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Thalidomide and Revlimid™ Issue

THE INTERNATIONAL MYELOMA FOUNDATION (IMF) is pleased to present our fourth issue of CITINGS for 2005. In this issue we are continuing our series focusing specifically on publications referring to thalidomide and its analogues. In addition to our usual summary of publications found in scientific journals, we have added to this issue summaries of all the major papers presented at the three large hematology meetings that have taken place so far in 2005. Below you will find summaries from:

- 1) the 10th International Myeloma Workshop held this year in Sydney, Australia from April 10–14,
- 2) the American Society of Clinical Oncology (ASCO) meeting held in Orlando from May 14–17 and,
- 3) the 10th Congress of the European Hematology Association held in Stockholm, Sweden, from June 2–5.

We hope you will find this issue of CITINGS 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

10th International Myeloma Workshop Presentations

A complete summary of the all plenary sessions that took place in Sydney can be found at *www.myeloma.org*. A printed guide to the workshop with a companion DVD containing key sessions and interviews will be published shortly by the IMF. Abstracts of the posters and presentations were published in a special supplement of the journal *Haematologica* as part of the April 20, 2005 issue.

[PL4.01] Maintenance treatment with thalidomide and pamidronate after autologous transplantation for myeloma: second analysis of a prospective randomized study of the Intergroupe Francophone du Myélome (IFM).

Attal M, Harousseau JL, Leyvraz S, et al.

In this study 1019 untreated myeloma patients (under 65 years) were enrolled in the IFM 99 protocol; 780 of them, without or with only one adverse prognostic factor (beta-2 microglobulin 33 mg/L or deletion of chromosome 13), were enrolled in the IFM 99 02 protocol. They received the following treatment: 1) 3-4 cycles of the VAD regimen; 2) a first autologous transplant prepared with melphalan 140 mg/m²; 3) a second autologous transplant prepared with melphalan 200 mg/m². Patients without progressive disease 2 months after the second transplant were randomized to receive: no maintenance treatment (arm A), maintenance treatment with pamidronate

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(arm B) or maintenance treatment with thalidomide and pamidronate (arm C). Inital results show thalidomide was found to improve the progression-free survival (PFS). Indeed, the 3-year post-randomization probability of PFS was 56% in the thalidomide arm versus 34% in arm A, and 37% in arm B.

[PL5.04] Phase I study of the safety and efficacy of bortezomib (Velcade) in combination with CC-5013 (Revlimid) in relapsed and refractory multiple myeloma (MM): The RevVel Study.

Richardson PG, Schlossman R, Munshi N, et al.

Velcade and Revlimid have both shown promise in myeloma but researchers have yet to determine the best place to use them within the treatment strategy or in what combinations with other agents. Both agents have unique mechanisms of action and directly promote apoptosis of myeloma cells, inhibit adhesion of myeloma to bone marrow stromal cells, inhibit cytokines important for myeloma cell growth and survival, are antiangiogenic, and have immunomodulatory effects. This is the first trial exploring the effectiveness and safety of their combination in relapsed patients. Doses of bortezomib are 1.0 or 1.3 mg/m² on days 1, 4, 8, and 11, with a 10-day rest. CC-5013 doses range from 5-20 mg/day on days 1-14. Each cycle is 21 days. Data will be presented later in 2005.

[F12.04] Mechanism of drug resistance towards thalidomide and its immunomodulatory derivatives in multiple myeloma cells: role of C/EBPb.

Janz M, Bargou R, Mapara MY, et al.

C/EBPb plays an important role in the regulation of cell proliferation and differentiation. Increased levels of C/EBPb have been found in different types of tumors, and mice deficient in C/EBPb show impaired generation of B lymphocytes, suggesting that C/EBPb plays a critical role in B lymphopoiesis. The promoter of IL-6, the most important growth and survival factor for myeloma cells, is activated by C/EBPb. This analysis revealed that treatment with CC-4047 (Actimid) resulted in a significant regulation of several genes, including FHF-2, C/EBPb, cmyb, and GFI-1. HUMSPARC.MM.1S cells (a particular myeloma cell line), which were sensitive to CC-4047, showed a strong down-regulation of C/EBPb.

[PO.119] Response to primary therapy with thalidomide and dexamethasone in multiple myeloma is not adversely affected by t(4;14) and del(13).

Terragna C, Renzulli M, Testoni N, et al.

The authors investigated the frequency of t(4;14) and del(13) in a series of 52 previously untreated patients with symptomatic myeloma who received first-line therapy of thalidomide and dexamethasone in preparation for subsequent autologous transplantation. The results showed that patients with translocation t(4; 14) and/or del(13) had the same probability of responding to thalidomide/dexamethasone therapy as patients who lacked these unfavorable karyotypic abnormalities.

[PO.120] t(4;14)-positive multiple myeloma is chemo-sensitive to dexamethasone and /or thalidomide but not alkylating agents: rapid relapse and not primary drug resistance explains poor outcomes.

Jaksic W, Trudel S, Chang H, et al.

This study analyzed 130 patients who were treated with induction chemotherapy followed by melphalan 200 mg/m2. Preliminary analysis demonstrates that t(4;14)-positive myeloma is not particularly responsive to alkylating agents, including high-dose melphalan; the authors have suggested that use of these agents (including ASCT) is generally of no long-term value in this patient population. Given the high response rates of 81% at induction and 64% at salvage, these authors favor induction and maintenance regimens containing high-dose dexamethasone and/or thalidomide.

[PO.122] Fibroblast growth factor receptor 3 (FGFR3) expression in maintenance thalidomide treatment following high-dose therapy in myeloma.

Joshua D, Jeffels M, Sze D, et al.

Translocation t(4;14) is found in 15% of myeloma patients and generally confers a poor prognosis in both standard and high-dose therapy. FGFR3, one of the candidate genes localized to del(14), is a tyrosine kinase receptor not normally expressed in plasma cells. It is up-regulated in approximately 2/3 of t(4;14) positive tumors. As thalidomide is an inhibitor of bFGF, one of the ligands of FGFR3, the authors investigated the effect of high-dose therapy with maintenance thalidomide and steroid in a Phase III randomized controlled trial (ALLG MM6) on FGFR3 expression. The complete results of this study have not yet been published.

[PO.136] Tumor necrosis factor-alpha 238A (TNF-alpha 238A) genotype is associated with an earlier onset of multiple myeloma and better response to thalidomide.

Kizil M, Soydan EA, Serbest E, et al.

The authors of this study looked at peripheral blood in 29 patients to analyze the association between the frequencies of the cytokines known to be important in the pathogenesis of myeloma, TNF-alpha, IL-6, IL-10, and response to thalidomide. The data showed that a cytokine gene SNP such as TNF-alpha 238A is associated with better response and earlier age of onset in myeloma [(83% vs. 39%) (p=0.054)]. However all the patients studied here carried the IL-6 genotype reported to be associated with high secretory pattern.

[PO.504] Primary treatment with pulsed melphalan, dexamethasone, and thalidomide for symptomatic patients with myeloma 75 years of age.

Anagnostopoulos A, Repoussis P, Terpos E, et al.

