



# 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 June 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](http://myeloma.org).

– Susie Novis, President, IMF

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## NOVEL THERAPIES PUBLICATIONS – JUNE 2011

### General Discussions & Reviews

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

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

*Leukemia*. 2011 Jun;25(6):899-905. doi: 10.1038/leu.2011.24. [Epub 2011 Feb 25.]



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

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

Much progress and significant therapeutic changes have been made in the field of tumor therapy in the past decades. Besides chemotherapy and radiotherapy, a special focus was laid on targeted therapies such as small molecule tyrosine kinase inhibitors (TKIs) and other immunomodulatory drugs, which have become standard therapies and important combination partners in a variety of malignancies. In contrast to the widely established use of these often anti-angiogenic drugs, many functional molecular mechanisms are yet not completely understood. Recent analyses focused not only on their direct anti-tumor responses, but also on their influence on tumor microenvironment, as well as on their effects on malignant and healthy cells. Different anti-angiogenic compounds targeting the vascular endothelial growth factor (VEGF) or platelet-derived growth factor pathways seem to be capable of modulating immune responses, in a positive, as well as apparently harmful manner. For an optimal clinical anti-cancer treatment, a better understanding of these immunomodulatory effects is necessary. Here we summarize recent reports on the immunomodulatory function of lately introduced clinically applied anti-angiogenic compounds, such as the humanized monoclonal antibody against VEGF bevacizumab, the small molecule TKIs sunitinib, sorafenib, imatinib, dasatinib, nilotinib and the proteasome inhibitor bortezomib.

#### **Is subcutaneous bortezomib ready for prime time?**

Lonial S.

*Curr Hematol Malig Rep*. 2011 Jun;6(2):73-4.



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

No abstract available.

### ***New immunomodulatory drugs in myeloma.***

Lacy MQ.

*Curr Hematol Malig Rep.* 2011 Jun;6(2):120-5.



<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.**

Multiple myeloma (MM) is an incurable malignancy of plasma cells. The introduction of thalidomide was a milestone in the treatment of MM. Thalidomide analogues termed immunomodulatory drugs (IMiDs) have been developed that are more effective and have less toxicity than thalidomide. The role of lenalidomide in relapsed MM has been well defined. 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. It also reviews our experience with pomalidomide, a new IMid with remarkable activity in relapsed, refractory MM.

### ***Proteasome inhibitors in cancer therapy.***

Crawford LJ, Walker B, Irvine AE.

*J Cell Commun Signal.* 2011 Jun;5(2):101-10. [Epub 2011 Jan 31.]



<http://www.ncbi.nlm.nih.gov/pubmed/21484190>

**This review summarizes the main mechanisms of action of proteasome inhibitors in cancer, the development of proteasome inhibitors as therapeutic agents and the properties and progress of next generation proteasome inhibitors in the clinic.**

The ubiquitin proteasome pathway plays a critical role in regulating many processes in the cell which are important for tumour cell growth and survival. Inhibition of proteasome function has emerged as a powerful strategy for anti-cancer therapy. Clinical validation of the proteasome as a therapeutic target was achieved with bortezomib and has prompted the development of a second generation of proteasome inhibitors with improved pharmacological properties. This review summarises the main mechanisms of action of proteasome inhibitors in cancer, the development of proteasome inhibitors as therapeutic agents and the properties and progress of next generation proteasome inhibitors in the clinic.

## Mechanisms & Pathways

### ***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 Jun 15. [Epub ahead of print.]



<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- $\gamma$ , 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.

 ***Integrin {beta}7-mediated regulation of multiple myeloma cell adhesion, migration, and invasion.***

Neri P, Ren L, Azab AK, Brentnall M, Gratton K, Klimowicz AC, Lin C, Duggan P, Tassone P, Mansoor A, Stewart DA, Boise LH, Ghobrial IM, Bahlis NJ.

*Blood.* 2011 Jun 9;117(23):6202-13. [Epub 2011 Apr 7.]



<http://www.ncbi.nlm.nih.gov/pubmed/21474670>

**This research supports a role for integrin-β7 (ITGB7) in myeloma cells adhesion, migration, bone marrow homing and pave the way for a novel therapeutic approach targeting this molecule, in part because of the finding that, functionally, shRNA-mediated silencing of ITGB7 reduces myeloma cells adhesion to extracellular matrix elements and reverses cell-adhesion mediated drug resistance sensitizing them to bortezomib and melphalan.**

Integrin-β7 (ITGB7) mRNA is detected in multiple myeloma (MM) cells and its presence is correlated with MAF gene activation. While the involvement of several integrin family members in MM-stoma cells interaction is well documented, the specific biological functions regulated by integrin-β7 in MM are largely unknown. Clinically we have correlated integrin-β7 expression in MM with poor survival outcomes post autologous stem cell transplantation and post salvage therapy with Bortezomib. Functionally, we have found that shRNA-mediated silencing of ITGB7 reduces MM cells adhesion to extracellular matrix elements (fibronectin, E-cadherin) and reverses cell-adhesion mediated drug resistance (CAM-DR) sensitizing them to Bortezomib and Melphalan. In addition, ITGB7 silencing abrogated MM cells transwell migration in response to SDF1α gradients, reduced vessel density in xenografted tumors and altered MM cells in vivo homing into the bone marrow. Mechanistically, ITGB7 knockdown inhibited FAK and Src phosphorylation, Rac1 activation and SUMOylation, reduced VEGF production in MM-BMSC co-cultures and attenuated p65-NF-κB activity. Our findings support a role for integrin-β7 in MM cells adhesion, migration, bone marrow homing and pave the way for a novel therapeutic approach targeting this molecule.

 ***Metabolism of thalidomide by human liver microsome cytochrome CYP2C19 is required for its antimyeloma and antiangiogenic activities in vitro.***

Li Y, Jiang Z, Xiao Y, Li L, Gao Y.

*Hematol Oncol.* 2011 Jun 3. doi: 10.1002/hon.992. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21638302>

**The authors use a system of human liver microsomes to investigate the antimyeloma and antiangiogenic activities of thalidomide. Their findings suggest that CYP2C19 is required for thalidomide to exhibit its antimyeloma and antiangiogenic activities.**

In this study, we used a system of human liver microsomes to investigate the antimyeloma and antiangiogenic activities of thalidomide. Myeloma cells and human umbilical vein endothelial cells (HUVECs) were treated with thalidomide alone or thalidomide incubated with human liver microsomal protein. We found that thalidomide alone had no direct effect on several multiple myeloma cell lines (U266, NCI-H929, RPMI 8226, LP-1, CZ-1) or on HUVECs in vitro. However, when incubated with human liver microsomal protein, thalidomide (100 µg/ml) caused a decrease of 34.9-46.7% in cell viability in myeloma cells and 12% in HUVECs. Cell cycle analysis and apoptosis detection indicated that the decreases in cell viability were correlated with the induction of apoptosis. Thalidomide incubated with microsomal protein also influenced HUVEC migration and tube formation. These effects were partially reversed by omeprazole (10 µmol/l), a potent inhibitor of CYP2C19, suggesting that CYP2C19 is required for thalidomide to exhibit its antimyeloma and antiangiogenic activities.

