



CITINGS

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Thalidomide and Revlimid® Issue

The International Myeloma Foundation (IMF) is pleased to present our fourth edition of *CITINGS* for 2007. This quarterly publication features citations to the most up-to-date studies on myeloma treatment. In this issue, we focus on thalidomide and Revlimid (lenalidomide) for the treatment of multiple myeloma. Inside you will find references to the latest published journal articles on both thalidomide and Revlimid from the fourth quarter of this year.

It is our hope that *CITINGS* will help keep you abreast of the latest developments in myeloma treatment. As always, we welcome your feedback; you may contact the IMF at (800) 452-CURE (2873) or at our website www.myeloma.org.

– Susie Novis, President, IMF

Thalidomide/Revlimid Publications 4th Quarter, 2007

Community-acquired lung abscess caused by *Legionella micdadei* in a myeloma patient receiving thalidomide treatment.

Girard LP, Gregson DB.

J Clin Microbiol. 2007 Sep;45(9):3135-7. [Epub 2007 Jul 3.]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17609324&ordinalpos=57&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors describe a case of cavitary *L. micdadei* community acquired pneumonia in a myeloma patient receiving thalidomide treatment and discuss the importance of considering pneumonia in the myeloma patient population.

Legionella infection causes 2 to 14% of community-acquired pneumonia (CAP). *Legionella micdadei* constitutes <1% of these infections. We describe a case of cavitary *L. micdadei* CAP in a myeloma patient receiving thalidomide treatment. The importance of considering pneumonia and problems in diagnosing pneumonia caused by *L. micdadei* in this patient population are reviewed.

Complications from vascular disrupting agents and angiogenesis inhibitors: aberrant control of hemostasis and thrombosis.

van Heeckeren WJ, Sanborn SL, Narayan A, Cooney MM, McCrae KR, Schmaier AH, Remick SC.

Curr Opin Hematol. 2007 Sep;14(5):468-80.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17934353&ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the hemorrhage and thrombosis side effects observed with from angiogenesis inhibitors and vascular disrupting agents, including thalidomide and lenalidomide.

PURPOSE OF REVIEW: To discuss thrombotic and hemorrhagic complications from angiogenesis inhibitors and vascular disrupting agents, pathogenesis, and recommendations for prophylaxis and management of those complications.

RECENT FINDINGS: Venous thromboembolism has been a significant complication of the angiogenesis inhibitors thalidomide and

lenalidomide. Prophylaxis with aspirin, low-molecular-weight heparin, or warfarin has been shown to decrease rates of venous thromboembolism in patients treated with these agents. Life-threatening hemorrhage and arterial thromboembolism have been observed in patients using treatments that inhibit the vascular endothelial growth factor signaling pathway. Patients should be screened for arterial thromboembolism and hemorrhage risk prior to using vascular endothelial growth factor signal inhibitors. It is not known how angiogenesis inhibitors and vascular disrupting agents upset normal hemostasis. It is likely that disruption of the function and/or integrity of vascular endothelium leads to an increased risk for thrombosis and/or hemorrhage.

SUMMARY: New angiogenesis inhibitors and vascular disrupting agents have been developed that have significant activity against neoplasms. Potentially life-threatening side effects of hemorrhage and thrombosis have been observed with many of these new agents. As new treatments that disrupt angiogenesis or existing tumor vasculature are developed, attention should be given to these toxicities in clinical practice and clinical trials.

Polymorphisms of CYP2C19 gene are associated with the efficacy of thalidomide based regimens in multiple myeloma.

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

Haematologica. 2007 Sep;92(9):1246-9. Epub 2007 Aug 1.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17666363&ordinalpos=56&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors' data suggests that the polymorphisms of the CYP2C19 gene are associated with the efficacy of thalidomide-based regimens in multiple myeloma.

In this study, CYP2C19 genotypes were tested by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method in 92 patients with multiple myeloma (MM). Sixty-two patients were treated with thalidomide plus dexamethasone (Thal+Dex) and 30 with thalidomide combined with chemotherapy (Thal+CC). The overall response rate of extensive metabolizers (EMs) was statistically higher than that of poor metabolizers (PMs) (62.6% vs. 33.3%, $p < 0.05$). Similar results were also observed in the Thal+Dex cohort. For the first time, our primary data suggested that the polymorphisms of CYP2C19 gene are associated with the efficacy of thalidomide based regimens in MM.

Ursolic acid inhibits STAT3 activation pathway leading to suppression of proliferation and chemosensitization of human multiple myeloma cells.

Pathak AK, Bhutani M, Nair AS, Ahn KS, Chakraborty A, Kadara H, Guha S, Sethi G, Aggarwal BB.

Mol Cancer Res. 2007 Sep;5(9):943-55.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17855663&ordinalpos=66&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that ursolic acid significantly potentiates the apoptotic effects of thalidomide and bortezomib in multiple myeloma cells and that ursolic acid may have a potential in prevention and treatment of myeloma.

The activation of signal transducers and activators of transcription 3 (STAT3) has been linked with the proliferation of a variety of human cancer cells, including multiple myeloma. Agents that can suppress STAT3 activation have potential for prevention and treatment of cancer. In the present report, we tested an agent, ursolic acid, found in basil, apples, prunes, and cranberries, for its ability to suppress STAT3 activation. We found that ursolic acid, a pentacyclic triterpenoid, inhibited both constitutive and interleukin-6-inducible STAT3 activation in a dose- and time-dependent manner in multiple myeloma cells. The suppression was mediated through the inhibition of activation of upstream kinases c-Src, Janus-activated kinase 1, Janus-activated kinase 2, and extracellular signal-regulated kinase 1/2. Vanadate treatment reversed the ursolic acid-induced down-regulation of STAT3, suggesting the involvement of a tyrosine phosphatase. Indeed, we found that ursolic acid induced the expression of tyrosine phosphatase SHP-1 protein and mRNA. Moreover, knockdown of SHP-1 by small interfering RNA suppressed the induction of SHP-1 and reversed the inhibition of STAT3 activation, thereby indicating the critical role of SHP-1 in the action of this triterpene. Ursolic acid down-regulated the expression of STAT3-regulated gene products such as cyclin D1, Bcl-2, Bcl-xL, survivin, Mcl-1, and vascular endothelial growth factor. Finally, ursolic acid inhibited proliferation and induced apoptosis and the accumulation of cells in G1-G0 phase of cell cycle. This triterpenoid also significantly potentiated the apoptotic effects of thalidomide and bortezomib in multiple myeloma cells. Overall, these results suggest that ursolic acid is a novel blocker of STAT3 activation that may have a potential in prevention and treatment of multiple myeloma and other cancers.

Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature.

Badros A, Goloubeva O, Dalal JS, Can I, Thompson J, Rapoport AP, Heyman M, Akpek G, Fenton RG.

Cancer. 2007 Sep 1;110(5):1042-9.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17654660&ordinalpos=50&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that 6 of 9 patients with peripheral neuropathy who received lenalidomide as salvage therapy after bortezomib treatment had significant improvement in their symptoms, warranting further investigation of lenalidomide in this context.

BACKGROUND: Bortezomib is active in heavily pretreated multiple myeloma patients; the dose-limiting toxicity is peripheral neuropathy (PN). **METHODS:** The authors retrospectively reviewed the incidence, severity, and risk factors for PN in 78 patients who received bortezomib. The median age was 57 years (range, 33-80 years), 62% of patients were men, and 37% of patients were African Americans. Seventeen patients (22%) had diabetes mellitus (DM), and 66 patients (85%) had received thalidomide. Before bortezomib treatment, 37% of the patients reported subjective, grade 1 or 2 PN. Patients received bortezomib alone (n = 10 patients) plus dexamethasone (n = 36 patients) and thalidomide (n = 20 patients) or chemotherapy (n = 12 patients). PN affected 52% of patients, including grade 3 and 4 PN in 15% and 7%, respectively.

RESULTS: Twelve patients stopped bortezomib because of side effects that included PN (n = 9 patients), diarrhea (n = 2 patients) and cytomegalovirus pneumonia (n = 1 patient); 11 patients had dose reductions because of PN. Grade 4 PN affected 6 patients (sensory, n = 4 patients; motor/sensory, n = 2 patients). The onset of grade 4 PN was sudden rather than cumulative. Factors that were predictive of PN grade were baseline PN (P = .002), prior thalidomide use (P = .03), and the presence of DM (P = .03). Multiple myeloma responses included complete, near complete, and partial responses in 5% of patients, 10% of patients, and 27% of patients, respectively. Responses were independent of PN and of whether bortezomib was combined with chemotherapy or thalidomide. Patients remained on therapy longer for a median of 5 cycles (range, 2-36 cycles) when they received bortezomib plus thalidomide versus 3 cycles (range, 1-19 cycles) for the other combinations. PN therapy was mostly supportive. It was noteworthy that 6 of 9 patients with PN who received lenalidomide as salvage therapy after bortezomib had significant improvement in their symptoms.

CONCLUSIONS: The risk of bortezomib-related PN was greater in patients who had PN and DM at baseline. The authors concluded that an unexpected, symptomatic improvement of PN on lenalidomide is worth further investigation.

Targeting MEK induces myeloma-cell cytotoxicity and inhibits osteoclastogenesis.

Tai YT, Fulciniti M, Hideshima T, Song W, Leiba M, Li XF, Rumizen M, Burger P, Morrison A, Podar K, Chauhan D, Tassone P, Richardson P, Munshi NC, Ghobrial IM, Anderson KC.

Blood. 2007 Sep 1;110(5):1656-63. Epub 2007 May 17.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17510321&ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that AZD6244 sensitizes myeloma cells to novel therapies, including lenalidomide, one of their observations that provide the preclinical framework for AZD6244 clinical trials to improve patient outcome in multiple myeloma.

Activation of the extracellular signal-regulated kinase1/2 (ERK1/2) signaling cascade mediates human multiple myeloma (MM) growth and survival triggered by cytokines and adhesion to bone marrow stromal cells (BMSCs). Here, we examined the effect of AZD6244 (ARRY-142886), a novel and specific MEK1/2 inhibitor, on human MM cell growth in the bone marrow (BM) milieu. AZD6244 blocks constitutive and cytokine-stimulated ERK1/2 phosphorylation and inhibits proliferation and survival of human MM cell lines and patient MM cells, regardless of sensitivity to conventional chemotherapy. Importantly, AZD6244 (200 nM) induces apoptosis in patient MM cells, even in the presence of exogenous interleukin-6 or BMSCs associated with triggering of caspase 3 activity. AZD6244 sensitizes MM cells to both conventional (dexamethasone) and novel (perifosine, lenalidomide, and bortezomib) therapies. AZD6244 down-regulates the expression/secretion of osteoclast (OC)-activating factors from MM cells and inhibits in vitro differentiation of MM patient PBMCs to OCs induced by ligand for receptor activator of NF-kappaB (RANKL) and macrophage-colony stimulating factor (M-CSF). Finally, AZD6244 inhibits tumor growth and prolongs survival in vivo in a human plasmacytoma xenograft model. Taken together, these results show that AZD6244 targets both MM cells and OCs in the BM microenvironment, providing the preclinical framework for clinical trials to improve patient outcome in MM.

Targeted treatments to improve stem cell outcome: old and new drugs.

Raab MS, Breitkreutz I, Anderson KC.

Bone Marrow Transplant. 2007 Sep 3; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17768392&ordinalpos=43&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the roles of thalidomide and lenalidomide in both induction therapy and maintenance treatment, as well as their potential roles in redefining the role of stem cell transplantation in first-line myeloma treatment.

Thalidomide, lenalidomide and bortezomib have been approved for the treatment of relapsed or refractory multiple myeloma in the recent years. These agents are now being increasingly integrated into therapeutic regimens for newly diagnosed patients. First data are available on the promising activity of these novel agents in induction therapy, as well as maintenance treatment to improve outcome after stem cell transplantation. Whether these early results will lead to prolonged overall survival and thereby ultimately redefine the role of stem cell transplantation in first-line treatment of multiple myeloma will be one of the most important questions to be answered in the coming years.

