



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 in July 2011.

As part of our ongoing efforts to make information about myeloma more accessible, we have implemented a new format for *CITINGS*, providing these citations on a monthly basis and organizing them by topic. We welcome your comments.

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 myeloma.org.

– Susie Novis, President, IMF

NOVEL THERAPIES PUBLICATIONS – JULY 2011

General Discussions & Reviews

Bortezomib for AL amyloidosis: moving forward.

Dimopoulos MA, Kastiritis E.

Blood. 2011 Jul 28;118(4):827-8.



<http://www.ncbi.nlm.nih.gov/pubmed/21799093>

No abstract available.

A Systematic Review on the Use of Bortezomib in Multiple Myeloma Patients with Renal Impairment: What Is the Published Evidence?

Piro E, Molica S.

Acta Haematol. 2011 Jul 21;126(3):163-168. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21778706>

This report presents the totality of evidence through a systematic review (1978-2010) that assesses either the efficacy or safety of bortezomib-based regimens in myeloma with renal impairment. Although many questions remain unanswered, the authors believe this report provides a relevant scientific and practical address for generating a diagnostic and therapeutic algorithm to be used in patients with renal impairment related to myeloma.

This report presents the totality of evidence through a systematic review that assessed either the efficacy or safety of bortezomib-based regimens in multiple myeloma with renal impairment. A systematic and comprehensive search of the literature was performed using MEDLINE databases from 1978 to December 1, 2010, and a hand search of references. We used the following medical subject headings (MESH) to identify potential studies: ‘myeloma renal failure’ (1,225 hits) and ‘bortezomib’ (2,554 hits). An additional search performed by combining the MESH terms ‘myeloma renal failure’ and ‘bortezomib’ yielded 50 citations. Five additional case-control studies judged relevant for the purpose of study were also included. In total, 6 case reports, 9 case series and 9 case-control studies were identified that reported on myeloma, renal failure and bortezomib. In this review, only the case series and case-control studies were considered. The results of our search led to the following conclusions: (1) bortezomib is feasible and well tolerated and its efficacy and safety are not substantially modified by renal failure patients, (2) renal failure should not induce physicians to reduce doses, since the efficacy of bortezomib is attained also in dialyzed patients

who may achieve dialysis independence, and (3) standard doses of bortezomib (i.e. 1.3 mg/m² on days 1, 4, 8, 11) associated with dexamethasone yield satisfactory tumor response, generally obtained shortly after starting therapy. Although many questions remain unanswered, our effort should be considered a relevant scientific and practical address for generating a diagnostic and therapeutic algorithm to be used in patients with renal impairment related to multiple myeloma.

Novel proteasome inhibitors to overcome bortezomib resistance.

Ruschak AM, Slassi M, Kay LE, Schimmer AD.

J Natl Cancer Inst. 2011 Jul 6;103(13):1007-17. [Epub 2011 May 23.]



<http://www.ncbi.nlm.nih.gov/pubmed/21606441>

This review discusses the structure and function of the proteasome, as well as the molecular biology, chemistry, and the preclinical and clinical efficacy of novel proteasome inhibitors as strategies to inhibit this target and overcome some forms of bortezomib resistance.

The proteasome is an intracellular enzyme complex that degrades ubiquitin-tagged proteins and thereby regulates protein levels within the cell. Given this important role in maintaining cellular homeostasis, it is perhaps somewhat surprising that proteasome inhibitors have a therapeutic window. Proteasome inhibitors have demonstrated clinical efficacy in the treatment of multiple myeloma and mantle cell lymphoma and are under evaluation for the treatment of other malignancies. Bortezomib is the first and only Food and Drug Administration-approved proteasome inhibitor that inhibits this enzyme complex in a reversible fashion. Although bortezomib improves clinical outcomes when used as a single agent, most patients do not respond to this drug and those who do respond almost uniformly relapse. As such, efforts are underway to develop proteasome inhibitors that act through mechanisms distinct from that of bortezomib. Specifically, inhibitors that bind the active site of the proteasome and inhibit the complex irreversibly have been developed and are in advanced clinical trials. Inhibitors that act on sites of the proteasome outside of the catalytic center have also been identified and are in preclinical development. In this review, we discuss the structure and function of the proteasome. We then focus on the molecular biology, chemistry, and the preclinical and clinical efficacy of novel proteasome inhibitors as strategies to inhibit this target and overcome some forms of bortezomib resistance.

Mechanisms & Pathways

Ex vivo graft purging and expansion of autologous blood progenitor cell products from patients with multiple myeloma.

Yang H, Robinson SN, Nieto Y, Jones RJ, Gocke CD, Lu J, Giralt SA, Jones RB, Decker WK, Xing D, Steiner D, Champlin RE, McMannis JD, Ng J, Thomas MW, Shah N, Andersson BS, Parmar S, Shpall EJ.

Cancer Res. 2011 Jul 15;71(14):5040-9. [Epub 2011 Jun 6.]



<http://www.ncbi.nlm.nih.gov/pubmed/21646477>

The authors report a sequential purging strategy targeting mature and immature clonogenic myeloma cell populations in the autograft. They find that overall, ex vivo treatment of apheresis products with rituximab, bortezomib and co-culture with normal donor mesenchymal stem cells deplete mature and immature myeloma cells from clinical aphereses, while expanding the normal hematopoietic progenitor cell compartment.

Autologous peripheral blood progenitor cell (PBPC) transplantation is the treatment of choice for selected myeloma patients. However, tumor cells contaminating the apheresis product are a potential source of relapse. Here we report a sequential purging strategy targeting mature and immature clonogenic myeloma cell populations in the autograft. Thawed PBPC products of myeloma patients were treated with rituximab to kill CD138(-)20(+) B cells (highly clonogenic immature cells), and bortezomib to target CD138(+) cells (normal and differentiated myeloma plasma cells), followed by co-culture with allogeneic mesenchymal stem cells (MSC) from normal donors. After 7 days of co-culture, non-adherent cells were removed and cultured in the absence of MSC for an additional 7 days. Then, efficacy of purging (removal of CD138(-)20(+) and CD138(+) cells) was assessed by flow cytometry and PCR. We used our ex vivo purging strategy to treat frozen aphereses from 16 patients. CD138(+) and CD138(-)20(+)19(+) cells present in the initial products were depleted more than 3 and 4 logs, respectively based on 10(6) flow acquisition events, and to levels below the limit of detection by PCR. In contrast, TNC, CD34(+) cell and colony-forming cell numbers were increased by approximately 12-20, 8 and 23 fold, respectively. Overall, ex vivo treatment of apheresis products with rituximab, bortezomib and co-culture with normal donor MSC depleted mature and immature myeloma cells from clinical aphereses, while expanding the normal hematopoietic progenitor cell compartment.