 ***Bortezomib attenuates acute graft-vs.-host disease through interfering with host immature dendritic cells.***

Tao Y, Zhang W, Fang Y, Yang D, Wang L, Zhou H, Wang J.

*Exp Hematol.* 2011 Jun;39(6):710-20. [Epub 2011 Mar 8.]



<http://www.ncbi.nlm.nih.gov/pubmed/21392555>

**The authors explore the conditions under which proteasome inhibitor bortezomib improves acute graft-vs.-host disease (aGVHD) and the mechanism underlying the differential effects of bortezomib on aGVHD. They find that manipulating host immature dendritic cells may represent a novel mechanism by which bortezomib improves aGVHD.**

OBJECTIVE: To explore the conditions under which proteasome inhibitor bortezomib improves acute graft-vs.-host disease (aGVHD) and the mechanism underlying the differential effects of bortezomib on aGVHD. MATERIALS AND METHODS: Murine aGVHD models (C57BL/6→BALB/c) of different severities were set up by infusing with decreasing doses of donor splenocytes (SC). Bortezomib were administered immediately or 6 days after bone marrow transplantation (BMT). Serum levels of tumor necrosis factor-α (TNF-α) and lipopolysaccharide along with the number of donor TNF-α(+) T cells in recipients before intervention were determined. Major histocompatibility complex II expression and interleukin-12 production were analyzed to evaluate the maturation state of host dendritic cells (DCs) before intervention. Phenotypic changes, apoptosis, allogeneic stimulation, and IκBα expression levels in bortezomib-treated mature DCs or immature DCs were analyzed in vitro.

RESULTS: Neither early bortezomib (day 0 BMT) administration in a modest ( $SC\ 1 \times 10^7$ ) or severe ( $SC\ 2 \times 10^7$ ) aGVHD model, nor delayed administration (day +6 BMT) could protect mice from aGVHD. Marked inhibition of aGVHD was observed in a mild aGVHD model ( $SC\ 5 \times 10^6$ ) with early intervention. This inhibition correlated with a relatively immature state of host DCs before intervention. Additional in vitro studies showed that, in comparison to mature DCs, bortezomib inhibited phenotypic and functional maturation as well as induced more potent apoptosis in immature DCs through suppression of nuclear factor- $\kappa$ B activity. CONCLUSIONS: Manipulating host immature DCs may represent a novel mechanism by which bortezomib improves aGVHD.

## New Combinations

### ***Bendamustine in combination with thalidomide and dexamethasone is an effective therapy for myeloma patients with end stage renal disease.***

Ramasamy K, Hazel B, Mahmood S, Corderoy S, Schey S.

*Br J Haematol.* 2011 Jun 21. doi: 10.1111/j.1365-2141.2011.08754.x. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21689088>

No abstract available.

### ***Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation.***

Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ, Navarro Coy N, Cook G, Feyler S, Byrne JL, Roddie H, Rudin C, Drayson MT, Owen RG, Ross FM, Jackson GH, Child JA.

*Blood.* 2011 Jun 7. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21652683>

**As part of the randomized MRC Myeloma IX trial, the authors compare an attenuated regimen of cyclophosphamide, thalidomide, and dexamethasone (CTDa) with melphalan and prednisolone (MP) in patients with newly diagnosed myeloma ineligible for autologous stem-cell transplantation. They find that in elderly newly diagnosed myeloma patients, CTDa produces higher response rates than MP, but is not associated with improved survival outcomes. They also highlight the importance of cytogenetic profiling at diagnosis and effective management of adverse events.**

As part of the randomized MRC Myeloma IX trial, we compared an attenuated regimen of cyclophosphamide, thalidomide, and dexamethasone (CTDa) ( $n = 426$ ) with melphalan and prednisolone (MP) ( $n = 423$ ) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for autologous stem-cell transplantation. The primary endpoints were overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). The ORR was significantly higher with CTDa than MP (63.8% vs 32.6%;  $P < .0001$ ), primarily due to increases in the rate of complete responses (13.1% vs 2.4%) and very good partial responses (16.9% vs 1.7%). PFS and OS were similar between groups. In this population, OS correlated with the depth of response ( $P < .0001$ ) and favorable interphase FISH profile ( $P < .001$ ). CTDa was associated with higher rates of thromboembolic events, constipation, infection, and neuropathy than MP. In elderly patients with NDMM (median age, 73 years), CTDa produced higher response rates than MP, but was not associated with improved survival outcomes. We highlight the importance of cytogenetic profiling at diagnosis and effective management of adverse events. This trial was registered at [www.ISRCTN.org](http://www.ISRCTN.org) as # 68454111.

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

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

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



<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 ( $< 5 \mu\text{M}$ ) 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.

### **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 Jun;112(6):1552-62. doi: 10.1002/jcb.23077.



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

**Using several myelogenous cell lines, the authors investigate the effect of genipin (an active compound of Gardenia fruit) on the STAT3 pathway and apoptosis. Their data suggest that genipin effectively potentiates the cytotoxic effect of chemotherapeutic agents, such as bortezomib, thalidomide, and paclitaxel in U266 cells, and that through regulation of Src and SHP-1, genipin antagonizes STAT3 for the induction of apoptosis in myeloma cells.**

It has drawn a lot of attention to target signal transducer and activator of transcription 3 (STAT3) as a potential strategy for cancer therapeutics. Using several myelogenous cell lines, the effect of genipin (an active compound of Gardenia fruit) on the STAT3 pathway and apoptosis was investigated. Genipin suppressed the constitutive STAT3 activation in U266 and U937 cells and stimulated Src homology 2 domain-containing phosphatase 1 (SHP-1), which dephosphorylates and inactivates STAT3. Specifically, genipin blocked STAT3 activation via repressing the activation of c-Src, but not Janus kinase 1 (JAK1). Genipin also downregulated the expression of STAT3 target genes including Bcl-2, Bcl-x(L), Survivin, Cyclin D1, and VEGF. Conversely, protein tyrosine phosphatase inhibitor pervanadate blocked genipin induced STAT3 inactivation. Using DNA fragmentation or TUNEL assays, we demonstrated the apoptotic effect of genipin on U266, MM.1S, and U937 cells. Furthermore, genipin effectively potentiated the cytotoxic effect of chemotherapeutic agents, such as bortezomib, thalidomide, and paclitaxel in U266 cells. Our data suggest that through regulation of Src and SHP-1, genipin antagonizes STAT3 for the induction of apoptosis in myeloma cells.

