



CITINGS

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Novel Therapies Issue

The International Myeloma Foundation (IMF) presents this edition of *Citings*, our premiere publication featuring the most up-to-date information on myeloma treatment, focused on the novel therapies currently under study and in use. This edition corresponds with articles published between December 2010 and March 2011.

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

– Susie Novis, President, IMF

NOVEL THERAPIES PUBLICATIONS

MARCH 2011

 ***Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial.***

Moreau P, Attal M, Pégourié B, Planche L, Hulin C, Facon T, Stoppa AM, Fuzibet JG, Grosbois B, Doyen C, Ketterer N, Sebban C, Kolb B, Chateix C, Dib M, Voillat L, Fontan J, Garderet L, Jaubert J, Mathiot C, Esseltine D, Avet-Loiseau H, Harousseau JL; for the IFM 2005-01 study investigators.

Blood. 2011 Mar 17;117(11):3041-3044. [Epub 2010 Nov 23.]



<http://www.ncbi.nlm.nih.gov/pubmed/21098740>

This post-hoc analysis of a trial investigating bortezomib-dexamethasone as induction therapy finds that progression-free survival is significantly improved with this therapy in patients with poor-risk cytogenetics and ISS stages 2 and 3, as compared to induction therapy with vincristine-adriamycin-dexamethasone.

 ***Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients.***

Gay F, Larocca A, Wijermans P, Cavallo F, Rossi D, Schaafsma R, Genuardi M, Romano A, Liberati AM, Siniscalchi A, Petrucci MT, Nozzoli C, Patriarca F, Offidani M, Ria R, Omedè P, Bruno B, Passera R, Musto P, Boccadoro M, Sonneveld P, Palumbo A.

Blood. 2011 Mar 17;117(11):3025-31. [Epub 2011 Jan 12.]



<http://www.ncbi.nlm.nih.gov/pubmed/21228328>

This retrospective analysis highlights a significant association between the achievement of complete response and long-term outcome, and supports the use of thalidomide and bortezomib to achieve maximal response in elderly myeloma patients, including those over 75 years.

 ***Shifts in the therapeutic paradigm for patients newly diagnosed with multiple myeloma: maintenance therapy and overall survival.***

Palumbo A, Attal M, Roussel M.

Clin Cancer Res. 2011 Mar 15;17(6):1253-63.



<http://www.ncbi.nlm.nih.gov/pubmed/21411441>

The authors discuss the wider array of treatment options now available to physicians providing care for newly diagnosed myeloma patients, including the uses of bortezomib, thalidomide and lenalidomide.

 **Treatment options for relapsed and refractory multiple myeloma.**

Lonial S, Mitsiades CS, Richardson PG.
Clin Cancer Res. 2011 Mar 15;17(6):1264-77.



<http://www.ncbi.nlm.nih.gov/pubmed/21411442>

The authors discuss newer treatment options for patients with relapsed myeloma, including use of bortezomib, thalidomide and lenalidomide.

 **Preclinical evaluation of the antitumor activity of bortezomib in combination with vitamin C or with epigallocatechin gallate, a component of green tea.**

Bannerman B, Xu L, Jones M, Tsu C, Yu J, Hales P, Monbaliu J, Fleming P, Dick L, Manfredi M, Claiborne C, Bolen J, Kupperman E, Berger A.

Cancer Chemother Pharmacol. 2011 Mar 13. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21400028>

The authors investigate whether clinically relevant levels of epigallocatechin gallate (EGCG, a component of green tea) or vitamin C (ascorbic acid) could antagonize bortezomib antitumor activity in CWR22 human prostate xenograft tumors. They find no antagonism of bortezomib in preclinical in vivo experiments, where EGCG or ascorbic acid plasma concentrations are commensurate with dietary or supplemental intake. The data suggest that patients receiving bortezomib treatment do not need to avoid normal dietary consumption of green tea, vitamin C-containing foods, or EGCG or vitamin C dietary supplements.

 **Treatment of Newly Diagnosed Multiple Myeloma in Transplant-Eligible Patients.**

Kumar S.

Curr Hematol Malig Rep. 2011 Mar 11. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21394431>

This review summarizes the current approach to the treatment of newly diagnosed myeloma in transplant-eligible patients, including the use of thalidomide, bortezomib and lenalidomide.

 **Aspirin, Warfarin, or Enoxaparin Thromboprophylaxis in Patients With Multiple Myeloma Treated With Thalidomide: A Phase III, Open-Label, Randomized Trial.**

Palumbo A, Cavo M, Bringhen S, Zamagni E, Romano A, Patriarca F, Rossi D, Gentilini F, Crippa C, Galli M, Nozzoli C, Ria R, Marasca R, Montefusco V, Baldini L, Elice F, Callea V, Pulini S, Carella AM, Zambello R, Benevolo G, Magarotto V, Tacchetti P, Pescosta N, Cellini C, Polloni C, Evangelista A, Caravita T, Morabito F, Offidani M, Tosi P, Boccadoro M.

J Clin Oncol. 2011 Mar 10;29(8):986-93. [Epub 2011 Jan 31.]



<http://www.ncbi.nlm.nih.gov/pubmed/21282540>

This randomized, open-label, multicenter trial compares aspirin (ASA) or fixed low-dose warfarin (WAR) versus low molecular weight heparin (LMWH) for preventing thromboembolism in patients with myeloma treated with thalidomide-based regimens. The authors find that ASA and WAR show similar efficacy in reducing serious thromboembolic events, acute cardiovascular events, and sudden deaths compared with LMWH, except in elderly patients where WAR shows less efficacy than LMWH.

 **IMiD(R) immunomodulatory compounds block C/EBP{beta} translation through eIF4E downregulation resulting in inhibition of MM.**

Li S, Pal R, Monaghan SA, Schafer P, Ouyang H, Mapara M, Galson DL, Lentzsch S.

Blood. 2011 Mar 9. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21389327>

The authors show that IMiD compounds (such as lenalidomide) downregulate CCAAT/enhancer-binding protein beta (C/EBPβ) resulting in abrogation of cell proliferation.

 **Characterization of haematological parameters with bortezomib-melphalan-prednisone versus melphalan-prednisone in newly diagnosed myeloma, with evaluation of long-term outcomes and risk of thromboembolic events with use of erythropoiesis-stimulating agents: analysis of the VISTA trial.**

Richardson P, Schlag R, Khuageva N, Dimopoulos M, Shpilberg O, Kropff M, Vekemans MC, Petrucci MT, Rossiev V, Hou J, Robak T, Mateos MV, Anderson K, Esseltine DL, Cakana A, Liu K, Deraedt W, van de Velde H, San Miguel JF.

Br J Haematol. 2011 Mar 6. doi: 10.1111/j.1365-2141.2011.08569.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21375521>

This analysis characterizes haematological toxicities and associated interventions in the phase III VISTA study of bortezomib plus melphalan/prednisone (VMP) versus MP in previously untreated myeloma patients ineligible for high-dose therapy, and evaluates the impact of erythropoiesis-stimulating agents (ESA) use or red-blood-cell (RBC) transfusions on outcomes and thromboembolic risk. The authors find that bortezomib does not add to melphalan haematological toxicity and that concomitant ESA use with VMP/MP in this patient population does not adversely affect time-to-progression or overall survival, or increase thromboembolic risk. However, RBC transfusion is associated with significantly shorter survival.

 **Similar efficacy of thalidomide- and bortezomib-based regimens for first relapse of multiple myeloma.**

Krejci M, Gregora E, Straub J, Minarik J, Scudla V, Adam Z, Krivanova A, Pour L, Zahradova L, Buchler T, Mayer J, Hajek R.

Ann Hematol. 2011 Mar 5. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21380511>

This retrospective study analyzes the outcomes of patients with first relapse of myeloma treated with thalidomide-based regimens or bortezomib-based regimens. The authors find both regimens to be equally effective in the treatment of first myeloma relapse.

 **Erratum to: pegylated liposomal doxorubicin in combination with dexamethasone and bortezomib (VMD) or lenalidomide (RMD) in multiple myeloma pretreated patients.**

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

Ann Hematol. 2011 Mar 4. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21373927>

No abstract available.

 **Bortezomib Retreatment in Relapsed Multiple Myeloma - Results from a Retrospective Multicentre Survey in Germany and Switzerland.**

Hrusovsky I, Emmerich B, von Rohr A, Voegeli J, Taverna C, Olie RA, Pliskat H, Frohn C, Hess G.