 ***Lenalidomide Enhances Antigen-Specific Activity and Decreases CD45RA Expression of T Cells from Patients with Multiple Myeloma.***

Neuber B, Herth I, Tolliver C, Schoenland S, Hegenbart U, Hose D, Witzens-Harig M, Ho AD, Goldschmidt H, Klein B, Hundemer M.

J Immunol. 2011 Jul 15;187(2):1047-56. [Epub 2011 Jun 15.]



<http://www.ncbi.nlm.nih.gov/pubmed/21677134>

The authors investigate whether the specific T cell response against the myeloma Ag HM1.24 is enhanced by the immunomodulatory drug lenalidomide. They show (for the first time, to their knowledge) that lenalidomide enhances the Ag-specific activation of T cells and the subsequent downregulation of CD45RA expression of T cells *in vitro* and *in vivo*.

The aim of this study was to investigate whether the specific T cell response against the multiple myeloma Ag HM1.24 is enhanced by the immunomodulatory drug lenalidomide (Revlimid). Ag-specific CD3(+)CD8(+) T cells against the HM1.24 Ag were expanded *in vitro* by dendritic cells in 29 healthy donors and 26 patients with plasma cell dyscrasias. Ag-specific activation was analyzed by IFN- γ , granzyme B, and perforin secretion using ELISA, ELISPOT assay, and intracellular staining, and generation of Ag-specific T cells was analyzed by tetramer staining. Expression of T cell maturation markers (CD45RA, CD45R0, CCR7, and CD28) was investigated by flow cytometry. We found that activation of HM1.24-specific T cells from healthy donors and patients with plasma cell dyscrasias was enhanced significantly by lenalidomide and furthermore that the impact of lenalidomide on T cells depends on the duration of the exposure. Notably, lenalidomide supports the downregulation of CD45RA on T cells upon activation, observed in healthy donors and in patients *in vitro* and also in patients during lenalidomide therapy *in vivo*. We showed for the first time, to our knowledge, that lenalidomide enhances the Ag-specific activation of T cells and the subsequent downregulation of CD45RA expression of T cells *in vitro* and *in vivo*.

 ***Identification of Genes Affecting the Toxicity of Anti-Cancer Drug Bortezomib by Genome-Wide Screening in *S. pombe*.***

Takeda K, Mori A, Yanagida M.

PLoS One. 2011;6(7):e22021. [Epub 2011 Jul 8.]



<http://www.ncbi.nlm.nih.gov/pubmed/21760946>

The authors aim to identify genes affecting the cytotoxicity of bortezomib in the fission yeast *S.pombe*, as the drug inhibits this organism's cell division cycle. They find that among the 2,815 genes screened, 19 genes, whose deletions induce strong synthetic lethality with bortezomib, are identified.

Bortezomib/PS-341/Velcade, a proteasome inhibitor, is widely used to treat multiple myeloma. While several mechanisms of the cytotoxicity of the drug were proposed, the actual mechanism remains elusive. We aimed to identify genes affecting the cytotoxicity of Bortezomib in the fission yeast *S.pombe* as the drug inhibits this organism's cell division cycle like proteasome mutants. Among the 2815 genes screened (covering 56% of total ORFs), 19 genes, whose deletions induce strong synthetic lethality with Bortezomib, were identified. The products of the 19 genes included four ubiquitin enzymes and one nuclear proteasome factor, and 13 of them are conserved in humans. Our results will provide useful information for understanding the actions of Bortezomib within cells.

New Combinations

 ***Lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone in newly diagnosed multiple myeloma: a phase 1/2 Multiple Myeloma Research Consortium trial.***

Jakubowiak AJ, Griffith KA, Reece DE, Hofmeister CC, Lonial S, Zimmerman TM, Campagnaro EL, Schlossman RL, Laubach JP, Raje NS, Anderson T, Mietzel MA, Harvey CK, Wear SM, Barrickman JC, Tendler CL, Esseltine DL, Kelley SL, Kaminski MS, Anderson KC, Richardson PG.

Blood. 2011 Jul 21;118(3):535-43. [Epub 2011 May 19.]



<http://www.ncbi.nlm.nih.gov/pubmed/21596852>

This phase I/II trial evaluates the combination of lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone (RVDD) in newly diagnosed myeloma patients. The authors find that RVDD is generally well tolerated and highly active, warranting further study in newly diagnosed myeloma patients.

This phase 1/2 trial evaluated combination lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone (RVDD) in newly diagnosed multiple myeloma (MM) patients. Patients received RVDD at 4 dose levels including the maximum tolerated dose (MTD). Patients with a very good partial response or better (\geq VGPR) after cycle 4 proceeded to autologous

stem-cell transplantation or continued treatment. The primary objectives were MTD evaluation and response to RVDD after 4 and 8 cycles. Seventy-two patients received a median of 4.5 cycles. The MTDs were lenalidomide 25 mg, bortezomib 1.3 mg/m², pegylated liposomal doxorubicin 30 mg/m², and dexamethasone 20/10 mg, as established with 3-week cycles. The most common adverse events were fatigue, constipation, sensory neuropathy, and infection; there was no treatment-related mortality. Response rates after 4 and 8 cycles were 96% and 95% partial response or better, 57% and 65% ≥VGPR, and 29% and 35% complete or near complete response, respectively. After a median follow-up of 15.5 months, median progression-free survival (PFS) and overall survival (OS) were not reached. Estimated 18-month PFS and OS are 80.8% and 98.6%, respectively. RVDD was generally well tolerated and highly active, warranting further study in newly diagnosed MM patients. This trial was registered at www.clinicaltrials.gov as #NCT00724568.

Monoclonal antibodies in the treatment of multiple myeloma.

Richardson PG, Lonial S, Jakubowiak AJ, Harousseau JL, Anderson KC.

Br J Haematol. 2011 Jul 21. doi: 10.1111/j.1365-2141.2011.08790.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21777223>

The authors discuss the role of monoclonal antibodies in the treatment of myeloma, including recently achieved clinically meaningful responses when combined with lenalidomide or bortezomib in patients with relapsed and relapsed/refractory myeloma.