### **Tanespimycin and bortezomib combination treatment in patients with relapsed or relapsed and refractory multiple myeloma: results of a phase 1/2 study.**

Richardson PG, Chanan-Khan AA, Lonial S, Krishnan AY, Carroll MP, Alsina M, Albitar M, Berman D, Messina M, Anderson KC.

*Br J Haematol.* 2011 Jun;153(6):729-40. doi: 10.1111/j.1365-2141.2011.08664.x. [Epub 2011 Apr 28.]



<http://www.ncbi.nlm.nih.gov/pubmed/21534941>

**This open-label, dose escalation, multicenter phase 1/2 trial was undertaken to determine the safety and tolerability of the heat shock protein 90 (HSP90) inhibitor tanespimycin plus bortezomib. Pharmacodynamic analyses indicate that tanespimycin plus bortezomib effectively inhibit the proteasome, as evidenced by decreased 20S proteasome activity, and inhibited HSP90, as reflected by increased HSP70 expression; the results of this study support additional studies of this combination approach in myeloma.**

This open-label, dose escalation, multicentre phase 1/2 trial was undertaken to determine the safety and tolerability of the heat shock protein 90 (HSP90) inhibitor tanespimycin ( $100\text{-}340 \text{ mg/m}^2$ ) + bortezomib ( $0.7\text{-}1.3 \text{ mg/m}^2$ ) given on days 1, 4, 8 and 11 in each 21-d cycle. Phase 2 expansion occurred at the highest tested dose of tanespimycin at  $340 \text{ mg/m}^2$  and bortezomib at  $1.3 \text{ mg/m}^2$ . Seventy-two patients (median age, 60 years) with relapsed or relapsed and refractory multiple myeloma (MM) were enrolled; 63 patients (89%) completed the study. Tanespimycin in combination with bortezomib was well tolerated; few patients experienced significant neutropenia, constipation and anorexia ( $<10\%$ ), and no patients developed severe peripheral neuropathy. Among 67 efficacy-evaluable patients, there were 2 (3%) complete responses and 8 (12%) partial responses, for an objective response rate (ORR) of 27%, including 8 (12%) minimal responses. Response rates were highest among bortezomib-naive patients and proved durable in all patient subgroups, including those with bortezomib-refractory disease. Pharmacodynamic analyses indicated that tanespimycin plus bortezomib effectively inhibited the proteasome, as evidenced by decreased 20S proteasome activity, and inhibited HSP90, as reflected by increased HSP70 expression. The results of this study support additional studies of this combination approach in MM.

## Newly Diagnosed

### ***Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from six randomized clinical trials.***

Fayers PM, Palumbo A, Hulin C, Waage A, Wijermans P, Beksaç M, Brinthen S, Mary JY, Gimsing P, Termorshuizen F, Haznedar R, Caravita T, Moreau P, Turesson I, Musto P, Benboubker L, Schaafsma M, Sonneveld P, Facon T.

*Blood.* 2011 Jun 13. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21670471>

**The authors oversee six randomized controlled trials, launched in or after 2000, comparing melphalan and prednisone alone (MP) and with thalidomide (MPT). They conclude that thalidomide added to MP improves overall survival and progression free survival in previously untreated elderly myeloma patients, extending the median survival time by on average 20%.**

The role of thalidomide for previously untreated elderly patients with multiple myeloma remains unclear. Six randomized controlled trials, launched in or after 2000, compared melphalan and prednisone alone (MP) and with thalidomide (MPT). The effect on overall survival (OS) varied across trials. We carried out a meta-analysis of the 1685 individual patients in these trials. The primary endpoint was OS, and progression-free survival (PFS) and one-year response rates were secondary endpoints. There was a highly significant benefit to OS from adding thalidomide to MP (HR 0.83, 95% CI 0.73-0.94,  $p=0.004$ ), representing increased median OS time of 6.6 months, from 32.7 months (MP) to 39.3 months (MPT). The thalidomide regimen was also associated with superior PFS (HR 0.68, 95% CI 0.61-0.76,  $p<0.0001$ ) and better one-year response rates (partial response or better was 59% on MPT and 37% on MP). Although the trials differed in terms of patient baseline characteristics and thalidomide regimens, there was no evidence that treatment affected OS differently according to levels of the prognostic factors. We conclude that thalidomide added to MP improves OS and PFS in previously untreated elderly patients with multiple myeloma, extending the median survival time by on average 20%.

### ***A randomized trial with melphalan and prednisone versus melphalan and prednisone plus thalidomide in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplant.***

Sacchi S, Marcheselli R, Lazzaro A, Morabito F, Fragasso A, Renzo ND, Balleari E, Neri S, Quarta G, Ferrara R, Vigliotti ML, Polimeno G, Musto P, Consoli U, Zoboli A, Buda G, Pastorini A, Masini L.

*Leuk Lymphoma.* 2011 Jun 12. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21663513>

**The authors evaluate the efficacy and toxicity of melphalan and prednisone (MP) versus MP plus thalidomide (MPT) in newly diagnosed myeloma patients who were transplant-ineligible or over age 65. Their results show an improved activity of MPT at a cost of increased toxicity, and they believe that MPT can be considered one of the new standard of care for elderly or transplant-ineligible myeloma patients.**

Several trials comparing the efficacy of standard melphalan and prednisone (MP) therapy with MP plus thalidomide (MPT) in elderly patients with multiple myeloma (MM) have been reported, with inconsistent results. The primary goal of our study was to evaluate the efficacy and toxicity of MP versus MPT in newly diagnosed patients with MM who were transplant-ineligible or over age 65. A total of 135 patients were enrolled. Either minimal response or better or partial response or better were more frequent with MPT treatment ( $p=0.001$ ). After a median follow-up of 30 months, median progression-free survival (PFS) and overall survival (OS) were 33 and 52 months for MPT versus 22 and 32 months for MP, respectively. The comparison showed a significant advantage for MPT versus MP in PFS ( $p=0.02$ ) and only a trend for OS ( $p=0.07$ ). Severe adverse events were observed more frequently with MPT. In conclusion, our results show an improved activity of MPT at a cost of increased toxicity. We believe that MPT can be considered one of the new standard of care for elderly or transplant-ineligible patients with MM.

### ***Treatment of newly diagnosed multiple myeloma in transplant-eligible patients.***

Kumar S.

*Curr Hematol Malig Rep.* 2011 Jun;6(2):104-12.