Oncology. 2011 Mar 3;79(3-4):247-254. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21372599>

This multicenter, retrospective survey evaluates the efficacy and safety of bortezomib retreatment in patients with relapsed myeloma who had responded to initial bortezomib treatment. The results demonstrate that this patient group has a sustained susceptibility to bortezomib and does not experience uncommon toxicity to retreatment.

 **Fewer bone disease events, improvement in bone remodelling, and evidence of bone healing with bortezomib plus melphalan-prednisone versus melphalan-prednisone, in the phase III VISTA trial in multiple myeloma.**

Delforge M, Terpos E, Richardson PG, Shpilberg O, Khuageva NK, Schlag R, Dimopoulos MA, Kropff M, Spicka I, Petrucci MT, Samoilova OS, Mateos MV, Magen-Nativ H, Goldschmidt H, Esseltine DL, Ricci DS, Liu K, Deraedt W, Cakana A, van de Velde H, San Miguel JF.

Eur J Haematol. 2011 Mar 2. doi: 10.1111/j.1600-0609.2011.01599.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21366694>

This post-hoc analysis of the phase III VISTA trial of bortezomib plus melphalan-prednisone (VMP) versus MP in previously untreated myeloma patients assesses clinical bone disease events and changes in alkaline phosphatase, a marker for osteoblast activation, and serum Dickkopf-1, an inhibitor of osteoblast differentiation, during treatment. The results suggest a positive effect of bortezomib on bone metabolism and potentially bone healing in myeloma.

 **Bortezomib as the first proteasome inhibitor anticancer drug: current status and future perspectives.**

Chen D, Frezza M, Schmitt S, Kanwar J, Dou QP.

Curr Cancer Drug Targets. 2011 Mar 1;11(3):239-53.



<http://www.ncbi.nlm.nih.gov/pubmed/21247388>

The authors discuss the emergence of bortezomib as front-line treatment for newly diagnosed myeloma patients, its established treatment uses and potential future roles.

 **Genetic factors underlying the risk of thalidomide-related neuropathy in patients with multiple myeloma.**

Johnson DC, Corthals SL, Walker BA, Ross FM, Gregory WM, Dickens NJ, Lokhorst HM, Goldschmidt H, Davies FE, Durie BG, Van Ness B, Child JA, Sonneveld P, Morgan GJ.

J Clin Oncol. 2011 Mar 1;29(7):797-804. [Epub 2011 Jan 18.]



<http://www.ncbi.nlm.nih.gov/pubmed/21245421>

The authors seek to identify genetic variation that can modulate and predict the risk of developing thalidomide-related peripheral neuropathy. Their results are consistent with the hypothesis that an individual's risk of developing a peripheral neuropathy after thalidomide treatment can be mediated by polymorphisms in genes governing repair mechanisms and inflammation in the peripheral nervous system.

 **Janus activated kinase 2/signal transducer and activator of transcription 3 pathway mediates icariside II-induced apoptosis in U266 multiple myeloma cells.**

Kim SH, Ahn KS, Jeong SJ, Kwon TR, Jung JH, Yun SM, Han I, Lee SG, Kim DK, Kang M, Chen CY, Lee JW, Kim SH.

Eur J Pharmacol. 2011 Mar 1;654(1):10-6. [Epub 2010 Dec 21.]



<http://www.ncbi.nlm.nih.gov/pubmed/21172343>

The authors find that icariside II enhances the apoptotic effects of thalidomide and bortezomib in U266 myeloma cells.

 **Lenalidomide is effective as salvage therapy in refractory or relapsed multiple myeloma: analysis of the Spanish Compassionate Use Registry in advanced patients.**

Alegre A, Aguado B, Giraldo P, Ríos E, Cánovas A, Ibáñez A, Castillo I, Hernández MT, Oriol A, Palomera L, Rodríguez JN, García FL, Calvo JM, Martínez-Chamorro C, de la Serna J, Lahuerta JJ.

Int J Hematol. 2011 Mar 1. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21360065>

This nationwide, multi-center retrospective study evaluates the clinical results of lenalidomide as a compassionate salvage therapy in refractory/relapsed myeloma patients. In this series of heavily pre-treated patients, the authors find similar efficacy to that reported in pivotal clinical trials, with acceptable tolerance.

 **Non-proteasomal targets of the proteasome inhibitors bortezomib and carfilzomib: a link to clinical adverse events.**

Arastu-Kapur S, Anderl JL, Kraus M, Parlati F, Shenk KD, Lee SJ, Muchamuel T, Bennett MK, Driessen C, Ball AJ, Kirk CJ.

Clin Cancer Res. 2011 Mar 1. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21364033>

The authors' data demonstrate that bortezomib-induced neurodegeneration in vitro occurs via a proteasome-independent mechanism, and that bortezomib inhibits several non-proteasomal targets in vitro and in vivo, which may play a role in its clinical adverse drug reaction profile.

 **Bortezomib and thalidomide, a steroid free regimen in newly diagnosed patients with multiple myeloma.**

Ghosh N, Ye X, Ferguson A, Huff CA, Borrello I.

Br J Haematol. 2011 Mar;152(5):593-9. doi: 10.1111/j.1365-2141.2010.08534.x. [Epub 2011 Jan 17.]



<http://www.ncbi.nlm.nih.gov/pubmed/21241279>

This Phase II clinical trial studies the toxicity and efficacy of a steroid-free combination of bortezomib and thalidomide as a first-line treatment in patients with symptomatic myeloma. The study demonstrates the efficacy of a steroid-free regimen, mostly reversible treatment-related peripheral neuropathy; and the absence of venous thrombotic events.

 **Chemotherapy-induced neuropathic pain.**

Farquhar-Smith P.

Curr Opin Support Palliat Care. 2011 Mar;5(1):1-7.



<http://www.ncbi.nlm.nih.gov/pubmed/21192267>

This review discusses the importance, clinical features, possible pathology and treatments of chemotherapy-induced neuropathic pain, including the use of newer biological agents such as bortezomib.

 **Combined treatment with bortezomib plus bafilomycin A1 enhances the cytotoxic effect and induces endoplasmic reticulum stress in U266 myeloma cells: crosstalk among proteasome, autophagy-lysosome and ER stress.**

Kawaguchi T, Miyazawa K, Moriya S, Ohtomo T, Che XF, Naito M, Itoh M, Tomoda A.

Int J Oncol. 2011 Mar;38(3):643-54. doi: 10.3892/ijo.2010.882. [Epub 2010 Dec 21.]



<http://www.ncbi.nlm.nih.gov/pubmed/21174067>

The authors pursue sequential treatment with bafilomycin A1 (BAF) and bortezomib, and find that it induces a further enhanced cytotoxicity as compared with the simultaneous combination of BAF and bortezomib. These data suggest crosstalk among the ubiquitin-proteasome system, the autophagy-lysosome system, and endoplasmic reticulum stress; controlling these interactions and kinetics appears to have important implications for optimizing clinical cancer treatment including myeloma therapy.

 **Emerging drugs for Waldenstrom's macroglobulinemia.**

Kastritis E, Terpos E, Dimopoulos MA.

Expert Opin Emerg Drugs. 2011 Mar;16(1):45-57.



<http://www.ncbi.nlm.nih.gov/pubmed/21352069>

The authors present recent advances on the treatment of Waldenstrom's macroglobulinemia, focusing on drugs that are under clinical investigation and for which data indicate promising activity and positive future prospects, including bortezomib.

 **Genetic variation associated with bortezomib-induced peripheral neuropathy.**

Favis R, Sun Y, van de Velde H, Broderick E, Levey L, Meyers M, Mulligan G, Harousseau JL, Richardson PG, Ricci DS.

Pharmacogenet Genomics. 2011 Mar;21(3):121-9.



<http://www.ncbi.nlm.nih.gov/pubmed/21228734>

The authors seek to develop a predictive genetic signature for the development of bortezomib-induced peripheral neuropathy. They find that genes associated with immune function (CTLA4, CTSS), reflexive coupling within Schwann cells (GJE1), drug binding (PSMB1), and neuron function (TCF4, DYNC1I1) associate with bortezomib.

-induced PN in this study.

 **High rate of stem cell mobilization failure after thalidomide and oral cyclophosphamide induction therapy for multiple myeloma.**

Auner HW, Mazzarella L, Cook L, Szydlo R, Saltarelli F, Pavlu J, Bua M, Giles C, Apperley JF, Rahemtulla A.

