



# CITINGS

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## Thalidomide and Revlimid® Issue

**The International Myeloma Foundation (IMF)** is pleased to present our first edition of CITINGS for 2008. This quarterly publication features citations to the most up-to-date studies on myeloma treatment. In this issue, we focus on thalidomide and Revlimid for the treatment of multiple myeloma. Inside you will find references to the latest published journal articles on both thalidomide and Revlimid from the first 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](http://www.myeloma.org).

– Susie Novis, President, IMF

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## Thalidomide/Revlimid Publications 1st Quarter, 2008

 **Improvement after thalidomide and dexamethasone treatment for advanced cardiac amyloidosis: a case report.**

Choi JS, Hwang EN, Kim YH, Jung Y, Kim HJ, Nam SH, Park JI.  
*Circ J.* 2007 Nov;71(11):1823-5.

 [http://www.ncbi.nlm.nih.gov/pubmed/17965510?ordinalpos=95&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17965510?ordinalpos=95&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

A case of advanced cardiac amyloidosis was treated with thalidomide. The patient showed early and significant improvement of diastolic cardiac function, as well as symptoms.

 **Successful antiangiogenic therapy for neuroblastoma with thalidomide.**

Gesundheit B, Moser A, Or R, Klement G.  
*J Clin Oncol.* 2007 Nov 20;25(33):5321-4.

 [http://www.ncbi.nlm.nih.gov/pubmed/18024879?ordinalpos=82&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18024879?ordinalpos=82&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

 **Effect of lenalidomide therapy on mobilization of peripheral blood stem cells in previously untreated multiple myeloma patients.**

Mazumder A, Kaufman J, Niesvizky R, Lonial S, Vesole D, Jagannath S.  
*Leukemia.* 2007 Nov 22. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18033320?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18033320?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

### ***Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.***

Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, San Miguel J, Hellmann A, Facon T, Foà R, Corso A, Masliak Z, Olesnyckij M, Yu Z, Patin J, Zeldis JB, Knight RD; Multiple Myeloma (010) Study Investigators.

*N Engl J Med.* 2007 Nov 22;357(21):2123-32.



[http://www.ncbi.nlm.nih.gov/pubmed/18032762?ordinalpos=81&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18032762?ordinalpos=81&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors find that lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in relapsed or refractory multiple myeloma.**

**BACKGROUND:** Lenalidomide is a structural analogue of thalidomide with similar but more potent biologic activity. This phase 3, placebo-controlled trial investigated the efficacy of lenalidomide plus dexamethasone in the treatment of relapsed or refractory multiple myeloma. **METHODS:** Of 351 patients who had received at least one previous antimyeloma therapy, 176 were randomly assigned to receive 25 mg of oral lenalidomide and 175 to receive placebo on days 1 to 21 of a 28-day cycle. In addition, all patients received 40 mg of oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles and subsequently, after the fourth cycle, only on days 1 to 4. Patients continued in the study until the occurrence of disease progression or unacceptable toxic effects. The primary end point was time to progression. **RESULTS:** The time to progression was significantly longer in the patients who received lenalidomide plus dexamethasone (lenalidomide group) than in those who received placebo plus dexamethasone (placebo group) (median, 11.3 months vs. 4.7 months;  $P < 0.001$ ). A complete or partial response occurred in 106 patients in the lenalidomide group (60.2%) and in 42 patients in the placebo group (24.0%,  $P < 0.001$ ), with a complete response in 15.9% and 3.4% of patients, respectively ( $P < 0.001$ ). Overall survival was significantly improved in the lenalidomide group (hazard ratio for death, 0.66;  $P = 0.03$ ). Grade 3 or 4 adverse events that occurred in more than 10% of patients in the lenalidomide group were neutropenia (29.5%, vs. 2.3% in the placebo group), thrombocytopenia (11.4% vs. 5.7%), and venous thromboembolism (11.4% vs. 4.6%). **CONCLUSIONS:** Lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in relapsed or refractory multiple myeloma.

### ***Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America.***

Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, Siegel D, Borrello I, Rajkumar SV, Chanan-Khan AA, Lonial S, Yu Z, Patin J, Olesnyckij M, Zeldis JB, Knight RD; Multiple Myeloma (009) Study Investigators.

*N Engl J Med.* 2007 Nov 22;357(21):2133-42.



[http://www.ncbi.nlm.nih.gov/pubmed/18032763?ordinalpos=80&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18032763?ordinalpos=80&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors find that lenalidomide plus dexamethasone is superior to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma.**

**BACKGROUND:** Lenalidomide, an oral immunomodulatory drug that is similar to thalidomide but has a different safety profile, has clinical activity in relapsed or refractory multiple myeloma. **METHODS:** Patients in the United States and Canada who had received at least one previous therapy for multiple myeloma but who required additional treatment were randomly assigned to receive either 25 mg of lenalidomide or placebo on days 1 to 21 of a 28-day cycle. Both groups also received 40 mg of oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles. After the fourth cycle, 40 mg of dexamethasone was administered only on days 1 to 4. Safety, clinical response, time to progression, and overall survival were assessed. **RESULTS:** We assigned 177 patients to the lenalidomide group and 176 to the placebo group. Complete, near-complete, or partial responses occurred in 108 patients (61.0%) in the lenalidomide group and in 35 patients (19.9%) in the placebo group ( $P < 0.001$ ); complete responses occurred in 14.1% and 0.6%, respectively ( $P < 0.001$ ). The median time to progression was 11.1 months in the lenalidomide group and 4.7 months in the placebo group ( $P < 0.001$ ). Median overall survival times in the two groups were 29.6 months and 20.2 months, respectively ( $P < 0.001$ ). Grade 3 or 4 adverse events were reported in 85.3% of the lenalidomide group and in 73.1% of the placebo group; these events resulted in study discontinuation in 19.8% and 10.2%, respectively. Grade 3 or 4 neutropenia and venous thromboembolism were more common in the lenalidomide group than in the placebo group (41.2% vs. 4.6% and 14.7% vs. 3.4%, respectively;  $P < 0.001$  for both comparisons). **CONCLUSIONS:** Lenalidomide plus dexamethasone is superior to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma.

 ***Lenalidomide – the phoenix rises.***

List AF.

*N Engl J Med.* 2007 Nov 22;357(21):2183-6.

 [http://www.ncbi.nlm.nih.gov/pubmed/18032768?ordinalpos=79&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18032768?ordinalpos=79&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

Comment on:

*N Engl J Med.* 2007 Nov 22;357(21):2123-32.

*N Engl J Med.* 2007 Nov 22;357(21):2133-42.

 ***Reply to ‘Effect of lenalidomide therapy on mobilization of peripheral blood stem cells in previously untreated multiple myeloma patients.’***

Kumar S, Gertz MA.

*Leukemia.* 2007 Nov 22. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18033319?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18033319?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

 ***Application and safety of thalidomide in the treatment of multiple myeloma.*** [Article in Japanese]

Hattori Y.

*Nippon Rinsho.* 2007 Dec;65(12):2296-301.

 [http://www.ncbi.nlm.nih.gov/pubmed/18069276?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069276?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses the recent expansion of thalidomide use for Japanese myeloma patients.**

Thalidomide is now regarded as one of the most promising salvage therapies for refractory or relapsed multiple myeloma. Appropriate use of this drug is indispensable to avoid repeating drug-induced disaster. Recently, its application has been expanded from refractory or relapsed cases also to untreated patients or post transplanted cases. Thus, it should be clarified which population of the Japanese patients with myeloma may truly benefit by this drug. Guideline, recently established by the Japanese Society of Clinical Hematology, has functioned for safety use of this drug. For future approval by Japanese government, strict but well-organized system for safety applicable to the clinical setting in Japan is necessary.

 ***The Arkansas approach to therapy of patients with multiple myeloma.***

Barlogie B, Anaissie E, van Rhee F, Pineda-Roman M, Zangari M, Shaughnessy J, Epstein J, Crowley J.

*Best Pract Res Clin Haematol.* 2007 Dec;20(4):761-81.

 [http://www.ncbi.nlm.nih.gov/pubmed/18070718?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18070718?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**This article gives an account of the experience of the Arkansas myeloma program since 1989 with transplant-supported high-dose melphalan, novel agents, and prognostic factors as they relate to standard laboratory features, gene expression profiling, and magnetic resonance imaging (MRI).**

This chapter gives an account of the experience of the Arkansas myeloma program since 1989 with transplant-supported high-dose melphalan, novel agents, and prognostic factors as they relate to standard laboratory features, gene expression profiling, and magnetic resonance imaging (MRI). Incorporation of novel agents and new concepts, such as post-tandem transplant consolidation therapy, has improved the rate and duration of complete response and prolonged event-free and overall survival rates. With Total Therapy 2, median survival exceeds 8 years, while Total Therapy 3 with added bortezomib has sustained complete remissions in more than 90% of patients at 2 years which, when used as a survival surrogate in Total Therapy 2, assured a high 6-year survival rate of 75%. Gene expression profiling identified 15% of patients with very short survival. MRI-defined focal lesions are associated with poor outcome, while their resolution - although slower than the time course of attaining clinical complete remission - conferred superior survival. Representing a frequent source of recurrence, with genetic profiles (in both plasma and stromal cells) distinct from those in random bone-marrow samples, therapeutic efforts are directed at hastening onset and increasing frequency of focal lesion resolution.

### ***Autologous stem cell transplantation in the elderly including pre- and post-treatment options.***

Kumar SK, Hayman SR, Kyle RA.

*Bone Marrow Transplant.* 2007 Dec;40(12):1115-21. Epub 2007 Aug 6.

 [http://www.ncbi.nlm.nih.gov/pubmed/17680019?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17680019?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss how the introduction of novel agents, including thalidomide and lenalidomide, has changed the paradigm for treatment of myeloma.**

Multiple myeloma (MM) is a disease of the elderly with a median age at diagnosis of 67 years in a referral population. High-dose chemotherapy (HDT) and autologous stem cell transplantation has been shown to improve survival in patients with MM in randomized trials and remains the preferred option for eligible patients. However, the randomized clinical trials demonstrating an advantage for HDT included only patients younger than 65 years and evidence supporting its role for the elderly patients has been based on retrospective reviews. The introduction of thalidomide, lenalidomide and bortezomib has changed the paradigm for treatment of myeloma and improved the outcome for these patients. Several ongoing clinical trials are evaluating the role of these novel agents in this population, specifically comparing these to HDT-based approaches. Other trials are examining the role of maintenance therapy post-HDT with these novel drugs with or without steroids. The role of HDT will be further redefined in the coming years with improvements in other therapies.

