barc). 2008 May 3;130(16):626-35.

 http://www.ncbi.nlm.nih.gov/pubmed/18482531?ordinalpos=119&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The article reviews the most important therapeutic innovations in the treatment of myeloma in terms of efficacy and cost-effectiveness, including a discussion of bortezomib.

 **The addition of liposomal doxorubicin to bortezomib, thalidomide and dexamethasone significantly improves clinical outcome of advanced multiple myeloma.**

Ciolli S, Leoni F, Casini C, Breschi C, Santini V, Bosi A.

Br J Haematol. 2008 Jun;141(6):814-9. [Epub 2008 Apr 10.]

 http://www.ncbi.nlm.nih.gov/pubmed/18410447?ordinalpos=84&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this study, liposomal doxorubicin is added to a bortezomib/thalidomide/ dexamethasone (VTD) treatment in relapsed/refractory myeloma patients. The authors find increased overall response rate and progression-free survival with this combination, compared to VTD alone and that toxicity is manageable although more pronounced.

 **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 Jun;19(6):1160-5. [Epub 2008 Mar 6.]

 http://www.ncbi.nlm.nih.gov/pubmed/18326520?ordinalpos=82&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors assess for the first time the combination of bortezomib, doxorubicin and low-dose dexamethasone (PAD) in the treatment of relapsed/refractory myeloma and find that PAD is an active salvage therapy with manageable toxicity in patients with relapsed/refractory myeloma.

 **Clinical implications of bortezomib in frontline treatment of newly-diagnosed multiple myeloma.**

[Article in Japanese]

Ohashi K.

Gan To Kagaku Ryoho. 2008 Jun;35(6):1029-32.

 http://www.ncbi.nlm.nih.gov/pubmed/18633240?ordinalpos=96&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This review focuses on the clinical data based on the previous studies of bortezomib in the treatment of newly diagnosed myeloma.

 **Features and risk factors of peripheral neuropathy during treatment with bortezomib for advanced multiple myeloma.**

El-Cheikh J, Stoppa AM, Bouabdallah R, de Lavallade H, Coso D, de Collela JM, Auran-Schleinitz T, Gastaut JA, Blaise D, Mohy M.

Clin Lymphoma Myeloma. 2008 Jun;8(3):146-52.

 http://www.ncbi.nlm.nih.gov/pubmed/18650177?ordinalpos=91&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This retrospective, single-center study aims to determine the characteristics of bortezomib-associated peripheral neuropathy (PN).

It concludes that, though relatively frequent, bortezomib-associated PN is reversible in a majority of patients and that bortezomib-associated PN seems to be dependent on previous therapy with thalidomide, suggesting that bortezomib followed by thalidomide could be an optimal sequence of administration of these drugs in the salvage setting.

 **Gastrointestinal side effects associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board.**

Smith LC, Bertolotti P, Curran K, Jenkins B; IMF Nurse Leadership Board.

Clin J Oncol Nurs. 2008 Jun;12(3 Suppl):37-52.

 http://www.ncbi.nlm.nih.gov/pubmed/18490256?ordinalpos=88&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The International Myeloma Foundation's Nurse Leadership Board develops a consensus statement for the management of gastrointestinal side effects associated with novel therapies, including bortezomib, to be used by healthcare providers in any medical setting.

 **Hemostatic effects of bortezomib treatment in patients with relapsed or refractory multiple myeloma.**

Zangari M, Guerrero J, Cavallo F, Prasad HK, Esseltine D, Fink L.

Haematologica. 2008 Jun;93(6):953-4.

 http://www.ncbi.nlm.nih.gov/pubmed/18515882?ordinalpos=97&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
No abstract available.

 **Maintenance treatment in multiple myeloma.**

Harousseau JL.

Ann Oncol. 2008 Jun;19 Suppl 4:iv54-5.

 http://www.ncbi.nlm.nih.gov/pubmed/18519405?ordinalpos=81&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
No abstract available.

 **Myelosuppression associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board.**

Miceli T, Colson K, Gavino M, Lilleby K; IMF Nurse Leadership Board.