The authors of this study wanted to create a thalidomide-containing regimen that would be well tolerated by elderly patients. Treatment consisted of melphalan 8 mg/m2 days 1-4, dexamethasone 12 mg/m2 on days 1-4 and 14-18, and thalidomide 300 mg on days 1-4 and 14-18. This regimen is repeated every 5 weeks for 3 courses; 40 patients have been enrolled so far; median age is 78 years (range: 75-85 years). On an intent-to-treat basis, 72% of patients achieved at least a partial response (EBMT criteria) including 10% of patients who achieved complete response. The incidence of deep vein thrombosis (DVT) and of peripheral neuropathy appears lower than that seen when thalidomide is administered continuously.

[PO.611] Interim results of a Phase II study to explore the efficacy and tolerability of thalidomide-containing regimens to reduce tumor cell load prior to hematopoietic stem cell (HSC) transplant in multiple myeloma and the feasibility of harvesting HSC following thalidomide-containing regimens.

Horvath N, To LB, Joshua D et al.

The regimen in this study included thalidomide 400mg/d x 21, pulsed dexamethasone 32mg TDS x 5d, followed by DT-PACEx2 (thalidomide 400mg/d, dexamethasone 40 mg/d x 4, cisplatin 10 mg/m²/d, doxorubicin 10 mg/m²/d, cyclophosphamide 400 mg/m²/d, etoposide 40 mg/m²/d 4 day infusion). Stem cells were harvested off the second cycle of DT-PACE. From the data compiled the authors concluded that the thalidomide-containing combination appears to be as efficacious as VAD/high-dose cyclophosphamide as first-line therapy in advanced myeloma and that the thalidomide-containing combinations are associated with tolerable but not insignificant toxicity. Unfortunately it also appears from this study that thalidomide-containing combinations may reduce stem cell harvests.

[PO.623] Thalidomide in relapsing multiple myeloma after the first autograft: a pilot study for the evaluation of experimental maintenance therapies.

Krivanová A, Hájek R, Krejci M, et al.

The authors tested maintenance therapy using thalidomide (MT-THAL) 100 mg daily after repeated autologous transplantation (AT) in patients with myeloma relapsing/progressing after the first AT. The data for 42 patients studied demonstrated that thalidomide has benefit in relapsing myeloma post autologous transplant (33% patients have prolonged event-free survival).

[PO.701] Long-term follow-up of combination therapy with thalidomide and dexamethasone in patients with newly diagnosed multiple myeloma not undergoing upfront autologous stem cell transplantation.

Dingli D, Rajkumar SV, Nowakowski G, MA Gertz, et al.

This is a retrospective analysis of a Phase II trial conducted at the Mayo Clinic (published, Journal of Clinical Oncology 20:4319-4323, 2002) that looked at thalidomide/dexamethasone as induction therapy before stem cell transplant. Here the authors reported the long-term status of the patients (24) that ended up not undergoing a transplant. Patients were treated with thalidomide at a dose of 200 mg/day orally and dexamethasone 40 mg daily on days 1-4, 9-12, 17-20 on odd months. During even months, the dexamethasone dose was 40 mg daily for 4 days. Each cycle was repeated every month. The overall survival was 30 months, with a progression-free survival of 19 months. The median time to progression was 20.5 months.

[PO.702] Low-dose thalidomide in combination with standard vincristine, Adriamycin and dexamethasone (VAD-t) yields higher response rates in treatment-naive multiple myeloma: preliminary results of an ongoing Phase II clinical study.

Chanan-Khan A, Miller KC, Koryzna A, et al.

Although this study is still in the accrual process, preliminary results suggest that VAD-t is well tolerated and is an effective regimen with improved overall response rate when compared to standard VAD in treatment of newly diagnosed myeloma patients. No increase in incidence of venous thromboembolism (VTE) was noted with the combination. Adequate stem cell collection was achieved in transplant-eligible patients.

[PO.703] Doxorubicin and dexamethasone followed by thalidomide and dexamethasone as initial therapy for symptomatic patients with multiple myeloma.

Hassoun H, Kewalramani T, Klimek VM, et al.

In this study the drugs were given to patients in a sequential fashion with the intent to reduce the high incidence of venous thromboembolic complications known to be associated with this combination of drugs. Doxorubicin and dexamethasone (AD; A=9 mg/m²/day, days 1-4; D=40 mg/day, days 1-4, 9-12, 17-20) are given for 3 months followed by thalidomide and dexamethasone (TD; T=200 mg nightly; D=as above) for 2 months with prophylactic antibiotics and daily aspirin (81 mg/day). At any point during therapy patients achieving a complete response were permitted to forgo further induction therapy and proceed with autologous stem cell transplantation. Results reported here show an overall response rate of 86.6%, including 20% complete responses, 26% very good partial responses, and 40% partial responses.

[PO.704] Thalidomide-dexamethasone versus melphalan-prednisolone as first-line treatment in elderly patients with multiple myeloma: an interim analysis.

Ludwig H, Drach J, Tóthová E, et al.

In this study patients were randomized to either thalidomide 200 mg/day and dexamethasone 40 mg, or melphalan 2.5 mg/kg days 1-4 and prednisolone 2 mg/kg days 1-4. Analysis of the two protocols revealed on overall response rate of 88% in the thalidomide/dexamethasone arm and of 68% in the melphalan/prednisolone group. Time to response and time to best response were significantly shorter with thalidomide/dexamethasone (8, 11 weeks, respectively) compared to the melphalan/prednisolone group (10, 39 weeks, respectively).

[PO.705] Thalidomide maintenance following high-dose therapy in multiple myeloma: a UK Myeloma Forum Phase II study.

Feyler S, Jackson G, Rawstron A, et al.

This is a British study looking at the long-term tolerance of thalidomide at 5 different dose levels; 50 mg, 100mg, 200 mg, 250 mg and 300 mg. One hundred patients were recruited, 20 patients in each cohort. Preliminary results show that 60 patients have stopped thalidomide, 20 following disease progression and 40 due to side effects. These include neuropathy (61 cases overall, 29 of these had to stop the drug), general lethargy and somnolence (39), constipation (30), rashes (17), dry skin and pruritus (14), dyspnoea (4), hypothyroidism (2), and only one deep vein thrombosis despite no routine anticoagulation. The 18 months progression-free survival is 79% for patients with intended dose of 200 mg or greater, and 63% for patients on intended dose less than 200 mg. 22 patients achieving partial response or minimal response at the start of thalidomide improved their disease status with a greater than 5 g/L reduction in protein.

[PO.707] Thalidomide in refractory and relapsed multiple myeloma: duration of response.

Cibeira MT, Rosiñol L, Esteve J, et al.

This study included forty-two patients (median age 61) with refractory/relapsed myeloma who were given thalidomide as a single agent. The median time from the onset of thalidomide to relapse was 15.8 months (range: 1.3-52.6). The median time to relapse for patients who had achieved a partial response (PR) was 22.6 months versus 11.2 months for those who had only achieved a minimal response (MR). The median duration of response was 10.3 months (range: 1-50) (19.3 months for PR vs. 8.3 months for MR).

[PO.710] Low-dose dexamethasone and thalidomide with higher frequency zoledronic acid (dtZ) for relapsed/refractory multiple myeloma.

Teoh G, Hwang W, Koh LP, et al.