Bone Marrow Transplant. 2011 Mar;46(3):364-7. [Epub 2010 Jun 21.]



<http://www.ncbi.nlm.nih.gov/pubmed/20562926>

This retrospective review of 136 patients with newly diagnosed myeloma shows that the combination of thalidomide and oral cyclophosphamide with dexamethasone during induction therapy impairs stem cell mobilization substantially.

 **Kidney dysfunction during lenalidomide treatment for AL amyloidosis.**

Specter R, Sanchowala V, Seldin DC, Shelton A, Fennessey S, Finn KT, Zeldis JB, Dember LM.

Nephrol Dial Transplant. 2011 Mar;26(3):881-6. [Epub 2010 Aug 5.]



<http://www.ncbi.nlm.nih.gov/pubmed/20693160>

The authors aim to characterize alterations in kidney function among patients with AL amyloidosis undergoing treatment with lenalidomide and conclude that worsening of kidney function occurs frequently during lenalidomide treatment. While a causal role of the drug has not been established, their findings suggest that kidney function should be monitored closely during treatment with this drug.

 **Low-dose Acyclovir is Effective for Prevention of Herpes Zoster in Myeloma Patients Treated with Bortezomib: A Report from the Korean Multiple Myeloma Working Party (KMMWP) Retrospective Study.**

Kim SJ, Kim K, Do YR, Bae SH, Yang DH, Lee JJ.

Jpn J Clin Oncol. 2011 Mar;41(3):353-7. [Epub 2010 Oct 14.]



<http://www.ncbi.nlm.nih.gov/pubmed/20947927>

This retrospective review finds that the administration of acyclovir 400 mg once daily during the bortezomib treatment of relapsed/refractory myeloma patients is an effective prophylaxis for herpes zoster in patients receiving bortezomib, irrespective of disease state and the type of chemotherapy regimen.

 **Management of older patients with multiple myeloma.**

Gay F, Palumbo A.

Blood Rev. 2011 Mar;25(2):65-73. [Epub 2011 Feb 4.]



<http://www.ncbi.nlm.nih.gov/pubmed/21295387>

The authors review, compare and contrast five randomized phase III studies addressing the traditional oral combination melphalan-prednisone (MP) with MP plus thalidomide in the management of myeloma patients, particularly those older than 75.

 **Transplantation vs. conventional-dose therapy for amyloidosis.**

Palladini G, Merlini G.

Curr Opin Oncol. 2011 Mar;23(2):214-20.



<http://www.ncbi.nlm.nih.gov/pubmed/21178616>

This review focuses on the role of autologous stem cell transplantation (ASCT) and conventional-dose therapy in light of advances in risk stratification and monitoring of patients with AL amyloidosis, and includes a discussion of the role of bortezomib.

 **Weekly bortezomib in combination with temsirolimus in relapsed or relapsed and refractory multiple myeloma: a multicentre, phase 1/2, open-label, dose-escalation study.**

Ghobrial IM, Weller E, Vij R, Munshi NC, Banwait R, Bagshaw M, Schlossman R, Leduc R, Chuma S, Kunsman J, Laubach J, Jakubowiak AJ, Maiso P, Roccaro A, Armand P, Dollard A, Warren D, Harris B, Poon T, Sam A, Rodig S, Anderson KC, Richardson PG.

Lancet Oncol. 2011 Mar;12(3):263-72. [Epub 2011 Feb 21.]



<http://www.ncbi.nlm.nih.gov/pubmed/21345726>

The authors aim to assess the response and safety of the combination of temsirolimus (an mTOR inhibitor) and bortezomib in patients with relapsed or refractory myeloma. They find that mTOR inhibitors could have a role in combination with weekly bortezomib for the treatment of this patient population, without the addition of steroids.

FEBRUARY 2011

 **Impact of response to thalidomide-, lenalidomide- or bortezomib- containing induction therapy on the outcomes of multiple myeloma patients undergoing autologous transplantation.**

Awan FT, Osman S, Kochuparambil ST, Gibson L, Remick SC, Abraham J, Craig M, Jillella A, Hamadani M.

Bone Marrow Transplant. 2011 Feb 28. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21358681>

No abstract available.

 **Immunomodulatory effects of anti-angiogenic drugs.**

Heine A, Held SA, Bringmann A, Holderried TA, Brossart P.

Leukemia. 2011 Feb 25. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21350557>

The authors summarize recent reports on the immunomodulatory function of lately introduced clinically applied anti-angiogenic compounds, including bortezomib.

 **Single nucleotide polymorphisms in the promoter region of the IL1B gene influence outcome in multiple myeloma patients treated with high-dose chemotherapy independently of relapse treatment with thalidomide and bortezomib.**

Vangsted AJ, Klausen TW, Abildgaard N, Andersen NF, Gimsing P, Gregersen H, Nexø BA, Vogel U.

Ann Hematol. 2011 Feb 24. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21347685>

The authors analyze the impact on outcome of high-dose treatment, INF- α maintenance treatment, and treatment with thalidomide and bortezomib at relapse, in relation to the major identified functional polymorphisms in the promoter region of IL1B. They find no relation to genotype and outcome for relapse patients treated with thalidomide or bortezomib.

 **Treatment of Newly Diagnosed Myeloma in Patients not Eligible for Transplantation.**

Mateos MV, San-Miguel J.

Curr Hematol Malig Rep. 2011 Feb 24. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21347656>

The authors discuss melphalan plus prednisone as the backbone for combinations based on novel agents, including thalidomide, bortezomib and lenalidomide, and compare and contrast efficacy and toxicity for various myeloma patient populations.

 **Recent advances in myeloma treatment.**

Schots R.

Transfus Apher Sci. 2011 Feb 22. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21349768>

The author discusses the role of novel agents, including thalidomide, bortezomib and lenalidomide in the first-line treatment and the advanced/refractory treatment of myeloma.

 **Signal transducer and activator of transcription 3 pathway mediates genipin-induced apoptosis in U266 multiple myeloma cells.**

Lee JC, Ahn KS, Jeong SJ, Jung JH, Kwon TR, Rhee YH, Kim SH, Kim SY, Yoon HJ, Zhu S, Chen CY, Kim SH.

J Cell Biochem. 2011 Feb 22. doi: 10.1002/jcb.23077. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21344490>

The authors find that genipin effectively potentiates the cytotoxic effect of chemotherapeutic agents, such as bortezomib and thalidomide, in U266 myeloma cells.

 **Multiple myeloma.**

Laubach J, Richardson P, Anderson K.

Annu Rev Med. 2011 Feb 18;62:249-64.



<http://www.ncbi.nlm.nih.gov/pubmed/21090965>

This review highlights important historical landmarks in the field of myeloma, examines the pathogenesis and clinical manifestations of the disease, and outlines principles of both diagnosis and treatment of myeloma, including use of thalidomide, lenalidomide and bortezomib.

 **Thiazole antibiotic thiostrepton synergize with bortezomib to induce apoptosis in cancer cells.**

Pandit B, Gartel AL.

PLoS One. 2011 Feb 18;6(2):e17110.



<http://www.ncbi.nlm.nih.gov/pubmed/21365012>

The authors investigate the therapeutic potential of the combination of thiostrepton and bortezomib on various human tumor cell lines and quantitatively demonstrate their synergistic relationship.

 **Previous thalidomide therapy may not affect lenalidomide response and outcome in relapse or refractory multiple myeloma patients.**

Guglielmelli T, Bringhen S, Rodehe S, Gay F, Cavallo F, Berruti A, Montefusco V, Piro E, Benevolo G, Petrucci MT, Caravita T, Offidani M, Corradini P, Boccadoro M, Saglio G, Palumbo A.

Eur J Cancer. 2011 Feb 17. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21334196>

This retrospective analysis aims to evaluate the impact of thalidomide therapy on lenalidomide response and outcome in relapse or refractory myeloma patients. The authors conclude that lenalidomide may be equally effective in heavily pre-treated myeloma patients who are thalidomide-resistant or thalidomide-sensitive to a previous therapy.

 **Is Subcutaneous Bortezomib Ready for Prime Time?**

Lonial S.

Curr Hematol Malig Rep. 2011 Feb 16. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21327564>

No abstract available.

 **New Immunomodulatory Drugs in Myeloma.**

Lacy MQ.

