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### Thalidomide and Revlimid<sup>TM</sup> Issue II

The INTERNATIONAL MYELOMA FOUNDATION (IMF)) is pleased to present our second edition of CITINGS, a new, quarterly publication featuring the most up-to-date information on treatment for multiple myeloma. Our second issue continues our focus on thalidomide and Revlimid<sup>TM</sup> for the treatment of myeloma. We have provided Internet links to the complete abstracts of the U.S. and internatonal studies listed here. We invite your feedback by calling (800)452-CURE or clicking on www.myeloma.org.

--Susie Novis, President, IMF

Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma. Palumbo A, Bertola A, Falco P, Rosato R, Cavallo F, Giaccone L, Bringhen S, Musto P, Pregno P, Caravita T, Ciccone G, Boccadoro M. The Hematology Journal (2004) 5(4):318-24.

http://www.nature.com/cgi-taf/DynaPage.taf?file=/thj/journal/v5/n4/abs/6200403a. html&dynoptions=doi1092260398 This article concludes that as first salvage regimen, thalidomide and dexamethasone (THAL-DEX) was

superior to CC; as second or third salvage regimen, it was equivalent to CC. THAL-DEX is not myelotoxic. It postpones the delivery of effective salvage chemotherapy. This might explain the survival benefit.

Thalidomide plus oral melphalan compared with thalidomide alone for advanced multiple myeloma. Offidani M, Corvatta L, Marconi M, Olivieri A, Catarini M, Mele A, Brunori M, Candela M, Malerba L, Capelli D, Montanari M, Leoni P. The Hematology Journal (2004) 5(4):312-7.

http://www.nature.com/cgi-taf/DynaPage.taf?file=/thj/journal/v5/n4/abs/6200401a. html&dynoptions=doi1092261269

The aim of this study was to compare the toxicity and efficacy of thalidomide alone and in combination with oral melphalan. Thalidomide administered with oral melphalan improved response rates and PFS in patients with advanced multiple myeloma (MM) without significantly increasing severe toxicity.

An update of novel therapeutic approaches for multiple myeloma. Richardson P, Hideshima T, Anderson KC.

Current Treatment Options in Oncology 2004 Jun;5(3):227-38.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_uid s=15115651

Recent studies have characterized the molecular mechanisms by which MM cell/host bone marrow (BM) interactions regulate tumor cell growth, survival, and migration in the BM milieu. These studies have not only enhanced our understanding of disease pathogenesis, but they have also provided the framework for a new treatment paradigm targeting the MM cell in its BM microenvironment to overcome drug resistance and improve patient outcome.

- Oct-5013 (Celgene). Mitsiades CS, Mitsiades N. Curr Opin Investig Drugs 2004 Jun;5(6):635-47.

## http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_uid s=15242253

Celgene, in collaboration with the National Cancer Institute, is developing CC-5013, the lead compound in a series of thalidomide derivatives that inhibit TNF-alpha overproduction, for the potential treatment of hematological and solid tumor cancers and inflammatory diseases.

Thalidomide treatment of patients with refractory myeloma in the institutes participating in the Japan Myeloma Study Group. [Article in Japanese] Murakami H, Handa H, Imai K, Kanakura Y, Kosaka M, Sawamura M, Shimazaki C, Suzuki K, Ishii A, Takagi T, Taniwaki M, Togawa A, Hata H, Wakayama T, Takatsuki K; Japan Myeloma Study Group. Rinsho Ketsueki 2004 Jun;45(6):468-72.

#### http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ui ds=15287523

Thalidomide was used in 73 patients with refractory myeloma in 15 of 45 institutes participating in the Japan Myeloma Study Group. The mean age and male/female ratio were 63.8 years and 0.92 (35/38), respectively. The authors concluded that low-dose thalidomide is a useful and safe tool for the treatment of refractory myeloma.

Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. Cavaletti G, Beronio A, Reni L, Ghiglione E, Schenone A, Briani C, Zara G, Cocito D, Isoardo G, Ciaramitaro P, Plasmati R, Pastorelli F, Frigo M, Piatti M, Carpo M.

Neurology 2004 Jun 22;62(12):2291-3.

#### http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ uids=15210898

The clinical and neurophysiologic data from 65 patients taking thalidomide were reviewed. Thalidomide sensory neurotoxicity was found to be cumulatively dose- dependent but occurs only when the total dose is relatively high (>20 g). The authors conclude that the risk of developing sensory neuropathy is around 10% below this threshold but increases with higher doses.

First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. Cavo M, Zamagni E, Tosi P, Cellini C, Cangini D, Tacchetti P, Testoni N, Tonelli M, De Vivo A, Palareti G, Tura S, Baccarani M. Haematologica 2004 Jul;89(7):826-31.

#### http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ uids=15257934

The authors concluded that the combination of thalidomide and dexamethasone is an effective and relatively well-tolerated induction regimen for previously untreated patients with MM. This combination may provide an oral alternative to vincristine-doxorubicin-dexamethasone in preparation for autologous stem cell transplantation.

Extramedullary multiple myeloma escapes the effect of thalidomide. Rosinol L, Cibeira MT, Blade J, Esteve J, Aymerich M, Rozman M, Segarra M, Cid MC, Filella X, Montserrat E. Haematologica 2004 Jul;89(7):832-6.

http://www.haematologica.org/journal/2004/7/832/ This study found that although thalidomide is effective in patients with advanced MM, extramedullary disease does not respond to thalidomide, as delivered in this series. The mechanisms to explain different response to therapy depending on tumor homing warrant further investigation.

- Thalidomide in cancer medicine. Eleutherakis-Papaiakovou V, Bamias A, Dimopoulos MA. Annals of Oncology 2004 Aug; 15(8):1151-60.
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ uids=15277253

Thalidomide, an oral agent with antiangiogenic and immunomodulatory properties, is being investigated extensively in the management of advanced cancer. Multiple studies with large numbers of patients have confirmed that this drug has significant activity in multiple myeloma.

### Plasma cell disorders in HIV-infected patients: from benign gammopathy to multiple myeloma. Dezube BJ, Aboulafia DM, Pantanowitz L... AIDS Read 2004 Jul;14(7):372-4, 377-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ui ds=15282866

Plasma cell disorders are not uncommonly reported in young patients with HIV infection. These disorders range from benign polyclonal hypergammaglobulinemia to indeterminate monoclonal gammopathy of unknown significance (MGUS) to malignant dyscrasias, including multiple myeloma and plasma cell leukemia. This study found that treatment with immunomodulatory agents (eg, thalidomide) and proteasome inhibitors (eg, bortezomib) may be worth considering. In the next few years, it is anticipated that these approaches will be applied more frequently to HIV-infected persons with myeloma.

Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. Richardson P, Schlossman R, Jagannath S, Alsina M, Desikan R, Blood E, Weller E, Mitsiades C, Hideshima T, Davies F, Doss D, Freeman A, Bosch J, Patin J, Knight R, Zeldis J, Dalton W, Anderson K.

Mayo Clin Proc 2004 Jul;79(7):875-82.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ui ds=15244383

The objective of this study was to determine the progression-free survival at 12 weeks, to evaluate the toxic effects, and to analyze the biological activity of thalidomide in patients with relapsed MM after high-dose chemotherapy and stem cell transplantation. The study concluded that the dose of thalidomide therapy should be based on the individual patient to ensure that it is well tolerated and that a response is achieved.

Modification of thrombomodulin plasma levels in refractory myeloma patients during treatment with thalidomide and dexamethasone. Corso A, Lorenzi A, Terulla V, Airo F, Varettoni M, Mangiacavalli S, Zappasodi P, Rusconi C, Lazzarino M. Annals of Hematology 2004 Jul 3.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ui ds=15235749

The authors conclude that the evidence of significant variations of thrombomodulin values in the first month of therapy, which is considered to involve the highest risk of thrombosis, might support a role for thrombomodulin in this complex mechanism.

Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. Tosi P, Zamagni E, Cellini C, Cangini D, Tacchetti P, Tura S, Baccarani M, Cavo M.

European Journal of Haematology 2004 Aug;73(2):98-103.

http://www.blackwell-synergy.com/openurl?genre=article&sid=nlm:pubmed&issn=1320-5463&date=2004&volume=54&issue=5&spage=285

This study was concerned with salvage therapy of patients with advanced, relapsed and refractory MM, which is often limited by poor marrow reserve and multi-organ impairment. The authors concluded that thalidomide can be safely administered in patients with advanced MM and renal failure.

Immunomodulatory derivative of thalidomide (IMiD CC-4047) [Actimid<sup>™</sup>]induces a shift in lineage commitment by suppressing erythropoiesis and promoting myelopoiesis. Koh KR, Janz M, Mapara MY, Lemke B, Stirling D, Dorken B, Zenke M, Lentzsch S. Blood (2004) Aug 3.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_ui ds=15292067

The authors investigated the effect of CC-4047 on lineage commitment and differentiation of hematopoietic stem cells. Their data indicate that CC-4047 might directly influence lineage commitment of hematopoietic cells by increasing the propensity of stem and/or progenitor cells to undergo myeloid cell development and concomitantly inhibiting red cell development. Therefore, CC-4047 provides a valuable tool to study the mechanisms underlying lineage commitment.

 Low-dose thalidomide and donor lymphocyte infusion as adoptive immunotherapy after allogeneic stem cell transplantation in patients with multiple myeloma. Kroger N, Shimoni A, Zagrivnaja M, Ayuk F, Lioznov M, Schieder H, Renges H, Fehse B, Zabelina T, Nagler A, Zander AR.

Blood (2004) Aug 3.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_uid s=15292062

To improve anti-myeloma effect of donor lymphocyte infusion (DLI) after allogeneic stem cell transplantation in multiple myeloma, the authors investigated in a phase I/II study the effect of low-dose thalidomide (100 mg) followed by DLI in 18 patients with progressive disease or residual disease and prior ineffective DLI after allografting. They concluded that adoptive immunotherapy with low-dose thalidomide and DLI induces strong anti-myeloma effect with low incidence of graft versus host disease.

Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. Schey SA, Fields P, Bartlett JB, Clarke IA, Ashan G, Knight RD, Streetly M, Dalgleish AG.

Journal of Clinical Oncology 2004 Aug 15;22(16):3269-76.

## http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_uids=15249589

This study demonstrates the safety and efficacy of CC-4047. The MTD of CC-4047 orally was 200 mg/dL. This is the first report demonstrating in vivo T-cell costimulation by this class of compound, supporting a potential role for CC-4047 as an immunostimulatory adjuvant treatment.

# Combination of the mTOR inhibitor rapamycin and Revlimid<sup>™</sup> (CC-5013) has synergistic activity in multiple myeloma.

Raje N, Kumar S, Hideshima T, Ishitsuka K, Chauhan D, Mitsiades C, Podar K, Le Gouill S, Richardson P, Munshi NC, Stirling DI, Antin JH, Anderson KC. *Blood (2004) Aug 19.* 

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_uid s=15319277

The authors examined the anti-MM activity of rapamycin, a specific mTOR inhibitor, combined with Revlimid<sup>™</sup>. Based on the Chou-Talalay method, combination indices of < 1 were obtained for all dose ranges of Revlimid<sup>™</sup> when combined with rapamycin, suggesting strong synergism. Importantly, this combination was able to overcome drug resistance when tested against MM cell lines resistant to conventional chemotherapy. Moreover, the combination, but not rapamycin alone, was able to overcome the growth advantage conferred on MM cells by Interleukin-6 (IL-6), Insulin-like growth factor-1 (IGF-1), or adherence to bone marrow stromal cells (BMSCs).