# 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 August 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 – AUGUST 2011

### General Discussions & Reviews

***Targeting the Ubiquitin-Proteasome Pathway: An Emerging Concept in Cancer Therapy.***

Frezza M, Schmitt S, Dou QP.

*Curr Top Med Chem. 2011 Aug 9. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21824109

**The clinical efficacy of the proteasome inhibitor bortezomib toward myeloma and other hematologic malignancies provides the "proof of concept" that targeting the proteasome is a promising strategy for cancer treatment; the authors discuss the clinical significance of targeting the tumor survival-associated proteasome pathway for cancer treatment, intervention and prevention.**

Selective degradation of proteins by the ubiquitin-proteasome pathway is a critical determinant for maintaining cellular homeostasis. Most intracellular proteins are degraded by the proteasome, a multicatalytic enzyme complex containing a 20S catalytic core and two 19S regulatory complexes. Many proteasome target proteins are involved in the regulation of important processes of carcinogenesis and cancer cell survival, such as cell cycle progression, cell proliferation, differentiation and apoptosis. Indeed, the ubiquitin-proteasome-dependent degradation pathway plays an essential role in both the up-regulation of cell proliferation and down-regulation of cell death in human cancer cells. Both in vitro and in vivo experimental and clinical results have demonstrated the potential use of proteasome inhibitors as novel anticancer drugs. Proteasome inhibition in cancer cells leads to accumulation of pro-apoptotic target proteins followed by induction of cell death. The clinical efficacy of the proteasome inhibitor bortezomib toward multiple myeloma and other hematologic malignancies provides the "proof of concept" that targeting the proteasome is a promising strategy for cancer treatment. Several other proteasome inhibitors have also been identified from natural resources, such as marine microbial metabolites, green tea polyphenols, flavonoids, and medicinal compounds. Additionally, the use of metal complexes as proteasome inhibitors has also been investigated as a potential anticancer strategy. The clinical significance of targeting the tumor survival-associated proteasome pathway for cancer treatment, intervention and prevention will be discussed.




*Funded by unrestricted educational grants from Celgene Corporation and Onyx Pharmaceuticals.*

### *IMiDs in hematology.*

Wémeau M, Gauthier J, Leleu X, Yakoub-Agha I.

*Bull Cancer. 2011 Aug 1;98(8):879-887.*

http://www.ncbi.nlm.nih.gov/pubmed/21827980

**The authors present an overview of IMiDs (such as thalidomide and lenalidomide) in hematology, including mechanisms of action and known significant side effects.**

IMiDs belong to a new pharmalogical class, whose principal therapeutic agents are the thalidomide and the lenalidomide. They have immunomodulatory and antiangiogenic properties, as well as a direct effect on tumor cells. Thalidomide and lenalidomide were first approved for multiple myeloma, and in 5q-myelodysplastic syndrome for lenalidomide. Several studies have shown the efficacy of these drugs in others hematologic malignancies. A third component has been developed, the pomalidomide, which may be more effective in certain indications. Here we present an overview of IMiDs in hematology, including mechanisms of action and known significant side effects.

### *Bortezomib for previously untreated multiple myeloma.*

de la Rubia J, Roig M.

*Expert Rev Hematol. 2011 Aug;4(4):381-98.*

http://www.ncbi.nlm.nih.gov/pubmed/21801129

**The authors present an overview of the results of bortezomib treatment when administered as a standard component of front-line therapy for myeloma patients.**

The treatment of newly diagnosed multiple myeloma (MM) has evolved rapidly over recent years. The availability of new effective drugs with novel mechanisms of action, such as bortezomib, in the last decade have resulted in a new scenario expected to impact favorably on the outcome of MM patients. In the transplant and nontransplant setting, several randomized trials have shown that front-line treatment with bortezomib-based combinations are superior to conventional treatment and have allowed for a significant increase of complete response rate, with a positive impact on progression-free survival. Furthermore, this drug appears to be active in patients with high-risk disease and comorbidities. Thus, bortezomib-containing regimens are now considered as a new standard of care for newly diagnosed myeloma patients. In this article, we will attempt to overview the results of bortezomib when administered as a standard component of front-line therapy for MM patients.

### *Targeting the extrinsic apoptosis signaling pathway for cancer therapy.*

Sayers TJ.

*Cancer Immunol Immunother. 2011 Aug;60(8):1173-80. [Epub 2011 Apr 6.]*

http://www.ncbi.nlm.nih.gov/pubmed/21626033

**The author provides a brief overview of apoptosis signaling by TRAIL and discussion of apoptosis-sensitizing agents, then primarily focuses on bortezomib and other novel sensitizers recently identified.**

The extrinsic apoptosis pathway is triggered by the binding of death ligands of the tumor necrosis factor (TNF) family to their appropriate death receptors (DRs) on the cell surface. One TNF family member, TNF-related apoptosis-inducing ligand (TRAIL or Apo2L), seems to preferentially cause apoptosis of transformed cells and can be systemically administered in the absence of severe toxicity. Therefore, there has been enthusiasm for the use of TRAIL or agonist antibodies to the TRAIL DR4 and DR5 in cancer therapy. Nonetheless, many cancer cells are very resistant to TRAIL apoptosis in vitro. Therefore, there is much interest in identifying compounds that can be combined with TRAIL to amplify its apoptotic effects. In this review, I will provide a brief overview of apoptosis signaling by TRAIL and discuss apoptosis-sensitizing agents, focusing mainly on the proteasome inhibitor bortezomib (VELCADE) and some novel sensitizers that we have recently identified. Alternative ways to administer TRAIL or DR agonist antibodies as therapeutic agents will also be described. Finally, I will discuss some of the gaps in our understanding of TRAIL apoptosis signaling and suggest some research directions that may provide additional information for optimizing the targeting of the extrinsic apoptosis pathway for future cancer therapy.