Curr Hematol Malig Rep. 2011 Feb 16. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21327565>

This review discusses the data regarding the upfront use of lenalidomide with dexamethasone or in multidrug combinations, as well as its potential role as maintenance therapy, in the treatment of myeloma.

 **Phase I study of the anti insulin-like growth factor 1 receptor (IGF-1R) monoclonal antibody, AVE1642, as single agent and in combination with bortezomib in patients with relapsed multiple myeloma.**

Moreau P, Cavallo F, Leleu X, Hulin C, Amiot M, Descamps G, Facon T, Boccadoro M, Mignard D, Harousseau JL. *Leukemia*. 2011 Feb 15. [Epub ahead of print.]

 <http://www.ncbi.nlm.nih.gov/pubmed/21321571>
No abstract available.

 **Rapid early monoclonal protein reduction after therapy with bortezomib or bortezomib and pegylated liposomal doxorubicin in relapsed/refractory myeloma is associated with a longer time to progression.**

Shah J, Bladé J, Sonneveld P, Harousseau JL, Lantz K, Londhe A, Lowery C, Orlowski RZ. *Cancer*. 2011 Feb 15. doi: 10.1002/encr.25937. [Epub ahead of print.]

 <http://www.ncbi.nlm.nih.gov/pubmed/21328327>

These analyses support the possibility that a robust early M protein response is a good prognostic factor for long-term outcome of myeloma patients with relapsed and/or refractory disease receiving bortezomib or pegylated liposomal doxorubicin + bortezomib.

 **Lenalidomide targets clonogenic side population in multiple myeloma: pathophysiologic and clinical implications.**

Jakubikova J, Adamia S, Kost-Alimova M, Klippel S, Cervi D, Daley JF, Cholujovala D, Kong SY, Leiba M, Blotta S, Ooi M, Delmore J, Laubach J, Richardson PG, Sedlak J, Anderson KC, Mitsiades CS. *Blood*. 2011 Feb 14. [Epub ahead of print.]

 <http://www.ncbi.nlm.nih.gov/pubmed/21321360>

These studies demonstrate a novel mechanism of action of lenalidomide targeting side population fraction, providing the framework for new therapeutic strategies targeting subpopulations of myeloma cells, including presumptive stem cells.

 **A novel panel of protein biomarkers for predicting response to thalidomide-based therapy in newly diagnosed multiple myeloma patients.**

Rajpal R, Dowling P, Meiller J, Clarke C, Murphy WG, O'Connor R, Kell M, Mitsiades C, Richardson P, Anderson KC, Clynes M, O'Gorman P. *Proteomics*. 2011 Feb 14. doi: 10.1002/pmic.201000471. [Epub ahead of print.]

 <http://www.ncbi.nlm.nih.gov/pubmed/21365752>

Using a novel panel of predictive biomarkers, the authors demonstrate the feasibility of predicting response to thalidomide-based therapy in previously untreated myeloma.

 **Fatal ischemic stroke in a patient receiving lenalidomide for multiple myeloma.**

Tannemaat MR, Vries EP, Molendijk WJ, Haan J. *Clin Neurol Neurosurg*. 2011 Feb 9. [Epub ahead of print.]

 <http://www.ncbi.nlm.nih.gov/pubmed/21315504>
No abstract available.

 **Lenalidomide restrains motility and overangiogenic potential of bone marrow endothelial cells in patients with active multiple myeloma.**

De Luisi A, Ferrucci A, Coluccia AM, Ria R, Moschetta M, de Luca E, Pieroni L, Maffia M, Urbani A, Di Pietro G, Guarini A, Ranieri G, Ditunno P, Berardi S, Caivano A, Basile A, Cascavilla N, Capalbo S, Quarta G, Dammacco F, Ribatti D, Vacca A. *Clin Cancer Res*. 2011 Feb 9. [Epub ahead of print.]

 <http://www.ncbi.nlm.nih.gov/pubmed/21307145>

The authors seek to determine the in vivo and in vitro antiangiogenic power of lenalidomide in myeloma patients. The study ultimately provides information on the molecular mechanisms associated with the antimigratory and antiangiogenic effects of lenalidomide in primary myeloma endothelial cells, thus giving new avenues for effective endothelium-targeted therapies in myeloma.

 **Optimizing the use of lenalidomide in relapsed or refractory multiple myeloma: consensus statement.**

Dimopoulos MA, Palumbo A, Attal M, Beksaç M, Davies FE, Delforge M, Einsele H, Hajek R, Harousseau JL, da Costa FL, Ludwig H, Mellqvist UH, Morgan GJ, San-Miguel JF, Zweegman S, Sonneveld P. *Leukemia*. 2011 Feb 4. [Epub ahead of print.]

 <http://www.ncbi.nlm.nih.gov/pubmed/21293488>

The authors report on an expert panel convened to reach a consensus regarding the optimal use of lenalidomide in combination with dexamethasone in patients with relapsed or refractory multiple myeloma.

 **How “immunomodulatory” are IMiDs?**

Mitsiades CS.

Blood. 2011 Feb 3;117(5):1440-1.



<http://www.ncbi.nlm.nih.gov/pubmed/21292783>

The author comments on the report that the immunostimulatory effect of lenalidomide on natural killer cell function is profoundly suppressed by concurrent dexamethasone therapy in myeloma patients.

 **RNAi screen of the druggable genome identifies modulators of proteasome inhibitor sensitivity in myeloma including CDK5.**

Zhu YX, Tiedemann R, Shi CX, Yin H, Schmidt JE, Bruins LA, Keats JJ, Braggio E, Sereduk C, Mousses S, Stewart AK.

Blood. 2011 Feb 2. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21289309>

The authors measure proliferation in myeloma cells transfected with 13,984 small interfering RNAs in the absence / presence of increasing concentrations of bortezomib and identify 37 genes which, when silenced, are not directly cytotoxic but do synergistically potentiate the growth inhibitory effects of bortezomib.

 **Bortezomib and donor lymphocyte infusion in multiple myeloma relapsed after allo-SCT does not result in durable remissions.**

Hoevenaren A, van Vulpen LF, Levenga H, Minnema MC, Raymakers R.

Bone Marrow Transplant. 2011 Feb;46(2):319-21. [Epub 2010 Mar 22.]



<http://www.ncbi.nlm.nih.gov/pubmed/20305701>

No abstract available.

 **Clinical impact of chromosomal aberrations in multiple myeloma.**

Nahi H, Sutlu T, Jansson M, Alici E, Gahrton G.

J Intern Med. 2011 Feb;269(2):137-47. doi: 10.1111/j.1365-2796.2010.02324.x. [Epub 2010 Dec 15.]



<http://www.ncbi.nlm.nih.gov/pubmed/21158983>

The authors discuss the role of chromosome analysis in the diagnosis and treatment of myeloma, including data regarding thalidomide, lenalidomide and bortezomib.

 **Coagulation profiles and thromboembolic events of bortezomib plus thalidomide and dexamethasone therapy in newly diagnosed multiple myeloma.**

Shen Y, Zhou X, Wang Z, Yang G, Jiang Y, Sun C, Wang J, Tong Y, Guo H.

Leuk Res. 2011 Feb;35(2):147-51. [Epub 2010 Sep 15.]



<http://www.ncbi.nlm.nih.gov/pubmed/20832859>

The authors characterize coagulation profiles and evaluate the incidence of thromboembolic events (TEEs) associated with the combination therapy of bortezomib-thalidomide-dexamethasone in Chinese patients with newly diagnosed myeloma. Their results indicate a low incident TEEs.

 **Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis.**

Lamm W, Willenbacher W, Lang A, Zojer N, Müldür E, Ludwig H, Schauer-Stalzer B, Zielinski CC, Drach J.

Ann Hematol. 2011 Feb;90(2):201-6. [Epub 2010 Sep 7.]



<http://www.ncbi.nlm.nih.gov/pubmed/20821326>

This retrospective evaluation of the efficacy and toxicity of bortezomib/dexamethasone in 26 patients with AL amyloidosis confirms its activity in this patient population and suggests that patients achieving a complete remission have a marked benefit for survival.

 **Immunoglobulin light chain amyloidosis: 2011 update on diagnosis, risk-stratification, and management.**

Gertz MA.

Am J Hematol. 2011 Feb;86(2):180-6. doi: 10.1002/ajh.21934.