Clin J Oncol Nurs. 2008 Jun;12(3 Suppl):13-20.

 http://www.ncbi.nlm.nih.gov/pubmed/18490253?ordinalpos=90&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The International Myeloma Foundation's Nurse Leadership Board developed a consensus statement that includes toxicity grading, strategies for monitoring and managing myelosuppression associated with novel therapies, including bortezomib, and offers educational recommendations for patients and their caregivers.

 **An observational, retrospective analysis of retreatment with bortezomib for multiple myeloma.**

Conner TM, Doan QD, Walters IB, LeBlanc AL, Beveridge RA.

Clin Lymphoma Myeloma. 2008 Jun;8(3):140-5.

 http://www.ncbi.nlm.nih.gov/pubmed/18650176?ordinalpos=92&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
This retrospective chart review of patients with myeloma aims to describe patterns of re-treatment with bortezomib-based therapy and responses to re-treatment in a community-based setting. It concludes that re-treatment with bortezomib-based therapy is feasible, with predictable toxicities; this observational analysis supports bortezomib alone or in combination as a re-treatment option after initial bortezomib treatment in patients with relapsed myeloma.

 **Peripheral neuropathy associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board.**

Tariman JD, Love G, McCullagh E, Sandifer S; IMF Nurse Leadership Board.

Clin J Oncol Nurs. 2008 Jun;12(3 Suppl):29-36.

 http://www.ncbi.nlm.nih.gov/pubmed/18490255?ordinalpos=89&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The International Myeloma Foundation Nurse Leadership Board provides specific management strategies for peripheral neuropathy caused by novel therapies, including bortezomib, based on the grade of severity and on signs and symptoms; strategies include dose and schedule modifications, pharmacologic interventions, nonpharmacologic approaches, and patient education.

The potential of proteasome inhibitors in cancer therapy.

Sterz J, von Metzler I, Hahne JC, Lamottke B, Rademacher J, Heider U, Terpos E, Sezer O.

Expert Opin Investig Drugs. 2008 Jun;17(6):879-95.



http://www.ncbi.nlm.nih.gov/pubmed/18491989?ordinalpos=94&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This review focuses both on preclinical results and on data from clinical trials with proteasome inhibitors in cancer and concludes that bortezomib as first-in-class proteasome inhibitor that has proven to be highly effective in some hematological malignancies, overcomes conventional chemoresistance, directly induces cell cycle arrest and apoptosis, and also targets the tumor microenvironment.

Proteasome Inhibitor Induces Apoptosis and Influences the Expression of Notch 1 and NF-kappaB in Multiple Myeloma RPMI8226 Cells. [Article in Chinese]

Wang H, Liu X, Xu B.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2008 Jun;16(3):531-7.



http://www.ncbi.nlm.nih.gov/pubmed/18549623?ordinalpos=109&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors investigate the effects of bortezomib inducing cell apoptosis and influencing the expression of Notch1 and NF-kappaB in multiple myeloma RPMI 8226 cells. They conclude that Notch1 and NF-kappaB signaling pathways participate in bortezomib-inducing RPMI8226 cell apoptosis and that there may be some correlation between the Notch 1 and NF-kappaB signaling pathways, indicating that Notch 1 signal may be a latent target in treating myeloma.

Updated follow-up of patients treated with bortezomib for relapsed multiple myeloma.

Santini D, Vincenzi B, Tonini G.

Nat Clin Pract Oncol. 2008 Jun;5(6):304-5. [Epub 2008 Apr 29.]



http://www.ncbi.nlm.nih.gov/pubmed/18446143?ordinalpos=106&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Comment on: *Blood. 2007 Nov 15;110(10):3557-60.*

Frontline treatment of multiple myeloma in elderly patients.

Moreau P, Hulin C, Facon T.

Blood Rev. 2008 Jun 10. [Epub ahead of print.]



http://www.ncbi.nlm.nih.gov/pubmed/18550234?ordinalpos=72&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This article discusses highly active new treatment options now available to treat elderly patients with myeloma, including melphalan-prednisone-bortezomib.