This study evaluated twenty-six consecutive patients with symptomatic myeloma who had received an average of 21.1 (0.2 to 135.6) months of prior therapy. They were treated with a low-toxicity dtZ regimen, which comprises weekly dexamethasone 20 mg for 4 days, thalidomide 50 mg/day, and three-weekly zoledronic acid 4 mg. The overall response rate was 61.6% and median time to progression was 26.9 months with a median overall survival of 29.9 months from commencement of treatment.

[PO.712] Thalidomide-induced peripheral neuropathy in newly diagnosed pre-treated multiple myeloma patients.

Tosi P, Zamagni E, Cellini C, et al.

This study attempted to quantify the peripheral neuropathy experienced by 74 patients who had been treated with thalidomide/dexamethasone for longer than 8 months [one group of newly diagnosed patients and one group of relapsed patients]. The severity of neuropathy varied greatly in the two groups of patients, as pretreated patients showed grade 2 and 3 toxicity in 32.5% and 27.5% of the cases, respectively, while the majority of newly diagnosed patients complained about grade 1 toxicity (57%), and none of them experienced grade 3 toxicity. In both groups thalidomide neurotoxicity was not related to sex, M protein isotope, and thalidomide daily dose. In pretreated patients, a significant correlation between grade 2+3 neurotoxicity and longer disease duration was found, from which the authors conclude that myeloma related neurotoxicity could favor drug-induced toxic effects.

[PO.713] Development of high-grade B-cell neoplasms following thalidomide therapy.

Saba S, Epstein A, Niesvizky R, et al.

It has been reported by several institutions that aggressive extramedullary disease (EMD) may appear after thalidomide treatment, and while the reasons for this phenomenon remain unclear, considerations include: a) selective inhibition of mature plasma cell clones; b) clonal evolution; or c) a change in the natural history of the disease given the lengthening of overall patient survival. The authors of this study conducted a retrospective review of their patients and the literature in order to explore this issue further. They suggested that the most probable explanation for this phenomenon is that thalidomide is effective in initially reducing a more mature plasma cell compartment confined to the marrow, and allows a relatively immature myeloma cell compartment to escape the bone marrow microenvironment.

[PO.715] A multi-center Phase II trial of thalidomide and celecoxib for relapsed and refractory multiple myeloma.

Prince HM, Mileshkin L, Roberts A, et al.

Recent data has suggested Cox-2 inhibition may impair plasma cell growth and be potentially synergistic with thalidomide; it is timely that this Phase II trial examined the addition of celecoxib to thalidomide in patients with relapsed/refractory myeloma. Thalidomide was used up to maximum dose 800 mg/day and celecoxib 400 mg. Overall response rate was 42% with 48% stable disease. At 20 months median follow-up, the actuarial median progression-free survival and overall survival were 6.8 and 21.4 months, respectively.

[PO.717] Thalidomide, dexamethasone and clarithromycin as salvage therapy for patients with advanced multiple myeloma.

Tam C, Spencer A

This study evaluated 14 patients with advanced myeloma treated with the combination of thalidomide (50-500 mg daily), dexamethasone (12-40 mg weekly) and clarithromycin (500 mg/day). Overall response was 71% with an overall survival of 52 weeks.

[PO.731] Velcade, Doxil and low-dose thalidomide as salvage regimen for patients with relapsed or refractory multiple myeloma and Waldenström's macroglobulemia: preliminary results of a Phase II study.

Chanan-Khan A, Miller KC, DiMiceli LA, et al.

The authors of this study have hypothesized that combining Velcade and thalidomide (which both target the bone marrow microenvironment) with Doxil (D) (which targets the actual myeloma cell) may help overcome resistance and enhance the activity of these agents, in patients with relapsed or refractory myeloma. While all three have shown promise as single agents the hope is that this type of strategic combination may create longer relapses. Eleven patients were evaluable for response; 8 (72%) showed a clinical response (1 complete response, 4 partial response, 1 minimal response, 2 stable disease) while 3 patients had progressive disease, 1 after 5 cycles and 2 after 2 cycles.

[PO.737] A multi-center, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide in subjects with relapsed and refractory multiple myeloma.

Richardson PG, Jagannath S, Hussein MA, et al.

At the time this abstract was published, 222 patients had been enrolled into the study. All patients had received at least 2 prior anti-myeloma treatments, including bortezomib, thalidomide, and stem cell transplant. Thus far at least a 25% reduction in paraprotein level has been achieved in 63 patients (28%). Lenalidomide (Revlimid) has been tolerated with acceptable toxicity.

[PO.738] A multi-center, randomized, parallel group, double blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma.

Weber DM, Chen C, Niesvizky R, et al.

This abstract introduces the large Phase III trial that was subsequently ended early after meeting its primary endpoints. Lenalidomide and high-dose dexamethasone (HDD) are given in 28-day cycles: lenalidomide 25 mg once daily on days 1-21 every 28 days and HDD 40 mg on days 1-4, 9-12, 17-20 every 28 days. After 4 cycles the HDD schedule is reduced to 40 mg on Days 1-4 every 28 days.

[PO.903] Induction of autophagy to myeloma cells by thalidomide and clarithromycin.

Nakamura M, Okuno Y, Takeya M, et al.

This is another study which explores the mechanism of action involved with thalidomide. Autophagy is a mechanism of recycling microorganelles when exposed to various stresses. It is believed that the proteasome rapidly degrades unnecessary proteins while some proteins are also degraded by autophagosomes. Although autophagy is necessary for survival of cells under unfavorable conditions, such as nutrient deficiency, it is also thought that autophagy may induce cell death in some situations. This study suggests that either thalidomide or clarithromycin may mediate autophagy as a single agent, which under these circumstances leads to cell death.

[PO.1104] The effect of a thalidomide analog (Actimid) on T-cell activation in patients with relapsed refractory myeloma.

Ahsan G, Kazmi MA, Fields PA, et al.

Actimid has been shown to have efficacy in treatment of relapsed myeloma but its exact mode of action remains unclear (Streetly M et al., ASH 2003). Preliminary work (S.Schey, JCO 2004) suggests that thalidomide analogues can activate T cells which may in part explain their mode of action. The aim of this study was to see if Actimid modulated serum levels of IL-2 and IL-15 and to see if these correlated with clinical response as assessed by use of the serum free light chain (SFL) assay. Here 14 patients were analyzed for changes in IL-2 and IL-15 serum levels. There was a significant increase in IL-2 levels on treatment (p<0.01) and a non-significant reduction in IL-15 levels (p=NS.).

[PO.1105] Increased number of T-cell receptor Vb expansions in patients on thalidomide maintenance therapy provides further evidence of the immunomodulatory action of thalidomide.

Murray A, Brown R, Ho PJ, et al.

Recent studies have demonstrated that following treatment with thalidomide there is increased T-cell activity and natural killer cell cytotoxicity in the blood of patients with myeloma. The data for this study was gathered from the Australian ALLG MM6 trial [a multi-center randomized Phase III study of low-dose thalidomide, prednisolone and Zometa versus prednisolone and Zometa for post-autologous stem cell transplant maintenance therapy]. The authors here assayed the peripheral blood for T-cell receptor Vb expansions in 35 patients enrolled in the MM6 trial. Expanded clones were seen in 54% (19/35) of patients prior to transplant. Of the patients in the thalidomide arm prior to transplant 47% had T-cell expansions and in the no thalidomide arm 62% of the patients had T-cell expansions. After thalidomide, 89% (17/19) of the patients had T-cell expansions compared with 56% in the control, (no thalidomide) group.