### ***Chemotherapy for multiple myeloma.*** [Article in Japanese]

Ishida T.

*Nippon Rinsho.* 2007 Dec;65(12):2280-4.

 [http://www.ncbi.nlm.nih.gov/pubmed/18069273?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069273?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses induction therapy, and the increased overall survival of myeloma patients treated with melphalan and prednisone (MP) in combination with thalidomide as compared to MP alone.**

The combination of the melphalan and prednisolone (MP) can induce objective responses in about 50% of patients with multiple myeloma (MM) since its introduction in 1960. Since then many combination chemotherapy regimens have been used, but a large metaanalysis showed that the combination of oral MP is as effective as combination regimens including intravenous drugs. In recent years, many novel agents (including bortezomib, thalidomide, and liposomal doxorubicin) have been developed for the MM treatment. More recently, MP has been used in combination with these novel agents. The combination treatment of MP and thalidomide, overall survival was significantly better than seen in the MP treatment. In the near future, primary induction therapy will be changed.

### ***Clinical updates and nursing considerations for patients with multiple myeloma.***

Faiman B.

*Clin J Oncol Nurs.* 2007 Dec;11(6):831-40.

 [http://www.ncbi.nlm.nih.gov/pubmed/18063542?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18063542?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses the oncology nurse's role in optimizing myeloma's new therapeutic options, including lenalidomide and thalidomide.**

Multiple myeloma accounts for approximately 1% of all new cancers and is characterized by abnormal plasma cell proliferation in the bone marrow. As a result, many patients develop bone lesions, hypercalcemia, anemia, and renal impairment. Although no cure exists for multiple myeloma, current treatments, such as oral melphalan and prednisone, can slow disease progression and prolong overall survival. Several new therapeutic options show promise: lenalidomide, thalidomide, liposomal doxorubicin, and bortezomib. Clinical research presented at the 2006 meeting of the American Society of Hematology, the 2007 meeting of the American Society of Clinical Oncology, and the 11th International Myeloma Workshop showed that newer therapeutic combinations were well tolerated and effective in patients with multiple myeloma. Oncology nurses, with their specialized knowledge of treatment administration and monitoring and their expertise in patient education, have an important role in the management of patients with multiple myeloma to help improve overall survival and quality of life. As newer regimens become available, oncology nurses must be aware of factors that optimize outcomes to help patients understand the benefits of treatment, how to manage side effects, and the importance of treatment adherence.

 **Development of thalidomide analogs for the treatment of multiple myeloma (MM).** [Article in Japanese]

Chou T.

*Nippon Rinsho.* 2007 Dec;65(12):2302-8.

 [http://www.ncbi.nlm.nih.gov/pubmed/18069277?ordinalpos=66&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069277?ordinalpos=66&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses phase II studies that show the anti-myeloma activity of lenalidomide.**

After the introduction of thalidomide (Thal) in the treatment of MM in 90's, several thalidomide analogs have been developed. Among them, CC-5013 (lenalidomide: Lenal) is the most potent and promising novel oral agent. Compared with Thal, Lenal is 50 to 2,000 times more potent at stimulating T cell proliferation and 50 to 100 times more potent at augmenting several cytokines. A phase I trial established a maximal tolerated oral dose for Lenal of 25 mg daily. Phase II study showed significant anti-MM activity of Lenal with less or no reports of significant somnolence, constipation, or neuropathy as with Thal therapy. Based on these findings, several phase III studies are on going internationally.

 **Diagnosis and management guideline of multiple myeloma.** [Article in Japanese]

Murakami H, Handa H, Saitoh T.

*Nippon Rinsho.* 2007 Dec;65(12):2167-76.

 [http://www.ncbi.nlm.nih.gov/pubmed/18069257?ordinalpos=71&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069257?ordinalpos=71&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**With the recent development of novel therapies, including thalidomide and lenalidomide, the authors propose diagnosis and management guidelines for Japanese myeloma patients.**

The prognosis of patients with multiple myeloma has been improved in the last decade due to the induction of autologous stem cell transplantation and novel drugs including thalidomide, lenalidomide, and bortezomib into the treatment. Recently, the UK Myeloma Forum and International Myeloma Foundation have successively proposed myeloma management guidelines. Because many novel drugs are not available in Japanese patients, we can not use the same treatment strategy in U.S.A. and Europe. In this chapter, the diagnosis and management guideline is proposed for Japanese patients with myeloma. For convenience, the recommendations are divided into: 1. Diagnostic criteria 2. Indications for starting therapy 3. Treatment(initial therapy, maintenance therapy, and therapy for refractory/relapsed patients) 4. Response criteria 5. Supportive care and management of specific complications.

 **Effects of as(2)o(3), dexamethasone and thalidomide on apoptosis and cytoplasmic [Ca(2+)] of myeloma cell line u266.** [Article in Chinese]

Lin RF, Lu H, Liu P, Wang YR, Shen WY, Wu YJ, Zhang JF, Fei XM, Ge Z, Li JY.

*Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2007 Dec;15(6):1200-3.

 [http://www.ncbi.nlm.nih.gov/pubmed/18088466?ordinalpos=73&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18088466?ordinalpos=73&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors investigate the influence of As(2)O(3), dexamethasone (Dex) and thalidomide (Thal) on apoptosis-induced myeloma cell line U266 cytoplasmic calcium concentrations ([Ca(2+)] i). They conclude that the raise of [Ca(2+)] i is one of the mechanisms for As(2)O(3) and Dex-induced U266 cells apoptosis, whereas Thal-induced U266 apoptosis has no significant relation to [Ca(2+)] i changes.**

To investigate the influence of As(2)O(3), dexamethasone (Dex) and thalidomide (Thal) on apoptosis-induced myeloma cell line U266 cytoplasmic calcium concentrations ([Ca(2+)] i), U266 cells were incubated in the culture of RPMI 1640 with 15% FBS in 24-well plate and exposed to different concentrations of As(2)O(3), Dex and Thal for 8 hours, respectively, then cell apoptosis was analyzed by fluorescence microscopy and flow cytometry (FCM) with Annexin V-FITC/PI double staining, and cytoplasmic free calcium were detected on FCM through Fluo-3/AM loading. The results indicated that (1) apoptotic cells were gradually increased with enhancement of As(2)O(3), Dex and Thal concentrations; (2) apoptotic cell rates increased from 0.56% in control to 31.54%, 28.35% and 21.97% respectively after treatment with As(2)O(3), Dex and Thal; (3) As(2)O(3), Dex induced U266 cell apoptosis accompanied with raise of [Ca(2+)] i; (4) [Ca(2+)] i had no statistically significant changes in Thal-induced apoptotic U266 cells. It is concluded that the raise of [Ca(2+)] i is one of the mechanisms for As(2)O(3) and Dex-induced U266 cells apoptosis, whereas Thal-induced U266 apoptosis has no significant relation to [Ca(2+)] i changes.

 ***Efficacy of thalidomide combined dexamethasone on newly diagnosed multiple myeloma.*** [Article in Chinese]

Yuan ZG, Hou J, Wang DX, Fu WJ, Chen YB, Xi H.

*Ai Zheng.* 2007 Dec;26(12):1369-72.

 [http://www.ncbi.nlm.nih.gov/pubmed/18076804?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18076804?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors find the combination of thalidomide and dexamethasone to be an effective induction regimen for newly diagnosed myeloma and may be considered as a replacement of VAD regimen.**

BACKGROUND & OBJECTIVE: Thalidomide is effective in treating refractory and relapsed multiple myeloma (MM). However, the efficacy of thalidomide in induction therapy for newly diagnosed MM remains unknown. This study was to evaluate the efficacy of thalidomide combined dexamethasone (TD induction regimen) on previously untreated MM, and observe the adverse events. METHODS: Thirty-nine patients with newly diagnosed MM received oral administration of thalidomide at a dose of 100-300 mg/day continuously and dexamethasone at a dose of 20-40 mg/day on Days 1-4, 9-12, 17-20 in odd months and on Days 1-4 in even months. TD regimen was repeated every 28 days. Thirty-six MM patients who received VAD regimen (vindesine, adriamycin, and dexamethasone) was regarded as a historical matched controls. The efficacy, survival time and adverse events were compared between the two groups. RESULTS: The overall response rates were 71.8% in TD group and 61.1% in VAD group ( $P > 0.05$ ). The median progression-free survival was 14 months in TD group and 9 months in VAD group ( $P > 0.05$ ). Within a median follow-up of 13 months (range, 1-30 months), median overall survival (OS) was not reached in TD group, and was 29 months in VAD group. The most common adverse events (always not higher than grade 2) were constipation, fatigue, dizziness and somnolence in TD group. More grade 3-4 adverse events, included leucopenia and thrombocytopenia, and higher infection rate were observed in VAD group as compared with those in TD group ( $P < 0.05$ ). CONCLUSIONS: The combination of thalidomide and dexamethasone is an effective induction regimen for newly diagnosed MM. It may be considered as a replacement of VAD regimen.

 ***The evolving background for high-dose treatment for myeloma.***

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

*Bone Marrow Transplant.* 2007 Dec;40(12):1097-100. [Epub 2007 Oct 1.]

 [http://www.ncbi.nlm.nih.gov/pubmed/17906702?ordinalpos=45&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17906702?ordinalpos=45&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss how the newer targeted myeloma treatments, such as thalidomide and lenalidomide, fit in with various transplantation strategies, with special emphasis on the attainment of very long-term survival.**

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.

 ***Frontline treatment in multiple myeloma patients not eligible for stem-cell transplantation.***

Facon T, Darre S.

*Best Pract Res Clin Haematol.* 2007 Dec;20(4):737-46.

 [http://www.ncbi.nlm.nih.gov/pubmed/18070716?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18070716?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss melphalan-prednisone-thalidomide and melphalan-prednisone-lenalidomide as therapeutic options for myeloma patients.**

Melphalan-prednisone-thalidomide (MPT) currently appears to be the treatment of choice for a large proportion of elderly patients ineligible for autologous stem-cell transplantation (ASCT). It seems certain that in the near future melphalan-prednisone-Velcade (MPV) and melphalan-prednisone-lenalidomide (MPR) will also be proved superior to melphalan-prednisone (MP), thus providing three therapeutic options (MPT, MPV and MPR) in this patient group with multiple myeloma (MM). These therapeutic options could lead to more personalized treatment approaches, based on patient comorbidities, as the three novel therapies have somewhat different toxicity profiles. MP would be appropriate for only a minority of patients with poor performance status and/or significant comorbidities, such as severe neuropathy or a contraindication to anticoagulants. Questions regarding the relative efficacy of melphalan-based regimens versus dexamethasone-based

regimens (preferably with low-dose dexamethasone) will require randomized phase-III trials. More intensive approaches with new drug combinations or with the incorporation of polyethylene glycolated (PEGylated) liposomal doxorubicin will also require additional studies. Additionally, the important issue of maintenance treatment needs to be further investigated, especially in elderly patients.