# Genetics

### *Genetic variations in multiple myeloma II: Association with effect of treatment.*

Vangsted A, Klausen TW, Vogel U.

*Eur J Haematol. 2011 Aug 28. doi: 10.1111/j.1600-0609.2011.01696.x. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21883476

**The authors discuss association studies on genetic variation to treatment effect, which may serve as a predictive marker for effect of treatment and can also uncover biological pathways behind drug effect. They address the study of single nucleotide polymorphisms (SNPs) in relation to thalidomide and bortezomib based therapy and conclude that further analysis of SNPs in clinical trials is needed, with collaboration between scientific groups.**

Association studies on genetic variation to treatment effect may serve as a predictive marker for effect of treatment but can also uncover biological pathways behind drug effect. Single nucleotide polymorphisms (SNPs) have been studied in relation to high-dose treatment (HDT), thalidomide and bortezomib based therapy, maintenance treatment with interferon-α and in relation to therapy related adverse effects caused by treatment. Candidate genes for prediction of effect of HDT include DNA repair genes, CYP genes and genes involved in inflammation and apoptosis such as IL1B and RAI. In thalidomide and bortezomib-based therapy candidate genes include TNFA and genes involved in the NF-κB pathway (NFKB2 and TRAF3), respectively. In maintenance treatment with interferon-α, a polymorphism in gene NFKB1 is a candidate gene for prediction for effect. Adverse effect includes infection, osteonecrosis of the jaw (ONJ), venous thrombotic events (VTE) and peripheral neuropathy (PN). A SNP in MBL2 and MPO gene was associated with septicaemia and a SNP in the gene CYP2C8 was strongly associated to ONJ. Several SNPs in genes encoding DNA repair, apoptosis, inflammation and genes involved in function of the nervous system has been associated to VTE induced by thalidomide and to PN induced by bortezomib. SNP analysis is simple and can be performed e.g. on blood and buccal cells. Further analysis of SNPs in clinical trials is needed and collaboration between scientific groups will be an advantage since SNP analysis required large number of patients.

### *Impact of gene expression profiling-based risk stratification in patients with myeloma receiving initial therapy with lenalidomide and dexamethasone.*

Kumar SK, Uno H, Jacobus SJ, Van Wier SA, Ahmann GJ, Henderson KJ, Callander NS, Haug JL, Siegel DS, Greipp PR, Fonseca R, Rajkumar SV.

*Blood. 2011 Aug 22. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21860025

**The authors examine the utility of two gene expression profiling (GEP)-based risk stratification systems among patients undergoing initial therapy with lenalidomide in the context of a phase 3 trial, demonstrating the prognostic value for GEP risk stratification in a group of patients primarily treated with novel agents.**

Detection of specific chromosomal abnormalities by FISH and metaphase cytogenetics allows risk stratification in multiple myeloma (MM); however, gene expression profiling (GEP) based signatures may enable more specific risk categorization. We examined the utility of two GEP-based risk stratification systems among patients undergoing initial therapy with lenalidomide in the context of a phase 3 trial. Among 45 patients studied at baseline, 7 (16%) and 10 (22%) respectively were high-risk using the GEP70 and GEP15 signatures. The median overall survival for the GEP70 high-risk group was 19 months vs. not reached for the rest (HR=14.1). While the medians were not reached, the GEP15 also predicted a poor outcome among the high-risk patients. The C-statistic for the GEP70, GEP15 and FISH based risk stratification systems was 0.74, 0.7, and 0.7, respectively. Here we demonstrate the prognostic value for GEP risk stratification in a group of patients primarily treated with novel agents.

### *Genomic stratification of multiple myeloma treated with novel agents.*

Jiang A, Reece D, Chang H.

*Leuk Lymphoma. 2011 Aug 8. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21823830

**The authors review recent studies that analyze the impact of specific genomic aberrations on the outcome of myeloma treated with bortezomib and/or lenalidomide.**

ABSTRACT Cytogenetic testing is now routinely performed for the prognostic workup of multiple myeloma (MM). The abnormalities del(17p), t(4;14), and del(13q) have been established as predictors of poor outcome in MM patients treated with conventional chemotherapy or stem cell transplant; chromosome 1q gains and 1p losses have also been identified as novel prognostic factors. In recent years, bortezomib and lenalidomide have emerged as effective treatments for both relapsed/refractory and newly diagnosed MM. However, the effect of cytogenetic abnormalities is unclear among MM patients treated with these novel agents. Here we review recent studies that analyze the impact of specific genomic aberrations on the outcome of MM treated with bortezomib and/or lenalidomide.

# New Combinations

### *Targeting heat shock protein 90 induces apoptosis and inhibits critical survival and proliferation pathways in multiple myeloma.*

Khong T, Spencer A.