[PO.1209] The combination of intermediate-dose thalidomide plus dexamethasone improves abnormal bone remodeling through the reduction of sRankL/osteoprotegerin ratio in patients with refractory/relapsed myeloma.

Terpos, E, Mihou D, Szydlo R, et al.

The researchers here looked at 35 patients who received thalidomide at a dose of 200 mg/daily. Dexamethasone was given at a dose of 40 mg/daily for 4 days every 15 days until response and then at 40 mg/daily for 4 days monthly. All patients were also given zoledronic acid monthly, both pre- and post-thalidomide/dexamethasone therapy. Patients who had a sRANKL/OPG ratio value of >15x10±2% had median survival of 13 months, while patients who had lower values had a median survival of 20 months. However, this difference was not significant due to the low number of patients in this study.

[PO.1407] Interim analysis of a Phase II study of risk-adapted intravenous melphalan followed by adjuvant dexamethasone and thalidomide for newly diagnosed patients with systemic AL amyloidosis.

Feldstein T, Filippa DA, Fleisher M, et al.

In this study, the authors investigated whether a risk-adapted approach to intravenous melphalan dosing could decrease therapy-related mortality for patients undergoing stem cell transplants, and whether adjuvant dexamethasone (D) ± thalidomide (T) could improve hematologic and amyloid-involved organ response rates. Patients with persistent clonal plasma cell disease at 3 months receive 9 months of adjuvant D+T or D alone (if history of deep venous thrombosis or neuropathy). Results show that adjuvant D ± T is feasible, has moderate toxicity, and has to date benefited 20% (4/20) of patients with persistent clonal plasma cell disease 3 months post stem cell transplant.

[PO.1410] Thalidomide treatment in 99 patients with AL amyloidosis: tolerability, clonal disease response, and clinical outcome.

Goodman HJB, Lachmann HJ, Gallimore R, et al.

For the patients in this study, thalidomide was taken for a median of 5 months (0.4-34), at a median dose of 100 mg/day (50-600). Overall survival for the whole cohort was estimated at 26 months from the start of treatment by Kaplan-Meier analysis. Overall survival was significantly better when dexamethasone was included as part of the regimen (p<0.012). Organ function improved or remained stable in 23% and 39% of evaluable cases respectively, and SAP scintigraphy showed regression of amyloid in 18% of patients. Adverse events occurred in 75 patients, including fatigue or somnolence (33), neuropathy (27), significant constipation (18), mental changes (9) and/or edema (8).

[PO.1411] Thalidomide alone and in combination with other agents in the treatment of patients with AL amyloidosis.

Abdalla SH, Goodman HJB, Hawkins PN, et al.

The authors of this study argue that although thalidomide can be badly tolerated in amyloid patients, in low doses and with careful attention it can be administered safely. Here five patients were given thalidomide: 100 mg daily in 3 patients and 200 mg in one patient. The fifth patient tolerated thalidomide poorly at 100 mg and the dose was therefore reduced to 25 mg for two weeks every 4 weeks. All patients showed variable but clinically useful responses. One patient showed a complete response and has discontinued treatment after 9 months, in a second patient the SFLC ratio became normal and there was an arrest of renal function deterioration. In the other two patients, the clonal serum free light chain levels were reduced by 75% and 68% of the levels at the start of treatment.

American Society of Clinical Oncology Presentations 2005

Results of Total Therapy 2 (TT 2), a Phase III randomized trial, to determine the role of thalidomide in the upfront management of multiple myeloma (MM).

Barlogie B, Tricot G, Shaughnessy J, et al.

Abstract No: LBA6502

http://www.asco.org/ac/1,1003,_12-002636-00_18-0034-00_19-0033929,00.asp

In this study, thalidomide was added on to the original TT2 regimen in Little Rock. The report here analyzes the impact that this addition had on 323 patients randomized to receive it. Dr. Barlogie and colleagues showed that thalidomide improves complete response (43% vs. 62%) and 5-year event free survival (40% vs. 55%); however at this point in the study there is no apparent impact on overall survival. This raises important questions about the most effective way in which thalidomide should be used in the overall treatment plan.

Thalidomide/dexamethasone versus melphalan/prednisolone as first-line treatment in elderly patients with multiple myeloma: an interim analysis.

Ludwig H, Drach J, Tóthová E, et al.

Abstract No: 6537

http://www.asco.org/ac/1,1003,_12-002636-00_18-0034-00_19-0033085,00.asp

This is a relatively large trial comparing what was the gold standard in myeloma treatment (melphalan/prednisolone) to what is fast becoming the most commonly used first-line choice (thalidomide/dexamethasone). So far 137 of 350 patients planned have been enrolled [median age: 72 yrs, stage I: 6 (4%), stage II: 52 (38%), stage III: 79 (58%)]. Patients are randomized to either thalidomide 200mg/d and dexamethasone 40mg, d1-4 and 15-18 on odd cycles and d1-4 on even cycles, or melphalan 2.5mg/kg d1-4 and prednisolone 2mg/kg d1-4, q 4-6 weeks. Results (time to response and overall response) thus far are significantly better in the thalidomide/dexamethasone arm of the study although the complete analysis has not yet been finished.

Final report of a Phase II study of oral cyclophosphamide, thalidomide, and prednisone (CTP) for patients with relapsed or refractory multiple myeloma: a Hoosier Oncology Group trial (HEM01-21).

Suvannasankha A, Fausel C, Juliar BE, et al.

Abstract No: 6591

http://www.asco.org/ac/1,1003,_12-002636-00_18-0034-00_19-0033882,00.asp

This study includes 37 patients, 16 of whom had prior high-dose therapy with stem cell transplant and 22 of whom had high-dose steroid [49 to 87 years old (median 65)]. Median follow-up time was 18.37 months. Response was observed in 22 patients (63%); 7 (22%) complete response, 2 (6%) near complete response, and 13 (41%) partial response.

Thalidomide and dexamethasone in newly diagnosed multiple myeloma: Long-term results in patients not undergoing upfront autologous stem cell transplantation.

Rajkumar SV, Dingli D, Nowakowski G, et al.

Abstract No: 6632

http://www.asco.org/ac/1,1003,_12-002636-00_18-0034-00_19-0033366,00.asp

This is a retrospective analysis of a previous trial at Mayo that looked at thalidomide and dexamethasone as a preparatory regimen for stem cell transplant. Here they followed the subset of patients (24 total, median age 65.5) in this group that did not end up having a transplant. Two (8%) patients achieved a complete response (CR), 11 (46%) had a partial response (PR) (overall CR+PR =57%), and 7 (29%) patients had stable disease. The median time to progression with upfront thalidomide and dexamethasone is 21 months.

Long-term treatment of newly diagnosed multiple myeloma with low-dose thalidomide, dexamethasone and zoledronate (TDZ).

Klueppelberg U, Shapira I, Chen L, et al.