### ***High-dose chemotherapy and autologous hematopoietic stem cell transplantation in myeloma patients under the age of 65 years.***

Mehta J, Singhal S.

*Bone Marrow Transplant.* 2007 Dec;40(12):1101-14. [Epub 2007 Aug 6.]



[http://www.ncbi.nlm.nih.gov/pubmed/17680020?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17680020?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss the uses of novel agents, such as thalidomide and lenalidomide, with respect to high-dose chemotherapy and stem cell transplantation for myeloma patients under 65 years of age.**

One or two cycles of high-dose chemotherapy with autologous hematopoietic stem cell transplantation have been shown to improve response rates and survival in myeloma. While this observation has largely been made in patients under the age of 65 years, there is evidence to suggest that the conclusions can be extrapolated to older individuals as well. In contrast to other hematologic malignancies treated with high-dose therapy, autografted myeloma patients continue to relapse several years after transplantation, and few patients are cured with this modality. However, up to a third of patients may be alive beyond a decade; some with excellent quality of life giving rise to the concept of 'operational cure'. Relapsing disease can be treated with novel agents or repeat high-dose chemotherapy and transplantation. The pressing questions to which answers are not obvious at the moment are whether tandem transplantation should be offered to all patients, and whether novel agents should be used before transplantation or reserved for relapse. Despite their excellent activity, there is no evidence so far that novel agents such as thalidomide, bortezomib and lenalidomide can replace high-dose chemotherapy and stem cell transplantation.

### ***How to prevent deep vein thrombosis in myeloma patients receiving thalidomide or lenalidomide.***

Kastritis E, Dimopoulos M.

*Leuk Lymphoma.* 2007 Dec;48(12):2295-7.



[http://www.ncbi.nlm.nih.gov/pubmed/18066998?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18066998?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

### ***Lenalidomide-associated hypothyroidism.***

Menon S, Habermann T, Witzig T.

*Leuk Lymphoma.* 2007 Dec;48(12):2465-7.



[http://www.ncbi.nlm.nih.gov/pubmed/18067027?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18067027?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

### ***Lenalidomide in multiple myeloma.***

Thomas SK, Richards TA, Weber DM.

*Best Pract Res Clin Haematol.* 2007 Dec;20(4):717-35.



[http://www.ncbi.nlm.nih.gov/pubmed/18070715?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18070715?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors describe the role of lenalidomide in patients with symptomatic multiple myeloma that is newly diagnosed, relapsed and/or refractory to other therapies, or concurrent with primary amyloidosis.**

For many years the treatment of multiple myeloma was limited to such regimens as melphalan-prednisone, high-dose dexamethasone, and vincristine-doxorubicin-dexamethasone (VAD). These combinations provided response rates of 45-55%, with complete remission rates of up to 10%. With the advent of thalidomide- and bortezomib-based combinations, response rates to induction therapy have risen to 85-95% in previously untreated patients and are associated with complete remission rates up to 25%. However, these agents are associated with such side-effects as somnolence, constipation and neuropathy. Lenalidomide, a thalidomide analog, was developed with the hope of improving both the efficacy and toxicity profile of thalidomide, and has subsequently shown significant clinical activity in patients with multiple myeloma. We describe the role of lenalidomide in patients with symptomatic multiple myeloma that is newly diagnosed, relapsed and/or refractory to other therapies, or concurrent with primary amyloidosis.

### ***The malignant clone and the bone-marrow environment.***

Podar K, Richardson PG, Hideshima T, Chauhan D, Anderson KC.

*Best Pract Res Clin Haematol.* 2007 Dec;20(4):597-612.



[http://www.ncbi.nlm.nih.gov/pubmed/18070708?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18070708?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors review current knowledge of the multiple myeloma (MM) cell clone, as well as the impact of the bone marrow microenvironment on tumor-cell growth, survival, migration and drug resistance because, although novel agents such as thalidomide and lenalidomide are now FDA-approved to treat MM, patients inevitably relapse and further improvements remain urgently needed.**

Multiple myeloma (MM) is characterized by the clonal expansion of monoclonal immunoglobulin-secreting plasma cells within the bone marrow (BM). It has become clear that the intimate reciprocal relationship between the tumor cell clone and the niches of the BM microenvironment plays a pivotal pathophysiologic role in MM. We and others have identified several new molecular targets and derived novel therapies which induce cytotoxicity against MM cells in the BM milieu, including thalidomide, bortezomib, and lenalidomide. Importantly, these agents induce tumor-cell death, as well as inhibit MM-cell-BM-stromal-cell (BMSC) adhesion and related tumor-cell growth, survival, and migration. Moreover, they block both constitutive and MM-cell binding-induced growth factor and cytokine secretion in BMSCs. Further, they also block tumor angiogenesis and can augment anti-MM immunity. Although all three of these agents are now FDA-approved to treat MM, patients inevitably relapse, and further improvements remain urgently needed. Here we review our current knowledge of the MM cell clone, as well as the impact of the BM microenvironment on tumor-cell growth, survival, migration and drug resistance. Delineating the mechanisms and sequelae of the reciprocal relationship between the MM cell clone, distinct BM extracellular matrix proteins, and accessory cell compartments may provide the basis for new effective therapeutic strategies to re-establish BM homeostasis and thereby improve MM patient outcome.

### ***The mechanism of action of thalidomide.*** [Article in Japanese]

Tsukagoshi S.

*Nippon Rinsho.* 2007 Dec;65(12):2291-5.



[http://www.ncbi.nlm.nih.gov/pubmed/18069275?ordinalpos=68&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069275?ordinalpos=68&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses the roles of thalidomide and lenalidomide in the treatment of myeloma.**

Thalidomide, N-phthalidoglutamide, is a well-known teratogenic agent when given to pregnant women. It was first synthesized by CIBA in 1953, but put on market in Germany as a sedative, but Dr. Rentz reported first the relation with the teratogenicity. However, its clinical activity to erythema nodosum leprosum was accidentally found. In 1997, thalidomide was found active to multiple myeloma, but its clinical use is not authorized yet in Japan. The mechanisms which so far reported are as follows. 1) The inhibitory activity of angiogenesis 2) NF-kappaB suppression 3) Suppression of GVHD, and other activity to immunity (suppression or augmentation), suppression of TNFa 4) Suppression of intracellular adhesion molecule 5) Binding to DNA From these reports, the teratogenicity or the clinical activities have been somewhat understood. Recently clinical studies of the analogue, Lenalidomide, have been reported.

### ***The molecular pathogenesis of myeloma for the therapeutic targets.*** [Article in Japanese]

Hanamura I.

*Nippon Rinsho.* 2007 Dec;65(12):2202-8.



[http://www.ncbi.nlm.nih.gov/pubmed/18069261?ordinalpos=70&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069261?ordinalpos=70&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author reviews the molecular pathogenesis of myeloma, especially the new findings related with NF-kappaB activation.**

Multiple myeloma (MM) is a neoplasia of plasma cells in bone marrow. High dose chemotherapy followed by stem cell transplantation and new drugs such as thalidomide and bortezomib have improved the survival in MM. However, most of patients with myeloma are incurable so there is a need for the new therapeutic approaches that have been developed against molecular targets and pathway. It has been reported that activation of NF-kappaB pathway was required to survival of myeloma cells and this pathway was the potential target for anti-MM therapy. Recently we reported diverse genetic aberrations that activated NF-kappaB signaling in MM. In this section, the molecular pathogenesis of myeloma, especially the new findings related with NF-kappaB activation, will be reviewed in Japanese.

 ***Molecular targeting therapy for multiple myeloma.*** [Article in Japanese]

Takatoku M.

*Nippon Rinsho.* 2007 Dec;65(12):2345-50.



[http://www.ncbi.nlm.nih.gov/pubmed/18069281?ordinalpos=63&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069281?ordinalpos=63&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses recent clinical data regarding thalidomide and lenalidomide for both newly diagnosed and relapsed/refractory myeloma.**

Molecular target therapy is the most progressive and promising anticancer therapy in last decade. Multiple myeloma is also one of the major therapeutic targets for using molecular based technology. The recent availability of clinical data regarding thalidomide-, lenalidomide-, and bortezomib-based regimens has provided new, effective treatment options for patients with both newly diagnosed and relapsed/refractory multiple myeloma. We are expecting that future clinical trials can be designed to achieve a high likelihood of success based on molecular studies, cell-signaling, and correlative science studies. Studies with these agents also provide new insight into the cancer biology underlying multiple myeloma in humans.

 ***Multiple myeloma and treatment-related thromboembolism: oncology nurses' role in prevention, assessment, and diagnosis.***

Wiley KE.

*Clin J Oncol Nurs.* 2007 Dec;11(6):847-51.



[http://www.ncbi.nlm.nih.gov/pubmed/18063543?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18063543?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses the oncology nurse's role in the prevention, diagnosis and management of thromboembolic events related to thalidomide and lenalidomide myeloma treatment regimens.**

Immunomodulating agents such as thalidomide and its newly emerged derivative, lenalidomide, are becoming increasingly popular in the treatment of multiple myeloma because of their ability to combat drug resistance. Clinical trials suggest that thalidomide and lenalidomide are effective in all stages of multiple myeloma treatment-new diagnoses, stem cell transplantations, maintenance therapy, and relapsed or refractory disease. The drugs are most efficacious when combined with additional chemotherapeutic agents and/or corticosteroids. However, deep vein thrombosis and other thromboembolic events are associated with the treatment regimens. Oncology nurses must understand the pharmacologic properties of the drugs and the potentially life-threatening complications associated with them. To provide the highest standard of care, oncology nurses must play a vital role in the prevention, diagnosis, and management of thromboembolic events through awareness of the clinical problem, assessment tools, and thromboembolic prophylactic regimens.