Recent major improvement in long-term survival of younger patients with multiple myeloma.

Brenner H, Gondos A, Pulte D.

Blood. 2007 Sep 27; [Epub ahead of print]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17901246&ordinalpos=36&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find a major increase in long-term survival of younger myeloma patients in recent years, which most likely reflects the impact of recent advances in therapy, including thalidomide and lenalidomide, and their dissemination in clinical practice.

In the past, most patients with multiple myeloma (MM) died within 5-10 years following diagnosis. Within the past decade, several new therapeutic interventions have been introduced, including autologous stem cell transplant, thalidomide, lenalidomide, and bortezomib. We estimated trends in age specific 5- and 10-year relative survival of MM patients in the United States from 1990-1992 to 2002-2004 from the 1973-2004 database of the Surveillance, Epidemiology, and End Results (SEER) Program. Techniques of period analysis were employed to disclose most recent developments. Overall, 5-year relative survival increased from 28.8% to 34.7% ($p < 0.0001$), and 10-year relative survival increased from 11.1% to 17.4% ($p < 0.0001$) between 1990-92 and 2002-04. Much stronger increases were seen in age group < 50 , leading to 5- and 10-year relative survival of 56.7% and 41.3% in 2002-04, and in age group 50-59, leading to 5- and 10-year relative survival of 48.2% and 28.6% in 2002-2004. By contrast, only moderate improvement was seen in age group 60-69, and essentially no improvement was achieved among older patients. Our period analysis discloses a major increase in long-term survival of younger patients with MM in recent years which most likely reflects the impact of recent advances in therapy and their dissemination in clinical practice.

Effect on survival of treatment-associated venous thromboembolism in newly diagnosed multiple myeloma patients.

Zangari M, Barlogie B, Cavallo F, Bolejack V, Fink L, Tricot G.

Blood Coagul Fibrinolysis. 2007 Oct;18(7):595-8.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17890944&ordinalpos=25&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors observe that patients who received intensive chemotherapy without thalidomide but developed a thrombosis experienced a significantly longer event-free survival compared with those without venous thromboembolism, suggesting a possible beneficial effect of anticoagulation on survival in patients treated for myeloma.

Venous thromboembolism (VTE) is a cancer complication associated with poor survival. We have analyzed the prognostic impact of the development of a thrombotic episode in newly diagnosed multiple myeloma patients who received chemotherapy either with or without thalidomide on our Total Therapy 2 protocol. Of 668 patients enrolled, 155 developed VTE complication during treatment. The overall and event-free survival of patients who experienced VTE was not inferior. Of interest, we observed that patients who received intensive chemotherapy without thalidomide but developed a thrombosis experienced a significantly longer event-free survival compared with those without VTE ($P = 0.02$). Our observation suggests a possible beneficial effect of anticoagulation on survival in patients treated for myeloma.

High-dose treatment with autologous stem cell transplantation in multiple myeloma: past, present, and future.

Björkstrand B, Gahrton G.

Semin Hematol. 2007 Oct;44(4):227-33.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17961721&ordinalpos=44&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the historical results of autologous stem cell transplantation in myeloma, along with its future role with the introduction of novel drugs, such as thalidomide and lenalidomide.

High-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) has been used in the treatment of multiple myeloma since the early 1980s. Its present position as the backbone of first-line treatment in patients up to 60 to 65 years of age is the result of several controlled randomized trials, where its superiority over standard chemotherapy has been demonstrated. However, the method is not considered to have curative potential, with the possible exception of a small proportion of about 5% to 10% of patients with very long-standing complete remissions (CRs) of more than 8 years. Over the years, there have been several attempts to improve the technique, where, for example, tandem transplants and post-transplant maintenance treatment have been successful, at least in certain subgroups of patients, while others, such as graft purging, have been of no value. Treatment results need further improvement, particularly in poor-prognosis disease-based on abnormal karyotype and high beta(2)-microglobulin-and the future will show if the introduction of novel drugs like bortezomib, thalidomide, and lenalidomide will lead to longer survival and prolongation of disease control in multiple myeloma.

Lenalidomide in multiple myeloma.

Bagchi S.

Lancet Oncol. 2007 Oct;8(10):872.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17974052&ordinalpos=13&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma.

Lacy MQ, Gertz MA, Dispenzieri A, Hayman SR, Geyer S, Kabat B, Zeldenrust SR, Kumar S, Greipp PR, Fonseca R, Lust JA, Russell SJ, Kyle RA, Witzig TE, Bergsagel PL, Stewart AK, Rajkumar SV.

Mayo Clin Proc. 2007 Oct;82(10):1179-84.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17908524&ordinalpos=10&itool=EntrezSysstem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors seek to determine the long-term effects of a combined regimen of lenalidomide and dexamethasone (Rev-Dex) on time to progression, progression-free survival, and overall survival (OS) in patients with multiple myeloma. They find that the Rev-Dex regimen is highly active in the treatment of newly diagnosed myeloma and that further study is needed to determine if this combination is better used early in therapy or should be reserved for later interventions.

OBJECTIVE: To determine the long-term effects of a combined regimen of lenalidomide and dexamethasone (Rev-Dex) on time to progression, progression-free survival, and overall survival (OS) in patients with multiple myeloma.

PATIENTS AND METHODS: From March 2004 through October 2004, 34 patients were registered for the study. They were treated with 25 mg/d of lenalidomide on days 1 through 21 of a 28-day cycle and 40 mg/d of dexamethasone on days 1 through 4, 9 through 12, and 17 through 20 of each cycle. After 4 cycles of therapy, patients were allowed to discontinue treatment to pursue autologous stem cell transplant (SCT). Treatment beyond 4 cycles was permitted at the physician's discretion.