*Mol Cancer Ther. 2011 Aug 22. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21859842

**The authors study NVP-HSP990 and find that it synergizes with azacytidine and bortezomib in cell lines and primary myeloma samples; the mechanism of HSP90 inhibition in myeloma warrants further evaluation.**

The second most commonly diagnosed haematologic malignancy, multiple myeloma (MM), affects predominantly older patients (>60s) and is characterised by paraprotein in the serum or urine. Clinical manifestations include anaemia, hypercalcaemia, progressive renal impairment and osteolytic bone destruction. Despite promising new therapies, MM eventually relapses in almost all patients. Heat shock proteins (HSP) are ubiquitous and highly conserved in prokaryotes and eukaryote organisms. Exposure to a broad range of stimuli results in increased HSP protein expression. These chaperone proteins are involved in protein transportation, prevent protein aggregation and ensure correct folding of nascent and stress-accumulated misfolded proteins. In cancer, HSP expression is dysregulated resulting in elevated expression which promotes cancer by preventing programmed cell death and supporting autonomous cells growth, ultimately leading to resistance to heat, chemotherapy and other stresses. Client proteins of HSP90 such as AKT, p53, MEK, STAT3 and Bcr-Abl are vital in tumour progression, including MM, and their maturation and stability is dependent on HSP90. Therefore inhibition of HSP90 via a HSP90 inhibitor (such as NVP-HSP990) should interrupt multiple signaling pathways essential for oncogenesis and growth in MM. Our study demonstrated that NVP-HSP990 triggered apoptosis in a panel of human MM cells, induced cell cycle arrest, PARP cleavage, down regulation of client proteins, inability to reactivate phospho-STAT3 following exogenous IL-6 stimulation and synergises with azacytidine and bortezomib in cell lines and primary MM samples. The mechanism of HSP90 inhibition in MM warrants further evaluation.

### *Monoclonal antibody-based therapy as a new treatment strategy in multiple myeloma.*

van de Donk NW, Kamps S, Mutis T, Lokhorst HM.

*Leukemia. 2011 Aug 19. doi: 10.1038/leu.2011.214. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21852787

**The authors provide an overview of various monoclonal antibodies (mAbs) targeting myeloma tumor cells directly or indirectly via effects on the bone marrow microenvironment. They give special focus to the combination of these mAbs with IMiDs and bortezomib.**

The introduction of autologous stem cell transplantation combined with the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors has significantly improved survival of multiple myeloma patients. However, ultimately the majority of patients will develop refractory disease, indicating the need for new treatment modalities. In preclinical and clinical studies, promising results have been obtained with several monoclonal antibodies (mAbs) targeting the myeloma tumor cell or the bone marrow microenvironment. The mechanisms underlying the therapeutic efficacy of these mAbs include direct induction of tumor cell apoptosis via inhibition or activation of target molecules, complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC). The capability of IMiDs to enhance ADCC and the modulation of various important signaling cascades in myeloma cells by both bortezomib and IMiDs forms the rationale to combine these novel agents with mAbs as new treatment strategies for myeloma patients. In this review, we will give an overview of various mAbs directly targeting myeloma tumor cells or indirectly via effects on the bone marrow microenvironment. Special focus will be on the combination of these mAbs with IMiDs or bortezomib.

### *In Vitro and In Vivo Selective Antitumor Activity of a Novel Orally Bioavailable Proteasome Inhibitor MLN9708 against Multiple Myeloma Cells.*

Chauhan D, Tian Z, Zhou B, Kuhn D, Orlowski R, Raje N, Richardson P, Anderson KC.

*Clin Cancer Res. 2011 Aug 15;17(16):5311-21. [Epub 2011 Jun 30.]*

http://www.ncbi.nlm.nih.gov/pubmed/21724551

**The authors evaluate the efficacy of the novel orally bioactive proteasome inhibitor MLN9708/MLN2238 in myeloma using well-established in vitro and in vivo models. They find that combining MLN2238 with lenalidomide triggers synergistic anti-myeloma activity.**

PURPOSE: The success of bortezomib therapy for treatment of multiple myeloma (MM) led to the development of structurally and pharmacologically distinct novel proteasome inhibitors. In the present study, we evaluated the efficacy of one such novel orally bioactive proteasome inhibitor MLN9708/MLN2238 in MM using well-established in vitro and in vivo models. EXPERIMENTAL DESIGN: MM cell lines, primary patient cells, and the human MM xenograft animal model were used to study the antitumor activity of MN2238. RESULTS: Treatment of MM cells with MLN2238 predominantly inhibits chymotrypsin-like activity of the proteasome and induces accumulation of ubiquitinated proteins. MLN2238 inhibits growth and induces apoptosis in MM cells resistant to conventional and bortezomib therapies without affecting the viability of normal cells. In animal tumor model studies, MLN2238 is well tolerated and inhibits tumor growth with significantly reduced tumor recurrence. A head-to-head analysis of MLN2238 versus bortezomib showed a significantly longer survival time in mice treated with MLN2238 than mice receiving bortezomib. Immununostaining of MM tumors from MLN2238-treated mice showed growth inhibition, apoptosis, and a decrease in associated angiogenesis. Mechanistic studies showed that MLN2238-triggered apoptosis is associated with activation of caspase-3, caspase-8, and caspase-9; increase in p53, p21, NOXA, PUMA, and E2F; induction of endoplasmic reticulum (ER) stress response proteins Bip, phospho-eIF2-α, and CHOP; and inhibition of nuclear factor kappa B. Finally, combining MLN2238 with lenalidomide, histone deacetylase inhibitor suberoylanilide hydroxamic acid, or dexamethasone triggers synergistic anti-MM activity. CONCLUSION: Our preclinical study supports clinical evaluation of MLN9708, alone or in combination, as a potential MM therapy.