Despite recent advances in treatment that have significantly improved overall survival, multiple myeloma (MM) remains incurable. Although rituximab, the first monoclonal antibody (MAB) evaluated in MM treatment, provided only very limited benefit, research is ongoing into a number of other MABs directed against a variety of MM-related target antigens. Given the inherent immune dysfunction associated with MM, newer strategies that may enhance immune function in conjunction with antibodies may also provide a more fruitful clinical approach. Potential MAB targets in MM include growth factors and their receptors, other signalling molecules, and antigens expressed exclusively or predominantly on MM cells. MAB therapy involves a range of mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, interference with receptor-ligand interactions, and MAB conjugation to radioisotopes or toxins. The antigens currently targeted in MM therapy are discussed, along with the development status of the corresponding MAB therapeutics. Elotuzumab, an anti-CS1 MAB, has recently achieved clinically meaningful responses when combined with lenalidomide or bortezomib in patients with relapsed and relapsed/refractory MM. Other MABs are also showing early promise. More ongoing clinical research is required to identify optimal combination regimens and biomarkers that may help predict response to specific MAB-based combinations.

Molecular Target Characterization and Antimyeloma Activity of the Novel, Insulin-like Growth Factor 1 Receptor Inhibitor, GTx-134.

Liang SB, Yang XZ, Trieu Y, Li Z, Zive J, Leung-Hagesteijn C, Wei E, Zozulya S, Coss CC, Dalton JT, Fantus IG, Trudel S.

Clin Cancer Res. 2011 Jul 15;17(14):4693-704. [Epub 2011 Jun 1.]



<http://www.ncbi.nlm.nih.gov/pubmed/21632854>

The authors describe GTx-134 and characterize its antitumor activity in preclinical models of myeloma. Their studies support the potential therapeutic efficacy of GTx-134 in myeloma, as well as providing a rationale for clinical application in combination with established anti-myeloma treatments and novel targeted therapies, including lenalidomide, which shows synergy when combined with GT-x-134 in vitro.

PURPOSE: Therapeutic strategies that target insulin-like growth factor 1 receptor (IGF-1R) hold promise in a wide variety of cancers including multiple myeloma (MM). In this study we describe GTx-134, a novel small molecule inhibitor of IGF-1R and insulin receptor (IR) and characterized its antitumor activity in preclinical models of MM. **EXPERIMENTAL DESIGN:** The activity of GTx-134 as a single agent and in combination was tested in MM cell lines and primary patient samples. Downstream effector proteins and correlation with apoptosis was evaluated. Cytotoxicity in bone marrow stroma co-culture experiments was assessed. Lastly, the in vivo efficacy was evaluated in a human myeloma xenograft model. **RESULTS:** GTx-134 inhibited the growth of 11 of 14 myeloma cell lines (< 5 μM) and induced apoptosis. Sensitivity to GTx-134 correlated with IGF-1R signal inhibition. Expression of MDR-1 and CD45 were associated with resistance to GTx-134. Co-culture with insulin-growth factor-1 (IGF-1) or adherence to bone marrow stroma conferred modest resistance, but did not overcome GTx-134-induced cytotoxicity. GTx-134 showed in vitro synergies when combined with dexamethasone or lenalidomide. Further, GTx-134 enhanced the activity of PD173074, a fibroblast growth factor receptor 3 (FGFR3) inhibitor, against t(4;14) myeloma cells. Therapeutic efficacy of GTx-134 was demonstrated against primary cells and xenograft tumors. Although dysregulation of glucose homeostasis was observed in GTx-134 treated mice, impairment of glucose tolerance was modest. **CONCLUSIONS:** These studies support the potential therapeutic efficacy of GTx-134 in MM. Further, they provide a rationale for clinical application in combination with established anti-myeloma treatments and novel targeted therapies.

Galectin-3C Inhibits Tumor Growth and Increases the Anticancer Activity of Bortezomib in a Murine Model of Human Multiple Myeloma.

Mirandola L, Yu Y, Chui K, Jenkins MR, Cobos E, John CM, Chiriva-Internati M.

PLoS One. 2011;6(7):e21811. [Epub 2011 Jul 13.]



<http://www.ncbi.nlm.nih.gov/pubmed/21765917>

The authors evaluate galectin-3C, an N-terminally truncated form of galectin-3 that is thought to act as a dominant negative inhibitor, as a potential treatment for myeloma. They find that the maximal effect is obtained with the combination of galectin-3C and bortezomib, affording a reduction of 94% in the mean tumor volume compared to the untreated controls at day 35.

Galectin-3 is a human lectin involved in many cellular processes including differentiation, apoptosis, angiogenesis, neoplastic transformation, and metastasis. We evaluated galectin-3C, an N-terminally truncated form of galectin-3 that is thought to act as a dominant negative inhibitor, as a potential treatment for multiple myeloma (MM). Galectin-3 was expressed at varying levels by all 9 human MM cell lines tested. In vitro galectin-3C exhibited modest anti-proliferative effects on MM cells and inhibited chemotaxis and invasion of U266 MM cells induced by stromal cell-derived factor (SDF)-1. Galectin-3C facilitated the anticancer activity of bortezomib, a proteasome inhibitor approved by the FDA for MM treatment. Galectin-3C and bortezomib also synergistically inhibited MM-induced angiogenesis activity in vitro. Delivery of galectin-3C intravenously via an osmotic pump in a subcutaneous U266 cell NOD/SCID mouse model of MM significantly inhibited tumor growth. The average tumor volume of bortezomib-treated animals was 19.6% and of galectin-3C treated animals was 13.5% of the average volume of the untreated controls at day 35. The maximal effect was obtained with the combination of galectin-3C with bortezomib that afforded a reduction of 94% in the mean tumor volume compared to the untreated controls at day 35. In conclusion, this is the first study to show that inhibition of galectin-3 is efficacious in a murine model of human MM. Our results demonstrated that galectin-3C alone was efficacious in a xenograft mouse model of human MM, and that it enhanced the anti-tumor activity of bortezomib in vitro and in vivo. These data provide the rationale for continued testing of galectin-3C towards initiation of clinical trials for treatment of MM.

Small compound 6-o-angeloylplenolin induces mitotic arrest and exhibits therapeutic potentials in multiple myeloma.

Liu Y, Chen XQ, Liang HX, Zhang FX, Zhang B, Jin J, Chen YL, Cheng YX, Zhou GB.

PLoS One. 2011;6(7):e21930. [Epub 2011 Jul 6.]



<http://www.ncbi.nlm.nih.gov/pubmed/21755010>

The authors investigate the effects and mechanisms of action of a sesquiterpene lactone 6-O-angeloylplenolin (6-OAP) on myeloma cells. They find that combined use of 6-OAP and bortezomib induces potentiated cytotoxicity with inactivation of ERK1/2 and activation of JNK1/2 and Casp-8/-3.