RESULTS: Thirteen patients proceeded to SCT after initial therapy and were censored at that time point for purposes of calculation of response. Thirty-one patients achieved an objective response, defined as a partial response or better (91%; 95% confidence interval, 79%-98%), with a complete response plus very good partial response rate of 56%. The complete response plus very good partial response among the 21 patients who received Rev-Dex without SCT was 67%. The 2-year progression-free survival rates for patients proceeding to SCT and patients remaining on Rev-Dex were 83% and 59%, respectively; the OS rates were 92% and 90% at 2 years and 92% and 85% at 3 years, respectively. The 3-year OS rate for the whole cohort was 88%.

CONCLUSION: The Rev-Dex regimen is highly active in the treatment of newly diagnosed multiple myeloma. Responses are durable with a low progression rate at 2 years. Randomized trials that incorporate quality-of-life measures are needed to determine if this and other combination regimens are better used early in therapy or should be reserved for later interventions.

 ***Monotherapy with low-dose thalidomide for relapsed or refractory multiple myeloma: better response rate with earlier treatment.***

Maisnar V, Radocha J, Büchler T, Bláha V, Malý J, Hájek R.

Eur J Haematol. 2007 Oct;79(4):305-9. [Epub 2007 Sep 4.]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17803678&ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that response rate with a monotherapy with low-dose thalidomide appears to be higher if treatment is started after the first relapse or progression in comparison with the second relapse or progression.

BACKGROUND: Thalidomide is an immunomodulatory drug used in the treatment of relapsed or refractory multiple myeloma (MM). The optimal dosing regimen of thalidomide is not known.

PATIENTS AND METHODS: We retrospectively analysed the overall response rate and response duration of 53 patients with relapsed MM who received thalidomide in a median dose of 100 mg daily. The aim of the study was to compare the response rates of thalidomide given as the second-line treatment to those of thalidomide given as the third-line therapy.

RESULTS: Of 33 patients receiving thalidomide as second line, 13 (39%) had overall treatment response. Of 20 patients treated with thalidomide monotherapy as the third-line treatment, there were three treatment responses (15%) ($P = 0.039$). The median duration of treatment response in the second-line thalidomide group (12 months, range 6-60 months) was twice as long as that in the third-line thalidomide group (6 months, range 3-57 months), although the difference was not statistically significant, probably due to low number of patients. Only 6% of patients (3/53) had to stop the treatment because of toxicity.

CONCLUSIONS: Monotherapy with low-dose thalidomide results in treatment responses in approximately 30% of patients with advanced MM. The response rate appears to be higher if thalidomide treatment is started after the first relapse or progression in comparison with the second relapse or progression. Treatment toxicity is acceptable even with prolonged exposure to the drug.

 ***New treatment of multiple myeloma.*** [Article in French]

Hulin C.

Rev Med Interne. 2007 Oct;28(10):682-688. [Epub 2007 May 24.]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17559982&ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author discusses the new novel therapies, including thalidomide and lenalidomide, which can be used successively or in combination in the effective treatment of myeloma.

PURPOSE: After decades of minimal progress, two new classes of drugs with novel mechanisms of action: immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib) have shown great activity for the treatment of multiple myeloma.

CURRENT KNOWLEDGE AND KEY POINTS: Thalidomide acts by a variety of mechanisms; its efficacy is well known in disease relapse especially associated with dexamethasone. Recent results prove that combination of thalidomide with melphalan and prednisone should be considered as the first line standard of care in elderly patient. The main side effects are peripheral neuropathy and deep-vein thrombosis. Bortezomib is the first proteasome inhibitor. It is approved for the treatment in first disease relapse. The combination with glucocorticoids is synergistic. This combination in induction treatment before autologous stem cell transplantation is promising, as well as the combination with melphalan and prednisone in elderly patient. The main toxicities are fatigue and peripheral neuropathy. Lenalidomide is a structural analogue of thalidomide. Its efficacy in combination with dexamethasone has been proved in relapsing patients. The main toxicity is hematologic. Utilisation as first line treatment is also promising.

FUTURE PROSPECTS AND PROJECTS: These three drugs have toxicities predictable and manageable and can be used successively or in combination for greater effectiveness. They have an impact on the multiple myeloma treatment strategies and on the disease course itself.

Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone +/- thalidomide for systemic light-chain amyloidosis: results of a phase II trial.

Cohen AD, Zhou P, Chou J, Teruya-Feldstein J, Reich L, Hassoun H, Levine B, Filippa DA, Riedel E, Kewalramani T, Stubblefield MD, Fleisher M, Nimer S, Comenzo RL.

Br J Haematol. 2007 Oct;139(2):224-33.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17897298&ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors perform a phase II trial of risk-adapted stem cell transplant (SCT) followed by adjuvant dexamethasone and thalidomide for systemic AL amyloidosis patients in an attempt to reduce treatment-related mortality (TRM) and improve response rates.

High-dose melphalan (MEL) with autologous stem cell transplant (SCT) is an effective therapy for systemic AL amyloidosis (AL), but treatment-related mortality (TRM) has historically been high. We performed a phase II trial of risk-adapted SCT followed by adjuvant dexamethasone (dex) and thalidomide (thal) in an attempt to reduce TRM and improve response rates. Patients (n = 45) with newly diagnosed AL involving < or = 2 organ systems were assigned to MEL 100, 140, or 200 mg/m² with SCT, based on age, renal function and cardiac involvement. Patients with persistent clonal plasma cell disease 3 months post-SCT received 9 months of adjuvant thal/dex (or dex if there was a history of deep vein thrombosis or neuropathy). Organ involvement was kidney (67%), heart (24%), liver/GI (22%) and peripheral nervous system (18%), with 31% having two organs involved. TRM was 4.4%. Thirty-one patients began adjuvant therapy, with 16 (52%) completing 9 months of treatment and 13 (42%) achieving an improvement in haematological response. By intention-to-treat, overall haematological response rate was 71% (36% complete response), with 44% having organ responses. With a median follow-up of 31 months, 2-year survival was 84% (95% confidence interval: 73%, 94%). Risk-adapted SCT with adjuvant thal/dex is feasible and results in low TRM and high haematological and organ response rates in AL patients.