Completion of premaintenance phases in total therapies 2 and 3 improves clinical outcomes in multiple myeloma: an important variable to be considered in clinical trial designs.

Barlogie B, Haessler J, Pineda-Roman M, Anaissie E, van Rhee F, Kiwan E, Steward D, Gurley J, Jenkins B, Crowley J.

Cancer. 2008 Jun 15;112(12):2720-5.



http://www.ncbi.nlm.nih.gov/pubmed/18433012?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study of treatment protocols results in data supporting the beneficial role of bortezomib in the treatment of myeloma.

The novel polyamine analogue CGC-11093 enhances the antimyeloma activity of bortezomib.

Carew JS, Nawrocki ST, Reddy VK, Bush D, Rehg JE, Goodwin A, Houghton JA, Casero RA Jr, Marton LJ, Cleveland JL.

Cancer Res. 2008 Jun 15;68(12):4783-90.



http://www.ncbi.nlm.nih.gov/pubmed/18559525?ordinalpos=70&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report that CGC-11093 selectively augments the in vitro and in vivo antimyeloma activity of bortezomib, findings that support the study of the use of the combination of bortezomib and CGC-11093 in myeloma patients who fail to respond to frontline therapy.

 **Molecular basis of bortezomib/Velcade(R) resistance: proteasome subunit {beta}5 (PSMB5) gene mutation and overexpression of PSMB5 protein.**

Oerlemans R, Franke NE, Assaraf YG, Cloos J, van Zantwijk I, Berkers CR, Scheffer GL, Debiprasad K, Vojtekova K, Lemos C, van der Heijden JW, Ylstra B, Peters GJ, Kaspers GL, Dijkmans BA, Schepers RJ, Jansen G.

Blood. 2008 Jun 18. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18565852?ordinalpos=65&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors' findings establish a novel mechanism of bortezomib-resistance associated with the selective overexpression of a mutant PSMB5 protein.

 **Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature.**

Argyriou AA, Iconomou G, Kalofonos HP.

Blood. 2008 Jun 23. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18574024?ordinalpos=62&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors review the pathogenesis, incidence, risk factors, diagnosis, characteristics and management of bortezomib-induced peripheral neuropathy and highlight areas of future research to pursue.

 **Bortezomib in the front-line treatment of multiple myeloma.**

Richardson PG, Mitsiades C, Schlossman R, Ghobrial I, Hideshima T, Munshi N, Anderson KC.

Expert Rev Anticancer Ther. 2008 Jul;8(7):1053-72.

 http://www.ncbi.nlm.nih.gov/pubmed/18588451?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors discuss the rapid evolution of front-line therapy for multiple myeloma with the development of new, highly active regimens based on novel agents such as bortezomib.

 **Chemotherapy-induced peripheral neuropathy: Prevention and treatment strategies.**

Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C.

Eur J Cancer. 2008 Jul;44(11):1507-15. [Epub 2008 Jun 18.]

 http://www.ncbi.nlm.nih.gov/pubmed/18571399?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
This article provides a review of studies conducted to look at ways of preventing or alleviating established chemotherapy-induced peripheral neuropathy (CIPN), including CIPN as a side effect of bortezomib treatment.

 **NF-kappaB in the pathogenesis and treatment of multiple myeloma.**

Li ZW, Chen H, Campbell RA, Bonavida B, Berenson JR.

Curr Opin Hematol. 2008 Jul;15(4):391-9.

 http://www.ncbi.nlm.nih.gov/pubmed/18536579?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
This review summarizes recent advances in the mechanisms through which the activation of the transcription factor NF-kappaB contributes to the pathogenesis of myeloma, including the finding that several drugs that are effective against myeloma, including bortezomib, also block activation of NF-kappaB.

 **Osteoprogenitor differentiation is not affected by immunomodulatory thalidomide analogs but is promoted by low bortezomib concentration, while both agents suppress osteoclast differentiation.**

Munemasa S, Sakai A, Kuroda Y, Okikawa Y, Katayama Y, Asaoku H, Kubo T, Shimose S, Kimura A.