Abstract No: 6697

http://www.asco.org/ac/1,1003,_12-002636-00_18-0034-00_19-0033114,00.asp

In this study, patients received thalidomide 100 mg/day, dexamethasone 10-40 mg on days 1-4, 9-12, and 17-20 monthly for 6 months; then only 4 days/month; and zoledronate 4 mg monthly, until progression. Mean duration of treatment with this combination was 12 months. Thus far 13 patients have been followed for 12-24 months. Age-adjusted one-year survival is 74.4% and no deaths occurred after 10 months. All HIV-positive patients remain in remission. These results have suggested there may be a synergistic effect between thalidomide/dexamethasone and zoledronate, allowing for lower doses of thalidomide than those used in earlier protocols.

Analysis of safety profile of thalidomide in multiple myeloma: A multi-center Indian experience.

Arora R, Mukhopadhyay A, Patel K, et al.

Abstract No: 6709

http://www.asco.org/ac/1,1003,_12-002636-00_18-0034-00_19-0032043,00.asp

This open-label, non-randomized, multi-center study was conducted across 8 centers in India to assess any difference in the safety and efficacy profile of thalidomide in an ethnic Indian population. Thalidomide was given either as a single agent at a dose of 100-200mg, or in combination with dexamethasone at a dose of 40 mg (oral) on days 1-4, 9-12, 17-20 of a 28-day cycle during odd cycles and days 1-4 of the even cycles. Thalidomide shows excellent tolerability in the Indian population and has responses similar to that reported in the Western literature.

10th Congress of the European Haematology Association

All of the abstracts from this meeting appear in a special supplement of the journal *Haematologica*, as part of the June 1, 2005 issue. *Haematologica* is a publication of the European Haematology Association.

[0235] First-line thalidomide/dexamethasone therapy in preparation for autologous stem cell transplantation in young patients with symptomatic multiple myeloma.

Abdelkefi A, Torjman L, Ben Romdhane N, et al.

This is one of several studies looking into the response when using thalidomide and dexamethasone as a firstline therapy; in this case, in preparation for a stem cell transplant. Thalidomide and dexamethasone was administered to 65 patients for 75 days (200mg/day) and 3 months (20 mg/m²/day for 4 days), respectively. On an intent-to-treat basis, the overall response rate was 84%, including 24% of patients who obtained a complete remission.

[0239] Intermediate dose of thalidomide in combination with dexamethasone and zoledronic acid is effective in refractory/relapsed myeloma, improves abnormal bone remodeling and reduces marrow angiogenesis.

Terpos E, Mihou D, Szydlo R, et al.

The aim of this study was to evaluate the effect of intermediate doses of thalidomide (200mg/day) and dexamethasone (40 mg/daily for 4 days every 15 days until maximum response, then monthly) plus zoledronic acid (monthly) on bone remodeling and angiogenesis in patients with refractory/relapsed myeloma. The study included 35 patients and recorded pre-treatment and 3 and 6 months post-treatment markers of osteoclast activation [sRANKL, OPG, tartrate resistant acid phosphatase isoform-5b (TRACP-5b)], markers of bone resorption [Ctelopeptide of collagen type-I (CTX)], markers of bone formation [bone alkaline phosphatase (bALP), osteocalcin (OC), and C-terminal propeptide of collagen type-I (CICP)], and OPN. In addition, serum levels of vascular endothelial growth factor (VEGF), basic-fibroblast growth factor (b-FGF), tumor necrosis factor-α (TNF-α), all of which have angiogenic potential, and interleukin-6 (IL-6), IL-1b, soluble IL-6 receptor (sIL-6R), and transforming growth factor-b (TGF-b), which are involved in the disease biology, were measured before treatment and then every 2 weeks for 8 weeks. Microvessel density (MVD) was evaluated in marrow biopsies before and after treatment. These results suggest that the combination of intermediate dose of thalidomide with dexamethasone is very effective in terms of overall response, reduction in MVD, and improving bone remodeling through the reduction of sRANKL/OPG ratio.

[0242] Thalidomide, dexamethasone and pegylated liposomal doxobubicin (THADD) in elderly/relapsed multiple myeloma patients.

Offidani M, Marconi M, Corvatta L, et al.

In this study 71 patients (59 evaluable) were given combination thalidomide 100 mg/day, dexamethasone 40 mg days 1-4 and 9-12 of each month, and pegylated liposomal doxorubicin 40mg/sqm on day 1. This regimen was administered every 4 weeks for 4-6 courses to patients with relapsed myeloma or newly diagnosed myeloma older than 65 years. Overall response rate was 88% (30% complete response, 10% very good partial response, 39% partial response and 9% minimal response) whereas 4 patients (7%) had progressive disease. Event-free survival at 2 years was 57% in elderly newly diagnosed patients; 37% in relapsed patients.

[0245] A Phase I study of bortezomib (Velcade) in combination with lenalidomide (Revlimid) in relapsed and refractory multiple myeloma.

Richardson PG, Schlossman R, Munshi N, et al.

This study was first presented in Sydney earlier this year, but the authors do include some updated data here. The study has now enrolled twelve patients into cohorts 1-4. Maximum tolerated dose was not reached in the first 3 cohorts. With a median of 6 cycles completed, patients have tolerated bortezomib 1.0-1.3 mg/m² and lenalidomide 5-10 mg/day without dose-limiting toxicity.

[0398] A prospective randomized trial of oral melphalan, prednisone, thalidomide (MPT) vs. oral melphalan, predisone (MP): An interim analysis.

Palumbo A, Bertola A, Caravita T, et al.

An interim analysis was conducted after the first 250 newly diagnosed myeloma patients, median age 72, range 56-85, entered the study, between January 2002 and December 2004. At the time this paper was published, 177 patients were evaluated for toxicity and response on an intent to treat basis. The MPT regimen included 6 monthly courses of oral melphalan 4 mg/m² and prednisone 40 mg/m² for 7 days every month plus thalidomide 100 mg/day continuously until any sign of progressive disease or relapse. According to the EBMT/IBMTR criteria, the response rate among patients who received MPT was: 22.2% immunofixation negative complete response (CR), 5.5% immunofixation positive near complete response (nCR), 49.4% partial remission (PR) (M-protein reduction 50-99%), 14.5% stable disease (SD) (M-protein reduction 0-49%), and 8.4% progressive disease (PD). The response rate after MP was 4.2% CR, 1.2% nCR, 41.3% PR, 25.3% SD, and 28% PD.

[0402] Evaluating oral lenalidomide (Revlimid) and dexamethasone versus placebo and dexamethasone in patients with relapsed or refractory multiple myeloma.

Dimopoulos M, Weber D, Chen C, et al.