### *Dihydroxypentamethoxyflavone Downregulates Constitutive and Inducible Signal Transducers and Activators of Transcription (STAT)-3 Through the Induction of Tyrosine Phosphatase SHP-1.*

Phromnoi K, Prasad S, Gupta SC, Kannappan R, Reuter S, Limtrakul P, Aggarwal BB.

*Mol Pharmacol. 2011 Aug 4. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21816954

**The authors identify a flavone from the leaves of a Thai plant, Gardenia obtusifolia, 5,3'-dihydroxy-3,6,7,8,4'-pentamethoxyflavone (PMF) that has ability to inhibit STAT3 activation. They find that PMF significantly potentiates the apoptotic effects of bortezomib and thalidomide in myeloma cells with overall results suggesting that PMF is a novel blocker of STAT3 activation and thus may have potential in suppression of tumor cell proliferation and reversal of chemoresistance in myeloma cells.**

Because constitutive activation of STAT3 has been linked with cellular transformation, survival, proliferation, chemoresistance, and angiogenesis of various tumor cells, agents that can suppress STAT3 activation have potential as cancer therapeutics. In the present report, we identified a flavone from the leaves of a Thai plant, Gardenia obtusifolia, 5,3'-dihydroxy-3,6,7,8,4'-pentamethoxyflavone (PMF) that has ability to inhibit STAT3 activation. PMF inhibited both constitutive and interleukin-6-inducible STAT3 activation in multiple myeloma (MM) cells, as indicated by suppression of STAT3 phosphorylation, nuclear translocation, DNA binding, and STAT3-regulated gene expression. The inhibition of STAT3 by PMF was reversible. We found that the activation of various kinases including Janus-activated kinase (JAK)-1, JAK-2, c-Src, ERK1/2, AKT and EGFR, implicated in STAT3 activation, were inhibited by the flavone. Interestingly, pervanadate suppressed the ability of PMF to inhibit the phosphorylation of STAT3, suggesting protein tyrosine phosphatase was involved. PMF induced the expression of SHP-1 and was linked to the dephosphorylation of STAT3, as its deletion by small interfering RNA abolished the PMF-induced constitutive as well as inducible STAT3 inhibition. STAT3 inhibition led to the suppression of proteins involved in proliferation (cyclin D1 and c-myc), survival (survivin, Mcl-1, Bcl-xL, Bcl-2 and cIAP-2), and angiogenesis (VEGF). Finally, PMF inhibited proliferation and induced apoptosis of MM cells. PMF also significantly potentiated the apoptotic effects of velcade and thalidomide in MM cells. Overall, these results suggest that PMF is a novel blocker of STAT3 activation and thus may have potential in suppression of tumor cell proliferation and reversal of chemoresistance in MM cells.

# Newly Diagnosed

### *Aspirin or enoxaparin thromboprophylaxis for newly-diagnosed multiple myeloma patients treated with lenalidomide.*

Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A, Cavalli M, Stanevsky A, Corradini P, Pezzati S, Patriarca F, Cavo M, Peccatori J, Catalano L, Carella AM, Cafro AM, Siniscalchi A, Crippa C, Petrucci MT, Ben Yehuda D, Beggiato E, Caravita Di Toritto T, Boccadoro M, Nagler A, Palumbo A.

*Blood. 2011 Aug 11. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21835953

**This prospective, open-label, randomized substudy of a phase 3 trial compares the efficacy and safety of thromboprophylaxis with low-dose aspirin (ASA) or low-molecular-weight heparin (LMWH) in newly-diagnosed myeloma patients treated with lenalidomide and low-dose dexamethasone induction and melphalan-prednisone-lenalidomide consolidation. The authors conclude that in previously untreated myeloma patients receiving lenalidomide with a low thromboembolic risk, ASA could be an effective and less-expensive alternative to LMWH thromboprophylaxis.**

Lenalidomide plus dexamethasone is effective in the treatment of multiple myeloma (MM) but is associated with an increased risk of venous thromboembolism (VTE). This prospective, open-label, randomized substudy of a phase 3 trial compared the efficacy and safety of thromboprophylaxis with low-dose aspirin (ASA) or low-molecular-weight heparin (LMWH) in newly-diagnosed MM patients, treated with lenalidomide and low-dose dexamethasone (Rd) induction and melphalan-prednisone-lenalidomide consolidation. Overall, 342 patients who did not have clinical indications or contraindications to antiplatelet or anticoagulant therapy, were randomized to receive ASA 100 mg/day (n=176) or LMWH enoxaparin 40 mg/day (n=166). The incidence of VTE was 2.27% in the ASA group and 1.20% in the LMWH group. Compared with LMWH, the absolute difference in the proportion of VTE was +1.07% (95% CI, -1.69 to 3.83; P = 0.452) in the ASA group. Pulmonary embolism was observed in 1.70% of patients in the ASA group and none in the LMWH group. No arterial thrombosis, acute cardiovascular events, or sudden deaths were reported. No major hemorrhagic complications were reported. In previously untreated MM patients receiving lenalidomide with a low thromboembolic risk, ASA could be an effective and less-expensive alternative to LMWH thromboprophylaxis. This study is registered at http://www.clinicaltrials.gov as NCT00551928.

