

Published by the International Myeloma Foundation

VOLUME II : ISSUE II : SPRING 2005

Thalidomide Issue

THE INTERNATIONAL MYELOMA FOUNDATION (IMF) is pleased to present our second issue of CITINGS for 2005. In this issue we are continuing our series focusing specifically on publications referring to thalidomide.

CITINGS is a relatively new, quarterly publication of the IMF. The goal of CITINGS is to provide the latest, most up-to-date list of publications on a key issue related to myeloma, along with a citation, web address, and brief summary of the study. CITINGS focuses on new treatments, drug regimens, and procedures that affect myeloma patients. We hope you will find this issue of CITINGS focused on thalidomide both interesting and useful. Please feel free to contact the IMF at (800) 452-CURE or by clicking on www.myeloma.org. --Susie Novis, President, IMF

Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma.

Cavo M, Zamagni E, Tosi P, et al.

Blood First Edition Paper, prepublished online 2005 March 10; DOI 10.1182/blood-2005-02-0522. http://www.bloodjournal.org/cgi/content/abstract/2005-02-0522v1

This study was a retrospective analysis of 200 patients who intended to undergo an autologous peripheral blood stem cell (PBSC) transplantation during the period 1996-2004. It compared the relative efficacy of thalidomide-dexamethasone (Thal-Dex) and vincristine-doxorubicin-dexamethasone (VAD) as a preparatory regimen for the transplant. In comparison with VAD, Thal-Dex resulted in a significantly higher response rate (52% versus 76%, respectively; P=0.0004) and effected more profound reduction in myeloma cell mass of both IgG (P=0.02) and IgA (P=0.03) types.

Thalidomide in combination with vincristine, epirubicin and dexamethasone (VED) for previously untreated patients with multiple myeloma.

Schutt P, Ebeling P, Buttkereit U, et al. Eur J Haematol, 2005 January; 74(1): 40-6.

http://highwire.stanford.edu/cgi/medline/pmid;15613105

The authors evaluated the efficacy and side effects of thalidomide (400 mg/d) in combination with vincristine, epirubicin and oral dexamethasone (VED). Thirty-one patients were enrolled, 12 patients were exclusively treated with thalidomide in combination with VED and 19 patients received high-dose melphalan, for consolidation. The results showed CR in 19%, PR in 61%, stable disease in 16%, and progressive disease in one patient (3.2%).

(800) 452 - CURE (2873)

Thalidomide salvage therapy following allogeneic stem cell transplantation for multiple myeloma: a retrospective study from the Intergroupe Francophone du Myélome (IFM) and the Société Française de Greffe de Moelle et Thérapie Cellulaire (SFGM-TC). Mohty M, Attal M, Marit G, et al.

Bone Marrow Transplant, 2005 January; 35(2): 165-9.

http://highwire.stanford.edu/cgi/medline/pmid;15531895 This retrospective study shows that thalidomide can be an effective therapy even for patients who have relapsed after high-dose therapy. The study involved 31 patients receiving thalidomide as salvage therapy after an allogeneic transplant. Nine patients responded with a partial response (PR) or very good partial response (VGPR) although three of these did develop graft versus host disease (GVHD).

Results of a "Multicenter Randomized Phase II Trial of Thalidomide and Prednisone Maintenance Therapy for Multiple Myeloma after Autologous Stem Cell Transplant." Stewart K, Chen CI, Howson-Jan K, et al.

Clin. Cancer Res., 2004 December; 10: 8170 - 8176.

http://clincancerres.aacrjournals.org/cgi/content/abstract/10/24/8170

All patients received 50 mg of prednisone by mouth on alternate days and thalidomide at a starting dose of either 200 or 400 mg daily by mouth. The primary end point was the incidence of dropout or dose reduction due to treatment toxicity within 6 months. Only the 200 mg of thalidomide arm of this trial met the definition of a tolerable maintenance therapy, defined as no dose reductions or discontinuation due to toxicity in at least 65% of patients for a minimum of 6 months, thus establishing a dosing schedule for phase III trials.

In vitro dendritic cell generation and lymphocyte subsets in myeloma patients: influence of thalidomide and high-dose chemotherapy treatment.

Schutt, Buttkereit U, Brandhorst D, Lindemann M, et al. Cancer Immunol Immunother 2005 May 1; 54(5): 506-12.

http://highwire.stanford.edu/cgi/medline/pmid;15750834

While vaccination with antigen-pulsed dendritic cells (DCs) represents a promising therapeutic strategy in multiple myeloma, there are still significant hurdles that need to be overcome. To identify potential problems with this approach, this study analyzed the influence of treatment parameters, in particular high-dose chemotherapy (HD-CTX) and thalidomide, on in vitro DC generation and peripheral blood lymphocyte subsets in myeloma patients. The results show that despite the well-known deficiencies in the immune system, adequate numbers of DCs can be generated in most myeloma patients. In patients treated with thalidomide, however, it remains to be seen whether the reduced expression of co-stimulatory molecules has functional relevance.

The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL).