Data from this trial has been presented at various times during the year. This is the first large-scale Phase III trial involving Revlimid in myeloma. Two randomized, multi-center, double-blind, placebo-controlled studies (MM-009 in North America (N=354); MM-010 in Europe and Australia (N=351) are fully enrolled. Patients with relapsed or refractory myeloma were randomized to receive oral lenalidomide (25 mg daily for 3 weeks every 4 weeks) plus dexamethasone (40 mg on Days 1-4, 9-12, 17-20 every 4 weeks for 4 months, then 40 mg on Days 1-4 every cycle thereafter) or placebo plus dexamethasone. Over 50% of patients in both studies had been treated with high-dose chemotherapy and stem cell transplantation and had failed at least 2 prior conventional chemotherapy regimens. The median time to progression (TTP) for lenalidomide/dexamethasone-treated patients was not reached in either study (exceeds 60 weeks and 47 weeks in MM-009 and MM-010, respectively). In contrast, the median TTP for patients in the dexamethasone alone group was 19.9 weeks in MM-009 and 20.4 weeks in MM-010. The difference was highly significant (p<0.00001). The overall response rate was significantly greater in patients treated with lenalidomide/dexamethasone compared to dexamethasone alone in both MM-009 (51.3% vs. 22.9%; p<0.0001) and MM 010 (47.6% vs. 18.4%; p<0.001). Grade 3 or 4 neutropenia adverse events were reported more frequently in patients given combination therapy than in patients treated with dexamethasone alone (MM-009, 24.1% vs 3.5%; MM-010, 16.5% vs 1.2%).

[0630] Melphalan, prednisone, thalidomide and Velcade (MPTV) combination therapy for relapsed multiple myeloma.

Palumbo A, Ambrosini1 MT, Cangialosi C, et al.

In newly diagnosed patients, the addition of thalidomide to the standard oral melphalan/prednisone combination significantly increased response rate and event free survival [Palumbo ASH 2004]. In heavily pretreated patients, the combination melphalan plus bortezomib induced a 67% overall response rate (>25% M protein reduction) [Berenson EHA 2004]; the combination Velcade, thalidomide and dexamethasone produced a 60% overall response rate [Zangari ASH 2004]. After 1 or 2 lines of treatment, relapsed/refractory myeloma patients were enrolled in the trial. The MPTV regimen included oral melphalan 6 mg/m² administered on days 1-5, oral prednisone 60 mg/m² on days 1-5, thalidomide 100 mg per day, and Velcade administered on days 1, 4, 15, 22 of each course, at 1 mg/m² in the first 10-patient cohort; 1.3 mg/sqm in the second 10-patient cohort, and 1.6 mg/m² in the third 10-patient cohort. In evaluable patients (n16), the response rate was: 20% near complete response, 30% partial response, 20% minimal response, and 30% stable disease.

[0633] Bortezomib (Velcade) in combination with pegylated liposomal doxorubicin and thalidomide yield high response rate in patients with relapsed or refractory multiple myeloma.

Chanan-Khan A, Miller KC, et al.

This study built on previous trials which successfully combined Velcade and thalidomide as well as Doxil and Velcade. In the current study (21 patients), early results showed objective clinical response (complete response + partial response + stable disease) in 11 (78%) pts, with 2 complete responses (14%), 6 partial responses (42.8%) and 3 stable disease (21.4%). Most commonly reported adverse events were Grade I/II fatigue (n=8) and constipation (n=5). Grade III/IV thrombocytopenia and neuropathy was noted in 5 (23.8%) and 2 (9.5%).

[0635] Response to primary therapy for myeloma with thalidomide/dexamethasone is not adversely affected by t(4,14) and del(13).

Terragna C, Matteo R, Zamagni E, et al.

This study investigated the frequency of t(4;14) and del (13) in a series of 52 previously untreated patients with symptomatic myeloma who received first-line remission induction therapy with thalidomide and dexamethasone in preparation for subsequent autologous transplantation. The frequency of t(4;14) in this series of patients was 29%, a value higher than that found in other series reported so far. Translocation t(4; 14) and/or del (13) had no adverse influence on response to primary therapy with thalidomide/dexamethasone, which the authors conclude can be considered as a valid treatment option in preparation for autologous transplantation even for patients with adverse chromosomal abnormalities.

[0637] Marked activity of VTD regimen comprising Velcade plus thalidomide and added dexamethasone for non-responders in advanced and refractory multiple myeloma.

Zangari M, Barlogie B, Elice F, et al.

This Phase I/II trial was initiated to determine the activity of the Velcade/thalidomide combination in patients with refractory myeloma and to investigate the cumulative toxicities. Velcade was given in group 1 at a dose of 1.0 mg/m² on days 1, 4, 8 and 11 every 21 days and, in the absence of > grade 2 neurotoxicity, thalidomide was added with the second cycle at dose increments of 50, 100, 150 and 200 mg daily in cohorts of at least 10 patients. A second group was then started at V 1.3 mg/m² with the addition of thalidomide in the same incremental dosing schedule. Dexamethasone was added as early as with cycle #4 if partial response (PR) was not achieved. A total of 85 patients have been enrolled and the data indicates good tolerance and activity of the VTD regimen in a very high-risk patient population. The quality of response and a higher dose of V (1.3 mg/m²), but not of T, were associated with better event-free survival (p=0.004).

[0848] Bendamustine in combination with thalidomide and prednisolone in patients with refractory or relapsed multiple myeloma. Preliminary results of a Phase I clinical trial.

Poenisch W, Rozanski M, Leiblein S, et al.

Although thalidomide has been shown to be very effective both as a single agent and in combination with other agents, neuropathy has been an issue. This study questioned whether lower doses of thalidomide in combination with weekly doses of bendamustine and prednisolone might be a more effective regimen with fewer side effects especially in relation to neurotoxicity in this setting. Although this trial is still ongoing, initial results show that BPT with a dose of 50 or 100 mg thalidomide daily is well tolerated in patients with relapsed or refractory myeloma.

[0948] Maintenance with low-dose thalidomide after autologous stem cell transplant in multiple myeloma.

Mettivier V, Pezzullo L, Rocco S, et al.

This study looked at 20 patients treated between 2001 and 2005. Median age was 58 years (range 51-72). Induction therapy was 4 cycles of VAD regimen followed by autologous stem cell transplant (auto-SCT). Half of the patients underwent double auto-SCT. Three months after SCT, 10 patients (5 single and 5 double SCT) began thalidomide 50 mg/day as maintenance therapy; the other half (5 single and 5 double SCT) received IFN-g (3/10), dexamethasone (3/10) or no therapy (4/10). The authors showed that in a small number of patients, low-dose thalidomide as maintenance after auto-SCT resulted in an improved progression-free survival and overall survival when compared with other or maintenance, with acceptable toxicity.

[1193] Efficacy of thalidomide and dexametheasone as salvage regimen for myeloma patients relapsing after autologous transplant.

Falco P, Ambrosini MT, Caravita T, et al.

In this study 90 multiple myeloma patients (median age 61) received first salvage treatment after an autologous stem cell transplant performed at diagnosis. Forty-three patients were treated with thalidomide /dexamethasone (100 mg/day and 40 mg on days 1-4 each month respectively), 19 patients were treated with doxorubicin - and/ or cyclophosphamide-containing regimens and 28 patients repeated autologous stem cell transplantation at first relapse (97% conditioned with melphalan 100 mg/m²). Response rate after thalidomide/dexamethasone was slightly lower than after a second autologous transplant but the time to progression was significantly prolonged. Median progression-free survival from relapse for TD was 20.3 months vs 9 months for autologous transplant and 4.5 months for cyclophosphamide regimen (p<0.001). Interestingly, 20% of patients treated with thalidomide/ dexamethasone showed a longer progression-free survival at relapse than at diagnosis.