Int J Oncol. 2008 Jul;33(1):129-36.

 http://www.ncbi.nlm.nih.gov/pubmed/18575758?ordinalpos=50&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors investigate the effects of bortezomib and immunomodulatory thalidomide analogs (including lenalidomide) on osteoblast and osteoclast differentiation in vitro. They conclude that by combining bortezomib with immunomodulatory compounds, it is possible to improve treatment strategy for myeloma patients without damaging BM stromal cells.

 **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 Jul;32(7):1078-84. [Epub 2008 Feb 1.]

 http://www.ncbi.nlm.nih.gov/pubmed/18241919?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors perform a prospective study in myeloma patients in whom coagulation factor levels are evaluated longitudinally before, during induction and after intensification. Patients are randomized to induction treatment consisting of adriamycin and dexamethasone, in combination with either vincristine, thalidomide, or bortezomib followed by high-dose melphalan and autologous stem cell transplant. The authors find that during induction treatment several changes in coagulation factor levels are observed, which may result in a prothrombotic state. They conclude that 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 myeloma patients.

 **VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma.**

Pineda-Roman M, Zangari M, van Rhee F, Anaissie E, Szymonifka J, Hoering A, Petty N, Crowley J, Shaughnessy J, Epstein J, Barlogie B.

Leukemia. 2008 Jul;22(7):1419-27. [Epub 2008 Apr 24.]

 http://www.ncbi.nlm.nih.gov/pubmed/18432260?ordinalpos=55&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this study, bortezomib was combined with thalidomide and dexamethasone in a phase I/II trial to determine dose-limiting toxicities and clinical activity of this regimen in 85 patients with advanced and refractory myeloma.

 **Bortezomib: a novel chemotherapeutic agent for hematologic malignancies.**

Utecht KN, Kolesar J.

Am J Health Syst Pharm. 2008 Jul 1;65(13):1221-31.

 http://www.ncbi.nlm.nih.gov/pubmed/18574011?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This article reviews the pharmacology, pharmacokinetics, clinical efficacy, safety, dosage and administration, place in therapy, and cost of bortezomib in the treatment of multiple myeloma and mantle cell lymphoma.

 **Multiple Myeloma, an update on diagnosis and treatment.**

Caers J, Vande Broek I, De Raeve H, Michaux L, Trullemans F, Schots R, Van Camp B, Vanderkerken K.

Eur J Haematol. 2008 Jul 11. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18637123?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This article updates the new approaches in the diagnosis and treatment of myeloma, including new agents such as bortezomib.

 **A novel therapeutic combination using PD 0332991 and bortezomib: study in the 5T33MM myeloma model.**

Menu E, Garcia J, Huang X, Di Liberto M, Toogood PL, Chen I, Vanderkerken K, Chen-Kiang S.

Cancer Res. 2008 Jul 15;68(14):5519-23.

 http://www.ncbi.nlm.nih.gov/pubmed/18632601?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that inhibition of Cdk4/6 by PD 0332991 effectively controls myeloma tumor expansion and sensitizes tumor cells to bortezomib killing in the presence of an intact immune system, thereby representing a novel and promising cell cycle-based combination therapy.

 **Dietary flavonoids inhibit the anti-cancer effects of the proteasome inhibitor Bortezomib.**

Liu FT, Agrawal SG, Movasagh Z, Wyatt PB, Rehman IU, Gribben JG, Newland AC, Jia L.

Blood. 2008 Jul 16. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18633129?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss data indicating that dietary flavonoids limit the efficacy of bortezomib.

 **Phase I-II Trial of Bortezomib Plus Oral Cyclophosphamide and Prednisone in Relapsed and Refractory Multiple Myeloma.**

Reece DE, Piza Rodriguez G, Chen C, Trudel S, Kukreti V, Mikhael J, Pantoja M, Xu W, Stewart AK.

J Clin Oncol. 2008 Jul 21. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18645194?ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors seek to improve the efficacy of the combination of oral weekly cyclophosphamide and alternate day prednisone regimen for relapsed/refractory multiple myeloma by adding bortezomib. They find that weekly bortezomib 1.5 mg/m²(2) plus oral cyclophosphamide and prednisone produces an unprecedented response rate and encouraging 1-year survival in relapsed/refractory patients with myeloma.