<http://www.ncbi.nlm.nih.gov/pubmed/21264900>

The author discusses the nature of Immunoglobulin light chain amyloidosis and its treatment, including the use of chemotherapy combinations involving thalidomide, bortezomib and lenalidomide.

 ***The impact of bortezomib on the risk of thrombosis in multiple myeloma.***

Connolly G.

Leuk Res. 2011 Feb;35(2):145-6. [Epub 2010 Oct 16.]



<http://www.ncbi.nlm.nih.gov/pubmed/20952063>

Comment on: *Leuk Res.* 2011 Feb;35(2):147-51.

 ***Inhibition of heat shock protein 90 (HSP90) as a therapeutic strategy for the treatment of myeloma and other cancers.***

Richardson PG, Mitsiades CS, Laubach JP, Lonial S, Chanan-Khan AA, Anderson KC.

Br J Haematol. 2011 Feb;152(4):367-79. doi: 10.1111/j.1365-2141.2010.08360.x. [Epub 2011 Jan 10.]



<http://www.ncbi.nlm.nih.gov/pubmed/21219297>

The authors find that Heat shock protein 90 inhibition is a promising strategy in the treatment of myeloma, especially in combination with bortezomib.

 ***Initial cytoreductive treatment with thalidomide plus bolus vincristine/doxorubicin and reduced dexamethasone followed by autologous stem cell transplantation for multiple myeloma.***

Jo JC, Kang BW, Sym SJ, Lee SS, Jang G, Kim S, Lee DH, Kim SW, Lee JS, Suh C.

Invest New Drugs. 2011 Feb;29(1):175-81. [Epub 2009 Oct 13.]



<http://www.ncbi.nlm.nih.gov/pubmed/19823768>

The authors assess the efficacy and toxicity of the combination of bolus vincristine/doxorubicin and reduced dose dexamethasone with thalidomide administered on an outpatient basis in untreated myeloma. They find that this induction therapy is efficient and relatively well tolerated in the treatment of myeloma.

 ***Management of relapsed or refractory multiple myeloma in French hospitals and estimation of associated direct costs: a multi-centre retrospective cohort study.***

Armoiry X, Fagnani F, Benboubker L, Facon T, Ferman J, Hulin C, Moreau P, Aulagner G.

J Clin Pharm Ther. 2011 Feb;36(1):19-26. doi: 10.1111/j.1365-2710.2009.01153.x.



<http://www.ncbi.nlm.nih.gov/pubmed/21198717>

The authors review the therapeutic management of relapsed and refractory myeloma patients in France and the associated costs of their treatment. They conclude that the use of novel agents such as thalidomide, bortezomib and lenalidomide for this population is highly prevalent in France from the first relapse; the associated medical cost is substantial, mainly due to the cost of these new agents.

 ***A modified regimen of pegylated liposomal doxorubicin, bortezomib, and dexamethasone is effective and well tolerated in the treatment of relapsed or refractory multiple myeloma.***

Waterman GN, Yellin O, Swift RA, Mapes R, Eades B, Ackerman E, Berenson JR.

Ann Hematol. 2011 Feb;90(2):193-200. [Epub 2010 Sep 1.]



<http://www.ncbi.nlm.nih.gov/pubmed/20809423>

This retrospective study evaluates the efficacy and safety of a more frequent low-dose schedule of pegylated liposomal doxorubicin (PLD), bortezomib, and intravenous dexamethasone – (DVD) – for patients with relapsed/refractory myeloma, many of whom were previously treated with bortezomib. The authors conclude that DVD appears to represent a well-tolerated regimen with a high response rate for the treatment of this patient population.

 ***A prospective evaluation of the biochemical, metabolic, hormonal and structural bone changes associated with bortezomib response in multiple myeloma patients.***

Zangari M, Yaccoby S, Pappas L, Cavallo F, Kumar NS, Ranganathan S, Suva LJ, Gruenewald JM, Kern S, Zhan F, Esseltine D, Tricot G.

Haematologica. 2011 Feb;96(2):333-6. [Epub 2010 Oct 15.]



<http://www.ncbi.nlm.nih.gov/pubmed/20952514>

The authors prospectively evaluate the bone changes associated with proteasome inhibition using single agent bortezomib in relapsed or refractory myeloma patients and demonstrate that the myeloma control produced by proteasome inhibition is associated with bone changes and to a discrete pattern of hormonal variation.

 **Safety Evaluation of Bortezomib in Multiple Myeloma Patients with Severe Renal Failure.**

[Article in Japanese]

Muta T, Nakanishi H, Yasunaga M, Senba S, Murakami H, Kan S, Ueda Y, Fujisaki T.

Gan To Kagaku Ryoho. 2011 Feb;38(2):237-241.



<http://www.ncbi.nlm.nih.gov/pubmed/21368487>

The authors retrospectively analyze the eight myeloma patients with renal failure who received bortezomib in their hospital and show the safety and efficacy of bortezomib in Japanese patients with myeloma complicated with renal failure.

 **Thalidomide, lenalidomide and bortezomib in the management of newly diagnosed multiple myeloma.**

Laubach JP, Schlossman RL, Mitsiades CS, Anderson KC, Richardson PG.

Expert Rev Hematol. 2011 Feb;4(1):51-60.



<http://www.ncbi.nlm.nih.gov/pubmed/21322778>

This article reviews the principles of management applied in the care of newly diagnosed myeloma, along with the clinical studies supporting the use of thalidomide, lenalidomide and bortezomib alone and in combination, and the management of treatment-related side effects.

 **Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab.**

van der Veer MS, de Weers M, van Kessel B, Bakker JM, Wittebol S, Parren PW, Lokhorst HM, Mutis T.

Haematologica. 2011 Feb;96(2):284-90. [Epub 2010 Nov 25.]



<http://www.ncbi.nlm.nih.gov/pubmed/21109694>

The authors evaluate the potential benefits of combining lenalidomide with daratumumab. Their results indicate that powerful and complementary effects may be achieved by this combination in the clinical management of myeloma.

JANUARY 2011

 **Feasibility and efficacy of administration of bortezomib-containing regimens to patients over the age of 70 years.**

Parrish C, Cromack J, Feyler S, Ashcroft J, Owen R, Cook G.

Br J Haematol. 2011 Jan 31. doi: 10.1111/j.1365-2141.2010.08565.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21275974>

No abstract available.

 **Re-transplantation after bortezomib-based therapy.**

Morris C, Cook G, Streetly M, Kettle P, Drake M, Quinn M, Cavet J, Tighe J, Kazmi M, Ashcroft J, Cook M, Snowden J, Olujohungbe A, Marshall S, Conn J, Oakervee H, Popat R, Cavenagh J.

Br J Haematol. 2011 Jan 31. doi: 10.1111/j.1365-2141.2010.08521.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21275960>

No abstract available.

 **Rates of Venous Thromboembolism in Multiple Myeloma Patients Undergoing Immunomodulatory Therapy with Thalidomide or Lenalidomide: A Systematic Review and Meta-Analysis.**

Carrier M, Le Gal G, Tay J, Wu C, Lee AY.

J Thromb Haemost. 2011 Jan 21. doi: 10.1111/j.1538-7836.2011.04215.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21255254>

The authors seek to determine the absolute rates of VTE with and without different thromboprophylactic agents in patients with newly diagnosed or previously treated myeloma receiving thalidomide- or lenalidomide-based regimens. They find that the benefit of various thromboprophylaxis is difficult to quantify in this patient group, especially in those receiving lenalidomide-based therapy or have previously treated myeloma.

 **Bortezomib as the First Proteasome Inhibitor Anticancer Drug: Current Status and Future Perspectives.**

Chen D, Frezza M, Schmitt S, Kanwar J, Dou QP.

Curr Cancer Drug Targets. 2011 Jan 19. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21247388>

The authors discuss the positive clinical benefits of bortezomib to induce chemo-/radio-sensitization or overcome drug resistance, as well as its mechanisms and current treatment limitations, all with an eye towards bortezomib's future applications.

 **Genetic Factors Underlying the Risk of Thalidomide-Related Neuropathy in Patients With Multiple Myeloma.**

Johnson DC, Corthals SL, Walker BA, Ross FM, Gregory WM, Dickens NJ, Lokhorst HM, Goldschmidt H, Davies FE, Durie BG, Van Ness B, Child JA, Sonneveld P, Morgan GJ.