BACKGROUND: Multiple myeloma (MM) is a disease of cell cycle dysregulation while cell cycle modulation can be a target for MM therapy. In this study we investigated the effects and mechanisms of action of a sesquiterpene lactone 6-O-angeloylplenolin (6-OAP) on MM cells. **METHODOLOGY/ PRINCIPAL FINDINGS:** MM cells were exposed to 6-OAP and cell cycle distribution were analyzed. The role for cyclin B1 to play in 6-OAP-caused mitotic arrest was tested by specific siRNA analyses in U266 cells. MM.1S cells co-incubated with interleukin-6 (IL-6), insulin-like growth factor-I (IGF-I), or bone marrow stromal cells (BMSCs) were treated with 6-OAP. The effects of 6-OAP plus other drugs on MM.1S cells were evaluated. The in vivo therapeutic efficacy and pharmacokinetic features of 6-OAP were tested in nude mice bearing U266 cells and Sprague-Dawley rats, respectively. We found that 6-OAP suppressed the proliferation of dexamethasone-sensitive and dexamethasone-resistant cell lines and primary CD138+ MM cells. 6-OAP caused mitotic arrest, accompanied by activation of spindle assembly checkpoint and blockage of ubiquitination and subsequent proteasomal degradation of cyclin B1. Combined use of 6-OAP and bortezomib induced potentiated cytotoxicity with inactivation of ERK1/2 and activation of JNK1/2 and Casp-8/-3. 6-OAP overcame the protective effects of IL-6 and IGF-I on MM cells through inhibition of Jak2/Stat3 and Akt, respectively. 6-OAP inhibited BMSCs-facilitated MM cell expansion and TNF- α -induced NF- κ B signal. Moreover, 6-OAP exhibited potent anti-MM activity in nude mice and favorable pharmacokinetics in rats. **CONCLUSIONS/SIGNIFICANCE:** These results indicate that 6-OAP is a new cell cycle inhibitor which shows therapeutic potentials for MM.

 **Transcriptomic rationale for the synergy observed with dasatinib + bortezomib + dexamethasone in multiple myeloma.**

de Queiroz Crusoe E, Maiso P, Fernandez-Lazaro D, San-Segundo L, Garayoa M, Garcia-Gomez A, Gutierrez NC, Delgado M, Colado E, Martin-Sanchez J, Lee FY, Ocio EM.

Ann Hematol. 2011 Jul 1. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21720745>

The authors explore the optimal combination for dasatinib in myeloma cells. They find a clear synergistic effect in the triple combination of dasatinib with bortezomib and dexamethasone, which is evident even in the presence of bone marrow microenvironment, and generate data that provides the rationale for the use of this novel combination in myeloma patients.

Despite the advantage observed with novel drugs such as bortezomib, thalidomide, or lenalidomide, multiple myeloma (MM) remains incurable and there is a clear need for new drugs or combinations based on the pathogenetic mechanism of MM. One of the proposed mechanisms in MM pathogenesis is the involvement of kinase molecules in the growth and survival of myeloma cells. In this study, we have explored the optimal combination for dasatinib, a tyrosine kinase inhibitor, in MM cells. A clear synergistic effect was observed with the triple combination of dasatinib with bortezomib and dexamethasone which was evident even in the presence of bone marrow microenvironment. Experiments performed on freshly isolated patients' cells also demonstrated potentiation of response in the triple as compared with the agents alone or in double combinations. Gene expression profiling experiments provided some clues on the transcriptional rationale underlying this potentiation, as the triple combination led to significant deregulation of genes involved in cell death, cell growth, proliferation, DNA replication, repair and recombination, and cell-cell signaling. Some of these results were further confirmed by apoptosis and cell cycle experiments and also by Western blot and PCR. These data provide the rationale for the use of this novel combination in MM patients.

 **A phase I safety study of enzastaurin plus bortezomib in the treatment of relapsed or refractory multiple myeloma.**

Ghobrial IM, Munshi NC, Harris BN, Shi P, Porter NM, Schlossman RL, Laubach JP, Anderson KC, Desai D, Myrand SP, Wooldridge JE, Richardson PG, Abonour R.

Am J Hematol. 2011 Jul;86(7):573-8. doi: 10.1002/ajh.22048. [Epub 2011 May 31.]



<http://www.ncbi.nlm.nih.gov/pubmed/21630305>

The authors assess the safety and identify the recommended doses of enzastaurin and bortezomib in combination for future Phase II studies in patients with relapsed or refractory myeloma. They find that the recommended Phase II doses are as follows: enzastaurin loading dose of 375 mg three times/day on Day 1 followed by 250 mg BID, with bortezomib 1.3 mg/m² on Days 1, 4, 8, and 11 of a 21-day cycle. The combination is well-tolerated and demonstrated some antimyeloma activity.

The purpose of this study was to assess the safety and identify the recommended doses of enzastaurin and bortezomib in combination for future Phase II studies in patients with relapsed or refractory multiple myeloma. Three dose levels (DLs) of oral enzastaurin and intravenous bortezomib were used according to a conventional "3 + 3" design. A loading dose of enzastaurin (250 mg twice/day [BID]) on Day 1 was followed by enzastaurin 125 mg BID for 1 week, after which bortezomib was added (Cycle 1, 28 days, 1.0 mg/m²; Days 8, 11, 15, and 18; seven subsequent 21-day cycles, 1.3 mg/m²; Days 1, 4, 8, and 11). Twenty-three patients received treatment; all patients received prior systemic therapy. Most patients received ≥ 3 regimens; 17 patients were bortezomib-refractory. A median of four treatment cycles (range 1-24) was completed. No dose-limiting toxicities were observed; thus, DL 3 was the recommended Phase II dose. The most common drug-related Grade 3/4 toxicities were thrombocytopenia (n = 6) and anemia (n = 2). No patients died on therapy. One patient (DL 1) achieved a very good partial response; three patients (DLs 2 and 3), a partial response; nine patients, stable disease; and four patients, progressive disease. The recommended Phase II doses in patients with relapsed or refractory multiple myeloma are as follows: enzastaurin loading dose of 375 mg three times/day on Day 1 followed by 250 mg BID, with bortezomib 1.3 mg/m² on Days 1, 4, 8, and 11 of a 21-day cycle. The combination was well-tolerated and demonstrated some antimyeloma activity.

 **A steroid-independent regimen of bortezomib, liposomal doxorubicin and thalidomide demonstrate high response rates in newly diagnosed multiple myeloma patients.**

Sher T, Ailawadhi S, Miller KC, Manfredi D, Wood M, Tan W, Wilding G, Czuczman MS, Hernandez-Ilizaliturri FJ, Hong F, Sood R, Soniwal A, Lawrence W, Jamshed S, Masood A, Iancu D, Lee K, Chanan-Khan A.

Br J Haematol. 2011 Jul;154(1):104-10. doi: 10.1111/j.1365-2141.2011.08703.x. Epub 2011 May 9.