The evolving background for high-dose treatment for myeloma.

Sirohi B, Powles R, Harousseau JL, Anderson KC.

Bone Marrow Transplant. 2007 Oct 1; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17906702&ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors address the challenge to optimize the use of stem cell transplantation into the emergence of the development, availability and regulatory approval of newer targeted therapies, such as thalidomide and lenalidomide.

In the constantly evolving field of myeloma, this special issue is slanted towards how the newer targeted treatments fit in with various transplantation strategies. High-dose treatment for myeloma with autologous stem cell transplantation started 25 years ago, with the consequence of producing complete remissions and a doubling of survival. Since then, its role has been refined and it has been accepted as standard treatment. The current challenge is to optimize its use into a background of the development, availability and regulatory approval of newer targeted therapies such as Thalidomide, Revlimid (Lenalidomide) and Velcade (Bortezomib). This special issue addresses these problems, and gives particular emphasis on the attainment of very long-term survival, with normal quality of life for patients with myeloma who do not necessarily need to be cured of their molecular disease, that is, they are 'operationally cured.' It is hoped that the reader will find the information in this issue useful in the day-to-day management of patients and we hope that this will also inspire new research directions designed to improve the outcome of patients with myeloma.

 ***Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA – Italian Multiple Myeloma Network.***

Palumbo A, Falco P, Corradini P, Falcone A, Di Raimondo F, Giuliani N, Crippa C, Ciccone G, Omedè P, Ambrosini MT, Gay F, Bringhen S, Musto P, Foà R, Knight R, Zeldis JB, Boccadoro M, Petrucci MT; GIMEMA-Italian Multiple Myeloma Network.

J Clin Oncol. 2007 Oct 1;25(28):4459-65. [Epub 2007 Sep 4.]

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17785703&ordinalpos=31&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors assess dosing, efficacy, and safety of melphalan, prednisone, and lenalidomide (MPR) in newly diagnosed elderly myeloma patients and find oral MPR to be a promising first-line treatment for this patient group.

PURPOSE: Lenalidomide has shown significant antimyeloma activity in clinical studies. Oral melphalan, prednisone, and thalidomide have been regarded as the standard of care in elderly multiple myeloma patients. We assessed dosing, efficacy, and safety of melphalan, prednisone, and lenalidomide (MPR) in newly diagnosed elderly myeloma patients.

PATIENTS AND METHODS: Oral melphalan was administered in doses ranging from 0.18 to 0.25 mg/kg on days 1 to 4, prednisone at a 2-mg/kg dose on days 1 to 4, and lenalidomide at doses ranging from 5 to 10 mg on days 1 to 21, every 28 days for nine cycles, followed by maintenance therapy with lenalidomide alone. Aspirin was given as a prophylaxis for thrombosis.

RESULTS: Fifty-four patients were enrolled and evaluated after completing the assigned treatment schedule. The maximum tolerated dose was defined as 0.18 mg/kg melphalan and 10 mg lenalidomide. With these doses, 81% of patients achieved at least a partial response, 47.6% achieved a very good partial response, and 23.8% achieved a complete immunofixation-negative response. In all patients, 1-year event-free and overall survival rates were 92% and 100%, respectively. At the maximum tolerated dose, grade 3 adverse events included neutropenia (38.1%), thrombocytopenia (14.2%), febrile neutropenia (9.5%), vasculitis (9.5%), and thromboembolism (4.8%); grade 4 adverse events were neutropenia (14.2%) and thrombocytopenia (9.5%).

CONCLUSION: Oral MPR therapy is a promising first-line treatment for elderly myeloma patients. Hematologic adverse events were frequent but manageable. A low incidence of nonhematologic adverse events was noted. Aspirin appears to provide adequate antithrombosis prophylaxis.

 ***Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial.***

Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, Renaud M, Harousseau JL, Guillerme G, Chaleteix C, Dib M, Voillat L, Maisonneuve H, Troncy J, Dorvaux V, Monconduit M, Martin C, Casassus P, Jaubert J, Jardel H, Doyen C, Kolb B, Anglaret B, Grosbois B, Yakoub-Agha I, Mathiot C, Avet-Loiseau H; Intergroupe Francophone du Myélome.

Lancet. 2007 Oct 6;370(9594):1209-18.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17920916&ordinalpos=18&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors assess whether the addition of thalidomide into the melphalan plus prednisone standard of care in elderly myeloma patients would improve survival. They find that the use of thalidomide in combination with melphalan and prednisone should become the reference treatment for previously untreated elderly patients with myeloma.

BACKGROUND: In multiple myeloma, combination chemotherapy with melphalan plus prednisone is still regarded as the standard of care in elderly patients. We assessed whether the addition of thalidomide to this combination, or reduced-intensity stem cell transplantation, would improve survival.

METHODS: Between May 22, 2000, and Aug 8, 2005, 447 previously untreated patients with multiple myeloma, who were aged between 65 and 75 years, were randomly assigned to receive either melphalan and prednisone (MP; n=196), melphalan and prednisone plus thalidomide (MPT; n=125), or reduced-intensity stem cell transplantation using melphalan 100 mg/m² (MEL100; n=126). The primary endpoint was overall survival. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00367185.

FINDINGS: After a median follow-up of 51.5 months (IQR 34.4-63.2), median overall survival times were 33.2 months (13.8-54.8) for MP, 51.6 months (26.6-not reached) for MPT, and 38.3 months (13.0-61.6) for MEL100. The MPT regimen was associated with a significantly better overall survival than was the MP regimen (hazard ratio 0.59, 95% CI 0.46-0.81, p=0.0006) or MEL100 regimen (0.69, 0.49-0.96, p=0.027). No difference was seen for MEL100 versus MP (0.86, 0.65-1.15, p=0.32).