 ***Prophylactic low-dose aspirin is effective antithrombotic therapy for combination treatments of thalidomide or lenalidomide in myeloma.***

Niesvizky R, Martínez-Baños D, Jalbrzikowski J, Christos P, Furst J, De Sancho M, Mark T, Pearse R, Mazumdar M, Zafar F, Pekle K, Leonard J, Jayabalan D, Coleman M.

*Leuk Lymphoma.* 2007 Dec;48(12):2330-7.



[http://www.ncbi.nlm.nih.gov/pubmed/18067007?ordinalpos=60&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18067007?ordinalpos=60&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**This report describes the use of low-dose aspirin (81 mg) as primary thromboprophylaxis in three series of multiple myeloma (MM) patients receiving thalidomide or lenalidomide with other drugs. The authors find that routine use of aspirin as antithrombotic prophylaxis in MM patients receiving immunomodulatory drugs with corticosteroids is warranted.**

Multiple myeloma (MM) patients have a propensity for thromboembolic events (TE), and treatment with thalidomide/dexamethasone or lenalidomide/dexamethasone increases this risk. This report describes the use of low-dose aspirin (81 mg) as primary thromboprophylaxis in three series of MM patients receiving thalidomide or lenalidomide with other drugs. In the first regimen (clarithromycin, thalidomide, dexamethasone), initiation of low-dose aspirin negated the occurrence of any further TE. In a second study, prophylactic aspirin given with thalidomide/dexamethasone resulted in a rate of TE similar to that seen with dexamethasone alone (without aspirin). A third study (n = 72) evaluated thrombosis rates with aspirin and a lenalidomide-containing regimen (clarithromycin, lenalidomide, dexamethasone). Of nine occurrences of thromboembolism, five were associated with aspirin interruption or poor compliance. Low-dose aspirin appears to reduce the incidence of thrombosis with these regimens. Routine use of aspirin as antithrombotic prophylaxis in MM patients receiving immunomodulatory drugs with corticosteroids is warranted.

 ***Role of autologous stem-cell transplantation in multiple myeloma.***

Attal M, Harousseau JL.

*Best Pract Res Clin Haematol.* 2007 Dec;20(4):747-59.



[http://www.ncbi.nlm.nih.gov/pubmed/18070717?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18070717?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss the current results of autologous stem-cell transplantation and the introduction of novel agents, such as thalidomide and lenalidomide.**

Multiple myeloma (MM) is one of the diseases in which the impact of dose intensity has been demonstrated. Consequently, in 2005 MM was the first disease for which autologous stem-cell transplantation (ASCT) was indicated in Europe and the US. However, ASCT is not curative, and most patients relapse in a median of 3 years. The introduction of novel agents such as thalidomide, bortezomib (Velcade((R))) or lenalidomide (Revlimid((R))) was logical to try to improve the high-dose strategy, and promising results have been reported. This article will focus on the current results of ASCT and will discuss the main research area to try to improve this strategy.

 ***The role of stem cell transplantation for multiple myeloma.*** [Article in Japanese]

Shimazaki C.

*Nippon Rinsho.* 2007 Dec;65(12):2338-44.



[http://www.ncbi.nlm.nih.gov/pubmed/18069280?ordinalpos=64&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18069280?ordinalpos=64&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (SCT) for newly diagnosed myeloma patients under 65 years of age, including how recently developed drugs, including thalidomide and lenalidomide, in combination with SCT might improve survival.**

The role of stem cell transplantation in the treatment of multiple myeloma (MM) is described. High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (SCT) is routinely recommended for most patients with newly diagnosed MM under 65 years of age. However, recently published meta-analysis of randomized controlled trials indicated PFS benefit but not OS benefit for HDT with autologous SCT performed early in MM. Tandem autologous SCT is superior to single transplantation in terms of event-free survival. Survival in recipients of autologous SCT followed by reduced-intensity conditioning allogeneic transplantation is superior to that in recipients of tandem autologous SCT. Recently developed new drugs including thalidomide, lenalidomide or bortezomib in combination with SCT might improve survival of myeloma patients.

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

Raab MS, Breitzkreutz I, Anderson KC.

*Bone Marrow Transplant.* 2007 Dec;40(12):1129-37. [Epub 2007 Sep 3.]



[http://www.ncbi.nlm.nih.gov/pubmed/17768392?ordinalpos=46&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17768392?ordinalpos=46&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss the increasingly integrated roles of thalidomide and lenalidomide in therapeutic regimens for newly diagnosed myeloma patients.**

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.

 ***Thalidomide.*** [Article in French]

Laffitte E, Revuz J.

*Ann Dermatol Venerol.* 2007 Dec;134(12):957-9.



[http://www.ncbi.nlm.nih.gov/pubmed/18166917?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18166917?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

### ***Thalidomide in the treatment of multiple myeloma.***

Kastritis E, Dimopoulos MA.

*Best Pract Res Clin Haematol.* 2007 Dec;20(4):681-99.



[http://www.ncbi.nlm.nih.gov/pubmed/18070713?ordinalpos=42&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18070713?ordinalpos=42&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors review the pharmacology, mechanisms of action, and toxicity of the thalidomide and focus on available data from clinical experience and randomized trials of thalidomide in the different settings of multiple myeloma.**

Thalidomide - either alone or in combination with dexamethasone or chemotherapy - has shown significant activity in relapsed/refractory disease. When used in the induction regimens in untreated patients, it significantly increases the response rates as well progression-free survival. Moreover, thalidomide as a maintenance therapy has become a very attractive option. However, the toxicity profile of the drug, mainly neurotoxicity and thrombotic events, mandate careful monitoring of patients treated with thalidomide, whether as the first line, in the relapsed setting, or as maintenance. In this chapter we will review the pharmacology, mechanisms of action, and toxicity of the drug, and will focus on available data from clinical experience and randomized trials of thalidomide in the different settings of multiple myeloma: refractory/relapsed disease, upfront treatment in patients who are eligible for high-dose therapy as well as those who are not, and finally the use of thalidomide as a maintenance treatment.

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

Peest D, Ganser A.

*Internist (Berl).* 2007 Dec;48(12):1343-1348.



[http://www.ncbi.nlm.nih.gov/pubmed/17960351?ordinalpos=58&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17960351?ordinalpos=58&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss approaches to the treatment of myeloma, including use of 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.

### ***Concurrent radiation therapy and lenalidomide in myeloma patient.***

Marchand V, Decaudin D, Servois V, Kirova YM.

*Radiother Oncol.* 2007 Dec 10 [Epub ahead of print].



[http://www.ncbi.nlm.nih.gov/pubmed/18077032?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18077032?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

### ***Low efficacy of thalidomide in improving response after induction in multiple myeloma patients who are candidates for high-dose therapy.***

Corso A, Mangiacavalli S, Barbarano L, Montalbetti L, Mazzone A, Fava S, Varettoni M, Zappasodi P, Morra E, Lazzarino M.

*Leuk Res.* 2007 Dec 18. [Epub ahead of print.]



[http://www.ncbi.nlm.nih.gov/pubmed/18096226?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18096226?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors explore intensive thalidomide-dexamethasone use for myeloma patients in the 3 months prior to transplant and find that the combination does not seem to be useful in this role.**

Giving the impact of complete response (CR) on outcome of multiple myeloma patients addressed to high-dose melphalan, we explored the role of a pre-transplant intensification with 3months thalidomide plus dexamethasone therapy (Thal-Dex), after pulse-VAD induction. Seventy-four multiple myeloma patients (MM pts) uniformly treated, were retrospectively studied. The response rate after pulse-VAD were: CR 6%, VGPR 40%, PR 23%, MR 23%, and progression 8%. The response rate after Thal-Dex were similar: CR 11%, VGPR 39%, PR 17%, MR 9%, and progression 24%. Giving no advantage in terms of response rate with an additive toxicity, Thal-Dex does not seem useful for intensification before transplant.

## ***Stem-Cell Transplantation for Multiple Myeloma in the Era of Novel Drugs.***

Bensinger W.

*J Clin Oncol.* 2007 Dec 19. [Epub ahead of print.]



[http://www.ncbi.nlm.nih.gov/pubmed/18056678?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18056678?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses the front-line efficacy of novel agents, including thalidomide and lenalidomide, in the treatment of myeloma, as it relates to the evolving role of transplantation.**

The treatment of multiple myeloma (MM) is changing rapidly. During the last 10 years, higher rates of complete response (CR) and prolonged progression-free and overall survival have been seen with high-dose chemotherapy plus autologous stem-cell transplantation (HDT-ASCT). Achievement of CR and good partial response have been shown to be key prognostic factors for prolonged survival, with eradication of minimal residual disease seeming crucial to long-term disease-free survival. Until recently, high rates of CR and other major responses were primarily seen with HDT-ASCT, but insights into the biology of MM have led to the development and approval of new drugs with significant activity, and new induction regimens based on these novel agents are offering improved responses. Thalidomide, bortezomib, and lenalidomide have been combined with corticosteroids, alkylators, and anthracyclines in front-line MM treatment. Phase II studies have indicated that high rates of response and CR may be achieved. The substantial activity seen with these new drug combinations has prompted a re-examination of the role of SCT in MM treatment. Will achievement of major responses with these new regimens translate into improved survival after consolidation with transplantation? Will these improved induction regimens reduce the need for tandem transplantation, or does achievement of CR obviate the need for front-line transplantation altogether? To help address these questions, randomized trials are needed, as well as tests with improved sensitivity to better define depth of remission.

## ***Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma.***

Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, Harousseau J, Zonder JA, Cavo M, Zangari M, Attal M, Belch A, Knop S, Joshua D, Ludwig H, Vesole D, Bladé J, Kyle R, Westin J, Weber D, Brinchen S, Niesvizky R, Waage A, von Lilienfeld-Toal M, Lonial S, Morgan GJ, Orlowski RZ, Shimizu K, Anderson KC, Boccadoro M, Durie BG, Sonneveld P, Hussein MA, Sezer O.

*Leukemia.* 2007 Dec 20. [Epub ahead of print.]