<http://www.ncbi.nlm.nih.gov/pubmed/21554260>

A phase II single institute, non-randomized clinical trial is conducted to investigate a novel steroid-free three-drug combination of bortezomib, pegylated liposomal doxorubicin, and thalidomide—the VDT regimen. The authors conclude that VDT is a tolerable and an effective regimen capable of inducing high response rates, and can be employed in patients considered to be poor candidates for steroid-based treatment regimens.

Novel agents have provided a new foundation for multiple myeloma therapies. When combined with other anti-myeloma agents, these compounds significantly enhance clinical efficacy. High-dose steroids are frequently used in anti-myeloma combination regimens; however, the doses employed are often poorly tolerated, especially in patients with concurrent comorbid conditions. We hypothesized that a steroid-independent combination regimen could be developed without significant compromise of efficacy. The availability of such a regimen will be important for patients whose concurrent ailments make them poor candidates for steroid containing anti-myeloma regimens. A phase II single institute, non-randomized clinical trial was conducted to investigate a novel steroid-free three-drug combination of bortezomib (V), pegylated liposomal doxorubicin (D), and thalidomide (T), the VDT regimen. Forty-three newly diagnosed multiple myeloma patients requiring treatment were enrolled on this study. The overall response rate and complete response (CR)+near complete response (nCR) rate was 78% and 35%, respectively. Median time to progression was 29.5 months. Fatigue, rash, neuropathy, constipation and infections were the most common side effects. We concluded that VDT is a tolerable and an effective regimen capable of inducing high response rates and can be employed in patients considered to be poor candidates for steroid-based treatment regimens.

Relapsed/Refractory Treatment

 **Bortezomib in a phase 1 trial for patients with relapsed AL amyloidosis: cardiac responses and overall effects.**

Dubrey SW, Reece DE, Sanchorawala V, Hegenbart U, Merlini G, Palladini G, Fermand JP, Vescio RA, Bladé J, Heffner LT, Hassoun H, Liu X, Enny C, Ramaswami P, Elsayed Y, Van De Velde H, Mortimer S, Cakana A, Comenzo RL; For The Velcade Can2007 Study Group.

QJM. 2011 Jul 13. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21752867>

In this phase 1 dose-escalation portion of the first prospective study of single-agent bortezomib in AL amyloidosis, 31 patients with relapsed disease, including 14 (45%) with cardiac involvement, receive bortezomib in seven dose cohorts on once-weekly and twice-weekly schedules. Results suggest that bortezomib may slow the progression of cardiac amyloid with limited toxicity.

BACKGROUND: Bortezomib is approved for the treatment of multiple myeloma and a role has been suggested in the treatment of systemic AL amyloidosis (AL). METHODS: In this phase 1 dose-escalation portion of the first prospective study of single-agent bortezomib in AL, 31 patients with relapsed disease, including 14 (45%) with cardiac involvement, received bortezomib in seven dose cohorts on once-weekly (0.7, 1.0, 1.3, 1.6 mg/m²) and twice-weekly (0.7, 1.0, 1.3 mg/m²) schedules. Electrocardiographic, Holter and echocardiographic studies were evaluated in all patients to determine safety and response. RESULTS: During therapy (median treatment period 210 days), no patient developed significant ventricular or supraventricular rhythm disturbance on 24-h Holter monitoring; however, no patient satisfied study criteria for cardiac response using echocardiographic assessment or New York Heart Association classification. Seven patients (23%) had a $\geq 10\%$ fall in left ventricular ejection fraction, but only one met criteria for cardiac deterioration. The predominant cardiac adverse events were peripheral edema (23%), orthostatic hypotension (13%) and hypotension (10%). Two patients developed grade 3 congestive heart failure, which resolved following treatment interruption. In this Phase 1 portion, the maximum tolerated dose of bortezomib on either schedule was not reached. Hematologic responses occurred in 14 patients (45%), including seven (23%) complete responses. In non-responders mean left ventricular wall thickness increased during the course of treatment. CONCLUSION: AL is frequently rapidly progressive; in these patients who had relapsed or progressed following previous conventional therapies, these results suggest that bortezomib may slow the progression of cardiac amyloid with limited toxicity.

 **Impact of lenalidomide dose on progression-free survival in patients with relapsed or refractory multiple myeloma.**

Dimopoulos MA, Hussein M, Swern AS, Weber D.

Leukemia. 2011 Jul 12. doi: 10.1038/leu.2011.126. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21747400>

This analysis assesses the effect of lenalidomide on progression-free survival (PFS). The authors' data suggest that to achieve maximum PFS benefit, patients with relapsed or refractory myeloma should be treated for 12 months with full-dose lenalidomide plus dexamethasone; thereafter, patients may benefit from lower-dose continued therapy.

This analysis assessed the effect of lenalidomide on progression-free survival (PFS). Patients with relapsed or refractory multiple myeloma (RRMM) who received lenalidomide plus dexamethasone in the MM-009 and MM-010 trials were pooled and those who had not progressed and were still receiving lenalidomide at 12 months were included. The median follow-up of surviving patients was 48 months. Of 353 patients who received lenalidomide plus dexamethasone, 116 (33%) had not progressed. Overall, 52 patients (45%) had no dose reductions, 25 (22%) had dose reductions at 12 months and 39 (34%) had dose reductions before 12 months. Patients who had dose reductions at 12 months had a significantly longer median PFS than those who had reductions before 12 months ($P=0.007$) or no dose reductions ($P=0.039$) (not reached vs 28.0 vs 36.8 months, respectively). In a multivariate Cox regression model, dose reduction at 12 months was an independent predictor of improved PFS (hazard ratio, 0.47; 95% confidence interval, 0.23-0.98) after adjusting for patient characteristics. The data suggest that to achieve maximum PFS benefit, patients with RRMM should be treated for at 12 months with full-dose lenalidomide plus dexamethasone. Thereafter, patients may benefit from lower-dose continued therapy; prospective studies are needed to confirm these findings.

 **Cost effectiveness of treatments for relapsed/refractory multiple myeloma: response to a methodology:**

RE: Hornberger J, Rickert J, Dhawan R, Liwing J, Aschan J, Löthgren M. The cost effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective.

***European Journal of Haematology* 2010; 85 (6):484-491.**

Ishak J, Rodrigues F.

Eur J Haematol. 2011 Jul;87(1):95. doi: 10.1111/j.1600-0609.2011.01624.x.



<http://www.ncbi.nlm.nih.gov/pubmed/21692852>

No abstract available.

Supportive Care

 **Efficacy of Continuous, Daily, Oral, Ultra-low-dose 200 mg Acyclovir to Prevent Herpes Zoster Events Among Bortezomib-treated Patients: A Report From Retrospective Study.**

Aoki T, Nishiyama T, Imahashi N, Kitamura K.