<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.**

Treatment of myeloma has changed significantly in the past decade as a result of better understanding of disease biology, more effective treatments, and improved supportive care. Autologous stem cell transplantation (SCT) is an effective treatment for myeloma and remains a critical component in its management. Given the potential impact of therapy on stem cell collection, initial treatment decisions in myeloma still depend on the patient's transplant eligibility. The goals of initial therapy remain rapid disease control allowing for reversal of disease complications, as well as reduction in the risk of early death—all with minimal

toxicity. The introduction of new drugs such as thalidomide, bortezomib, and lenalidomide has enabled us to achieve this goal, and combinations of these drugs have also led to unprecedented response depth. In addition, the newer drugs are being explored as maintenance therapy following SCT. This review summarizes the current approach to the treatment of newly diagnosed myeloma in transplant-eligible patients.

### **Treatment of newly diagnosed myeloma in patients not eligible for transplantation.**

Mateos MV, San-Miguel J.

*Curr Hematol Malig Rep.* 2011 Jun;6(2):113-9.



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

**The authors discuss the standards of care for the treatment of elderly patients with newly diagnosed myeloma, including the use of novel agents (including bortezomib and lenalidomide) and their treatment-related adverse events.**

Melphalan plus prednisone (MP) has long been considered the gold-standard treatment for elderly patients with newly diagnosed myeloma, and it still forms the backbone for combinations based on novel agents. MP plus thalidomide (MPT), bortezomib (VMP), or lenalidomide (MPR), as induction plus maintenance, have proved to be superior to MP and are currently the treatment of choice for this population. Low-dose dexamethasone in combination with thalidomide and cyclophosphamide (CTDa) or with lenalidomide can be an alternative option for these patients. The benefit of these novel agents in terms of prolonged survival is accompanied by increases in treatment-related adverse events, however, which may be particularly pronounced in older individuals. In managing these patients, efficacy and toxicity should be balanced, and thus prophylactic measures to avoid adverse effects are mandatory. Moreover, reduced-intensity regimens are recommended for fragile or very elderly patients. Finally, the wide array of new treatment options will facilitate individualized treatment approaches, based on characteristics of the disease, patient comorbidities, and personal and social circumstances.

## Relapsed/Refractory Treatment

### **Thalidomide, dexamethasone and lovastatin with autologous stem cell transplantation as a salvage immunomodulatory therapy in patients with relapsed and refractory multiple myeloma.**

Hus M, Grzasko N, Szostek M, Pluta A, Helbig G, Woszczyk D, Adamczyk-Cioch M, Jawniak D, Legiec W, Morawska M, Kozinska J, Waciński P, Dmoszynska A.

*Ann Hematol.* 2011 Jun 23. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21698395>

**The results of this study suggest that the addition of lovastatin to a thalidomide-dexamethasone regimen may improve the response rate in patients with relapsed or refractory myeloma.**

The treatment of patients with multiple myeloma usually includes many drugs including thalidomide, lenalidomide and bortezomib. Lovastatin and other inhibitors of HMG-CoA reductase demonstrated to exhibit antineoplastic and proapoptotic properties in numerous in vitro studies involving myeloma cell lines. We treated 91 patients with relapsed or refractory multiple myeloma with thalidomide, dexamethasone and lovastatin (TDL group, 49 patients) or thalidomide and dexamethasone (TD group, 42 patients). A clinical response defined of at least 50% reduction of monoclonal band has been observed in 32% of TD patients and 44% of TDL patients. Prolongation of overall survival and progression-free survival in the TDL group as compared with the TD group has been documented. The TDL regimen was safe and well tolerated. The incidence of side effects was comparable in both groups. Plasma cells have been cultured in vitro with thalidomide and lovastatin to assess the impact of both drugs on the apoptosis rate of plasma cells. In vitro experiments revealed that the combination of thalidomide and lovastatin induced higher apoptosis rate than apoptosis induced by each drug alone. Our results suggest that the addition of lovastatin to the TD regimen may improve the response rate in patients with relapsed or refractory myeloma.

### **Bortezomib-Cyclophosphamide-Dexamethasone for Relapsing Multiple Myeloma.**

Fu W, Delasalle K, Wang J, Song S, Hou J, Alexanian R, Wang M.

*Am J Clin Oncol.* 2011 Jun 18. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21694573>

**The authors treat 44 patients with relapsing myeloma with the combination of bortezomib-cyclophosphamide-dexamethasone, which they find is an effective, well-tolerated combination for the treatment of relapsing myeloma.**

**OBJECTIVES:** In vitro studies have shown synergistic antimyeloma effects with the combination of bortezomib and alkylating agents. Combinations of bortezomib, cyclophosphamide, and dexamethasone are rational with the prospect of superior antitumor activity with independent toxicity. **METHODS:** Between December 2004 and April 2007, we treated 44 patients with relapsing

multiple myeloma with the combination of bortezomib 1.3 mg/m intravenously on days 1, 4, 8, 11; dexamethasone 20 mg/m orally daily for 4 days beginning on days 1, 9 and 17; and cyclophosphamide 70 mg/m orally twice daily for 4 days. A second course was given 1 month later. RESULTS: Clinical response was observed in 32 patients (73%) including 26 with disease in partial remission (59%), and 6 with disease in complete remission (14%). Side effects were uncommon and mild, except for grade 3 thrombocytopenia in 15%, infection in 5% and constipation in 2% of patients. The median remission time of responding patients was 10 months that contributed to significantly longer median survival for patients with responsive disease (33 mo) than for those with unresponsive disease (12 mo) ( $P < 0.01$ ). CONCLUSION: Bortezomib-cyclophosphamide-dexamethasone was an effective, well-tolerated combination for the treatment of relapsing multiple myeloma.

 ***Efficacy of retreatment with immunomodulatory drugs (IMiDs) in patients receiving IMiDs for initial therapy of newly diagnosed multiple myeloma.***

Madan S, Lacy MQ, Dispenzieri A, Gertz MA, Buadi F, Hayman SR, Detweiler-Short K, Dingli D, Zeldenrust S, Lust J, Greipp PR, Rajkumar SV, Kumar S.