J Clin Oncol. 2011 Jan 18. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21245421>

The authors seek to identify genetic variation that can modulate and predict the risk of developing thalidomide-related peripheral neuropathy. Their results are consistent with the hypothesis that an individual's risk of developing a peripheral neuropathy after thalidomide treatment can be mediated by polymorphisms in genes governing repair mechanisms and inflammation in the peripheral nervous system.

 **Targeting the Proteasome With Bortezomib in Multiple Myeloma: Update on Therapeutic Benefit as an Upfront Single Agent, Induction Regimen for Stem-Cell Transplantation and as Maintenance Therapy.**

Driscoll JJ, Burris J, Annunziata CM.

Am J Ther. 2011 Jan 18. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21248621>

The authors discuss bortezomib's use as an upfront therapy, as an induction regimen before stem-cell transplantation, and as maintenance therapy in the treatment of myeloma.

 **Bortezomib and thalidomide, a steroid free regimen in newly diagnosed patients with multiple myeloma.**

Ghosh N, Ye X, Ferguson A, Huff CA, Borrello I.

Br J Haematol. 2011 Jan 17. doi: 10.1111/j.1365-2141.2010.08534.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21241279>

This phase II clinical trial studies the toxicity and efficacy of a steroid-free combination of bortezomib and thalidomide as a first-line treatment in patients with symptomatic myeloma. The authors find this regimen to be effective, with mostly reversible treatment-related peripheral neuropathy and an absence of venous thrombotic events.

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

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

Leukemia. 2011 Jan 14. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21233832>

This meta-analysis demonstrates that in previously untreated, transplant ineligible, elderly myeloma patients, the addition of thalidomide to melphalan-prednisone (MP) results in significantly improved response rates and progression-free survival, with a trend towards improvement in overall survival compared with MP alone, but at a cost of significantly greater toxicity.

 **Polymorphisms of NF- κ B family genes are associated with development of multiple myeloma and treatment outcome in patients undergoing bortezomib-based regimens.**

Du J, Huo J, Shi J, Yuan Z, Zhang C, Fu W, Jiang H, Yi Q, Hou J.

Haematologica. 2011 Jan 12. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21228035>

The authors find that NF- κ B family member gene polymorphisms play a role in myeloma development and in response to bortezomib therapy.

 **Complete atrioventricular block secondary to bortezomib use in multiple myeloma.**

Lee WS, Kim DH, Shin SH, Woo SI, Kwan J, Park KS, Park SD, Yi HG, Jeon SH.

Yonsei Med J. 2011 Jan 1;52(1):196-8.



<http://www.ncbi.nlm.nih.gov/pubmed/21155055>

The authors describe a patient with dyspnea and general weakness because of a complete atrioventricular block while receiving bortezomib. After immediately stopping bortezomib and inserting a permanent VDD pacemaker, the patient's symptoms disappeared.

 **Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group.**

Beksac M, Haznedar R, Firatli-Tuglular T, Ozdogu H, Aydogdu I, Konuk N, Sucak G, Kaygusuz I, Karakus S, Kaya E, Ali R, Gulbas Z, Ozet G, Goker H, Undar L.

Eur J Haematol. 2011 Jan;86(1):16-22. doi: 10.1111/j.1600-0609.2010.01524.x. [Epub 2010 Nov 22.]



<http://www.ncbi.nlm.nih.gov/pubmed/20942865>

In this prospective trial, the authors find that although myeloma patients treated with melphalan-prednisone-thalidomide are relatively younger and had more frequent renal impairment than in myeloma patients receiving melphan-prednisone, they also result better responses and less early mortality, throughout all age groups.

 **Bone scan images reveal increased osteoblastic function after bortezomib treatment in patients with multiple myeloma.**

Lee SE, Min CK, Yahng SA, Cho BS, Eom KS, Kim YJ, Kim HJ, Lee S, Cho SG, Kim DW, Lee JW, Min WS, Park CW.

Eur J Haematol. 2011 Jan;86(1):83-6. doi: 10.1111/j.1600-0609.2010.01523.x. [Epub 2010 Nov 11.]



<http://www.ncbi.nlm.nih.gov/pubmed/20946110>

The authors' findings suggest that bortezomib has potent anti-myeloma activity and bone-protecting effects, with enhanced osteoblast function.

 **Hematology: Bortezomib and dexamethasone induction for multiple myeloma.**

Laubach J, Richardson P.

Nat Rev Clin Oncol. 2011 Jan;8(1):8-10.



<http://www.ncbi.nlm.nih.gov/pubmed/21179054>

No abstract available.

 **Impact of cytogenetics in patients with relapsed or refractory multiple myeloma treated with bortezomib: Adverse effect of 1q21 gains.**

Chang H, Trieu Y, Qi X, Jiang NN, Xu W, Reece D.

Leuk Res. 2011 Jan;35(1):95-8. [Epub 2010 May 26.]



<http://www.ncbi.nlm.nih.gov/pubmed/20537706>

The authors investigate the influence of genetic risk factors on the clinical response to bortezomib in 85 relapsed/refractory myeloma patients. Multivariate analysis confirms that 1q21 gain is an independent risk factor progression-free survival (PFS) and overall survival (OS); there was no significant difference in response rate, response duration, PFS or OS for any of the other genetic risk factors tested.

 **Managing the teratogenic risk of thalidomide and lenalidomide: an industry perspective.**

Bwire R, Freeman J, Houn F.

Expert Opin Drug Saf. 2011 Jan;10(1):3-8. [Epub 2010 Dec 2.]



<http://www.ncbi.nlm.nih.gov/pubmed/21121869>

The authors present experiences and perspectives on the successes and challenges of managing pregnancy prevention programs for patients using thalidomide and lenalidomide.

 **Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management.**

Rajkumar SV.

Am J Hematol. 2011 Jan;86(1):57-65.



<http://www.ncbi.nlm.nih.gov/pubmed/21181954>

The author discusses recent myeloma treatment updates, including the most beneficial uses of lenalidomide and bortezomib.

 **NF- κ B localization in multiple myeloma plasma cells and mesenchymal cells.**

Conticello C, Giuffrida R, Adamo L, Anastasi G, Martinetti D, Salomone E, Colarossi C, Amato G, Gorgone A, Romano A, Iannolo G, De Maria R, Giustolisi R, Gulisano M, Di Raimondo F.

Leuk Res. 2011 Jan;35(1):52-60. [Epub 2010 Jul 31.]



<http://www.ncbi.nlm.nih.gov/pubmed/20674018>

The authors find that bortezomib has a consistent antitumor activity against both chemoresistant and chemosensitive myeloma-cells, regardless the NF- κ B localization, thus suggesting the existence of other molecular targets of proteasome inhibitors in myeloma.

 **Novel agents improve survival of transplant patients with multiple myeloma including those with high-risk disease defined by early relapse (<12 months).**

Venner CP, Connors JM, Sutherland HJ, Shepherd JD, Hamata L, Mourad YA, Barnett MJ, Broady R, Forrest DL, Hogge DE, Nantel SH, Narayanan S, Nevill TJ, Nitta J, Power MM, Toze CL, Smith CA, Song KW.

Leuk Lymphoma. 2011 Jan;52(1):34-41. [Epub 2010 Dec 6.]



<http://www.ncbi.nlm.nih.gov/pubmed/21133716>

This population-based study seeks to assess improvements in survival, as well as to characterize the relevance of early relapse and the International Staging System (ISS) in the era of novel agents thalidomide, lenalidomide and bortezomib. The authors find that exposure to novel agents conferred a better post-relapse survival, with those who relapse late continuing to do better. They also find that the ISS remains an important prognostic tool in relapse, but only in the late relapsing cohort.

 **Pharmacokinetic and pharmacodynamic study of two doses of bortezomib in patients with relapsed multiple myeloma.**

Reece DE, Sullivan D, Lonial S, Mohrbacher AF, Chatta G, Shustik C, Burris H 3rd, Venkatakrisnan K, Neuwirth R, Riordan WJ, Karol M, von Moltke LL, Acharya M, Zannikos P, Keith Stewart A.

Cancer Chemother Pharmacol. 2011 Jan;67(1):57-67. [Epub 2010 Mar 20.]



<http://www.ncbi.nlm.nih.gov/pubmed/20306195>

The authors find that bortezomib pharmacokinetics change with repeat dose administration, characterized by a reduction in plasma clearance and associated increase in systemic exposure. Their findings support the current clinical dosing regimen.