Jpn J Clin Oncol. 2011 Jul;41(7):876-81. [Epub 2011 May 25.]



<http://www.ncbi.nlm.nih.gov/pubmed/21616919>

The authors address herpes zoster, the most common infection in myeloma patients treated with bortezomib-containing regimens, and find that continuous prophylaxis by oral 200 mg/day acyclovir in myeloma patients receiving bortezomib treatment is effective and sufficient in preventing the infection.

OBJECTIVE: Herpes zoster is the most common infection in patients treated with bortezomib-containing regimens for multiple myeloma. Some clinical trials have reported on the use of acyclovir prophylaxis to decrease the incidence of herpes zoster. However, the appropriate acyclovir dose and duration of prophylaxis remain unclear. The primary objective of this study was to evaluate the efficacy of continuous oral 200 mg/day acyclovir prophylaxis and the secondary objective was to determine the risk factors for developing herpes zoster. **METHODS:** We collected medical information from consecutive patients who received bortezomib with or without acyclovir prophylaxis for relapsed or refractory multiple myeloma at our hospital and retrospectively analyzed the efficacy of acyclovir prophylaxis and the parameters for predicting the risk factors for developing herpes zoster. The definition of acyclovir prophylaxis was oral continuous administration of 200 mg of once daily, without cessation, during the entire period of bortezomib treatment. **RESULTS:** Six of the 33 patients in the study developed herpes zoster during bortezomib treatment. No varicella-zoster virus reactivation was observed in the 19 patients in the acyclovir prophylaxis group. The incidence of herpes zoster was significantly higher in the group that did not receive acyclovir prophylaxis (43%, 6 of 14 patients) than in the group that did (0%, 0 of 19; $P = 0.003$). The predictive factors for varicella-zoster virus reactivation were male sex ($P = 0.035$) and the use of acyclovir ($P = 0.003$). **CONCLUSIONS:** Continuous prophylaxis by oral 200 mg/day acyclovir in multiple myeloma patients receiving bortezomib treatment is effective and sufficient in preventing herpes zoster.

Practical management of adverse events in multiple myeloma: Can therapy be attenuated in older patients?

Palumbo A, Mateos MV, Brinchen S, San Miguel JF.
Blood Rev. 2011 Jul;25(4):181-91. [Epub 2011 Apr 16.]



<http://www.ncbi.nlm.nih.gov/pubmed/21497966>

This article provides practical guidance on the management of bortezomib-, thalidomide-, and lenalidomide-associated adverse events to maximize treatment feasibility and active drug delivered, and thus help minimize toxicity and maximize outcomes.

The current standard of care for elderly patients with newly diagnosed multiple myeloma is melphalan and prednisone (MP) in combination with either bortezomib (VMP) or thalidomide (MPT), with lenalidomide plus dexamethasone increasingly being employed. The addition of bortezomib or thalidomide to the established MP regimen significantly improves outcomes and prolongs survival in elderly and transplant-ineligible patients. However, these benefits are accompanied by increases in treatment-related adverse events (AEs), which may be particularly pronounced in older individuals. Patients receiving bortezomib as part of a VMP regimen commonly experience transient and cyclical thrombocytopenia and neutropenia, along with gastrointestinal AEs. Fortunately, these AEs can be managed with appropriate supportive care and, when necessary, adjustments in dose. Peripheral neuropathy (PN) is the most important side effect of bortezomib, and although it is reversible in a high proportion of patients, it affects their quality of life. Furthermore, PN can require temporary or permanent withholding of bortezomib, which will reduce treatment efficacy. PN is also a common adverse effect of thalidomide; thromboembolic events are also a key concern, requiring thromboprophylaxis in patients receiving thalidomide in combination. For lenalidomide in combination with dexamethasone, the most clinically important adverse effects are hematologic toxicity (particularly neutropenia) and thromboembolic events. Recent phase III studies in newly diagnosed elderly patients are providing further insight into the most appropriate treatment regimens to maximize outcomes and minimize toxicity in individual patients. Of note, once-weekly bortezomib dosing (in combination with MP±T) was shown to reduce the incidence of peripheral neuropathy and gastrointestinal events compared with twice-weekly dosing, while maintaining efficacy. Elderly patients may be less able to withstand the AEs associated with newer treatment regimens and combinations of multiple drugs, and may experience greater declines in quality of life and, subsequently, reduced treatment adherence. It is therefore critical that these patients are closely monitored and any emergent AEs promptly and appropriately managed. For very elderly, frail patients, tailored therapy, reduced intensity regimens, and adverse event management are necessary to encourage treatment adherence and reduce discontinuation. This article will provide practical guidance on the management of bortezomib-, thalidomide-, and lenalidomide-associated AEs, to maximize treatment feasibility and active drug delivered, and thus help minimize toxicity and maximize outcomes.

Toxicities & Adverse Effects

Genetic factors underlying the risk of bortezomib induced peripheral neuropathy in multiple myeloma patients.

Corthals SL, Kuiper R, Johnson DC, Sonneveld P, Hajek R, van der Holt B, Magrangeas F, Goldschmidt H, Morgan GJ, Avet-Loiseau H.

Haematologica. 2011 Jul 26. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21791469>

To identify genetic risk factors associated with development of peripheral neuropathy in bortezomib-treated myeloma patients, a pharmacogenetic association study is performed using a discovery set and a validation set. None of the 2,149 single nucleotide polymorphisms tested reveal any significant association with bortezomib-induced peripheral neuropathy. However, 56 single nucleotide polymorphisms demonstrate an association with bortezomib induced peripheral neuropathy with pointwise, uncorrected significance and a clear enrichment of major bortezomib metabolizing genes is found. Univariate evaluation of these 56 polymorphisms demonstrate one single nucleotide polymorphism with pointwise significance: rs619824 in CYP17A1.

Bortezomib induced peripheral neuropathy is a dose-limiting side effect and a major concern in the treatment of multiple myeloma. To identify genetic risk factors associated with development of this side effect in bortezomib treated multiple myeloma patients, a pharmacogenetic association study was performed using a discovery set (IFM 2005-01; n=238) and a validation set (HOVON65/GMMG-HD4 and a Czech dataset; n=231). After multiplicity correction, none of the 2149 single nucleotide polymorphisms tested revealed any significant association with bortezomib induced peripheral neuropathy. However, 56 single nucleotide polymorphisms demonstrated an association with bortezomib induced peripheral neuropathy with pointwise, uncorrected significance. Pathway analysis of these polymorphisms demonstrated involvement of neurological disease (FDR <20%). Also a clear enrichment of major bortezomib metabolizing genes was found. Univariate evaluation of these 56 polymorphisms in the validation set demonstrated one single nucleotide polymorphism with pointwise significance: rs619824

Transplantation & Induction Therapies

Sequential vincristine, adriamycin, dexamethasone (VAD) followed by bortezomib, thalidomide, dexamethasone (VTD) as induction, followed by high-dose therapy with autologous stem cell transplant and consolidation therapy with bortezomib for newly diagnosed multiple myeloma: results of a phase II trial.