[http://www.ncbi.nlm.nih.gov/pubmed/18094721?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18094721?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The risk of VTE is higher in multiple myeloma patients who receive thalidomide or lenalidomide, especially in combination with dexamethasone or chemotherapy. The authors summarize various prophylaxis strategies and make recommendations according to a risk-assessment model.**

The incidence of venous thromboembolism (VTE) is more than 1 per thousand annually in the general population and increases further in cancer patients. The risk of VTE is higher in multiple myeloma (MM) patients who receive thalidomide or lenalidomide, especially in combination with dexamethasone or chemotherapy. Various VTE prophylaxis strategies, such as low-molecular-weight heparin (LMWH), warfarin or aspirin, have been investigated in small, uncontrolled clinical studies. This manuscript summarizes the available evidence and recommends a prophylaxis strategy according to a risk-assessment model. Individual risk factors for thrombosis associated with thalidomide/lenalidomide-based therapy include age, history of VTE, central venous catheter, comorbidities (infections, diabetes, cardiac disease), immobilization, surgery and inherited thrombophilia. Myeloma-related risk factors include diagnosis and hyperviscosity. VTE is very high in patients who receive high-dose dexamethasone, doxorubicin or multiagent chemotherapy in combination with thalidomide or lenalidomide, but not with bortezomib. The panel recommends aspirin for patients with  $\leq 1$  risk factor for VTE. LMWH (equivalent to enoxaparin 40 mg per day) is recommended for those with two or more individual/myeloma-related risk factors. LMWH is also recommended for all patients receiving concurrent high-dose dexamethasone or doxorubicin. Full-dose warfarin targeting a therapeutic INR of 2-3 is an alternative to LMWH, although there are limited data in the literature with this strategy. In the absence of clear data from randomized studies as a foundation for recommendations, many of the following proposed strategies are the results of common sense or derive from the extrapolation of data from many studies not specifically designed to answer these questions. Further investigation is needed to define the best VTE prophylaxis.

**👁️ *Thalidomide in consecutive multiple myeloma (MM) patients: single center analysis on practical aspects, efficacy, side effects and prognostic factors with lower thalidomide doses.***

Haas PS, Denz U, Ihorst G, Engelhardt M.

*Eur J Haematol.* 2007 Dec 21. [Epub ahead of print.]



[http://www.ncbi.nlm.nih.gov/pubmed/18182082?ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18182082?ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**In a single center analysis, the authors assess whether lower thalidomide doses are feasible and result in favorable treatment response in multiple myeloma patients and find that the strategy doses seems a feasible and attractive approach.**

Purpose: In this single center analysis, we assessed whether lower thalidomide doses are feasible and result in favourable treatment response in multiple myeloma (MM) patients. Results: Between 5/01 and 10/06, 38 consecutive MM patients received thalidomide. Their median age was 62.4 years, all had stage II/III MM and 31.6% had deletion 13q14 (del13q14). Prior to thalidomide, patients had received a median of two treatment lines. The median thalidomide dose was 100mg/day (d; range; 50-800) and the median treatment duration was 34 weeks. The median cumulative thalidomide dose was 24g. Sixteen patients received thalidomide as a single-agent and 22 in combination (+ dexamethasone; n=18, others; n=4). The median time to treatment failure (TTF) after thalidomide initiation was 30.4 weeks. Analysis of prognostic factors showed a significantly prolonged TTF without del13q14 (38.1 vs. 8.9 weeks with del13q14; p=0.006). Our analysis of TTF between thalidomide given alone vs. in combinations showed a better TTF for the combination (23.6 vs. 30.6 weeks), albeit not reaching significance (p=0.20). Other parameters, such as age, stage, prior SCT showed no difference in TTF. Peripheral polyneuropathy (PNP) frequencies were increased with longer (>28 weeks) and increased cumulative thalidomide doses (>40g), which emphasizes the need a) to carefully escalate thalidomide from 50 to 200mg/d, thereby reducing side effects and increasing patient compliance, and b) that PNP occurs more frequently with longer and higher thalidomide doses. Conclusion: The strategy to lower thalidomide doses seems a feasible and attractive approach in MM patients, this being currently tested in prospective randomized trials.

**👁️ *Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma.***

Lokhorst HM, Schmidt-Wolf I, Sonneveld P, van der Holt B, Martin H, Barge R, Bertsch U, Schlenzka J, Bos GM, Croockewit S, Zweegman S, Breitkreuz I, Joosten P, Scheid C, van Marwijk-Kooy M, Salwender HJ, van Oers MH, Schaafsma R, Naumann R, Sinnige H, Blau I, Verhoef G, de Weerd O, Wijermans P, Wittebol S, Duersen U, Vellenga E, Goldschmidt H; Dutch-Belgian HOVON; German GMMG.

*Haematologica.* 2008 Jan;93(1):124-7.



[http://www.ncbi.nlm.nih.gov/pubmed/18166796?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18166796?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**In the prospective phase 3 trial, patients randomized to TAD (thalidomide, doxorubicin, dexamethasone) have a significantly higher response rate after induction compared with patients randomized to VAD (vincristine, adriamycin, dexamethasone).**

In the prospective phase 3 HOVON-50/GMMG-HD3 trial, patients randomized to TAD (thalidomide, doxorubicin, dexamethasone) had a significantly higher response rate (at least PR) after induction compared with patients randomized to VAD (vincristine, adriamycin, dexamethasone, 72% vs. 54%, p<0.001). Complete remission (CR) and very good partial remission (VGPR) were also higher after TAD. After High Dose melphalan 200mg/m<sup>2</sup> response was comparable in both arms, 76% and 79% respectively. However, CR plus VGPR were significantly higher in the patients randomized to TAD (49% vs. 32%, p<0.001). CTC grade 3-4 adverse events were similar in both arms.

### ***An update on drug combinations for treatment of myeloma.***

Srikanth M, Davies FE, Morgan GJ.

Expert Opin Investig Drugs. 2008 Jan;17(1):1-12.



[http://www.ncbi.nlm.nih.gov/pubmed/18095914?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18095914?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss the enormous potential of using novel therapies in combination, such as thalidomide and lenalidomide, as challenges for both drug development and clinical trial evaluation.**

Multiple myeloma is the second most common haematological malignancy. It is becoming increasingly manageable with conventional and high-dose chemotherapy but there remains a critical need to develop both new drugs and combinations to improve long-term outcomes. Novel biological therapies that specifically target myeloma cells and/or their microenvironmental interactions are being developed that are highly effective, both as single agents and as combinations. Chief among these new agents are the proteasome inhibitor, bortezomib, and the immunomodulatory agents, thalidomide and lenalidomide. These drugs show improved single agent activity that is enhanced in combination. However, many drugs that are being developed in this setting may only have limited single agent activity, but combination use with these and other agents represents a very exciting way of targeting important pathogenic pathways crucial in myeloma development. This represents a challenge for both drug development and clinical trial evaluation, which has the potential to revolutionise the clinical management of myeloma and a paradigm for drug development in other diseases.

### ***Bone marrow angiogenesis and angiogenic factors in multiple myeloma treated with novel agents.***

Cibeira MT, Rozman M, Segarra M, Lozano E, Rosiñol L, Cid MC, Filella X, Bladé J.

*Cytokine*. 2008 Jan 3. [Epub ahead of print.]



[http://www.ncbi.nlm.nih.gov/pubmed/18178097?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18178097?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors study bone marrow angiogenesis in multiple myeloma treated with novel agents, including thalidomide and lenalidomide. They find that there is no relationship between microvessel density estimation and baseline serum levels of angiogenic cytokines.**

**Introduction.** An increased bone marrow (BM) angiogenesis is associated with poor outcome in multiple myeloma (MM). **Objective.** Angiogenesis study in MM treated with novel antimyeloma agents: thalidomide, lenalidomide, bortezomib, and with dexamethasone. **Patients and methods.** Forty-four patients with MM (14 newly diagnosed, 30 refractory/relapsed) were treated with novel agents at our institution. A BM biopsy was obtained before the initiation of therapy in 19. Angiogenesis was assessed by microvessel density (MVD) estimation in BM biopsies stained with the monoclonal anti-CD34 antibody, and by serum levels of angiogenic factors (VEGF, bFGF, and HGF) and cytokines (IL-6 and TNF-alpha). **Results.** A positive correlation was found between BM plasma cell involvement and MVD estimation ( $p=0.01$ ). However, MVD was not significantly correlated with either disease phase ( $p=0.065$ ) or response to therapy ( $p=0.79$ ). Neither baseline serum levels of angiogenic cytokines correlated to response to treatment. No significant correlation was found between BM MVD and serum levels of angiogenic cytokines. Serum levels of angiogenic cytokines before and after therapy showed a significant increase of bFGF ( $p=0.008$ ). **Conclusion.** There is no relationship between MVD estimation and baseline serum levels of angiogenic cytokines, neither between each of them and response to therapy.

### ***Recent advances in analytical determination of thalidomide and its metabolites.***

Bosch ME, Sánchez AJ, Rojas FS, Ojeda CB.

*J Pharm Biomed Anal*. 2008 Jan 7;46(1):9-17. [Epub 2007 Oct 9.]



[http://www.ncbi.nlm.nih.gov/pubmed/18023317?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18023317?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**This overview of thalidomide includes the most relevant analytical methodologies used in its determination.**

Thalidomide, a racemate, is coming into clinical use as immuno-modulating and anti-inflammatory drug. Thalidomide was approved by the FDA in July 1998 for the treatment of erythema nodosum leprosum associated with leprosy. Recently, thalidomide is proving to be a promising drug in the treatment of a number of cancers and inflammatory diseases, such as multiple myeloma, inflammatory bowel disease (Crohn's disease), HIV and cancer associated cachexia. These effects may chiefly be exerted by S-thalidomide, but the enantiomers are inter-converted in vivo. Thalidomide is given orally, although parenteral administration would be desirable in some clinical situations. Thalidomide has been determined in formulations and, principally in biological fluids by a variety of methods such as high-performance liquid chromatography with ultraviolet detection and liquid chromatography coupled with tandem mass spectrometry. The overview includes the most relevant analytical methodologies used in its determination.

### ***Stem-cell transplantation for multiple myeloma in the era of novel drugs.***

Bensinger W.

*J Clin Oncol.* 2008 Jan 20;26(3):480-92. [Epub 2007 Dec 3.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18056678?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18056678?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses how the substantial activity of new drug affects the role of stem-cell transplantation as myeloma treatment.**

The treatment of multiple myeloma (MM) is changing rapidly. During the last 10 years, higher rates of complete response (CR) and prolonged progression-free and overall survival have been seen with high-dose chemotherapy plus autologous stem-cell transplantation (HDT-ASCT). Achievement of CR and good partial response have been shown to be key prognostic factors for prolonged survival, with eradication of minimal residual disease seeming crucial to long-term disease-free survival. Until recently, high rates of CR and other major responses were primarily seen with HDT-ASCT, but insights into the biology of MM have led to the development and approval of new drugs with significant activity, and new induction regimens based on these novel agents are offering improved responses. Thalidomide, bortezomib, and lenalidomide have been combined with corticosteroids, alkylators, and anthracyclines in front-line MM treatment. Phase II studies have indicated that high rates of response and CR may be achieved. The substantial activity seen with these new drug combinations has prompted a re-examination of the role of SCT in MM treatment. Will achievement of major responses with these new regimens translate into improved survival after consolidation with transplantation? Will these improved induction regimens reduce the need for tandem transplantation, or does achievement of CR obviate the need for front-line transplantation altogether? To help address these questions, randomized trials are needed, as well as tests with improved sensitivity to better define depth of remission.