*Blood*. 2011 Jun 14. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21673347>

**The authors study 140 patients who received either thalidomide-dexamethasone or lenalidomide-dexamethasone as first line therapy of myeloma followed by repeat IMiD as one of the salvage regimens. They find that response rates with lenalidomide retreatment are higher compared with repeat administration of thalidomide.**

The efficacy of retreatment with immunomodulatory drugs (IMiDs) among patients with multiple myeloma (MM) who received this class of drugs for initial therapy is unknown. We studied 140 patients who received either thalidomide-dexamethasone (81; 58%) or lenalidomide-dexamethasone (59; 42%) as first line therapy of MM followed by repeat IMiD [thalidomide (34; 24%) or lenalidomide (106; 76%)] as one of the salvage regimens. A median of 2 treatments (range, 1-6), including a stem cell transplant (SCT) in 105 (75%) patients, was administered prior to IMiD based salvage therapy. The median time from diagnosis to repeat exposure to IMiD was 28 months. Among the 113 evaluable patients, 50 (44%) patients achieved at least a partial response and 63 (56%) patients achieved less than a partial response to repeat IMiD. Response rates with lenalidomide retreatment were higher compared with repeat administration of thalidomide.

 ***Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation.***

Fenk R, Liese V, Neubauer F, Bruns I, Kondakci M, Balleisen S, Saure C, Schröder T, Haas R, Kobbe G.

*Leuk Lymphoma*. 2011 Jun 10. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21657961>

**This retrospective study reports on 55 patients who were treated with salvage high-dose therapy (HDT) with a conditioning regimen of melphalan, melphalan and busulfan, or melphalan and bortezomib. The authors find that salvage HDT followed by autologous peripheral blood stem cell transplantation is an effective treatment option for patients with relapsed or refractory myeloma, but that patients with an early relapse after their first transplant do not benefit from this treatment modality.**

For patients with relapsed or refractory multiple myeloma (MM) treated with a prior high-dose therapy (HDT) followed by autologous peripheral blood stem cell transplantation (PBSCT), the reapplication of HDT is a widely used salvage strategy. In this retrospective study, we report on 55 patients who were treated with salvage HDT at our institution. The conditioning regimen consisted of melphalan 200 mg/m<sup>2</sup> (27%), melphalan 140 mg/m<sup>2</sup> and busulfan 12 mg/kg body weight (40%), or melphalan 200 mg/m<sup>2</sup> and bortezomib 1.3 mg/m<sup>2</sup> (33%). Treatment-related mortality was 5% and response rates were as follows: 9% complete remission, 9% very good partial remission, 56% partial remission, 11% minimal response + stable disease, and 4% progressive disease (5% not assessable). Toxicity was moderate and the median event-free (EFS) and overall survival (OS) were 14 months and 52 months, respectively. The different conditioning regimens did not result in differences in terms of remission rates, EFS and OS, or toxicity. In multivariate analysis a duration of remission of more than 12 months after the first transplant was the only predictive factor for both EFS ( $p < 0.0001$ ) and OS ( $p = 0.0001$ ). In conclusion, salvage HDT followed by autologous PBSCT is an effective treatment option for patients with relapsed or refractory MM, while patients with an early relapse after their first transplant do not benefit from this treatment modality.

 ***Lenalidomide is active for extramedullary disease in refractory multiple myeloma.***

Nakazato T, Mihara A, Ito C, Sanada Y, Aisa Y.

*Ann Hematol*. 2011 Jun 7. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21647581>

No abstract available.

### **Treatment of relapsed and refractory multiple myeloma in the era of novel agents.**

van de Donk NW, Lokhorst HM, Dimopoulos M, Cavo M, Morgan G, Einsele H, Kropff M, Schey S, Avet-Loiseau H, Ludwig H, Goldschmidt H, Sonneveld P, Johnsen HE, Bladé J, San-Miguel JF, Palumbo A.

*Cancer Treat Rev.* 2011 Jun;37(4):266-83. [Epub 2010 Sep 21.]



<http://www.ncbi.nlm.nih.gov/pubmed/20863623>

**This review provides an overview of the various salvage regimens and gives recommendations for treatment of patients with relapsed/refractory myeloma in different clinical settings.**

The introduction of the Immunomodulatory drugs (IMiDs) and proteasome inhibitors, used either as a single-agent or combined with classic anti-myeloma therapies, has improved the outcome for patients with relapsed myeloma. However, there is currently no generally accepted standard treatment for relapsed/refractory myeloma patients, partly because of the absence of trials comparing the efficacy of the novel agents in relapsed/refractory myeloma. Choice of a new treatment regimen depends on both patient and disease-specific characteristics. A lenalidomide-based regimen is the first choice in patients with neuropathy, while bortezomib has the highest efficacy in patients with renal insufficiency and is not associated with increased risk of thromboembolism. A second autologous stem cell transplantation (auto-SCT) can be applied in patients with a progression-free period of  $\geq 18$ -24 months after the first auto-SCT. In high-risk relapse such as occurring early after auto-SCT consolidation with allogeneic SCT can be considered. In this review we provide an overview of the various salvage regimens and give recommendations for treatment of patients with relapsed/refractory myeloma in different clinical settings.

## Supportive Care

### **Renal improvement in myeloma with bortezomib plus plasma exchange.**

Burnette BL, Leung N, Rajkumar SV.

*N Engl J Med.* 2011 Jun 16;364(24):2365-6.



<http://www.ncbi.nlm.nih.gov/pubmed/21675906>

No abstract available.

### **Activation of coagulation by a thalidomide-based regimen.**

Hoshi A, Matsumoto A, Chung J, Iozumi Y, Koyama T.

*Blood Coagul Fibrinolysis.* 2011 Jun 10. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21670663>

**The authors investigate the procoagulant effects of thalidomide when combined with chemotherapeutic agents in vitro, focusing on tissue factor (TF) and phosphatidylserine. They find that when thalidomide is given in combination with chemotherapies or dexamethasone, endothelial cell and monocyte procoagulant activity may be induced through phosphatidylserine exposure, or TF expression. Induction may be protracted by thalidomide, which has an antiangiogenic activity. They therefore conclude that prophylactic anticoagulant strategies should be considered in thalidomide-based combination regimens.**

Combining thalidomide (Thal) with chemotherapeutic agents or steroid preparations led to improved response rates in the treatment of multiple myeloma. However, deep vein thrombosis (DVT) is one of the most serious side-effects noted with this regimen, and how a Thal-based regimen causes DVT is unclear. We investigated the procoagulant effects of Thal when combined with chemotherapeutic agents in vitro, focusing on tissue factor (TF) and phosphatidylserine. We examined the effects of the chemotherapeutic doxorubicin hydrochloride (Dox) and the steroid dexamethasone (Dex), with or without Thal. Our study used the human vascular endothelial, monocytic, and myeloma cell lines, EAhy926, THP-1, and RPMI8226, respectively. In EAhy926 and THP-1, Dex treatment increased expression of TF, which may induce procoagulant activity (PCA). Upregulation of TF mRNA correlated with activation of the Egr-1 pathway. In Thal and Dex treatments, the increase of PCA induction from phosphatidylserine exposure was modest. In contrast, Dox and Thal-Dox increased phosphatidylserine exposure in both cell types. In THP-1 cells, cell surface phosphatidylserine exposure correlated with increased PCA by Dox. Thal alone showed a modest increase in phosphatidylserine exposure in endothelial cells and monocytes. When Thal is given in combination with chemotherapies or Dex, endothelial cell and monocyte PCA may be induced through phosphatidylserine exposure, or TF expression. Induction may be protracted by Thal, which has an antiangiogenic activity. Therefore, prophylactic anticoagulant strategies should be considered in Thal-based combination regimens.