 **Advances in and applications of proteasome inhibitors.**

Moore BS, Eustáquio AS, McGlinchey RP.

Curr Opin Chem Biol. 2008 Jul 24. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18656549?ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This review highlights recent advances in the development and application of proteasome inhibitors, including bortezomib.

 **Targeting TRAIL death receptors.**

Oldenhuis C, Steghuis J, Walenkamp A, de Jong S, de Vries E.

Curr Opin Pharmacol. 2008 Jul 28. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18625341?ordinalpos=25&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors in part discuss the mechanisms to sensitize tumors cells to rhTRAIL by combination with bortezomib.

 **The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma.**

Niesvizky R, Richardson PG, Rajkumar SV, Coleman M, Rosiñol L, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Boral AL, Esseltine DL, Anderson KC, Bladé J.

Br J Haematol. 2008 Jul 31. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18673366?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study assesses bortezomib versus dexamethasone in relapsed myeloma and the relationship between quality of response to bortezomib and clinical benefit. The authors conclude that bortezomib had substantial activity in relapsed myeloma patients and that complete remission may be a surrogate marker for significant clinical benefit with bortezomib.

 **Bortezomib and the increased incidence of herpes zoster in patients with multiple myeloma.**

Kim SJ, Kim K, Kim BS, Lee HJ, Kim H, Lee NR, Nam SH, Kwon JH, Kim HJ, Sohn SK, Won JH, Lee JH, Suh C, Yoon SS, Kim HJ, Kim I, Do YR, Lee WS, Joo YD, Shin HJ.

Clin Lymphoma Myeloma. 2008 Aug;8(4):237-40.

 http://www.ncbi.nlm.nih.gov/pubmed/18765311?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors perform a retrospective analysis of the incidence of herpes zoster among 282 patients treated with a bortezomib-containing regimen and conclude that bortezomib can increase the incidence of herpes zoster regardless of disease duration, previous treatments, and concomitantly administered drugs; the occurrence of herpes zoster should therefore be monitored during bortezomib treatment.

 **Bortezomib-resistant nuclear factor-*kappaB* activity in multiple myeloma cells.**

Markovina S, Callander NS, O'Connor SL, Kim J, Werndli JE, Raschko M, Leith CP, Kahl BS, Kim K, Miyamoto S.

Mol Cancer Res. 2008 Aug;6(8):1356-64.

 http://www.ncbi.nlm.nih.gov/pubmed/18708367?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report an unexpected finding that constitutive NF-*kappaB* activity in 10 of 14 primary myeloma samples analyzed is refractory to inhibition by bortezomib.

 **Caspase-2 functions upstream of mitochondria in endoplasmic reticulum stress-induced apoptosis by bortezomib in human myeloma cells.**

Gu H, Chen X, Gao G, Dong H.

Mol Cancer Ther. 2008 Aug;7(8):2298-307.

 http://www.ncbi.nlm.nih.gov/pubmed/18723477?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors' data strongly suggest that caspase-2 can serve as a proximal caspase that functions upstream of mitochondrial signaling during endoplasmic reticulum stress-induced apoptosis by bortezomib in multiple myeloma cells.

 **Clinical study of bortezomib in combination with dexamethasone for the treatment of multiple myeloma.**

[Article in Chinese]

Wang LX, Lu H, Shen WY, Qian SX, Qiu HX, Wu HX, Zhang JF, Wu YJ, Li JY.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2008 Aug;16(4):943-5.

 http://www.ncbi.nlm.nih.gov/pubmed/18718096?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors evaluate the efficiency and safety of bortezomib for the treatment of myeloma by administering it as first-line treatment in combination with dexamethasone in 7 newly diagnosed patients. They conclude that bortezomib demonstrates efficiency in the treatment of newly diagnosed and refractory/relapsed multiple myeloma, and the side effects from treatment are acceptable and manageable.

 **Pathogenesis and treatment of renal failure in multiple myeloma.**

Dimopoulos MA, Kastritis E, Rosinol L, Bladé J, Ludwig H.