### *Bortezomib, Liposomal Doxorubicin and Dexamethasone (BDD) Followed by Thalidomide and Dexamethasone (TD) Is an Effective Treatment for Newly Diagnosed Multiple Myeloma Patients with ISS stage II or III, or Extramedullary Disease.*

Landau H, Pandit-Taskar N, Hassoun H, Cohen A, Lesokhin A, Lendvai N, Drullinsky P, Schulman P, Jhanwar S, Hoover E, Bello C, Riedel E, Nimer SD, Comenzo RL.

*Leuk Lymphoma. 2011 Aug 9. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21824051

**The authors evaluate sequential bortezomib, liposomal doxorubicin and dexamethasone (BDD) followed by thalidomide and dexamethasone (TD) or bortezomib and TD (BTD) in untreated myeloma patients with ISS stage II/III or extramedullary disease. They conclude that BDD followed by TD or BTD is effective initial therapy for this higher risk myeloma population and results in rapid disease control and a high response rate.**

ABSTRACT We evaluated sequential bortezomib, liposomal doxorubicin and dexamethasone (BDD) followed by thalidomide and dexamethasone (TD) (if ≥ partial response (PR)) or bortezomib and TD (BTD) if < PR in untreated multiple myeloma patients with ISS stage II/III or extramedullary disease. Of the 42 patients enrolled, two thirds had cytogenetic abnormalities including high risk findings (del(13q) by karyotype, t(4;14), loss of p53 or gain 1q) in one third. After the planned 3 cycles of BDD, the overall response rate (ORR) was 81% with 40% ≥ very good partial response (VGPR), including 26% near complete and complete responses (nCR/CR). After the additional 2 cycles of TD or BTD, ORR was 83% with 60% ≥ VGPR including 43% nCR/CR, indicating deeper responses following sequential therapy (P = 0.008). Two-thirds of patients who presented with significant renal impairment had improved renal function. All patients undergoing stem cell harvest had a successful collection. BDD followed by TD or BTD is effective initial therapy for this higher risk myeloma population and results in rapid disease control and a high response rate.

### *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, Coy NN, Cook G, Feyler S, Byrne JL, Roddie H, Rudin C, Drayson MT, Owen RG, Ross FM, Jackson GH, Child JA; for the NCRI Haematological Oncology Study Group.

*Blood. 2011 Aug 4;118(5):1231-1238. [Epub 2011 Jun 7.]*

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 as # 68454111.

### *Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials.*

Fayers PM, Palumbo A, Hulin C, Waage A, Wijermans P, Beksaç M, Bringhen 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; on behalf of the Nordic Myeloma Study Group, Italian Multiple Myeloma Network, Turkish Myeloma Study Group, Hemato-Oncologie voor Volwassenen Nederland, Intergroupe Francophone du Myélome, and European Myeloma Network.

*Blood. 2011 Aug 4;118(5):1239-1247. [Epub 2011 Jun 13.]*

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%.

### *Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial.*

Kumar SK, Lacy MQ, Hayman SR, Stewart K, Buadi FK, Allred J, Laumann K, Greipp PR, Lust JA, Gertz MA, Zeldenrust SR, Bergsagel PL, Reeder CB, Witzig TE, Fonseca R, Russell SJ, Mikhael JR, Dingli D, Rajkumar SV, Dispenzieri A.

*Am J Hematol. 2011 Aug;86(8):640-5. doi: 10.1002/ajh.22053. [Epub 2011 May 31.]*

http://www.ncbi.nlm.nih.gov/pubmed/21630308

**This trial studies the combination of cyclophosphamide, lenalidomide, and dexamethasone (CRd) as initial therapy for myeloma. The authors find that CRd is an effective and well-tolerated regimen for upfront therapy of myeloma with high response rates and excellent two-year overall survival, and is suitable for long-term therapy.**

The combination of lenalidomide and low-dose dexamethasone is an effective treatment for multiple myeloma (MM). Addition of alkylating agents to lenalidomide or thalidomide results in increased response rates and deeper responses. We designed this trial to study the combination of cyclophosphamide, lenalidomide, and dexamethasone (CRd) as initial therapy for MM. Fifty-three patients with previously untreated symptomatic MM was enrolled. Patients received 4-week treatment cycles consisting of lenalidomide (25 mg daily for 3 weeks), dexamethasone (40 mg weekly), and cyclophosphamide (300 mg/m$^2$ weekly for 3 weeks). A partial response or better was seen in 85% of patients including 47% with a very good partial response or better. The toxicities were manageable with over 80% of planned doses delivered; six patients went off study for toxicity. The median progression free survival (PFS) for the entire group was 28 months (95% CI: 22.7-32.6) and the overall survival (OS) at 2 years was 87% (95% CI: 78-96). Importantly, 14 patients with high-risk MM had similar PFS and OS as the standard-risk patients (n = 39). CRd is an effective and well-tolerated regimen for upfront therapy of MM with high response rates and excellent 2-year OS, and is suitable for long-term therapy.