INTERPRETATION: The results of our trial provide strong evidence to indicate that the use of thalidomide in combination with melphalan and prednisone should, at present, be the reference treatment for previously untreated elderly patients with multiple myeloma.

 ***A new standard of care for elderly patients with myeloma.***

Palumbo A, Boccadoro M.

Lancet. 2007 Oct 6;370(9594):1191-2.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17920906&ordinalpos=19&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Comment on: *Lancet.* 2007 Oct 6;370(9594):1209-18.

 ***Single autologous stem cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial.***

Abdelkefi A, Ladeb S, Torjman I, Ben Othman T, Lakhal A, Ben Romdhane N, El Omri H, Elloumi M, Belaaj H, Jeddi R, Aissaoui L, Ksouri H, Ben Hassen A, Msadek F, Saad A, Hsairi M, Boukef K, Amouri A, Louzir H, Dellagi K, Ben Abdeladhim A.

Blood. 2007 Oct 16; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17875806&ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that up-front single autologous transplant followed by 6 months of maintenance therapy with thalidomide is an effective therapeutic strategy to treat myeloma patients, and appears superior to tandem transplant within their study setting.

From April 2003 to December 2006, 195 patients with de novo symptomatic myeloma and less than 60 years of age, were randomly assigned to receive either tandem transplantation up-front [Arm A, n=97] or one autologous stem cell transplantation followed by a maintenance therapy with thalidomide (day +90, 100 mg per day during 6 months) [Arm B, n=98]. Patients included in arm B received a second transplant at disease progression. In both arms, autologous stem cell transplantation was preceded by first-line therapy with thalidomide-dexamethasone and subsequent collection of peripheral blood stem cells with high-dose cyclophosphamide (4 g/m²) and granulocyte colony stimulating factor. Data were analyzed on an intent-to-treat basis. With a median follow-up of 33 months (range, 6-46 months), the 3-year overall survival was 63% in arm A, and 88% in arm B (P= .05). The 3-year progression-free survival was 57% in arm A, and 85% in arm B (P= .03). Up-front single autologous transplant followed by 6 months of maintenance therapy with thalidomide (with second transplant in reserve for relapse or progression) is an effective therapeutic strategy to treat multiple myeloma patients, and appears superior to tandem transplant in this setting. This study was registered at <http://clinicaltrials.gov>.

 ***Bortezomib in combination with thalidomide and dexamethasone-a successful treatment regimen in refractory extramedullary multiple myeloma.***

Dytfeld D, Matuszak M, Lewandowski K, Komarnicki M.

Ann Hematol. 2007 Oct 23; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17955241&ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

 ***Therapy of multiple myeloma: indications and options.*** [Article in German]

Peest D, Ganser A.

Internist (Berl). 2007 Oct 26; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17960351&ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors provide an overview of treatment options, including thalidomide and lenalidomide.

The multiple myeloma (MM) has an incidence of 3-4/100,000 in the Caucasian population. MM has to be distinguished from smouldering MM and monoclonal gammopathy of uncertain significance (MGUS). In younger patients (<65 years) a good long-term remission is the aim of therapy, while in the elderly patients with comorbidities the aim is a good partial remission with good quality of life. In the elderly this can be achieved with a combination of melphalan and prednisone. High-dose chemotherapy, often as a tandem transplantation, is part of standard therapy of MM patients <65 years. However, allogeneic stem cell transplantation is the only curative approach. New substances approved for treatment of relapsed MM include bortezomib, thalidomide, and lenalidomide.

Management of multiple myeloma: The changing landscape.

Reece DE.

Blood Rev. 2007 Nov;21(6):301-14. Epub 2007 Aug 29.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17761373&ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The author highlights some of the key recent findings in multiple myeloma and describes areas for future research, including the roles of thalidomide and lenalidomide.

Many changes have been incorporated into the approach to multiple myeloma over the last few years, due to improvements in our understanding of the disease biology. New diagnostic and prognostic criteria from the International Myeloma Working Group have clarified the initial clinical approach to this disease. The prognostic impact of chromosomal abnormalities is now recognized, and the detection of specific abnormal cytogenetics is beginning to influence therapeutic decisions. The introduction of the novel agents thalidomide, bortezomib and lenalidomide has expanded treatment options at different points in the disease course; these agents are being evaluated in conjunction with conventional chemotherapy and stem cell transplantation. This report highlights some of the key recent findings in multiple myeloma, and describes areas for future research.

Novel therapies in myeloma.

Hayden PJ, Mitsiades CS, Anderson KC, Richardson PG.

Curr Opin Hematol. 2007 Nov;14(6):609-15.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17898564&ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors summarize some of the trials leading to the approval of immunomodulatory drugs thalidomide and lenalidomide, and the current evidence for their clinical use.

PURPOSE OF REVIEW: Several novel therapies have been licensed for the treatment of myeloma in recent years. We summarize some of the trials leading to their approval and the current evidence for their clinical use. A number of promising agents undergoing phase I/II trial evaluation are also discussed.

RECENT FINDINGS: The immunomodulatory drugs, thalidomide and lenalidomide, and the proteasome inhibitor, bortezomib, have been shown to be effective agents, both alone and as part of combination regimens, for the treatment of myeloma. Studies are now focusing on the optimal sequencing of these drugs throughout the disease course, with a view to maximizing antitumor efficacy and minimizing overlapping toxicities. New protocols are increasingly based on preclinical evidence of synergy. The incorporation of these agents into transplant-based treatment protocols has improved outcomes. Other examples of novel agents undergoing assessment at present include arsenic trioxide, hsp90 inhibitors and histone deacetylase inhibitors. Future developments are likely to include individualized treatment plans based on patient-specific parameters including cytogenetic analysis and gene expression profiling.

SUMMARY: Thalidomide, lenalidomide and bortezomib can now be considered as standard options both as first-line agents and beyond for the treatment of myeloma, with respective combinations also emerging as valid choices for all stages of the disease.

Successful desensitization in a patient with lenalidomide hypersensitivity.

Phillips J, Kujawa J, Davis-Lorton M, Hindenburg A.