 **Delayed treatment with vitamin C and N-acetyl-L: -cysteine protects Schwann cells without compromising the anti-myeloma activity of bortezomib.**

Nakano A, Abe M, Oda A, Amou H, Hiasa M, Nakamura S, Miki H, Harada T, Fujii S, Kagawa K, Takeuchi K, Watanabe T, Ozaki S, Matsumoto T.

*Int J Hematol.* 2011 Jun;93(6):727-35. [Epub 2011 Apr 28.]



<http://www.ncbi.nlm.nih.gov/pubmed/21526377>

The authors screen for cytoprotective agents to devise a method of rescuing Schwann cells from the cytotoxic effects of bortezomib without compromising its anti-myeloma effects. They find that delayed addition of vitamin C and/or N-acetyl-L: -cysteine after the exposure to bortezomib alleviates the cytotoxicity in Schwann cells but not myeloma cells. These results suggest that delayed treatment with these agents may be instrumental in prophylaxis of bortezomib-induced peripheral neuropathy.

Bortezomib-induced peripheral neuropathy (BIPN) emerges as a disabling adverse effect. As rat models for BIPN have demonstrated damage in nerve Schwann cells, we screened for cytoprotective agents to devise a method of rescuing Schwann cells from the cytotoxic effects of bortezomib without compromising its anti-myeloma effects. Schwann cells underwent macroautophagy along with cytoplasmic inclusion body and vacuole formation, and appeared much less susceptible to bortezomib-induced cytotoxicity than did myeloma cells. Vitamin C or N-acetyl-L: -cysteine (NAC) achieved near-complete rescue of Schwann cells treated with bortezomib at 30 nM or less, and these agents in combination are able to cooperatively inhibit the morphological changes and the cytotoxicity in Schwann cells with higher doses of bortezomib. The delayed addition of vitamin C and/or NAC after the exposure to bortezomib alleviated the cytotoxicity in Schwann cells but not myeloma cells. These results suggest that delayed treatment with these agents may be instrumental in prophylaxis of BIPN.

## Toxicities & Adverse Effects

 **Stevens-Johnson syndrome after lenalidomide therapy for multiple myeloma: a case report and a review of treatment options.**

Allegra A, Alonci A, Penna G, Russo S, Gerace D, Greve B, D'Angelo A, Catena S, Musolino C.

*Hematol Oncol.* 2011 Jun 23. doi: 10.1002/hon.1000. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21702057>

The authors describe a patient with Stevens- Johnson syndrome (SJS) while receiving lenalidomide in combination with prednisolone for treatment-naïve myeloma. They conclude that although SJS has been reported rarely as an adverse reaction to lenalidomide, it should be considered, and that the increased use of lenalidomide therapy for myeloma should stress the awareness of its potentially serious side effects.

Stevens- Johnson syndrome (SJS) is a severe and life-threatening condition. Although allopurinol, an antihyperuricemia drug, is the drug most commonly associated with SJS, more than 100 different causative drugs have been reported. Among hematologic drugs recently introduced into the market, drugs such as rituximab, imatinib, and bortezomib are reported. Here, we describe a patient with SJS while receiving lenalidomide in combination with prednisolone for treatment-naïve multiple myeloma. Although SJS has been reported rarely as an adverse reaction to Lenalidomide, this drug should be considered in the etiology of SJS, and the increased number of prescriptions of Lenalidomide for the therapy of multiple myeloma has to stress the awareness of its potentially serious side-effects.

 **Follow-Up Psychophysical Studies in Bortezomib-Related Chemoneuropathy Patients.**

Boyette-Davis JA, Cata JP, Zhang H, Driver LC, Wendelschafer-Crabb G, Kennedy WR, Dougherty PM.

*J Pain.* 2011 Jun 22. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21703938>

This is the first article to address the persistence, and potential contributing factors, of bortezomib chemoneuropathy, and its results indicate a persistent, painful peripheral neuropathy in patients treated with bortezomib.

Many frontline chemotherapeutic agents produce robust neuropathy as a dose-limiting side effect; however, the persistence of chemotherapy-related sensory disturbances and pain are not well documented. We have previously investigated the qualities of bortezomib-induced pain, and now seek to determine the ongoing nature of this pain. Twenty-six control subjects and 11 patients who had previously been treated with bortezomib and who were experiencing ongoing pain consented to recurring quantitative sensory testing. A pilot immunohistochemistry study of skin innervation was also performed on patient-obtained biopsies. Psychophysical testing in patients revealed persistent changes including decreased skin temperature in the area of pain, diminished touch and sharpness detection, increased pegboard completion times, and decreased sensitivity to skin heating. Additionally, the intensity of pain, as captured by the use of a visual analog scale and pain descriptors, was reported by patients

to be unchanged during the retest despite similar morphine equivalent daily doses. The patient skin biopsies displayed a marked decrease in the density of epidermal nerve fibers and Meissner's corpuscles. These results signify a persistent and severe impairment of A $\beta$ , A $\delta$ , and C fibers in patients with chronic bortezomib-induced chemoneuropathy. Further, this study reports a loss of both epidermal nerve fibers and Meissner's corpuscles. PERSPECTIVE: The results of this article indicate a persistent, painful peripheral neuropathy in patients treated with bortezomib. Pilot data indicates a loss of nerve fibers innervating the area of pain. This is the first paper to address the persistence, and potential contributing factors, of bortezomib chemoneuropathy.

### ***Bisphosphonate-related osteonecrosis of the jaws - Characteristics, risk factors, clinical features, localization and impact on oncological treatment.***

Otto S, Schreyer C, Hafner S, Mast G, Ehrenfeld M, Stürzenbaum S, Pautke C.