## Relapsed/Refractory Treatment

### *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 Aug 18;118(7):1763-5. [Epub 2011 Jun 14.]*

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.

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

Shah J, Bladé J, Sonneveld P, Harousseau JL, Lantz K, Londhe A, Lowery C, Orlowski RZ.

*Cancer. 2011 Aug 15;117(16):3758-62. doi: 10.1002/cncr.25937. [Epub 2011 Feb 15.]*

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

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

BACKGROUND: A rapid and early monoclonal (M) protein response during initial therapy in patients with multiple myeloma had been identified as a predictor of superior long-term outcome in some-but not all-studies. METHODS: To determine if the parameter of M protein reduction was of value in the relapsed and/or refractory setting, retrospective landmark analyses were performed at the end of cycles 2 and 4 of a phase 3 study, which randomized such patients to receive bortezomib alone or pegylated liposomal doxorubicin (PLD) with bortezomib. RESULTS: Compared with a <25% reduction in M protein at the landmark time point, patients with a 50% to <75% reduction after cycle 2 had a significantly lower hazard ratio (HR) for time to progression (HR = 0.41; 95% confidence interval [CI], 0.26-0.64; P <.001), as did those with a ≥75% reduction (HR = 0.26; 95% CI, 0.15-0.45; P < .001). In all of these groups, PLD + bortezomib provided superior outcomes to bortezomib alone, and did so without an increase in the risk of adverse events overall and with a predictable toxicity profile. CONCLUSIONS: These analyses supported the possibility that a robust early M protein response is a good prognostic factor for long-term outcome of myeloma patients with relapsed and/or refractory disease receiving bortezomib or PLD + bortezomib.

### *Phase II randomized trial of bevacizumab versus bevacizumab and thalidomide for relapsed/refractory multiple myeloma: a California Cancer Consortium trial.*

Somlo G, Lashkari A, Bellamy W, Zimmerman TM, Tuscano JM, O'Donnell MR, Mohrbacher AF, Forman SJ, Frankel P, Chen HX, Doroshow JH, Gandara DR.

*Br J Haematol. 2011 Aug;154(4):533-535. doi: 10.1111/j.1365-2141.2011.08623.x. [Epub 2011 Apr 26.]*

http://www.ncbi.nlm.nih.gov/pubmed/21517811

No abstract available.

### *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 Aug;52(8):1455-62. [Epub 2011 Jun 10.]*

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$^2$ (27%), melphalan 140 mg/m$^2$ and busulfan 12 mg/kg body weight (40%), or melphalan 200 mg/m$^2$ and bortezomib 1.3 mg/m$^2$ (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.

# Transplantation & Induction Therapy

### *Bortezomib and high dose melphalan conditioning for stem cell transplantation for AL amyloidosis: a pilot study.*

Sanchorawala V, Quillen K, Sloan JM, Andrea NT, Seldin DC.

*Haematologica. 2011 Aug 22. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21859734

No abstract available.

### *Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment prior to autologous stem cell transplantation in newly diagnosed multiple myeloma.*

Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, Doyen C, Garderet L, Randriamalala E, Araujo C, Lepeu G, Marit G, Caillot D, Escoffre M, Lioure B, Benboubker L, Pégourié B, Kolb B, Stoppa AM, Fuzibet JG, Decaux O, Dib M, Berthou C, Chaleteix C, Sebban C, Traullé C, Fontan J, Wetterwald M, Lenain P, Mathiot C, Harousseau JL.

*Blood. 2011 Aug 17. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21849487

**This randomized trial compares bortezomib-dexamethasone (VD) as induction prior to high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) to a combination consisting of reduced doses of bortezomib and thalidomide plus dexamethasone (vtD) in patients with myeloma. The authors find that vtD, including reduced doses of bortezomib and thalidomide, yields higher very good partial response rates as compared with VD and can be considered as a new effective triplet combination prior to HDT/ASCT.**

The IFM conducted a randomized trial to compare bortezomib-dexamethasone (VD) as induction prior to high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) to a combination consisting of reduced doses of bortezomib and thalidomide plus dexamethasone (vtD) in patients with multiple myeloma. Overall, a total of 199 patients were centrally randomly assigned to receive VD (99 patients) or vtD (100 patients). After four cycles, the complete response (CR) rate was the same in both groups (13% in the vtD arm, 12% in the VD arm, $p = 0.74$). However, the CR + very good partial response (VGPR) rate was significantly higher in the vtD arm (49% versus 36%, $p = 0.05$). After ASCT, the CR + VGPR rate was significantly higher in the vtD arm (74% versus 58%, $p = 0.02$). The reduced doses of bortezomib and thalidomide in the vtD arm translated into a reduced incidence of peripheral neuropathy (PN): grade ≥ 2 PN were reported in 34% in the VD arm versus 14% in the vtD arm ($p=0.001$). vtD including reduced doses of bortezomib and thalidomide yields higher VGPR rates as compared with VD and can be considered as a new effective triplet combination prior to HDT/ASCT. This study is registered with www.ClinicalTrials.gov (NCT00910897) and EudraCT (no. 2007-005204-40).