Am J Hematol. 2007 Nov;82(11):1030.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17617781&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

 ***Thalidomide maintenance following high-dose therapy in multiple myeloma: a UK myeloma forum phase 2 study.***

Feyler S, Rawstron A, Jackson G, Snowden JA, Cocks K, Johnson RJ.

Br J Haematol. 2007 Nov;139(3):429-33.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17910633&ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors address thalidomide maintenance's unresolved issues regarding dosage and toxicity and find that lower doses enabled more patients to stay on the drug for a useful period of time.

Thalidomide maintenance has unresolved issues regarding dosage and toxicity. We evaluated this in five dose cohorts in 100 patients. At a median follow-up of 32.3 months, 23 patients had stopped thalidomide for disease progression, 54 for side effects. 3-year overall and progression-free survival was 76% and 41% respectively. Dosage did not influence disease outcome but greatly affected toxicity. Fifteen patients converted from partial remission to complete remission on thalidomide at a median of 13.5 months. Maintenance doses >200 mg were largely unachievable and peripheral neuropathy was the main toxicity. Lower doses enabled more patients to stay on the drug for a useful period of time.

 ***Improved survival in multiple myeloma and the impact of novel therapies.***

Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, Dingli D, Russell SJ, Lust JA, Greipp PR, Kyle RA, Gertz MA.

Blood. 2007 Nov 1; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17975015&ordinalpos=18&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors demonstrate the improved outcome of patients using novel therapies, including thalidomide and lenalidomide, both in the relapsed setting as well as at diagnosis.

Treatments for myeloma have expanded in the last decade, but it is not clear if the introduction of novel therapies and the increased use of high dose therapy have translated into better outcome for patients with myeloma. We examined the outcome of two groups of patients seen at a single institution, one from time of diagnosis and the other from the time of relapse, to examine the survival trends over time. Among 387 patients relapsing after stem cell transplant, a clear improvement in overall survival from the time of relapse was seen, with those relapsing after 2000 having a median overall survival of 23.9 vs. 11.8 months ($P < 0.001$) for those who relapsed prior to this date. This improvement was independent of other prognostic factors. Patients treated with one or more of the newer drugs (thalidomide, lenalidomide, bortezomib) had longer survival from relapse (30.9 vs. 14.8 months; $P < 0.001$). In a larger group of 2981 patients with newly diagnosed myeloma, those diagnosed in the last decade had a 50% improvement in overall survival (44.8 vs. 29.9 months; $P < 0.001$). In this study, we demonstrate improved outcome of patients with myeloma in recent years, both in the relapsed setting as well as at diagnosis.

 ***BiRD (Biaxin(R)[clarithromycin]/Revlimid(R)[lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma.***

Niesvizky R, Jayabalan DS, Christos PJ, Furst JR, Naib T, Ely S, Jalbrzikowski J, Pearse RN, Zafar F, Pekle K, Larow A, Lent R, Mark T, Cho HJ, Shore T, Tepler J, Harpel J, Schuster MW, Mathew S, Leonard JP, Mazumdar M, Chen-Kiang S, Coleman M.

Blood. 2007 Nov 7; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17989313&ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study aims to determine the safety and efficacy of the BiRD combination regimen as first-line therapy for myeloma and finds that BiRD is an effective regimen with manageable side effects in the treatment of symptomatic, newly diagnosed myeloma.

The aim of this trial was to determine the safety and efficacy of the combination regimen clarithromycin (Biaxin(R)), lenalidomide (Revlimid(R)), and dexamethasone (BiRD) as first-line therapy for multiple myeloma. Patients received BiRD in 28-day cycles. Dexamethasone (40 mg) was given orally once weekly, clarithromycin (500 mg) was given orally twice daily, and lenalidomide (25 mg) was given orally daily on days 1-21. In cycle 1, patients received dexamethasone on 3 consecutive days, and lenalidomide was begun on day 3 for pharmacokinetic studies. Objective response was defined by standard criteria (i.e. decrease in serum monoclonal protein [M-protein] by $\geq 50\%$, and a decrease in urine M-protein by $\geq 90\%$). Of the 72 patients enrolled, 65 had an objective response (90.3%). A combined stringent and conventional complete response rate of 38.9% was achieved, and 73.6% of the patients achieved a $\geq 90\%$ decrease in M-protein levels. This regimen did not interfere with hematopoietic stem cell harvest. Fifty-two patients who did not go on to receive transplantation received continued therapy (complete response 37%, very good partial response 33%). The major toxicities were

thromboembolic events, corticosteroid-related morbidity, and cytopenias. BiRD is an effective regimen with manageable side effects in the treatment of symptomatic, newly diagnosed multiple myeloma.

👁️ *Single autologous stem cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial.*

Abdelkefi A, Ladeb S, Torjman L, Ben Othman T, Lakhal A, Ben Romdhane N, El Omri H, Elloumi M, Belaaj H, Jeddi R, Aissaoui L, Ksouri H, Ben Hassen A, Msadek F, Saad A, Hsairi M, Boukef K, Amouri A, Louzir H, Dellagi K, Ben Abdeladhim A.

Blood. 2007 Nov 8; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17875806&ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors conclude that up-front single autologous transplant followed by 6 months of maintenance therapy with thalidomide (with second transplant in reserve for relapse or progression) is an effective therapeutic strategy to treat multiple myeloma patients, and appears superior to tandem transplant in this setting.

From April 2003 to December 2006, 195 patients with de novo symptomatic myeloma and less than 60 years of age, were randomly assigned to receive either tandem transplantation up-front [Arm A, n=97] or one autologous stem cell transplantation followed by a maintenance therapy with thalidomide (day +90, 100 mg per day during 6 months) [Arm B, n=98]. Patients included in arm B received a second transplant at disease progression. In both arms, autologous stem cell transplantation was preceded by first-line therapy with thalidomide-dexamethasone and subsequent collection of peripheral blood stem cells with high-dose cyclophosphamide (4 g/m²) and granulocyte colony stimulating factor. Data were analyzed on an intent-to-treat basis. With a median follow-up of 33 months (range, 6-46 months), the 3-year overall survival was 65% in arm A, and 85% in arm B (P= .04). The 3-year progression-free survival was 57% in arm A, and 85% in arm B (P= .02). Up-front single autologous transplant followed by 6 months of maintenance therapy with thalidomide (with second transplant in reserve for relapse or progression) is an effective therapeutic strategy to treat multiple myeloma patients, and appears superior to tandem transplant in this setting.