### ***Thalidomide in consecutive multiple myeloma patients: single-center analysis on practical aspects, efficacy, side effects and prognostic factors with lower thalidomide doses.***

Haas PS, Denz U, Ihorst G, Engelhardt M.

*Eur J Haematol.* 2008 Jan 21 [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18182082?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18182082?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors assess whether lower thalidomide doses are feasible and result in favorable treatment response in multiple myeloma (MM) patients and find that the strategy to lower thalidomide doses seems a feasible and attractive approach.**

Purpose: In this single-center analysis, we assessed whether lower thalidomide doses are feasible and result in favourable treatment response in multiple myeloma (MM) patients. Results: Between May 2001 and October 2006, 38 consecutive MM patients received thalidomide. Their median age was 62.4 yr, all had stage II/III MM and 31.6% had deletion 13q14 (del13q14). Prior to thalidomide, patients had received a median of two treatment lines. The median thalidomide dose was 100 mg/d (range 50-800) and the median treatment duration was 34 wk. The median cumulative thalidomide dose was 24 g. Sixteen patients received thalidomide as a single agent and 22 in combination (+ dexamethasone n = 18; others n = 4). The median time-to-treatment failure (TTF) after thalidomide initiation was 30.4 wk. Analysis of prognostic factors showed a significantly prolonged TTF without del13q14 (38.1 vs. 8.9 wk with del13q14; P = 0.006). Our analysis of TTF between thalidomide given alone vs. in combinations showed a better TTF for the combination (23.6 vs. 30.6 wk), albeit not reaching significance (P = 0.20). Other parameters, such as age, stage, and prior SCT showed no difference in TTF. Peripheral polyneuropathy (PNP) frequencies were increased with longer (>28 wk) and increased cumulative thalidomide doses (>40 g), which emphasizes (a) the need to carefully escalate thalidomide from 50 to 200 mg/d, thereby reducing side effects and increasing patient compliance, and (b) that PNP occurs more frequently with longer and higher thalidomide doses. Conclusion: The strategy to lower thalidomide doses seems a feasible and attractive approach in MM patients, this being currently tested in prospective randomized trials.

### ***Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma.***

Paripati H, Stewart AK, Cabou S, Dueck A, Zepeda VJ, Pirooz N, Ehlenbeck C, Reeder C, Slack J, Leis JF, Boesiger J, Torloni AS, Fonseca R, Bergsagel PL.

*Leukemia.* 2008 Jan 24 [Epub ahead of print]

 [http://www.ncbi.nlm.nih.gov/pubmed/18216870?ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18216870?ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

 ***Lenalidomide: A new therapy for multiple myeloma.***

Palumbo A, Miguel JS, Sonneveld P, Moreau P, Drach J, Morgan G, Einsele H.

*Cancer Treat Rev.* 2008 Jan 28. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18230411?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18230411?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors discuss the current and future roles of lenalidomide in myeloma treatment, alone and in combination.**

The last decade has seen rapid evolution in the management of multiple myeloma. Cytogenetic, molecular, and proteomic techniques have led to a better understanding of the pathophysiology and prognostic markers of this heterogeneous malignancy. New immunomodulatory drugs, such as lenalidomide, which interrupt myeloma growth and survival pathways have entered into clinical usage. Combined with dexamethasone, oral lenalidomide has proved to be highly effective in patients whose disease has become resistant to conventional therapy. Currently, several clinical trials are ongoing in order to define the optimal use of this new agent and its combinations across the spectrum of patients with myeloma. Whether the ultimate outcome of future research will be a single-treatment solution for all patients, or whether treatments will become better-tailored to the individual (based on prognostic markers and pre-existing co-morbidities) has yet to be determined.

 ***Prospective evaluation of coagulopathy in multiple myeloma patients before, during and after various chemotherapeutic regimens.***

van Marion AM, Auwerda JJ, Lisman T, Sonneveld P, de Maat MP, Lokhorst HM, Leebeek FW.

*Leuk Res.* 2008 Jan 30. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18241919?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18241919?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors perform a prospective study in 138 multiple myeloma patients in whom coagulation factor levels are evaluated longitudinally before, during induction and after intensification. During induction treatment several changes in coagulation factor levels are observed, which they find may result in a prothrombotic state. Larger studies are required to establish whether the changes in these coagulation factors during induction treatment contribute to the increased risk of venous thromboembolism in multiple myeloma patients.**

BACKGROUND: Venous thromboembolism (VTE) occurs frequently in multiple myeloma patients, especially during induction treatment with thalidomide in combination with anthracyclines and/or dexamethasone. Several coagulation abnormalities have been described in untreated myeloma patients, but these have not been prospectively evaluated during and after treatment. PATIENTS AND METHODS: We performed a prospective study in 138 multiple myeloma patients in whom coagulation factor levels were evaluated longitudinally before, during induction and after intensification. Patients were randomized to induction treatment consisting of adriamycin and dexamethason, in combination with either vincristin (VAD), thalidomide (TAD), or bortezomib (PAD) followed by high-dose melphalan (HDM) and autologous stem cell transplant (ASCT). RESULTS: Factor VIII:C (FVIII:C) and von Willebrand factor (VWF) were significantly elevated before treatment (median FVIII:C 2.26U/ml, VWF:Ag 1.95U/ml). Irrespective of the type of induction regimen, these variables increased strongly during induction therapy (FVIII:C 2.55U/ml and VWF:Ag 2.96U/ml). Fibrinogen also showed a significant increase after induction therapy (3.5g/l pre-treatment and 4.0g/l after treatment, respectively,  $P < 0.001$ ). This was significantly higher in TAD than VAD treated patients. Three to six month after ASCT levels of VWF and FVIII:C had decreased to values lower than observed before treatment (1.71 and 1.67U/ml respectively). There was no correlation between the increased levels at start and the response of multiple myeloma to treatment. High levels of VWF, fibrinogen and FVIII:C before start of treatment were significantly associated with mortality. Fourteen patients (10%) developed a venous thrombotic event (VTE). The coagulation factor abnormalities before and during treatment were not associated with the development of VTE. CONCLUSION: During induction treatment several changes in coagulation factor levels are observed, which may result in a prothrombotic state. Larger studies are required to establish whether the changes in these coagulation factors during induction treatment contribute to the increased risk of venous thromboembolism in multiple myeloma patients.

 ***Arterial and venous thrombotic complications with thalidomide in multiple myeloma.***

Alkindi S, Dennison D, Pathare A.

*Arch Med Res.* 2008 Feb;39(2):257-8. [Epub 2007 Nov 19.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18164975?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18164975?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

### ***Bone building with bortezomib.***

Roodman GD.

*J Clin Invest.* 2008 Feb;118(2):462-4.

 [http://www.ncbi.nlm.nih.gov/pubmed/18219395?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18219395?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The author discusses several myeloma treatments, including thalidomide and lenalidomide, which block the activity of bone-resorbing osteoclasts.**

In this issue of the JCI, Mukherjee et al. report that bortezomib, a clinically available proteasome inhibitor active against myeloma, induces the differentiation of mesenchymal stem/progenitor cells (MSCs)--rather than mature osteoprogenitor cells--into osteoblasts, resulting in new bone formation (see the related article beginning on page 491). These results were observed when MSCs were implanted subcutaneously in mice or were used to treat a mouse model of postmenopausal bone loss. Others have reported that immunomodulatory drugs (e.g., thalidomide and lenalidomide), which are active against myeloma, also block the activity of bone-resorbing osteoclasts. These results reflect the utility of targeting endogenous MSCs for the purpose of tissue repair and suggest that combining different classes of agents that are antineoplastic and also inhibit bone destruction and increase bone formation should be very beneficial for myeloma patients suffering from severe bone disease.

### ***Novel tubulin-polymerization inhibitor derived from thalidomide directly induces apoptosis in human multiple myeloma cells: possible anti-myeloma mechanism of thalidomide.***

Iguchi T, Yachide-Noguchi T, Hashimoto Y, Nakazato S, Sagawa M, Ikeda Y, Kizaki M.

*Int J Mol Med.* 2008 Feb;21(2):163-8.

 [http://www.ncbi.nlm.nih.gov/pubmed/18204782?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18204782?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**To ascertain the exact anti-myeloma mechanism of thalidomide in vivo, the authors perform structural development studies of thalidomide. Their results suggest that the tubulin-polymerization inhibiting activity of thalidomide might be a possible mechanism for inducing the apoptosis of myeloma cells by thalidomide.**

To ascertain the exact anti-myeloma mechanism of thalidomide in vivo, we performed structural development studies of thalidomide, and obtained various analogues with specific molecular properties. Among these derivatives, we found that a new thalidomide analogue, 2-(2,6-diisopropylphenyl)-5-hydroxy-1H-isindole-1,3-dione (5HPP-33) had the most potent anti-myeloma effect and tubulin-polymerization-inhibiting activity. 5HPP-33 directly inhibited the growth and survival of various myeloma cell lines (RPMI8226, U266, and IM9) in a dose-dependent manner with IC50 of 1-10 microM. In contrast, thalidomide itself did not inhibit cellular growth of RPMI8226 cells. Cultivation with 10 microM 5HPP-33 induced G2/M phase cell cycle arrest, followed by apoptosis of myeloma cells. Treatment with 5HPP-33 induced caspase-3 activity and PARP cleavage. A tubulin polymerization assay using microtubule protein from porcine brain revealed that 5HPP-33 showed potent tubulin-polymerization-inhibiting activity with IC50 of 8.1 microM, comparable to that of the known tubulin-polymerization inhibitor, rhizoxin. Moreover, its activity was more potent than that of a known thalidomide metabolite, 5-hydroxythalidomide. Notably, the structural requirement for its activity was critical, as other analogues and derivatives of 5HPP-33 showed only slight tubulin-polymerization-inhibiting activity. Our data suggest that 5HPP-33 is a promising candidates for a therapeutic agent of multiple myeloma. In addition, these results suggest that the tubulin-polymerization inhibiting activity of thalidomide might be a possible mechanism for inducing the apoptosis of myeloma cells by thalidomide.