*J Craniomaxillofac Surg.* 2011 Jun 13. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21676622>

**This single-center study collated medical records (2003-2009) of all patients that suffered from osteonecrosis of the jaw (ONJ) within the Department of Oral and Maxillofacial Surgery, Ludwig-Maximilians-University of Munich, Germany. The authors conclude that the development of ONJ has a multi-factorial aetiology and the clinical presentation can vary markedly; ONJ cannot only impair the quality of life but also the treatment of the underlying disease.**

**INTRODUCTION:** Osteonecrosis of the jaw (ONJ) is a serious side-effect of intravenous nitrogen-containing bisphosphonate therapy frequently used in the treatment of malignant diseases. Despite numerous case series published so far studies with detailed investigations into risk factors, the precise localization of ONJ and impact of ONJ on the oncological treatment remain sparse. **PATIENTS AND METHODS:** This single-centre study collated medical records (2003-2009) of all patients that suffered from ONJ within the Department of Oral and Maxillofacial Surgery, Ludwig-Maximilians-University of Munich, Germany. In total, 126 patients fulfilled the case criteria of ONJ and were examined clinically. The complete medical history including detailed questionnaires was collected of 66 patients, focussing in particular on the identification of underlying risk factors, clinical features, ONJ localization as well as the impact on the oncological treatment. **RESULTS:** The majority of ONJ cases occurred in patients suffering from malignant diseases (n=117; 92.8%), in particular breast cancer (n=57; 45.2%), multiple myeloma (n=37; 29.4%) and prostate cancer (n=13; 10.3%), all received nitrogen-containing bisphosphonates intravenously. ONJ was also diagnosed in 9 patients (7.1%) suffering from osteoporosis or rheumatoid arthritis. The most prevalent clinical feature was exposed necrotic bone (93.9%) in the oral cavity which was accompanied in 78.8% of cases by pain. A predilection for the mandible and in particular for molar and premolar regions in both jaws was shown. Although no recommendation concerning the oncologic treatment was made, the manifestation of ONJ resulted (in a significant proportion of the patients) in a change of medication and schedule. The most frequent co-medications were steroids and anti-angiogenic drugs, such as thalidomide. **DISCUSSION:** The predilection for mandibular molar and premolar regions, and the infectious conditions that often precede the onset of ONJ support recent pathogenesis theories stating that local inflammation and associated pH-changes may trigger the release and activation of nitrogen-containing bisphosphonates ultimately resulting in necrosis. **CONCLUSION:** The development of ONJ has a multi-factorial aetiology and the clinical presentation can vary markedly. ONJ cannot only impair the quality of life but also the treatment of the underlying disease.

### ***Inflammatory autoimmune neuropathy, presumably induced by bortezomib, in a patient suffering from multiple myeloma.***

Schmitt S, Goldschmidt H, Storch-Hagenlocher B, Pham M, Fingerle-Rowson G, Ho AD, Neben K.

*Int J Hematol.* 2011 Jun;93(6):791-4. [Epub 2011 May 7.]



<http://www.ncbi.nlm.nih.gov/pubmed/21553020>

**The authors report here the case of a 65-year-old female myeloma patient who was initially treated with bortezomib, doxorubicin, and dexamethasone (PAD). They conclude that the identification of an inflammatory autoimmune neuropathy, presumably associated with bortezomib, is a rare but important complication. An extensive neurological examination should be performed in patients who develop severe or unusual sensory or motor deficits under therapy with bortezomib, so as to differentiate autoimmune from toxic neuropathies, as therapeutic strategies differ for each.**

Bortezomib is a proteasome inhibitor demonstrating substantial activity in multiple myeloma. One of its key toxicities is peripheral neuropathy, which is reversible in most patients. The possibility that bortezomib might in rare cases induce severe neuropathies by auto-inflammatory mechanisms remains controversial. We report here the case of a 65-year-old female myeloma patient who was initially treated with bortezomib, doxorubicin, and dexamethasone (PAD). At the end of the second cycle of PAD, the patient presented with a rapid and severe onset of paresis of the left arm, accompanied by progressive sensory neuropathy and increasing neuropathic pain. After an extensive neurological work-up, including electrophysiological and laboratory evaluations as well as magnet resonance tomography imaging, we diagnosed an inflammatory autoimmune neuropathy, presumably induced

by bortezomib, with accentuation of the left arm nerve plexus. We subsequently initiated regular treatment with polyvalent immunoglobulins, which gradually improved the neurological symptoms. In conclusion, the identification of an inflammatory autoimmune neuropathy, presumably associated with bortezomib, is a rare but important complication. An extensive neurological examination should be performed in patients who develop severe or unusual sensory or motor deficits under therapy with bortezomib, so as to differentiate autoimmune from toxic neuropathies, as therapeutic strategies differ for each.

### **Thyroid abnormalities in patients treated with lenalidomide for hematological malignancies: Results of a retrospective case review.**

Figaro MK, Clayton W Jr, Usoh C, Brown K, Kassim A, Lakhani VT, Jagasia S.

*Am J Hematol.* 2011 Jun;86(6):467-70. doi: 10.1002/ajh.22008. [Epub 2011 May 4.]



<http://www.ncbi.nlm.nih.gov/pubmed/21544854>

**The authors review medical records of patients treated with lenalidomide at a single center from 2005 to 2010 and extracted demographic, clinical, and laboratory data; 148 were treated for myeloma and 6% had thyroid abnormalities attributable only to lenalidomide. The authors conclude that because symptoms of thyroid dysfunction could be alleviated by appropriate treatment, thyroid function should be evaluated during the course of lenalidomide to improve patients' quality of life.**

Lenalidomide is an antiangiogenic drug associated with hypothyroidism. We describe a case-series of lenalidomide use in hematological cancers and the prevalence of thyroid abnormalities. We reviewed medical records of patients treated with lenalidomide at a single center from 2005 to 2010 and extracted demographic, clinical, and laboratory data. Of 170 patients with confirmed lenalidomide use (age 64.9±15 years), 148 were treated for multiple myeloma and 6% had thyroid abnormalities attributable only to lenalidomide. In patients with a previous diagnosis of thyroid dysfunction, the addition of lenalidomide therapy was associated with a higher incidence of subsequent TFTF abnormality (17%) as compared to patients with no previous diagnosis of thyroid dysfunction (6%) (P=0.0001). Many patients (44%) with pre-existing disease and a change in thyroid function before or while on lenalidomide had no further follow-up of their thyroid abnormalities. Of 20 patients who did not undergo any thyroid function testing either before starting or while on lenalidomide for a median of 9.4 months (±6.5), 35% developed new symptoms compatible with hypothyroidism, including worsened fatigue, constipation or cold intolerance. Symptoms of thyroid dysfunction overlap with side effects of lenalidomide. Thyroid hormone levels are not regularly evaluated in patients on lenalidomide. While on this treatment, thyroid abnormalities can occur in patients with no previous diagnoses and in patients with pre-existing abnormalities. Because symptoms of thyroid dysfunction could be alleviated by appropriate treatment, thyroid function should be evaluated during the course of lenalidomide to improve patients' quality of life.