### *Allogeneic Stem Cell Transplantation in Multiple Myeloma Relapsed After Autograft: A Multicenter Retrospective Study Based on Donor Availability.*

Patriarca F, Einsele H, Spina F, Bruno B, Isola M, Nozzoli C, Nozza A, Sperotto A, Morabito F, Stuhler G, Festuccia M, Bosi A, Fanin R, Corradini P.

*Biol Blood Marrow Transplant. 2011 Aug 3. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21820394

**The authors investigate the role of reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) in patients with myeloma who relapsed after autologous stem cell transplantation and were then treated with a salvage therapy based on novel agents. This study provides evidence for a significant progression-free survival benefit of salvage treatment with novel drugs (including bortezomib, thalidomide and lenalidomide) followed by RIC allo-SCT in patients with relapsed myeloma who have a suitable donor.**

Allogeneic stem cell transplantation (allo-SCT) using reduced-intensity conditioning (RIC) is a feasible procedure in selected patients with relapsed multiple myeloma (MM), but its efficacy remains a matter of debate. The mortality and morbidity related to the procedure and the rather high relapse risk make the use of allo-SCT controversial. In addition, the availability of novel antimyeloma treatments, such as bortezomib and immunomodulatory agents, have made allo-SCT less appealing to clinicians. We investigated the role of RIC allo-SCT in patients with MM who relapsed after autologous stem cell transplantation and were then treated with a salvage therapy based on novel agents. This study was structured similarly to an intention-to-treat analysis and included only those patients who underwent HLA typing immediately after the relapse. Patients with a donor (donor group) and those without a suitable donor (no-donor group) were compared. A total of 169 consecutive patients were evaluated retrospectively in a multicenter study. Of these, 75 patients found a donor and 68 (91%) underwent RIC allo-SCT, including 24 from an HLA-identical sibling (35%) and 44 from an unrelated donor (65%). Seven patients with a donor did not undergo

allo-SCT for progressive disease or concomitant severe comorbidities. The 2-year cumulative incidence of nonrelapse mortality was 22% in the donor group and 1% in the no-donor group (P < .0001). The 2-year progression-free survival (PFS) was 42% in the donor group and 18% in the no-donor group (P < .0001). The 2-year overall survival (OS) was 54% in the donor group and 53% in the no-donor group (P = .329). In multivariate analysis, lack of a donor was a significant unfavorable factor for PFS, but not for OS. Lack of chemosensitivity after salvage treatment and high-risk karyotype at diagnosis significantly shortened OS. In patients who underwent allo-SCT, the development of chronic graft-versus-host disease had a significant protective effect on OS. This study provides evidence for a significant PFS benefit of salvage treatment with novel drugs followed by RIC allo-SCT in patients with relapsed MM who have a suitable donor.

### *Novel agents-based regimens as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis of randomized controlled trials.*

Wang L, Ran X, Wang B, Sheng Z, Liu L.

*Hematol Oncol. 2011 Aug 2. doi: 10.1002/hon.1007. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21809367

**In order to investigate the effect of novel agents like bortezomib, lenalidomide and thalidomide as part of induction treatment prior to autologous stem-cell transplantation (ASCT) for previously untreated patients with myeloma, the authors perform a meta-analysis of randomized controlled trials. Their analysis shows that novel agents as induction treatment prior to ASCT improve complete response and progression-free survival, but not overall survival.**

To investigate the effect of novel agents like bortezomib, lenalidomide and thalidomide as part of induction treatment prior to autologous stem-cell transplantation (ASCT) for previously untreated patients with multiple myeloma, we performed a meta-analysis of randomized controlled trials (RCTs). Medline, Embase, the Cochrane controlled trials register and the Science Citation Index were searched for RCTs of novel agents as part of induction therapy before ASCT. Three RCTs of bortezomib, two RCTs of thalidomide and no RCT of lenalidomide were identified, covering a total of 2,316 subjects. Due to different mechanisms of action, we performed a subgroup analysis by type of agent (thalidomide or bortezomib). The weighted risk ratios of a complete response (CR) were 4.25 [95% CI: 2.44-7.41] ($p < 0.001$) for bortezomib and 1.66 [95% CI: 1.15-2.38] ($p=0.007$) for thalidomide, respectively. The summary hazard ratios for progression-free survival (PFS) were 0.73 [95% CI: 0.59-0.89] ($p=0.002$) for bortezomib and 0.68 [95% CI: 0.59-0.79] ($p<0.001$) for thalidomide, respectively. The corresponding ratios for overall survival (OS) were 0.87 [95% CI: 0.64-1.18] ($p=0.37$) and 0.88 [95% CI: 0.73-1.05] ($p=0.14$), respectively. Additionally, there was a statistically significant heterogeneity between subgroups (thalidomide and bortezomib) for CR ($p=0.005$) but non-significant for PFS ($p=0.64$) and OS ($p=0.97$). In conclusion, our analysis showed novel agents as induction treatment prior to ASCT improved CR and PFS but not OS.

## and More

### *Successful bone reconstruction after bortezomib therapy in a myeloma patient.*

Tanaka T, Yamasaki R, Omura H, Hino N.

*Int J Hematol. 2011 Aug 23. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21861100

No abstract available.

### *Cereblon expression is required for the anti-myeloma activity of lenalidomide and pomalidomide.*

Zhu YX, Braggio E, Shi CX, Bruins LA, Schmidt JE, Van Wier S, Chang XB, Bjorklund CC, Fonseca R, Bergsagel PL, Orlowski RZ, Stewart AK.