 **Risk factors for, and reversibility of, peripheral neuropathy associated with bortezomib-melphalan-prednisone in newly diagnosed patients with multiple myeloma: subanalysis of the phase 3 VISTA study.**

Dimopoulos MA, Mateos MV, Richardson PG, Schlag R, Khuageva NK, Shpilberg O, Kropff M, Spicka I, Palumbo A, Wu KL, Esseltine DL, Liu K, Deraedt W, Cakana A, Van De Velde H, San Miguel JF.

Eur J Haematol. 2011 Jan;86(1):23-31. doi: 10.1111/j.1600-0609.2010.01533.x. [Epub 2010 Nov 15.]



<http://www.ncbi.nlm.nih.gov/pubmed/20874823>

This subanalysis of the phase 3 VISTA trial aims to assess the frequency, characteristics and reversibility of, and prognostic factors for, bortezomib-associated peripheral neuropathy (PN) in newly diagnosed patients with myeloma ineligible for high-dose therapy who receive bortezomib plus melphalan-prednisone. The authors find that rates of bortezomib-induced PN in the frontline setting are similar to those in relapsed patients and resolved in most cases.

 **Safety and efficacy of a combination therapy with Revlimid, Adriamycin and dexamethasone (RAD) in relapsed/refractory multiple myeloma (MM): a single-centre experience.**

Caravita T, Siniscalchi A, Tendas A, Cupelli L, Ales M, Perrotti A, Niscola P, de Fabritiis P.

Ann Hematol. 2011 Jan;90(1):115-6. [Epub 2010 Apr 27.]



<http://www.ncbi.nlm.nih.gov/pubmed/20422414>

No abstract available.

 **Stem cell collection in patients with multiple myeloma: impact of induction therapy and mobilization regimen.**

Nazha A, Cook R, Vogl DT, Mangan PA, Gardler M, Hummel K, Cunningham K, Luger SM, Porter DL, Schuster S, O'Doherty U, Siegel D, Stadtmauer EA.

Bone Marrow Transplant. 2011 Jan;46(1):59-63. [Epub 2010 May 3.]



<http://www.ncbi.nlm.nih.gov/pubmed/20421869>

This retrospective data analysis of 364 myeloma patients who underwent stem cell mobilization and attempted harvest suggests that lenalidomide does not prevent the harvest of adequate numbers of CD34 cells for autologous stem cell transplant, but mobilization with G-CSF and CY may be required to obtain adequate numbers of stem cells; the number of lenalidomide cycles does not correlate with stem cell yield.

 **Thalidomide after lenalidomide: a possible treatment regimen in relapse refractory multiple myeloma patients.**

Guglielmelli T, Petrucci MT, Saglio G, Palumbo A.

Br J Haematol. 2011 Jan;152(1):108-10. doi: 10.1111/j.1365-2141.2010.08416.x. [Epub 2010 Nov 18.]



<http://www.ncbi.nlm.nih.gov/pubmed/21083653>

No abstract available.

 ***Thalidomide versus bortezomib based regimens as first-line therapy for patients with multiple myeloma: a systematic review.***

Kumar A, Hozo I, Wheatley K, Djulbegovic B.

Am J Hematol. 2011 Jan;86(1):18-24.



<http://www.ncbi.nlm.nih.gov/pubmed/21120867>

This indirect meta-analysis seeks to assess the treatment effects of melphalan-prednisone-bortezomib versus melphalan-prednisone-thalidomide using the systematic review and meta-analytical techniques. The authors' conclude that there is an uncertainty about definitive superiority of one type of regimen over the other and therefore suggest direct head-to-head comparison between these regimens.

 ***Thromboembolism with immunomodulatory agents in the treatment of multiple myeloma.***

Singh A, Gajra A.

Cardiovasc Hematol Agents Med Chem. 2011 Jan;9(1):7-13.



<http://www.ncbi.nlm.nih.gov/pubmed/20874693>

This review discusses incidence, pathogenesis and management of thrombotic events with the use of immunomodulatory agents, including thalidomide and lenalidomide, in the setting of myeloma, as well as recent recommendations regarding appropriate prophylaxis and preventive measures.

 ***Treatment of multiple myeloma in the elderly: realities and hopes.***

De La Rubia J, Sanz MA.

Leuk Lymphoma. 2011 Jan;52(1):9-14. [Epub 2010 Nov 15.]



<http://www.ncbi.nlm.nih.gov/pubmed/21077740>

This review summarizes the currently available data in the front-line treatment of elderly patients with MM, including use of thalidomide and bortezomib, and discusses questions that are still unsolved in the management of this subset of patients.

 ***Treatment of patients with multiple myeloma: an overview of systematic reviews.***

Kumar A, Gale S, Djulbegovic B.

Acta Haematol. 2011;125(1-2):8-22. [Epub 2010 Dec 8.]



<http://www.ncbi.nlm.nih.gov/pubmed/21150183>

This overview summarizes all existing systematic reviews on treatments in myeloma, including the use of thalidomide.

DECEMBER 2010

 ***Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232).***

Zonder JA, Crowley J, Hussein MA, Bolejack V, Moore DF Sr, Whittenberger BF, Abidi MH, Durie BG, Barlogie B.

Blood. 2010 Dec 23;116(26):5838-41. [Epub 2010 Sep 27.]



<http://www.ncbi.nlm.nih.gov/pubmed/20876454>

This randomized trial compares lenalidomide (LEN) plus dexamethasone (DEX) to placebo plus DEX in newly diagnosed myeloma. The authors find that one-year progression-free survival, overall response rate, and very good partial response rate were superior with LEN-DEX, but that its toxicities were also more pronounced.

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

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

Ann Hematol. 2010 Dec 22. [Epub ahead of print.]



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

No abstract available.

 **Combined treatment with bortezomib plus bafilomycin A1 enhances the cytotoxic effect and induces endoplasmic reticulum stress in U266 myeloma cells: Crosstalk among proteasome, autophagy-lysosome and ER stress.**

Kawaguchi T, Miyazawa K, Moriya S, Ohtomo T, Che XF, Naito M, Itoh M, Tomoda A.

Int J Oncol. 2010 Dec 21. doi: 10.3892/ijo.2010.882. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21174067>

In order to synchronize endoplasmic reticulum (ER) stress, the authors pre-treat U266 cells with bafilomycin A1 (BAF) followed by bortezomib. They find that this sequential treatment induces a further enhanced cytotoxicity, compared with simultaneous combination. These data suggest crosstalk among the ubiquitin-proteasome system, the autophagy-lysosome system, and ER stress and that controlling these interactions and kinetics appears to have important implications for optimizing clinical cancer treatment including myeloma therapy.

 **Janus activated kinase 2/signal transducer and activator of transcription 3 pathway mediates icariside II-induced apoptosis in U266 multiple myeloma cells.**

Kim SH, Ahn KS, Jeong SJ, Kwon TR, Jung JH, Yun SM, Han I, Lee SG, Kim DK, Kang M, Chen CY, Lee JW, Kim SH.

Eur J Pharmacol. 2010 Dec 21. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21172343>

The authors find that icariside II enhances the apoptotic effects of thalidomide and bortezomib in U266 cells, and that icariside II could be a potential therapeutic intervention agent alone or in combination with these agents for myeloma as a novel blocker of STAT3 signaling cascades at multiple levels, contributing to its anti-proliferative and anti-apoptosis.

 **Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study.**

Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, Di Raimondo F, Crippa C, Zamagni E, Palumbo A, Offidani M, Corradini P, Narni F, Spadano A, Pescosta N, Deliliers GL, Ledda A, Cellini C, Caravita T, Tosi P, Baccarani M; GIMEMA Italian Myeloma Network.

Lancet. 2010 Dec 18;376(9758):2075-85. [Epub 2010 Dec 9.]



<http://www.ncbi.nlm.nih.gov/pubmed/21146205>

The authors aim to assess the efficacy and safety of addition of bortezomib to thalidomide versus thalidomide alone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed myeloma. They find that bortezomib-thalidomide induction therapy before double autologous stem-cell transplantation significantly improves rate of complete or near complete response, and represents a new standard of care for patients with myeloma who are eligible for transplant.

 **A new standard of care in newly diagnosed multiple myeloma.**

Richardson PG.

Lancet. 2010 Dec 18;376(9758):2043-4. [Epub 2010 Dec 9.]