## **Transplantation & Induction Therapies**

### **Lenalidomide maintenance following non-myeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 trial.**

Kneppers E, van der Holt B, Kersten MJ, Zweegman S, Meijer E, Huls G, Cornelissen JJ, Janssen JJ, Huisman C, Cornelisse PB, Bruijnen CP, Emmelot M, Sonneveld P, Lokhorst HM, Mutis T, Minnema MC.

*Blood.* 2011 Jun 20. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21690556>

**To improve the outcome of allogeneic stem cell transplantation (allo-SCT) in myeloma as part of first line treatment, the authors prospectively investigate the feasibility and efficacy of lenalidomide maintenance. They conclude that lenalidomide maintenance 10 mg daily after non myeloablative allo-SCT with unmanipulated graft in myeloma patients is not feasible, mainly due to the rapid induction of acute graft versus host disease.**

To improve the outcome of allogeneic stem cell transplantation (allo-SCT) in Multiple Myeloma (MM) as part of first line treatment we prospectively investigated the feasibility and efficacy of lenalidomide maintenance. Patients started with maintenance 1-6 months after non myeloablative (NMA) allo-SCT. Lenalidomide was dosed 10 mg on day 1-21 of a 28 day schedule for a total of 24 cycles. Peripheral blood samples were taken to evaluate immune modulating effects. Thirty five eligible patients were enrolled and 30 started with lenalidomide. After 2 cycles, 14 patients (47%) had to stop treatment, mainly because of the development of acute graft versus host disease (GvHD). In total, 13 patients (43%) stopped treatment due to development of GvHD, 5 patients (17%) due to other adverse events and 5 patients (17%) due to progression. Responses improved in 37% of patients and the estimated 1 year PFS from start of maintenance was 69% (90% CI, 53-81%). Lenalidomide increased the frequency of HLA-DR+ T cells and regulatory T cells but this did not correlate with clinical parameters. In conclusion, lenalidomide maintenance 10 mg daily after NMA allo-SCT with unmanipulated graft in MM patients is not feasible, mainly due to the rapid induction of acute GvHD. The trial was registered at [www.trialregister.nl](http://www.trialregister.nl) under ID number NTR1645.

 **International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation.**

Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Bladé J, Sezer O, Ludwig H, Dimopoulos MA, Attal M, Sonneveld P, Boccadoro M, Anderson KC, Richardson PG, Bensinger W, Johnsen HE, Kroeger N, Gahrton G, Bergsagel PL, Vesole DH, Einsele H, Jagannath S, Niesvizky R, Durie BG, San Miguel J, Lonial S; on behalf of the International Myeloma Working Group.

*Blood.* 2011 Jun 9;117(23):6063-6073. [Epub 2011 Mar 29.]



<http://www.ncbi.nlm.nih.gov/pubmed/21447828>

**This manuscript reviews the current literature and provides important perspectives and guidance on the major issues surrounding the optimal current management of younger, transplant-eligible myeloma patients, including the use of thalidomide, lenalidomide and bortezomib.**

The role of high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) in the treatment of multiple myeloma (MM) continues to evolve in the novel agent era. The choice of induction therapy has moved from conventional chemotherapy to newer regimens incorporating the immunomodulatory derivatives (IMiDs) thalidomide or lenalidomide, and the proteasome inhibitor bortezomib. These drugs combine well with traditional therapies and with one another to form various doublet, triplet and quadruplet regimens. Up-front use of these induction treatments, in particular three-drug combinations, has effected unprecedented rates of complete response that rival those previously seen with conventional chemotherapy and subsequent ASCT. Autotransplantation applied after novel-agent-based induction regimens provides further improvement in the depth of responses, a gain which translates into extended progression-free survival and, potentially, overall survival. High activity shown by IMiDs and bortezomib before ASCT has recently led to their successful use as consolidation and maintenance therapies after autotransplantation. Novel agents and ASCT are complementary treatment strategies for MM. This manuscript reviews the current literature and provides important perspectives and guidance on the major issues surrounding the optimal current management of younger, transplant-eligible MM patients.

 **Stem cell mobilization in patients with newly diagnosed multiple myeloma after lenalidomide induction therapy.**

Cavallo F, Bringhen S, Milone G, Ben-Yehuda D, Nagler A, Calabrese E, Cascavilla N, Montefusco V, Lupo B, Liberati AM, Crippa C, Rossini F, Passera R, Patriarca F, Cafro AM, Omedè P, Carella AM, Peccatori J, Catalano L, Caravita T, Musto P, Petrucci MT, Boccadoro M, Palumbo A.

*Leukemia.* 2011 Jun 3. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21637283>

**This prospective study investigates the influence of lenalidomide on stem cell collection in newly diagnosed patients. They confirm that a short induction with lenalidomide allows sufficient stem cells collection to perform autologous transplantation in 91% of newly diagnosed patients.**

Lenalidomide has raised concerns regarding its potential impact on the ability to collect stem cells for autologous stem cell transplantation, especially after prolonged exposure. The use of cyclophosphamide plus granulocyte colony-stimulating factor (G-CSF) to mobilize peripheral blood stem cells may overcome this concern. In newly diagnosed multiple myeloma (MM) patients, we investigated the influence of lenalidomide on stem cell collection. In a prospective study, 346 patients received four cycles of lenalidomide-dexamethasone (Rd). Stem cells were mobilized with cyclophosphamide and G-CSF. Patients failing to collect a minimum of  $4 \times 10^6$  CD34(+)/kg cells received a second mobilization course. After mobilization, a median yield of  $8.7 \times 10^6$  CD34(+)/kg was obtained from patients receiving Rd induction. After first mobilization, inadequate yield was observed in 21% of patients, whereas only 9% of patients failed to collect the target yield after the second mobilization attempt. In conclusion, we confirm that a short induction with lenalidomide allowed sufficient stem cells collection to perform autologous transplantation in 91% of newly diagnosed patients.

 **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, Olujuhungbe A, Marshall S, Conn J, Oakervee H, Popat R, Cavenagh J.

*Br J Haematol.* 2011 Jun;153(5):666-8. doi: 10.1111/j.1365-2141.2010.08521.x. [Epub 2011 Jan 31.]



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

No abstract available.

## ...and More

### **Donor cell leukaemia after allogeneic haematopoietic SCT followed by prolonged thalidomide maintenance for multiple myeloma.**

Chan TS, Au WY, Lam K, Lam YF, So CC, Leung AY, Tse E, Lie AK, Kwong YL.

*Bone Marrow Transplant.* 2011 Jun 27. doi: 10.1038/bmt.2011.136. [Epub ahead of print.]



<http://www.ncbi.nlm.nih.gov/pubmed/21706063>

No abstract available.

### **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 S, 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 Jun 6. [Epub ahead of print.]



<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.



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