### ***Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma.***

Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, Harousseau J, Zonder JA, Cavo M, Zangari M, Attal M, Belch A, Knop S, Joshua D, Sezer O, Ludwig H, Vesole D, Bladé J, Kyle R, Westin J, Weber D, Brinchen S, Niesvizky R, Waage A, von Lilienfeld-Toal M, Lonial S, Morgan GJ, Orłowski RZ, Shimizu K, Anderson KC, Boccadoro M, Durie BG, Sonneveld P, Hussein MA; International Myeloma Working Group.

*Leukemia.* 2008 Feb;22(2):414-23. [Epub 2007 Dec 20.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18094721?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18094721?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**This article summarizes the available evidence related to incidents of venous thromboembolism related to thalidomide and lenalidomide treatment of myeloma, and recommends a prophylaxis strategy according to a risk-assessment model.**

The incidence of venous thromboembolism (VTE) is more than 1 per thousand annually in the general population and increases further in cancer patients. The risk of VTE is higher in multiple myeloma (MM) patients who receive thalidomide or lenalidomide, especially in combination with dexamethasone or chemotherapy. Various VTE prophylaxis strategies, such as low-molecular-weight heparin (LMWH), warfarin or aspirin, have been investigated in small, uncontrolled clinical studies. This manuscript summarizes the available evidence and recommends a prophylaxis strategy according to a risk-assessment model. Individual risk factors for thrombosis associated with thalidomide/lenalidomide-based therapy include age, history of VTE, central venous catheter, comorbidities (infections, diabetes, cardiac disease), immobilization, surgery and inherited thrombophilia. Myeloma-related risk factors include diagnosis and hyperviscosity. VTE is very high in patients who receive high-dose dexamethasone, doxorubicin or multiagent chemotherapy in combination with thalidomide or lenalidomide, but not with bortezomib. The panel recommends aspirin for patients with < or = 1 risk factor for VTE. LMWH (equivalent to enoxaparin 40 mg per day) is recommended for those with two or more individual/myeloma-related risk factors. LMWH is also recommended for all patients receiving concurrent high-dose dexamethasone or doxorubicin. Full-dose warfarin targeting a therapeutic INR of 2-3 is an alternative to LMWH, although there are limited data in the literature with this strategy. In the absence of clear data from randomized studies as a foundation for recommendations, many of the following proposed strategies are the results of common sense or derive from the extrapolation of data from many studies not specifically designed to answer these questions. Further investigation is needed to define the best VTE prophylaxis.

### ***BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naïve 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.* 2008 Feb 1;111(3):1101-9. [Epub 2007 Nov 7.]

 [http://www.ncbi.nlm.nih.gov/pubmed/17989313?ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17989313?ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors determine the safety and efficacy of the combination regimen clarithromycin (Biaxin), lenalidomide (Revlimid), and dexamethasone (BiRD) as first-line therapy for multiple myeloma and find BiRD to be an effective regimen with manageable side effects in the treatment of symptomatic, newly diagnosed myeloma.**

This trial determined the safety and efficacy of the combination regimen clarithromycin (Biaxin), lenalidomide (Revlimid), 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 to 21. Objective response was defined by standard criteria (ie, decrease in serum monoclonal protein [M-protein] by at least 50%, and a decrease in urine M-protein by at least 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 at least a 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 transplants received continued therapy (complete response, 37%; very good partial response, 33%). The major adverse events 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.

### ***Thalidomide for treatment of multiple myeloma: 10 years later.***

Palumbo A, Facon T, Sonneveld P, Blade J, Offidani M, Gay F, Moreau P, Waage A, Spencer A, Ludwig H, Boccadoro M, Harousseau JL.

*Blood*. 2008 Feb 1. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18245666?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18245666?ordinalpos=40&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors review the most effective uses of thalidomide in the treatment of myeloma, as well as treatment side effects.**

Thalidomide, bortezomib and lenalidomide have recently changed the treatment paradigm of myeloma. In young newly diagnosed patients, the combination of thalidomide and dexamethasone has been widely used as induction treatment before autologous transplant (ASCT). In two randomised studies, consolidation or maintenance with low-dose thalidomide has extended both progression-free and overall survival in patients who received ASCT at diagnosis. In elderly newly diagnosed patients, two independent randomised studies have reported that the oral combination of melphalan and prednisone plus thalidomide (MPT) is better than the standard melphalan and prednisone (MP). These studies have shown better progression-free survival, and two have shown improved overall survival for patients assigned to MPT. In refractory-relapsed disease, combinations including thalidomide with dexamethasone, melphalan, doxorubicin or cyclophosphamide have been extensively investigated. The risks of side-effects are greater when thalidomide is used in combination with other drugs. Thromboembolism and peripheral neuropathy are the major concern. The introduction of anticoagulant prophylaxis has reduced the rate of thromboembolism to less than 10%. Immediate thalidomide dose-reduction or discontinuation when paresthesia is complicated by pain or motor deficit has decreased the severity of neuropathy. Future studies will define the most effective or the best sequence of combinations which could improve life expectancy.

### ***Bisphosphonate-induced osteonecrosis of the jaws: Prospective study of 80 patients with multiple myeloma and other malignancies.***

Boonyapakorn T, Schirmer I, Reichart PA, Sturm I, Massenkeil G.

*Oral Oncol*. 2008 Feb 15. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18282788?ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18282788?ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**This prospective study is performed in 80 patients receiving bisphosphonates in order to determine frequency of occurrence, risk factors, clinical presentation, radiology, pathology and proper treatment of osteonecrosis of the jaw (ONJ). The authors find no association of ONJ with thalidomide.**

A prospective study was performed in 80 patients receiving bisphosphonates in order to determine frequency of occurrence, risk factors, clinical presentation, radiology, pathology and proper treatment of osteonecrosis of the jaw (ONJ). Of 80 patients, 22 (28%) developed ONJ. There were 11 male and 11 female patients. Median age was 65 years. Ten patients (46%) had multiple myeloma (MM), 5 (23%) had breast cancer and 7 (32%) had other malignancies. Of 22 patients with ONJ, 14 patients (64%) received zoledronate, 3 (14%) received pamidronate, 4 (18%) received pamidronate later followed by zoledronate and 1 patient received ibandronate later followed by zoledronate. The median time of exposure in ONJ group was 32 months compared with 27 months in patients without ONJ. The mean induction time until bone exposure was 26 months for patients who received zoledronate, 54 months for pamidronate and 48 months for pamidronate followed by zoledronate. Thirteen patients (59%) had ONJ with bone exposure of mandible, 6 (27%) of maxilla and 3 (14%) of both jaws. ONJ occurred spontaneously in 5 patients (23%) and in 17 patients (77%) occurred after tooth extractions and surgical tooth removals ( $P < 0.001$ ). Nine patients (41%) had previous extractions of molars, 6 (27%) of premolars and 2 (9%) of front teeth. The cumulative hazard is significantly higher in zoledronate group ( $P = 0.015$ ). It was 3.48 times higher than the other group (pamidronate alone; pamidronate followed by zoledronate; ibandronate alone; etidronate alone; ibandronate followed by pamidronate; ibandronate followed by zoledronate; ibandronate followed by pamidronate and zoledronate). There was no association of ONJ with age, sex, use of high-dose or conventional chemotherapy or the use of corticosteroids, thalidomide or bortezomib ( $P > 0.05$ ). Patients diagnosed with multiple myeloma and breast cancer were found significantly associated with ONJ ( $P = 0.001$  and  $P = 0.014$ , respectively). Long-term use of bisphosphonates ( $> 2.5$  years) increases the risk for development of ONJ. Intravenous application of zoledronate and previous dental extractions or surgical tooth removals are important risk factors of ONJ. Neither treatment with high-dose chemotherapy with autologous stem cell transplantation nor treatment with corticosteroids, thalidomide or bortezomib is a risk factor in this study.

**👁️ *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, Othman TB, Lakhal A, Romdhane NB, Omri HE, Elloumi M, Belaaj H, Jeddi R, Aissaoui L, Ksouri H, Hassen AB, Msadek F, Saad A, Hsairi M, Boukef K, Amouri A, Louzir H, Dellagi K, Abdeladhim AB; on behalf of the Tunisian Multiple Myeloma Study Group.

*Blood.* 2008 Feb 15;111(4):1805-1810. [Epub 2007 Sep 17.]

 [http://www.ncbi.nlm.nih.gov/pubmed/17875806?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17875806?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

appears superior to tandem transplant in this setting.

**The authors find that up-front single autologous transplantation 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 younger 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/m<sup>2</sup>) 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 transplantation 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

**👁️ *Thromboembolic events with lenalidomide-based therapy for multiple myeloma.***

Menon SP, Rajkumar SV, Lacy M, Falco P, Palumbo A.

*Cancer.* 2008 Feb 15. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18278812?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18278812?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors evaluate the incidence and risk factors of thromboembolism associated with lenalidomide therapy in newly diagnosed myeloma and find the incidence of deep vein thrombosis is lower than previously reported in the literature.**

BACKGROUND.: The purpose was to evaluate the incidence and risk factors of thromboembolism associated with lenalidomide therapy in newly diagnosed myeloma. METHODS.: A pooled analysis was performed of patients with previously untreated multiple myeloma enrolled in clinical trials of lenalidomide-based therapy at the Mayo Clinic, Rochester, Minnesota, and the Italian Myeloma Network, Italy. The incidence of thrombosis, the effect of risk factors such as steroid dose and erythropoietin supplementation, and the effect of prophylaxis were examined. RESULTS.: In all, 125 patients enrolled in 3 clinical trials were identified. Patients were stratified based on the concomitant corticosteroid dose. Fifty-two patients were in the high-dose group (dexamethasone 40 mg, 12 days a month); 73 patients were in the low-dose group (prednisone at any dose; or dexamethasone 40 mg, 4 days a month). A total of 110 patients were initiated on thromboprophylaxis; of these, 104 patients (95%) received aspirin. Ten patients (8%) developed deep vein thrombosis, including 4 who were not receiving any thromboprophylaxis at the time of the event. The rate of thromboembolic events was not different between patients who received concomitant erythropoietin therapy and those who did not, 4.8% and 8.6%, respectively (P = .54). A higher number of venous thrombotic episodes occurred in the high-dose corticosteroid group compared with the low-dose corticosteroid therapy group (12% vs 6%), but the difference was not statistically significant (P = .3). CONCLUSIONS.: The incidence of deep vein thrombosis is lower than previously reported in the literature. There was a trend to a higher incidence of thrombosis in patients receiving high-dose corticosteroid therapy.