QUARTER II THALIDOMIDE AND REVLIMID PUBLICATIONS

Phase II study of G3139, a Bcl-2 antisense oligonucleotide, in combination with dexamethasone and thalidomide in relapsed multiple myeloma patients.

Badros AZ, Goloubeva O, Rapoport AP, et al.

J Clin Oncol. 2005 Jun 20;23(18):4089-99. Epub 2005 May 2.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15867202&query_hl=1

Thalidomide and dexamethasone in combination have shown promising results when used at various points in the treatment of myeloma. This study looks at how the actions of these two drugs are affected by the addition of G3139 [a Bcl-2 antisense oligonucleotide produced by Genta]. Bcl-2 regulates the mitochondrial apoptosis pathway that promotes chemotherapy resistance. Thirty-three relapsed patients (median age, 60 years; range, 28 to 76 years) were enrolled and all received 220 cycles. Fifty-five percent of patients had objective responses, including two complete responses, four near complete responses, and 12 partial responses; six patients had minimal responses. The median duration of response was 13 months, and estimated progression-free and overall survival time is 17.4 months.

First-line thalidomide-dexamethasone therapy in preparation for autologous stem cell transplantation in young patients (<61 years) with symptomatic multiple myeloma.

Abdelkefi A, Torjman L, Ben Romdhane N, et al.

Bone Marrow Transplant. 2005 Jun 13; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15968290&query_hl=1

Thalidomide and dexamethasone therapy was given to patients under 61 years old with previously untreated symptomatic multiple myeloma. The aim of this study was to assess the efficacy and toxicity of this combination as first-line therapy, as well as to determine its effect on stem cell collection and engraftment. On an intent-to-treat basis, the overall response (spartial response) rate was 74%, including 24% of patients who obtained a complete remission. Authors assert that this combination does not affect stem cell mobilization.

Thalidomide downregulates angiogenic genes in bone marrow endothelial cells of patients with active multiple myeloma.

Vacca A, Scavelli C, Montefusco V, et al.

J Clin Oncol. 2005 Jun 6; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15939924&query_hl=1

The exact method of action through which thalidomide works is not completely understood, although it is thought to limit production of new blood vessels (antiangiogenesis). This study expands on that idea by comparing the expression of known angiogenic genes in bone marrow endothelial cells (ECs) of patients with active and non-active multiple myeloma, monoclonal gammopathies unattributed/unassociated (MGUS), non-Hodgkin's lymphoma, in a Kaposi's sarcoma (KS) cell line, and in healthy human umbilical vein ECs (HUVECs), following exposure to therapeutic doses of thalidomide. Results have shown that thalidomide markedly down-regulates the genes in a dose-dependent fashion in active MMECs and KS cell lines, but upregulates them or is ineffective in non-active MMECs, MGUS-ECs, NHL-ECs, and in HUVECs. Secretion of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and hepatocyte growth factor also diminishes according to the dose in culture-conditioned media.

Dow-dose thalidomide in combination with oral weekly cyclophosphamide and pulsed dexamethasone is a well tolerated and effective regimen in patients with relapsed and refractory multiple myeloma.

Kyriakou C, Thomson K, D'Sa S, et al. Br J Haematol. 2005 Jun;129(6):763-70

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15953002&query_hl=1

This study looked at the feasibility and efficacy of a regimen of oral weekly cyclophosphamide; monthly, pulsed dexamethasone; and low-dose thalidomide (CDT) in 52 patients with relapsed or refractory multiple myeloma. Results show about 17% of the patients achieved complete response, 62% partial response, 11% minimal response, 6% stable disease and 4% progressive disease, meaning an objective response rate (a least a minimal response) of 90% was achieved.

Long-term outcomes of previously untreated myeloma patients: responses to induction chemotherapy and high-dose melphalan incorporated within a risk stratification model can help to direct the use of novel treatments.

Alvares CL, Davies FE, Horton C, et al. Br J Haematol. 2005 Jun;129(5):607-14.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15916682&query_hl=1

In the UK, induction VAD chemotherapy followed by high-dose melphalan (HDM) is the standard treatment for patients with myeloma. The place of bortezomib and the thalidomide analogues within this treatment paradigm is yet to be established. After an intention-to-treat analysis involving 383 newly diagnosed patients, the authors proposed a multi-parametric risk-adapted model that includes response to induction chemotherapy and HDM, for identifying patients who may benefit from novel approaches to treatment.

Immunomodulatory derivative of thalidomide (Actimid or CC-4047) induces a shift in lineage commitment by suppressing erythropoiesis and promoting myelopoiesis.

Koh KR, Janz M, Mapara MY, et al.

Blood. 2005 May 15;105(10):3833-40. Epub 2004 Aug 3.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15292067&query_hl=1

There is a lot of optimism surrounding the potential of the two derivatives of thalidomide; Revlimid (CC-5013) and Actimid (CC-4047). However, as with thalidomide, the method of action with these drugs is not fully understood. This study explored the effect that Actimid has on normal hematopoiesis. The investigators found that Actimid effectively inhibits erythroid cell colony formation from CD34+ cells and increases the frequency of myeloid colonies. The development of both erythropoietin-independent and erythropoietin-dependent red cell progenitors was strongly inhibited while terminal red cell differentiation was unaffected.

Thalidomide influences the function of macrophages and increases the survival of plasmodium berghei-infected CBA mice.

Muniz-Junqueira MI, Silva FO, de Paula-Junior MR, *et al.* Acta Trop. 2005 May;94(2):128-38. Epub 2005 Apr 7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15817259&query_hl=1

It is recognized that thalidomide decreases TNF production and may modulate several functions of the immune system. This work expanded on this concept by evaluating the influence of thalidomide on macrophage functions, and its ability to protect against severe disease. The results of this study showed that thalidomide correlated with a 26.5% increase of the mean of macrophage phagocytic index versus the control, and augmented in 13% the mean of the production of hydrogen peroxide, and in 45% the mean of nitric oxide production by macrophages.

Markers of endothelial and haemostatic function in the treatment of relapsed myeloma with the immunomodulatory agent Actimid (CC-4047) and their relationship with venous thrombosis.

Streetly M, Hunt BJ, Parmar K, et al. Eur J Haematol. 2005 Apr;74(4):293-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15777340&query_hl=1

In an attempt to further understand the method of action for Actimid, the authors of this study evaluated the serum/plasma levels of cytokines [interleukin (IL)-6, vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-beta2] and markers of coagulation, fibrinolysis, and endothelial and platelet activation during the first 4 weeks of treatment with Actimid in 15 patients with relapsed/refractory myeloma. There was evidence of activation of endothelium (soluble vascular cell adhesion molecule, sVCAM), coagulation (prothrombin fragment 1 + 2, PF1 + 2) and fibrinolysis (D-dimers), but no evidence of platelet activation or endothelial cell damage in myeloma patients. Three of four patients with baseline D-dimer levels >500 microg/L subsequently developed deep vein thrombosis (DVT). The authors suggest that D-dimer level >500 microg/L may predict for those patients most at risk of thromboembolism with myeloma.

Thalidomide inhibits growth of tumors through COX-2 degradation independent of antiangiogenesis.

Du GJ, Lin HH, Xu QT, et al.