*Blood. 2011 Aug 22. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21860026

**The authors investigate the role of cereblon (CRBN), a primary teratogenic target of thalidomide, in the anti-myeloma activity of IMiDs. They find that CRBN is an essential requirement for IMiD activity, and a possible biomarker for the clinical assessment of anti-myeloma efficacy.**

The precise molecular mechanism of action and targets through which thalidomide and related immunomodulatory drugs (IMiDs) exert their anti-tumor effects remains unclear. We investigated the role of cereblon (CRBN), a primary teratogenic target of thalidomide, in the anti-myeloma activity of IMiDs. CRBN depletion is initially cytotoxic to human myeloma cells but surviving cells with stable CRBN depletion become highly resistant to both lenalidomide and pomalidomide, but not to the unrelated drugs bortezomib, dexamethasone and melphalan. Acquired deletion of CRBN was found to be the primary genetic event differentiating isogenic MM1.S cell lines cultured to be sensitive or resistant to lenalidomide and pomalidomide.

Gene expression changes induced by lenalidomide were dramatically suppressed in the presence of CRBN depletion further demonstrating that CRBN is required for lenalidomide activity. Downstream targets of CRBN include interferon regulatory factor 4 (IRF4) previously reported to also be a target of lenalidomide. Patients exposed to and putatively resistant to lenalidomide had lower CRBN levels in paired samples before and after therapy. In summary, CRBN is an essential requirement for IMiD activity, and a possible biomarker for the clinical assessment of anti-myeloma efficacy.

### *Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN).*

Palumbo A, Bringhen S, Ludwig H, Dimopoulos MA, Bladé J, Mateos MV, Rosiñol L, Boccadoro M, Cavo M, Lokhorst H, Zweegman S, Terpos E, Davies F, Driessen C, Gimsing P, Gramatzki M, Hàjek R, Johnsen HE, Leal Da Costa F, Sezer O, Spencer A, Beksac M, Morgan G, Einsele H, San Miguel JF, Sonneveld P.

*Blood. 2011 Aug 12. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/21841166

**This article discusses improved outcomes due to the introduction of novel agents, such as thalidomide, bortezomib and lenalidomide; however, elderly myeloma patients are more susceptible to side effects and are often unable to tolerate full drug doses. The authors conclude that for these patients, lower-dose-intensity regimens improve the safety profile and thus optimize treatment outcome; further research into the best treatment strategies for vulnerable elderly patients is urgently needed.**

The majority of patients with newly diagnosed multiple myeloma (MM) are aged >65 years with 30% aged >75 years. Many elderly patients are also vulnerable due to comorbidities that complicate the management of MM. The prevalence of MM is expected to rise over time due to an aging population. Most elderly MM patients are ineligible for autologous transplantation and the standard treatment has, until recently, been melphalan plus prednisone. The introduction of novel agents, such as thalidomide, bortezomib and lenalidomide, has improved outcomes; however, elderly MM patients are more susceptible to side effects and are often unable to tolerate full drug doses. For these patients, lower-dose-intensity regimens improve the safety profile and thus optimize treatment outcome. Further research into the best treatment strategies for vulnerable elderly patients is urgently needed. Appropriate screening for vulnerability and an assessment of cardiac, pulmonary, renal, hepatic and neurological function, as well as age >75 years, at the start of therapy allows treatment strategies to be individualized and drug doses to be tailored to improve tolerability and optimize efficacy. Similarly, occurrence of serious non-hematologic adverse events during treatment should be carefully taken into account to adjust doses and optimize outcomes.

### *Identification and evaluation of a panel of serum biomarkers for predicting response to thalidomide in multiple myeloma patients.*

Xiong Q, Ge F.

*Expert Rev Proteomics. 2011 Aug;8(4):439-42.*

http://www.ncbi.nlm.nih.gov/pubmed/21819299

**The authors evaluate a study by Rajpal R, Dowling P, Meiller J et al, which developed a novel panel of protein biomarkers for predicting response to thalidomide-based therapy in newly diagnosed myeloma patients; this panel of biomarkers may not only guide initial therapy, but can also provide direct implications for personalized medicine in myeloma patients.**

Evaluation of: Rajpal R, Dowling P, Meiller J et al. A novel panel of protein biomarkers for predicting response to thalidomide-based therapy in newly diagnosed multiple myeloma patients. Proteomics 11(8), 1391-1402 (2011). Predicting response to thalidomide-based therapy remains a challenging task faced by clinicians in the treatment of multiple myeloma. The pioneering work reported by Rajpal et al. moves one step further towards solving this challenge. They developed a proteomics-based approach that combines immunodepletion, 2D-difference gel electrophoresis analysis and mass spectrometry to search for serum proteins with expressions that show significant correlations to thalidomide treatment. This integrated approach allowed them to identify a panel of protein biomarkers. By using ELISA-based validation and strict statistical analysis, the authors have achieved an overall 84.0% predictive accuracy, with associated sensitivity and specificity values of 81.8 and 86.2%, respectively. Their methods and significant findings are reviewed within this article. This panel of biomarkers may not only guide initial therapy, but can also provide direct implications for personalized medicine in multiple myeloma patients.


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