Leukemia. 2008 Jun 5. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18528426?ordinalpos=76&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors discuss renal failure as a frequent complication in patients with multiple myeloma, and address data that suggest that bortezomib may be beneficial in this population.

 **The role of high-dose chemotherapy followed by peripheral blood stem cell transplantation for the treatment of multiple myeloma.**

Siddiqui M, Gertz M.

Leuk Lymphoma. 2008 Aug;49(8):1436-51.

 http://www.ncbi.nlm.nih.gov/pubmed/18608872?ordinalpos=42&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
This review summarizes the role of stem cell transplantation in myeloma and how the advent of novel therapies, such bortezomib, have started to redefine the role of peripheral stem cell transplantation.

 **Safety and efficacy of bortezomib and melphalan combination in patients with relapsed or refractory multiple myeloma: updated results of a phase 1/2 study after longer follow-up.**

Berenson JR, Yang HH, Vescio RA, Nassir Y, Mapes R, Lee SP, Wilson J, Yellin O, Morrison B, Hilger J, Swift R.

Ann Hematol. 2008 Aug;87(8):623-31. [Epub 2008 May 8.]

 http://www.ncbi.nlm.nih.gov/pubmed/18463870?ordinalpos=36&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
The authors present updated data from their phase 1/2 study assessing the safety and efficacy of bortezomib plus melphalan in relapsed/refractory myeloma. They conclude that bortezomib plus melphalan is a steroid- and immunomodulatory drug-free regimen that may provide a treatment alternative for elderly patients and patients with significant comorbidity.

 **Treatment of relapsed and refractory myeloma.**

Reece DE, Leitch HA, Atkins H, Voralia M, Canning LA, Leblanc R, Belch AR, White D, Kovacs MJ.

Leuk Lymphoma. 2008 Aug;49(8):1470-85.

 http://www.ncbi.nlm.nih.gov/pubmed/18608859?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
This article reviews the literature for the treatment of relapsed/refractory myeloma and considers the influence of prior therapy, optimal sequencing of regimens, sequential versus combination use of agents, and the role of cytogenetic and other prognostic factors, both for established regimens and newer regimens incorporating thalidomide, bortezomib and lenalidomide.

 **Weekly treatment with bortezomib for patients with recurrent or refractory multiple myeloma: a phase 2 trial of the Minnie Pearl Cancer Research Network.**

Hainsworth JD, Spigel DR, Barton J, Farley C, Schreeder M, Hon J, Greco FA.

Cancer. 2008 Aug 15;113(4):765-71.

 http://www.ncbi.nlm.nih.gov/pubmed/18543319?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study evaluates the efficacy and toxicity of weekly bortezomib in the treatment of patients with recurrent/refractory multiple myeloma and finds it to be a reasonable option for patients who have logistic difficulties receiving a twice-weekly schedule, and is an attractive schedule for incorporation into combination regimens.

 **Analysis of Herpes Zoster Events Among Bortezomib-Treated Patients in the Phase III APEX Study.**

Chanan-Khan A, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, Neuwirth R, Anderson KC, Richardson PG.

J Clin Oncol. 2008 Aug 18. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18711175?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The study aims to determine if bortezomib treatment is associated with increased incidence of varicella-zoster virus (VZV) reactivation in patients with relapsed multiple myeloma and concludes that though further studies are needed, for patients treated with bortezomib or bortezomib-containing regimens, the risk of VZV reactivation should be monitored and routine use of antiviral prophylaxis considered.

 **Characterisation of haematological profiles and low risk of thromboembolic events with bortezomib in patients with relapsed multiple myeloma.**

Lonial S, Richardson PG, San Miguel J, Sonneveld P, Schuster MW, Bladé J, Cavenagh J, Rajkumar SV, Jakubowiak AJ, Esseltine DL, Anderson KC, Harousseau JL.

Br J Haematol. 2008 Aug 18. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18713253?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors characterize thrombocytopenia and neutropenia in a phase 3 study of bortezomib versus high-dose dexamethasone in relapsed myeloma. Their preliminary data suggest bortezomib may reduce the thrombogenic potential of combination regimens via inhibition of platelet function or other mechanism-specific effects on coagulation.