Vascul Pharmacol. 2005 Jun 24; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15982930&query_hl=9

There has been recent interest in the role that the COX-2 enzyme plays in myeloma. Ladetto and his Italian colleagues recently published research that indicates that the presence of this enzyme is an independent predictor of poor outcome. This study attempted to clarify the antiangiogenic effects of thalidomide, and during the process found that thalidomide might inhibit growth of tumors through COX-2 degradation independent of antiangiogenesis. Thalidomide reduced COX-2 expression, accompanied by a decrease of BCl-2 protein, TNFalpha, VEGF, GSH and an increased cytochrome c, but had no effect on that of COX-1, in MCF-7 or HL-60. Moreover, cells not expressing COX-2 were insensitive to thalidomide's effects on growth inhibition and cytokines.

CLINICAL TRIALS UPDATE

Phase III Special Protocol Assessment (SPA) Trials Show REVLIMID Significantly Delays Time to Disease Progression in Previously Treated Multiple Myeloma Patients; Data Presented at ASCO 2005 Meeting.

- The median time-to-disease progression in the North American Phase III Trial (MM-009) with REVLIMID plus dexamethasone was 60.1 weeks, compared with the median time-to-disease progression of 20.7 weeks for placebo plus dexamethasone.
- The median time-to-disease progression in the International Phase III Trial (MM-010) with REVLIMID plus dexamethasone was 53.4 weeks, compared with median time-to-disease progression of 20.6 weeks for placebo plus dexamethasone.
- Best response rate in the North American trial with REVLIMID plus dexamethasone was 61.2%, compared with a response rate of 22.8% for placebo plus dexamethasone; Complete response rate of REVLIMID plus dexamethasone was 26.5%, compared with 4.1% for placebo plus dexamethasone in the North American trial.
- Best response rate in the international trial with REVLIMID plus dexamethasone was 58.0% compared with a response rate of 21.7% for placebo plus dexamethasone. Complete response rate of REVLIMID plus dexamethasone was 13.6%, compared with 4.0% with placebo plus dexamethasone in the international trial.

Other current trials include:

UARK 2003-26 (NCT00090493) – Phase II/III Study of MAGE-A3 and NY-ESO-1 Immunotherapy in Combo with DTPACE Chemo and Auto Transplantation in Multiple Myeloma

CALGB-100104 (NCT00114101, ECOG-CALGB-100104) – Phase III Randomized Study of Lenalidomide as Maintenance Therapy After Autologous Stem Cell Transplantation in Patients With Multiple Myeloma

UARK 2005-01 (NCT00111748) – Phase III Study of Velcade, Thalidomide, and Dexamethasone (VTD) with or without Adriamycin[®] in Relapsed/Refractory Patients

ECOG-E4A03 (NCT00098475) – Phase III Randomized Study of Lenalidomide With Standard-Dose Versus Low-Dose Dexamethasone With or Without Salvage Therapy Comprising Thalidomide and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma

DO04-23-006 (NCT00097981) – Thal/Dex (Thalidomide and Dexamethasone) Versus Dd-T (Doxil, Dexamethasone and Thalidomide) in Multiple Myeloma Patients

CKVO-2001-02 (EU-20133, NCT00028886) – Phase III Randomized Study of Doxorubicin, Dexamethasone, and High-Dose Melphalan With or Without Thalidomide in Patients With Myeloma

CAN-NCIC-MY10 (NCT00049673) – Phase III Randomized Study of Thalidomide and Prednisone as Maintenance Therapy After Autologous Stem Cell Transplantation in Patients With Multiple Myeloma

SWOG-S0232 (NCT00064038) – Phase III Randomized Study of Dexamethasone With or Without Lenalidomide in Patients With Newly Diagnosed Stage I, II, or III Multiple Myeloma

NCT00093028 - Study of Bortezomib and REVLIMID for Patients Relapsing or Progressing on Total Therapy II

CHNMC-04064 (NCT00112827) – Phase I/II Study of Tandem Ablative Therapy Comprising High-Dose Melphalan and Total Marrow Irradiation Followed By Autologous Peripheral Blood Stem Cell Transplantation and Maintenance Therapy Comprising Dexamethasone and Thalidomide in Patients With Stage I, II, or III Multiple Myeloma

SWOG-S0204 (NCT00040937) – Phase II Study of Thalidomide and Dexamethasone Induction Followed By Tandem Melphalan and Peripheral Blood Stem Cell Transplantation Followed By Prednisone and Thalidomide Maintenance in Patients With Multiple Myeloma

MSGCC-210421 (NCT00049374, NCI-5824) – Phase II Study of Oblimersen, Thalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma

MSKCC-02031 – Phase II Study of Risk-Adapted Melphalan Followed By Thalidomide and Dexamethasone in Patients With Newly Diagnosed, Previously Untreated Primary Systemic (AL) Amyloidosis

BUMC-H-23235 (CELGENE-RV-AMYL-PI-003) – Phase II Study of CC-5013 With or Without Dexamethasone in Patients With Primary Systemic (AL) Amyloidosis

UARK 98-036 (NCT00083382) – Phase II Combination Bisphosphonate and Anti-Angiogenesis Therapy with Pamidronate and Thalidomide

CC-5013-MM-011 (NCT00091624) – Phase I Study of CC-5013 in combination with Doxil, Vincristine and Decadron (DVd) in Subjects with Relapsed or Refractory Multiple Myeloma A Phase I Study of DVd +/ CC-5013 in Relapsed Refractory Multiple Myeloma (MM)

Phase II study of Biaxin, REVLIMID and Dexamethasone in patients with newly-diagnosed multiple myeloma, New York Presyterian/Cornell-Weill Medical Center

Phase II Trial on the Combination of Melphalan, Intermediate-dose Dexamethasone and Thalidomide in Poor Risk Patients, Amyloid Center, Pavia, Italy

Phase I Study of Velcade with REVLIMID in Relapsed and Refractory MM: The RevVelStudy, Dana Farber Cancer Institute, Boston.

LICENSING UPDATE:

- The Food and Drug Administration (FDA) has accepted Celgene Corporation's New Drug Application (NDA) for REVLIMID and granted a priority review. The application was based on favorable clinical trial data as a treatment for low- and intermediate- risk myelodysplastic syndromes (MDS). A decision is expected by the end of the 2005. If the FDA accepts the application for MDS, REVLIMID will also become available "off-label" for the treatment of multiple myeloma. Although this would be fantastic news for myeloma patients the "off label" status may cause difficulties when attempting to recover reimbursments from insurance providers.
- Celegene has begun an "expanded access program" (EAP) for REVLIMID in patients with myeloma. Through this program REVLIMID will be available on a limited basis through-out the U.S. An EAP is a mechanism for making unapproved drugs with clear benefit available to patients who have a specific need before approval.
- Celgene has submitted its response to the FDA's "approvable letter" for THALOMID®'s supplemental New Drug Application (NDA) for multiple myeloma. The FDA's letter made it clear the FDA would be willing to approve THALOMID for use in myeloma when additional data is presented. Although thalidomide is widely used as a treatment for myeloma, it is actually only approved in the U.S. for the treatment of leprosy, and therefore all use in myeloma is technically "off label." There may be more progress on this issue later in 2005.
- For the most up-to-date information on any of these items please visit our website at www.myeloma.org or visit Celgene Corporation's site at www.celgene.com.