Kim HJ, Yoon SS, Lee DS, Sohn SK, Eom HS, Lee JL, Chung JS, Kim K, Suh C, Won JH, Kim JS, Park JS, Kang HJ, Seong CM, Kim CS, Lee SJ, Lee JH.

Ann Hematol. 2011 Jul 26. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21789621>

In this study, patients receive 2 cycles of vincristine, adriamycin, dexamethasone (VAD) and then 2 cycles of bortezomib, thalidomide, dexamethasone (VTD) chemotherapy as an induction treatment. Followed by autologous stem cell transplantation and bortezomib as a consolidation therapy. The authors find that sequential VAD and VTD induction therapy in patients with newly diagnosed myeloma is active with manageable toxicity and excellent stem cell yields. The incorporation of bortezomib as a consolidation therapy improves the clinical outcome with the expense of rather frequent development of peripheral neuropathy.

Incorporation of novel agents has resulted in an improved response rate and reduced side effects in multiple myeloma. This has prompted combining novel agents in induction chemotherapy in patients with newly diagnosed multiple myeloma. Our patients received 2 cycles of vincristine, adriamycin, dexamethasone (VAD) and then 2 cycles of bortezomib, thalidomide, dexamethasone (VTD) chemotherapy as an induction treatment. Subsequently, autologous stem cell transplantation was performed, and bortezomib was administered as a consolidation therapy. Seventy-one patients were enrolled, and 65 were evaluable for response. After 2 cycles of VAD, the overall response rate was 69%. After VTD, the response rate improved to 97% with a complete response (CR) and near CR rate of 27%. Importantly, patients with cytogenetics, having poor prognostic features, all responded after VTD. Autologous stem cells were successfully collected in all 58 patients with a median CD34+ cell count of 7.12×10^6 /kg (range, $1.94\text{--}44.7 \times 10^6$ /kg), except in 1 patient (2%). After ASCT, 36 patients completed bortezomib maintenance with a combined CR and near CR rate approaching 75%. Median time to response was rapid (1.6 months). With a median follow-up duration of 52.7 months, the median TTP was 29.4 months and median OS was not reached. Toxicities proved manageable. In conclusion, sequential VAD and VTD induction therapy in patients with newly diagnosed multiple myeloma was active with manageable toxicity and excellent stem cell yields. The incorporation of bortezomib as a consolidation therapy improved the clinical outcome with the expense of rather frequent development of peripheral neuropathy.

Results of the first bortezomib-based induction therapy in the treatment of multiple myeloma.

Kortüm M, Einsele H.

Expert Opin Pharmacother. 2011 Jul;12(10):1661-3. [Epub 2011 May 10.]



<http://www.ncbi.nlm.nih.gov/pubmed/21554151>

Commenting on a phase III trial comparing the efficacy and the safety of a bortezomib-containing induction regimen with conventional chemotherapy before autologous stem-cell transplantation in myeloma patients, the authors find that the difference in progression-free survival (PFS) is not statistically significant but a trend to longer PFS is seen to favor to the bortezomib-containing regimen. They therefore support the study's conclusion proposing bortezomib and dexamethasone to be the standard of care.

This is a comment on the IFM 2005 - 01 Phase III trial that compared, for the first time, the efficacy and the safety of a bortezomib-containing induction regimen with conventional chemotherapy before autologous stem-cell transplantation in multiple myeloma (MM) patients. Between 2005 and 2008, 482 patients were randomized to vincristine/doxorubicin/dexamethasone (VAD), VAD + dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) consolidation, bortezomib + dexamethasone and bortezomib + dexamethasone + DCEP consolidation followed by autologous stem-cell transplantation. The trial was conducted in 89 sites in France, Belgium and Switzerland. The novel agent-based induction therapy (bortezomib/dexamethasone) achieved higher complete remission (CR)/nearCR rates, as well as less treatment-related mortality, but higher rates of polyneuropathy than the conventional chemotherapy-based induction therapy (VAD/VAD + DCEP). The difference in progression-free survival (PFS) difference was not statistically significant but a trend to longer PFS was seen to favor to the bortezomib-containing regimen; bortezomib and dexamethasone (BD) was, therefore, proposed to be a standard of care by the authors of the study.

and More

In vitro effects of perifosine, bortezomib and lenalidomide against hematopoietic progenitor cells from healthy donors.

Schmidt-Hieber M, Dabrowski R, Aicher B, Lohneis P, Busse A, Tietze-Buerger C, Reufi B, Thiel E, Blau IW. *Invest New Drugs*. 2011 Jul 13. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21750922>

The authors study the in vitro effects of the novel agents perifosine, bortezomib and lenalidomide in addition to adriamycin against normal human hematopoietic progenitor cells (HPC) using different clonogenic and non-clonogenic assays. They find that all of these novel agents typically induce only slight or moderate suppression of the clonogenic potential or loss of viability of normal HPC at clinically achievable plasma concentrations, assuming that hematotoxicity is manageable and functional HPC can be collected after treatment with these compounds.

The novel AKT inhibitor perifosine possesses myelopoiesis-stimulating effects in rodents. We studied the in vitro effects of the novel agents perifosine, bortezomib and lenalidomide in addition to adriamycin against normal human hematopoietic progenitor cells (HPC) using different clonogenic and non-clonogenic assays. All agents inhibited colony-forming unit (CFU) formation, perifosine inhibiting mainly CFU-granulocyte/macrophage formation and the other agents burst-forming unit-erythroid formation. Perifosine combined with lenalidomide or adriamycin tended to act antagonistically in suppressing CFU formation. Despite their inhibition of CFU formation, perifosine, bortezomib and lenalidomide induced only slight or moderate cytotoxicity in CD34(+) selected HPC, as assessed using different assays such as flow cytometry-based detection of activated caspases and immunohistochemistry studies (e.g., Ki-67 staining). In contrast to its myelopoiesis-stimulating effects in rodents, perifosine - like bortezomib and lenalidomide - suppresses the clonogenic potential of HPC from healthy donors in vitro and thus probably plays no role in preventing neutropenia or in shorting its duration after intensive chemotherapy. However, all these novel agents typically induce only slight or moderate suppression of the clonogenic potential or loss of viability of normal HPC at clinically achievable plasma concentrations, assuming that hematotoxicity is manageable and functional HPC can be collected after treatment with these compounds.