 ***Bone marrow angiogenesis and angiogenic factors in multiple myeloma treated with novel agents.***

Cibeira MT, Rozman M, Segarra M, Lozano E, Rosiñol L, Cid MC, Filella X, Bladé J.

*Cytokine*. 2008 Mar;41(3):244-53. [Epub 2008 Jan 4.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18178097?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18178097?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors perform an angiogenesis study in myeloma treated with thalidomide, lenalidomide, bortezomib, and with dexamethasone.**

INTRODUCTION: An increased bone marrow (BM) angiogenesis is associated with poor outcome in multiple myeloma (MM). OBJECTIVE: Angiogenesis study in MM treated with novel antimyeloma agents: thalidomide, lenalidomide, bortezomib, and with dexamethasone. PATIENTS AND METHODS: Forty-four patients with MM (14 newly diagnosed, 30 refractory/relapsed) were treated with novel agents at our institution. A BM biopsy was obtained before the initiation of therapy in 19. Angiogenesis was assessed by microvessel density (MVD) estimation in BM biopsies stained with the monoclonal anti-CD34 antibody, and by serum levels of angiogenic factors (VEGF, bFGF, and HGF) and cytokines (IL-6 and TNF-alpha). RESULTS: A positive correlation was found between BM plasma cell involvement and MVD estimation ( $p=0.01$ ). However, MVD was not significantly correlated with either disease phase ( $p=0.065$ ) or response to therapy ( $p=0.79$ ). Neither baseline serum levels of angiogenic cytokines correlated to response to treatment. No significant correlation was found between BM MVD and serum levels of angiogenic cytokines. Serum levels of angiogenic cytokines before and after therapy showed a significant increase of bFGF ( $p=0.008$ ). CONCLUSION: There is no relationship between MVD estimation and baseline serum levels of angiogenic cytokines, neither between each of them and response to therapy.

 ***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*. 2008 Mar;87(3):253-4. [Epub 2007 Oct 23.]

 [http://www.ncbi.nlm.nih.gov/pubmed/17955241?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17955241?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

 ***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*. 2008 Mar 1;111(5):2516-20. [Epub 2007 Nov 1.]

 [http://www.ncbi.nlm.nih.gov/pubmed/17975015?ordinalpos=25&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17975015?ordinalpos=25&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 2 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 transplantation, 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 versus 11.8 months ( $P < .001$ ) 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;  $P < .001$ ). 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;  $P < .001$ ). In this study, we demonstrate improved outcome of patients with myeloma in recent years, both in the relapsed setting as well as at diagnosis.

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

Brenner H, Gondos A, Pulte D.

*Blood*. 2008 Mar 1;111(5):2521-6. [Epub 2007 Sep 27.]

 [http://www.ncbi.nlm.nih.gov/pubmed/17901246?ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17901246?ordinalpos=26&itool=EntrezSystem2.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 to 10 years after diagnosis. Within the past decade, several new therapeutic interventions have been introduced, including autologous stem-cell transplantation, thalidomide, lenalidomide, and bortezomib. We estimated trends in age-specific 5- and 10-year relative survival of patients with MM 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 used to show most recent developments. Overall, 5-year relative survival increased from 28.8% to 34.7% ( $P < .001$ ), and 10-year relative survival increased from 11.1% to 17.4% ( $P < .001$ ) between 1990-1992 and 2002-2004. Much stronger increases were seen in the age group younger than 50 years, leading to 5- and 10-year relative survival of 56.7% and 41.3% in 2002-2004, and in the age group 50 to 59 years, leading to 5- and 10-year relative survival of 48.2% and 28.6% in 200-2004. By contrast, only moderate improvement was seen in the age group 60 to 69 years, 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 effect of recent advances in therapy and their dissemination in clinical practice.

 ***Completely reversible agranulocytosis in a multiple myeloma patient treated with thalidomide-dexamethasone.***

Magalini F, Stella A, Sansoni P.

*Intern Emerg Med*. 2008 Mar 5. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18320148?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18320148?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

 ***Impact of pretransplant therapy in patients with newly diagnosed myeloma undergoing autologous SCT.***

Kumar SK, Dingli D, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Rajkumar SV, Litzow MR, Gertz MA.

*Bone Marrow Transplant*. 2008 Mar 10. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18332915?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18332915?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors study 472 patients undergoing autologous stem cell transplant (ASCT) within 12 months of myeloma diagnosis and find that the nature of initial treatment utilized (including combinations incorporating thalidomide and lenalidomide) has no long-term impact on the outcome of ASCT.**

Autologous SCT (ASCT) remains an effective therapy for eligible patients with myeloma. Previous studies have suggested a lack of impact of the initial therapy on the outcome after ASCT. It is not clear if incorporation of new agents in the initial treatment regimens will have any impact on the outcome after ASCT. We studied 472 patients undergoing ASCT within 12 months of diagnosis to assess the effect of initial therapy on the outcome after ASCT. Patients received initial therapy with vincristine, adriamycin and dexamethasone (VAD), dexamethasone, thalidomide and dexamethasone or lenalidomide and dexamethasone. While patients treated with dexamethasone alone had higher disease burden at ASCT, no differences were observed in the response rates to ASCT, post transplant complications or treatment-related mortality among the groups. The median time to progression after ASCT was 27.1, 24.7, 21.1 months and did not reach the VAD, Dex, Thal-Dex and Len-Dex group, respectively,  $P=0.11$ . The median overall survival from ASCT was 62 months for VAD, 69.6 months for Dex and were not reached for Thal-Dex and Len-Dex groups,  $P=0.2$ . For patients undergoing early ASCT for myeloma, the nature of initial treatment utilized has no long-term impact on the outcome of ASCT.

 ***The insulin-like growth factor-I receptor inhibitor NVP-AEW541 provokes cell cycle arrest and apoptosis in multiple myeloma cells.***

Maiso P, Ocio EM, Garayoa M, Montero JC, Hofmann F, García-Echeverría C, Zimmermann J, Pandiella A, San Miguel JF.  
*Br J Haematol.* 2008 Mar 12. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18341634?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18341634?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors find that NVP-AEW541 potentiates the action of myeloma drugs, including lenalidomide.**

Multiple myeloma (MM) is a B-cell malignancy characterized by accumulation of monoclonal plasma cells in the bone marrow (BM). Despite recent advances in the treatment, MM represents an incurable disease for which development of new therapies is required. We report the antimyeloma effect of NVP-AEW541, a small molecule that belongs to the pyrrolo[2,3-d]pyrimidine class, identified as a selective inhibitor of the insulin-like growth factor-I receptor (IGF-IR) in vitro kinase activity. NVP-AEW541 had a potent cytotoxic effect on fresh cells and in a murine MM model. NVP-AEW541 partially abrogated the proliferative advantage conferred by the coculture with BM stromal cells and the presence of growth factors produced by the BM microenvironment. In addition, NVP-AEW541 potentiated the action of drugs, such as bortezomib, lenalidomide, dexamethasone or melphalan. Moreover the triple combination of NVP-AEW541, dexamethasone and bortezomib resulted in a significant increase in growth inhibition. Mechanistic studies indicated that NVP-AEW541 provoked a marked cell cycle blockade accompanied by pRb downregulation. Interestingly, NVP-AEW541 increased the levels of p27 associated with a reduction in the CDK2 activity. Finally, NVP-AEW541 induced cell death through caspase-dependent and -independent mechanisms. All these data, suggest the potential effect of IGF-IR kinase inhibitors as therapeutic agents for MM patients.

 ***Does the addition of thalidomide to MP or low-intensity SCT improve survival in elderly multiple myeloma patients?***

Corradini P, Montefusco V.

*Nat Clin Pract Oncol.* 2008 Mar 18. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18349855?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18349855?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

No abstract available.

 ***Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Thalidomide Plus Dexamethasone Compared With Dexamethasone As Initial Therapy for Newly Diagnosed Multiple Myeloma.***

Rajkumar SV, Rosiñol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, Olesnyckyj M, Yu Z, Knight R, Zeldis JB, Bladé J.  
*J Clin Oncol.* 2008 Mar 24. [Epub ahead of print.]

 [http://www.ncbi.nlm.nih.gov/pubmed/18362366?ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18362366?ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)

**The authors compare thalidomide plus dexamethasone versus placebo plus dexamethasone (placebo/dex) as primary therapy for newly diagnosed myeloma and find that thal/dex results in significantly higher response rates and significantly prolongs time to progression compared with dexamethasone alone in patients with newly diagnosed myeloma.**

**PURPOSE:** The long-term impact of thalidomide plus dexamethasone (thal/dex) as primary therapy for newly diagnosed multiple myeloma (MM) is unknown. The goal of this study was to compare thalidomide plus dexamethasone versus placebo plus dexamethasone (placebo/dex) as primary therapy for newly diagnosed MM. **PATIENTS AND METHODS:** In this double-blind, placebo-controlled trial, patients with untreated symptomatic MM were randomized to thal/dex (arm A) or to placebo plus dexamethasone (dex) (arm B). Patients in arm A received oral thalidomide 50 mg daily, escalated to 100 mg on day 15, and to 200 mg from day 1 of cycle 2 (28-day cycles). Oral dex 40 mg was administered on days 1 through 4, 9 through 12, and 17 through 20 during cycles 1 through 4 and on days 1 through 4 only from cycle 5 onwards. Patients in arm B received placebo and dex, administered as in arm A. The primary end point of the study was time to progression. This study is registered at <http://ClinicalTrials.gov> (NCT00057564). **RESULTS:** A total of 470 patients were enrolled (235 randomly assigned to thal/dex and 235 to placebo/dex). The overall response rate was significantly higher with thal/dex compared with placebo/dex (63% v 46%),  $P < .001$ . Time to progression (TTP) was significantly longer with thal/dex compared with placebo/dex (median, 22.6 v 6.5 months,  $P < 0.001$ ). Grade 4 adverse events were more frequent with thal/dex than with placebo/dex (30.3% v 22.8%). **CONCLUSION:** Thal/dex results in significantly higher response rates and significantly prolongs TTP compared with dexamethasone alone in patients with newly diagnosed MM.



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