👁️ *Management of newly diagnosed myeloma.*

Rajkumar SV, Palumbo A.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1141-56.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996592&ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the dramatic changes in myeloma treatment over the last decade, including the introduction of thalidomide and lenalidomide.

The treatment of multiple myeloma has changed dramatically in the last decade with the introduction of thalidomide, bortezomib, and lenalidomide. Patients eligible for autologous stem cell transplantation (ASCT) are treated with non-alkylating agent-containing regimens as initial therapy; typically thalidomide-dexamethasone or lenalidomide-dexamethasone. For patients not eligible for ASCT, the current standard of care is melphalan, prednisone, and thalidomide. Ongoing trials will soon assess if combinations including melphalan and prednisone plus bortezomib or MP plus lenalidomide may be considered an attractive option. Patients who have risk factors, such as deletion 13 or translocation t(4;14) or t(14;16), are candidates for novel, more aggressive treatments.

👁️ *Management of relapsed and relapsed refractory myeloma.*

Kastritis E, Mitsiades CS, Dimopoulos MA, Richardson PG.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1175-215.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996594&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the accumulating experience from ongoing trials of bortezomib/lenalidomide/dexamethasone combinations in patients who have relapsed/refractory or newly diagnosed myeloma.

Studies of bortezomib, thalidomide, and lenalidomide have shown promising clinical activity in relapsed/refractory multiple myeloma (MM). Bortezomib alone and in combination with other agents is associated with high response rates, consistently high rates of complete response, and a predictable and manageable profile of adverse events. Thalidomide-based regimens have also shown substantial clinical activity. The accumulating experience from ongoing trials of bortezomib/lenalidomide/dexamethasone combinations in patients who have relapsed/refractory or newly diagnosed MM will provide critical information that will determine the possible role of this combination as the basic backbone for combination regimens for management of advanced MM.

Post-transplant outcomes of induction therapy for myeloma: Thalidomide and dexamethasone versus doxorubicin, vincristine, and dexamethasone prior to high-dose melphalan with autologous stem cell support.

Vogl DT, Liu SV, Chong EA, Luger SM, Porter DL, Schuster SJ, Tsai DE, Perl A, Loren AW, Goldstein SC, Nasta SD, Andreadis C, Mangan PA, Hummel K, Siegel DL, Glatstein E, Stadtmauer EA.

Am J Hematol. 2007 Dec;82(12):1071-5.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17696204&ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors' findings suggest that the use of thalidomide during induction therapy may lead to improved long-term outcomes after transplant.

High-dose melphalan with autologous stem cell support improves survival as part of initial therapy for myeloma. Previous studies of pre-transplant induction regimens have compared paraprotein response rates but not long-term outcomes after transplant. We reviewed the records of all patients with multiple myeloma who received an autologous stem cell transplant at the University of Pennsylvania Medical Center. We compared outcomes for 69 patients who received high-dose melphalan conditioning after January 1, 2003 as part of initial therapy for myeloma, including 41 patients who received anthracycline-based induction (VAD or DVD) and 28 patients who received thalidomide and dexamethasone induction. Baseline characteristics in these two groups were not different, though potentially clinically important differences were apparent in assignment to post-transplant consolidation and maintenance therapy. Despite similar response rates during induction therapy, thalidomide and dexamethasone induction was associated with better progression-free survival (hazard ratio 0.18, $P = 0.011$) after transplant. This effect persisted in multivariable regression models including baseline characteristics and post-transplant treatment. Overall survival was not different between the two groups. These results suggest that the use of thalidomide during induction therapy may lead to improved long-term outcomes after transplant. Future trials comparing induction therapies should examine progression-free and overall survival after transplant to confirm this benefit.

Preclinical studies of novel targeted therapies.

Hideshima T, Anderson KC.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1071-91.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996589&ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss how novel therapies, such as thalidomide and lenalidomide, are usefully directed not only at myeloma cells but also at the bone marrow milieu.

The bone marrow (BM) milieu confers drug resistance in multiple myeloma (MM) cells to conventional therapies. Novel biologically based therapies are therefore needed. Preclinical studies have identified and validated molecular targeted therapeutics in MM. In particular, recognition of the biologic significance of the BM microenvironment in MM pathogenesis and as a potential target for novel therapeutics has already derived several promising approaches. Thalidomide, lenalidomide (Revlimid), and bortezomib (Velcade) are directed not only at MM cells but also at the BM milieu and have moved rapidly from the bench to the bedside and United States Food and Drug Administration approval to treat MM.

Role of stem cell transplantation.

Harousseau JL.

Hematol Oncol Clin North Am. 2007 Dec;21(6):1157-74.

The author concludes that the role of allogeneic stem cell transplantation remains controversial, even with reduced intensity conditionings, given the introduction of novel agents, such as thalidomide and lenalidomide.

 http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17996593&ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Hematopoietic stem cell transplantation (SCT) was introduced in the treatment of multiple myeloma in the 1980s. In the autologous setting, the use of peripheral blood stem cells instead of bone marrow has markedly improved feasibility. In fit patients who have normal renal function and are younger than 65 years of age, randomized studies have shown the superiority of autologous stem cell transplantation (ASCT) compared with conventional chemotherapy. ASCT is now considered the standard of care in this population of patients. It is currently challenged, however, by the introduction of novel agents, such as thalidomide, bortezomib, and lenalidomide. The role of allogeneic SCT remains controversial, even with reduced intensity conditionings. Prospective studies still are needed to evaluate the impact of both autologous and allogeneic SCT in this new era.



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