Palladini G, Perfetti V, Perlini S, Merlini G, et al. Blood 2005 April 1; 105 (7):2949-2951.

http://www.bloodjournal.org/cgi/content/abstract/105/7/2949

The study showed that the combination of thalidomide and dexamethasone is rapidly effective and may represent a valuable second-line treatment for AL. The study evaluated the combination of thalidomide (100 mg/d, with 100-mg increments every 2 weeks, up to 400 mg) and dexamethasone (20 mg on days 1-4) every 21 days in 31 patients with primary amyloidosis (AL) whose disease was refractory to or had relapsed after first-line therapy. Overall, 15 (48%) patients achieved hematologic response, with 6 (19%) complete remissions and 8 (26%) organ responses.

Thalidomide in combination with dexamethasone for pretreated patients with multiple myeloma: serum level of soluble interleukin-2 receptor as a predictive factor for response rate and for survival.

Schutt P, Ebeling P, Buttkereit U, et al. Ann Hematol, 2005 March 3; [Epub ahead of print]

http://highwire.stanford.edu/cgi/medline/pmid;15744524 In this study cycles of dexamethasone (20mg/m²/d for 4 consecutive days every 3 weeks) were given until maximal decline of myeloma protein was achieved, whereas therapy with thalidomide (400 mg/d) was maintained until disease progression. In multivariate analysis, pretreatment serum levels of soluble interleukin-2 receptor (sIL-2R) were a significant prognostic factor for event free survival (EFS), and those of ß2 microglobulin (ß2M) and sIL-2R for overall survival (OS). Serum levels of sIL-2R significantly increased after 3 weeks of treatment in 89% of patients, possibly representing lymphocyte activation induced by thalidomide.

Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma.

Tosi P, Zamagni E, Cellini C, *et al. Eur J Haematol, 2005 March 1; 74(3): 212-6.*

http://highwire.stanford.edu/cgi/medline/pmid;15693790

The study analyzed long-term toxicity of 40 patients who received salvage therapy with thalidomide and/or dexamethasone for longer than 12 months. All the patients had achieved at least stable disease on treatment with thalidomide alone (200-400 mg/d) or thalidomide (200 mg/d) and dexamethasone (40 mg/d for 4 d every 4 wk). The results suggest that long-term thalidomide therapy in MM may be hampered by the neurotoxicity of the drug at the doses being given, and that a neurological evaluation should be given prior to thalidomide treatment.

Thalidomide-induced anti-angiogenic action is mediated by ceramide through depletion of VEGF receptors, and antagonized by sphingosine-1-phosphate. Yabu T, Tomimoto H, Taguchi Y, et al.

Blood First Edition Paper, prepublished online, 2005 March 1; DOI 10.1182/blood-2004-09-3679.

http://www.bloodjournal.org/cgi/content/abstract/2004-09-3679v1

This study attempts to explain some of the anti-angiogenic effects seen with thalidomide. They suggest that the effect is regulated by the balance between ceramide (C2-ceramide) and sphingosine-1-phosphate (S1P) signals causing the depletion of vascular endothelial growth factor (VEGF) receptors such as neuropilin-1 and Flk-1.

Thalidomide: present and future in multiple myeloma. Hussein MA

Expert Rev Anticancer Ther, 2005 February 1; 5(1): 25-31.

http://highwire.stanford.edu/cgi/medline/pmid;15757435

Thalidomide, the first of the immunomodulatory family to be used in the management of multiple myeloma, proved not only to be effective in the treatment of multiple myeloma, but also instigated a wide range of in vitro and in vivo studies to define the pathophysiology of the plasma cell dyscrasia The drug has a sideeffect profile that, if managed appropriately, provides the most unique active molecule in the management of the disease, where it maintains the same response rate in newly diagnosed patients as in advanced relapsed/refractory multiple myeloma patients.

Thalidomide radiosensitizes tumors through early changes in the tumor microenvironment. Ansiaux R, Baudelet C, Jordan BF, et al.

Clin. Cancer Res., 2005 January; 11: 743 – 750.

http://clincancerres.aacrjournals.org/cgi/content/abstract/11/2/743

This study focused on the changes in tumor microenvironment with special focus on a possible "normalization" of the tumor vasculature that could be exploited to improve radiotherapy. They found that the changes induced by thalidomide were sufficient to radiosensitize tumors. The fact that thalidomide radiosensitization was not observed *in vitro*, and that *in vivo* radiosensitization occurred in a narrow time window, implies that initial vascular normalization by thalidomide is responsible.

Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application.

Hayashi T, Hideshima T, Akiyama M, Podar K, *et al.* Br J Haematol. 2005 Jan;128(2):192-203.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1 5638853

It has been reported that thalidomide increased serum interleukin-2 (IL-2) levels and natural killer (NK) cell numbers in the peripheral blood of responding myeloma patients. This study investigated the mechanisms whereby IMiDs augment NK cell cytotoxicity. IMiDs facilitated the nuclear translocation of nuclear factor of activated T cells-2 and activator protein-1 via activation of phosphoinositide-3 kinase signalling, with resultant IL-2 secretion.