Bortezomib in patients with renal impairment.

Kaygusuz I, Toptas T, Aydin F, Uzay A, Firatli-Tuglular T, Bayik M. *Hematology*. 2011 Jul;16(4):200-8.



<http://www.ncbi.nlm.nih.gov/pubmed/21756535>

The authors aim to explore the efficacy and toxicity profiles of bortezomib in 56 patients with myeloma, 24 of whom had moderate to severe renal failure. They find that bortezomib appears to be active; however, when used alone, it may cause more frequent and severe adverse events in patients with myeloma and renal failure.

Renal failure is a common manifestation of multiple myeloma (MM). Bortezomib is primarily metabolized by cytochrome p450 isoforms. It also has a cytochrome-independent metabolism by excretion through the bile and kidney. Based on our observations, we aimed to explore the efficacy and toxicity profiles of bortezomib in 56 patients with MM, 24 of which had moderate to severe renal failure. Overall response and complete response, as well as very good partial response rates, were comparable between patients with normal renal functions and renal impairment. The median overall survivals for patients with estimated glomerular filtration rates of <60 and ≥60 ml/minute were similar. Although there was a tendency for shorter overall survival along lower estimated glomerular filtration rates, this difference did not reach a statistical significance. Overall and severe adverse events, and dose modification and treatment discontinuation rates were higher in patients with renal impairment. Patients with renal failure had more thrombocytopenia and diarrhea. While thrombocytopenia was mild to moderate and manageable, diarrhea, which led to serious adverse events, was more severe in patients with renal failure who received bortezomib as monotherapy. Bortezomib appears to be active; however, when used alone, it may cause more frequent and severe adverse events in patients with MM and renal failure.

Efficacy of thalidomide- or lenalidomide-based therapy in proliferative multiple myeloma.

Kapoor P, Kumar S, Mandrekar SJ, Laumann KM, Dispenzieri A, Lacy MQ, Dingli D, Gertz MA, Kyle RA, Greipp PR, Rajkumar SV, Witzig TE.

Leukemia. 2011 Jul;25(7):1195-7. doi: 10.1038/leu.2011.54. [Epub 2011 Apr 5.]



<http://www.ncbi.nlm.nih.gov/pubmed/21468037>

No abstract available.

 ***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 Jul;90(7):863.



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

No abstract available.

 ***Lenalidomide can induce long-term responses in patients with multiple myeloma relapsing after multiple chemotherapy lines, in particular after allogeneic transplant.***

Spina F, Montefusco V, Crippa C, Citro A, Sammassimo S, Olivero B, Gentili S, Galli M, Guglielmelli T, Rossi D, Pia Falcone A, Grasso M, Patriarca F, De Muro M, Corradini P.

Leuk Lymphoma. 2011 Jul;52(7):1262-70. [Epub 2011 May 3.]



<http://www.ncbi.nlm.nih.gov/pubmed/21534872>

Evidence of long-term response to lenalidomide in heavily pretreated patients with myeloma is lacking. This study seeks to assess whether long-term responders exist, long-term responders' characteristics, and predictive factors of a long-term response. The authors find that patients treated with lenalidomide can become long-term responders; allogeneic transplant and response quality predict long-term response.

Evidence of long-term response to lenalidomide in heavily pretreated patients with multiple myeloma is lacking. This study sought to assess whether long-term responders exist, long-term responders' characteristics, and predictive factors of a long-term response. One hundred and four patients with multiple myeloma treated with lenalidomide and dexamethasone after ≥ 2 therapy lines (median, 3) were analyzed. Long-term response was defined as at least a partial response (\geq PR) lasting ≥ 12 months. The overall response rate was 73%, and 80.3% of the responses were achieved within 5 months. The median response was 14.3 months. Patients evaluable for long-term response numbered 87, and a total of 47% were long-term responders. Compared to non-long-term responders, long-term responders had better overall survival, less light-chain multiple myeloma, and higher incidence of t(11;14). Previous allogeneic transplant (alloSCT) and the response quality predicted a long-term response. In conclusion, patients treated with lenalidomide can become long-term responders; alloSCT and response quality predict long-term response.

 ***Successful use of bortezomib in a patient with systemic lupus erythematosus and multiple myeloma.***

Fröhlich K, Holle JU, Aries PM, Gross WL, Moosig F.

Ann Rheum Dis. 2011 Jul;70(7):1344-5. [Epub 2010 Dec 20.]



<http://www.ncbi.nlm.nih.gov/pubmed/21173019>

No abstract available.

 ***Superior overall survival of patients with myeloma achieving very good partial response or better to initial treatment with bortezomib, pegylated liposomal doxorubicin, and dexamethasone, predicted after two cycles by a free light chain- and M-protein-based model: extended follow-up of a phase II trial.***

Dytfeld D, Griffith KA, Friedman J, Lebovic D, Harvey C, Kaminski MS, Jakubowiak AJ.

Leuk Lymphoma. 2011 Jul;52(7):1271-80.



<http://www.ncbi.nlm.nih.gov/pubmed/21699382>

In this study of bortezomib, pegylated liposomal doxorubicin, and dexamethasone (VDD) in 40 patients with newly diagnosed myeloma 2-4-year overall survival (OS) estimates were 95.7%/86.5% versus 82.4%/58.2% for patients achieving \geq very good partial response (VGPR) versus $<$ VGPR to VDD. These findings emphasize the importance of achieving \geq VGPR to initial therapy, associated with prolonged OS. The predictive model provides a potential basis for developing individualized therapy.

In myeloma, achievement of very good partial response (VGPR) post-transplant is associated with prolonged overall (OS) and progression-free survival (PFS). In this study of bortezomib, pegylated liposomal doxorubicin, and dexamethasone (VDD) in 40 patients with newly diagnosed myeloma (median follow-up 45.1 months), 2-4-year OS estimates were 95.7%/86.5% versus 82.4%/58.2% for patients achieving \geq VGPR versus $<$ VGPR to VDD ($p=0.0241$). In 30 patients undergoing transplant, PFS ($p=0.0357$) and OS ($p=0.0272$) were longer in patients achieving \geq VGPR to VDD. Achievement of \geq VGPR was predicted by a novel model based on occurrence after two cycles of $\geq 90\%$ involved free light chain reduction, free light kappa/lambda ratio normalization, and/or $\geq 90\%$ M-protein reduction. Prediction of \geq VGPR was associated with superior PFS and OS in patients with transplant. These findings emphasize the importance of achieving \geq VGPR to initial therapy, associated with prolonged OS. The predictive model provides a potential basis for developing individualized therapy, which requires further study.



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