<http://www.ncbi.nlm.nih.gov/pubmed/21146204>

Comment on: *Lancet.* 2010 Dec 18;376(9758):2075-85.

 **Successful treatment with a modified bortezomib schedule of weekly and longer intervals for patients with refractory/resistance multiple myeloma.**

Tokuhira M, Watanabe R, Nemoto T, Hanzawa K, Sagawa M, Tomikawa T, Mori S, Kizaki M.

Leuk Res. 2010 Dec 15. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21167601>

The authors present the cases of nine patients with refractory myeloma whose bortezomib administration schedule was modified from twice weekly to an interval of once weekly or longer – the first report of this kind.

 **Successful treatment with bortezomib and thalidomide for POEMS syndrome.**

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

Ann Hematol. 2010 Dec 10. [Epub ahead of print.]



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

No abstract available.

 **Myeloma: making sense of a complex blood cancer.**

Kelly MB, Meenaghan T, Dowling M.

Br J Nurs. 2010 Dec 9-2011 Jan 13;19(22):1415-21.



<http://www.ncbi.nlm.nih.gov/pubmed/21139523>

From a nursing perspective, the authors address the use of thalidomide, lenalidomide and bortezomib as part of a significant shift in approach to myeloma treatment and an improvement in patients' quality of life.

 **Significantly reduced regulatory T cell population in patients with untreated multiple myeloma.**

Gupta R, Ganeshan P, Hakim M, Verma R, Sharma A, Kumar L.

Leuk Res. 2010 Dec 9. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21146215>

Increases in regulatory T-cells have been demonstrated in hematological malignancies but conflicting results have been reported in multiple myeloma (MM). In this study, we report a decrease in frequency of regulatory T-cells as well as reduced expression of FoxP3 in untreated MM patients which increased significantly after treatment. Regulatory T-cells of MM patients exhibited immunosuppressive activity in an in vitro assay. Reduced regulatory T-cells in untreated MM patients which increased after treatment with thalidomide, suggests the analysis of treated and untreated patients as a single cohort as cause of conflicting results in earlier studies on regulatory T-cells in MM.

 **Chromosomal aberrations +1q21 and del(17p13) predict survival in patients with recurrent multiple myeloma treated with lenalidomide and dexamethasone.**

Klein U, Jauch A, Hielscher T, Hillengass J, Raab MS, Seckinger A, Hose D, Ho AD, Goldschmidt H, Neben K.

Cancer. 2010 Dec 4. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21132814>

This study suggests that the prognostic significance of t(4;14) may be ameliorated or eliminated in patients treated with lenalidomide/dexamethasone, whereas the presence of del(17p13) or +1q21 is still associated with a dismal overall survival. The presence of t(11;14) and del(13q14) as exclusive chromosomal aberrations indicates no impact on outcome. Because of its rarity in myeloma, a confirmation of the prognostic role of the t(14;16) aberration is still pending.

 **Efficacy and safety of once-weekly bortezomib in multiple myeloma patients.**

Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, Gentili S, Patriarca F, Nozzoli C, Levi A, Guglielmelli T, Benevolo G, Callea V, Rizzo V, Cangialosi C, Musto P, De Rosa L, Liberati AM, Grasso M, Falcone AP, Evangelista A, Cavo M, Gaidano G, Boccadoro M, Palumbo A.

Blood. 2010 Dec 2;116(23):4745-53. [Epub 2010 Aug 31.]



<http://www.ncbi.nlm.nih.gov/pubmed/20807892>

The authors find that, for this protocol, the reduction to once-weekly bortezomib infusions does not impact the efficacy of the regimen.

 **Increases in B-type natriuretic peptide (BNP) during treatment with lenalidomide in AL amyloidosis.**

Tapan U, Seldin DC, Finn KT, Fennessey S, Shelton A, Zeldis JB, Sanchorawala V.

Blood. 2010 Dec 2;116(23):5071-2.



<http://www.ncbi.nlm.nih.gov/pubmed/21127185>

No abstract available.

 **Lenalidomide in combination with melphalan and dexamethasone in patients with newly diagnosed AL amyloidosis: a multicenter phase 1/2 dose-escalation study.**

Moreau P, Jaccard A, Benboubker L, Royer B, Leleu X, Bridoux F, Salles G, Leblond V, Roussel M, Alakl M, Hermine O, Planche L, Harousseau JL, Feraud JP.

Blood. 2010 Dec 2;116(23):4777-82. [Epub 2010 Aug 19.]



<http://www.ncbi.nlm.nih.gov/pubmed/20724537>

The authors find that lenalidomide 15 mg/day plus melphalan-dexamethasone is a new effective combination therapy in patients with newly diagnosed AL amyloidosis.

 **A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma.**

Chauhan D, Singh AV, Aujay M, Kirk CJ, Bandi M, Ciccarelli B, Raje N, Richardson P, Anderson KC.

Blood. 2010 Dec 2;116(23):4906-15. [Epub 2010 Aug 30.]



<http://www.ncbi.nlm.nih.gov/pubmed/20805366>

The authors find that ONX 0912 enhances anti-myeloma activity of bortezomib and lenalidomide.

👁️ *Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial.*

Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, Offidani M, Patriarca F, Nozzoli C, Guglielmelli T, Benevolo G, Callea V, Baldini L, Morabito F, Grasso M, Leonardi G, Rizzo M, Falcone AP, Gottardi D, Montefusco V, Musto P, Petrucci MT, Ciccone G, Boccadoro M.

J Clin Oncol. 2010 Dec 1;28(34):5101-9. [Epub 2010 Oct 12.]



<http://www.ncbi.nlm.nih.gov/pubmed/20940200>

This phase III study examines the efficacy of the four-drug combination of bortezomib-melphalan-prednisone-thalidomide (VMPT) followed by maintenance with bortezomib-thalidomide (VMPT-VT) compared with VMP treatment alone in untreated myeloma patients who are ineligible for autologous stem-cell transplantation. The authors find that VMPT followed by VT as maintenance is superior to VMP alone.

👁️ *Ten years of improvement in the management of multiple myeloma: 2000-2010.*

Harousseau JL.

Clin Lymphoma Myeloma Leuk. 2010 Dec 1;10(6):424-42.



<http://www.ncbi.nlm.nih.gov/pubmed/21156460>

The author discusses the introduction of thalidomide, lenalidomide and bortezomib as critical factors for the dramatic progress that has been made in the management of myeloma.

👁️ *The clinical utility of lenalidomide in multiple myeloma and myelodysplastic syndromes.*

Bonkowski J, Vermeulen LC, Kolesar JM.

J Oncol Pharm Pract. 2010 Dec;16(4):223-32. [Epub 2009 Nov 12.]



<http://www.ncbi.nlm.nih.gov/pubmed/19910392>

The authors review the pharmacology, pharmacokinetics, pharmacodynamics, clinical utility, adverse effects, dosage, and cost of lenalidomide and find that is an effective agent for the treatment of relapsed or refractory myeloma.

👁️ *The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective.*

Hornberger J, Rickert J, Dhawan R, Liwing J, Aschan J, Löthgren M.

Eur J Haematol. 2010 Dec;85(6):484-91. doi: 10.1111/j.1600-0609.2010.01526.x.



<http://www.ncbi.nlm.nih.gov/pubmed/20846301>

The authors seek to estimate the cost-effectiveness of bortezomib compared with both dexamethasone and lenalidomide/dexamethasone for the treatment of relapsed/refractory myeloma in Sweden. They find that bortezomib and lenalidomide/dexamethasone are projected to prolong survival relative to dexamethasone, and that – from a Swedish perspective – bortezomib is cost-effective compared to dexamethasone and lenalidomide/dexamethasone.

👁️ *Prophylactic antivirals may be helpful in prevention of varicella-zoster virus reactivation in myeloma, but are they safe?*

Dasanu CA, Alexandrescu DT.

J Oncol Pharm Pract. 2010 Dec;16(4):266-8. [Epub 2009 Dec 4.]



<http://www.ncbi.nlm.nih.gov/pubmed/19965947>

This article explores the potential risks and pitfalls linked to routine acyclovir prophylaxis in bortezomib-treated myeloma. The authors conclude that long-term acyclovir prophylaxis in myeloma patients treated with bortezomib may cause severe renal and neurological toxicity. Prevention of these complications can be achieved through either withholding of the antivirals or a very close monitoring of both neurologic status and renal function in this patient population.



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