 **Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma.**

San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, Dmoszynska A, Abdulkadyrov KM, Schots R, Jiang B, Mateos MV, Anderson KC, Esseltine DL, Liu K, Cakana A, van de Velde H, Richardson PG; VISTA Trial Investigators.

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

 http://www.ncbi.nlm.nih.gov/pubmed/18753647?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This phase 3 study compares the use of melphalan and prednisone with or without bortezomib in previously untreated patients with myeloma who were ineligible for high-dose therapy. The authors find that bortezomib plus melphalan-prednisone was superior to melphalan-prednisone alone.

 **Treatment of myeloma – are we making progress?**

Durie BG.

N Engl J Med. 2008 Aug 28;359(9):964-6.

 http://www.ncbi.nlm.nih.gov/pubmed/18753654?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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

 **New drugs in multiple myeloma.**

Berenson JR, Yellin O.

Curr Opin Support Palliat Care. 2008 Sep;2(3):204-10.

 http://www.ncbi.nlm.nih.gov/pubmed/18685422?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This review discusses new antimyeloma arsenal, including combinations involving bortezomib, that has shown its worth in both the relapsed/refractory and frontline setting.

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

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

Haematologica. 2008 Sep 2. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18768528?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

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

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

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

Leukemia. 2008 Sep 4. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18769451?ordinalpos=25&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

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

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

Hongming H, Jian H.

Leuk Res. 2008 Sep 6. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18778854?ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

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

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

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

Br J Haematol. 2008 Sep 6. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18783399?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

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

 **Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature.**

Argyriou AA, Iconomou G, Kalofonos HP.

Blood. 2008 Sept 7. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18574024?ordinalpos=62&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors review the pathogenesis, incidence, risk factors, diagnosis, characteristics and management of bortezomib-induced peripheral neuropathy and highlight areas of future research to pursue.

 **Multiple myeloma - an update on diagnosis and treatment.**

Caers J, Vande Broek I, De Raeve H, Michaux L, Trullemans F, Schots R, Van Camp B, Vanderkerken K.

Eur J Haematol. 2008 Sep 13. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/pubmed/18637123?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This myeloma treatment update addresses the optimization of different treatment options and schedules, including the use of bortezomib.

 **Many facets of bortezomib resistance/susceptibility.**

Kumar S, Rajkumar SV.

Blood. 2008 Sep 15;112(6):2177-8.

 http://www.ncbi.nlm.nih.gov/pubmed/18779399?ordinalpos=9&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

 **Pulse treatment with the proteasome inhibitor bortezomib inhibits osteoclast resorptive activity in clinically relevant conditions.**

Boissy P, Andersen TL, Lund T, Kupisiewicz K, Plesner T, Delaissé JM.

Leuk Res. 2008 Nov;32(11):1661-8. [Epub 2008 Apr 18.]

 http://www.ncbi.nlm.nih.gov/pubmed/18394701?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors test bortezomib on cultured osteoclasts in conditions mimicking the pulse treatment used in the clinic, and demonstrate a direct inhibition of osteoclasts by bortezomib in conditions relevant to treatment of myeloma.

 **Arsenic trioxide and 2-methoxyestradiol reduce beta-catenin accumulation after proteasome inhibition and enhance the sensitivity of myeloma cells to Bortezomib.**

Zhou L, Hou J, Fu W, Wang D, Yuan Z, Jiang H.

Leuk Res. 2008 Nov;32(11):1674-83. [Epub 2008 May 15.]

 http://www.ncbi.nlm.nih.gov/pubmed/18485479?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors prove that beta-catenin protein levels are negatively associated with myeloma cells' sensitivity to bortezomib.

 **Bortezomib directly inhibits osteoclast function in multiple myeloma: implications into the management of myeloma bone disease.**

Terpos E.

Leuk Res. 2008 Nov;32(11):1646-7. [Epub 2008 Jul 9.]

 http://www.ncbi.nlm.nih.gov/pubmed/18614229?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.



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