CITINGS

Published by the International Myeloma Foundation — Volume II : Issue III : Spring 2005

Revlimid™ (lenalidomide) Issue

***The International Myeloma Foundation** (IMF) is pleased to present our third issue of CITINGS for 2005. In this issue we are continuing our series focusing specifically on publications referring to Revlimid™.*

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 Revlimid™ 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

Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro.

Dredge K, Horsfall R, Robinson SP, Zhang LH, *et al.*

Microvasc Res. 2005 Jan;69 (1-2):56-63.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15797261

It has been shown that lenalidomide inhibits angiogenesis in both rat and human in vitro models but does not affect endothelial cell proliferation. This study demonstrates that oral administration of lenalidomide attenuates growth factor-induced angiogenesis in vivo and significantly inhibits growth factor-induced endothelial cell migration. This correlates with the inhibitory effect of lenalidomide on growth factor-induced Akt phosphorylation, thereby providing a potential mechanism for its anti-migratory and subsequent anti-angiogenic effects.

Combination of the mTOR inhibitor rapamycin and CC-5013 has synergistic activity in multiple myeloma.

Raje N, Kumar S, Hideshima T, Ishitsuka K, *et al.*

Blood, 2004 December 15, 104 (13); 4188-4193.

http://www.bloodjournal.org/cgi/content/abstract/104/13/4188

This study showed that rapamycin and Revlimid together are able to overcome drug resistance when tested against myeloma cell lines resistant to conventional chemotherapy. Moreover, the combination, but not rapamycin alone, is able to overcome the growth advantage conferred on myeloma cells by interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), or adherence to bone marrow stromal cells (BMSCs).

Funded by an educational grant from Celgene Corporation.

Toward a rational combinaTORial therapy for multiple myeloma.
Jernberg-Wiklund H, Nilsson K
Blood, 2004 December 15 2004: 104(13); 3845-3846.
http://www.bloodjournal.org/cgi/content/full/104/13/3845?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=CC5013&andorexactfulltext=and&searchid=1112046420261_8120&stored_search=&FIRSTINDEX=0&sortspec=date&resourcetype=1&journalcode=bloodjournal
The article argues that phosphatidylinositol 3-kinase/Akt (PI3-K/Akt) signaling pathway regulates growth and survival in multiple myeloma (MM) in vitro. Of the many substrates regulating caspase activity and apoptosis downstream of Akt, the mammalian target of rapamycin, mTOR, has been thought to act as a special survival checkpoint kinase in several cell types. This pathway can be disrupted effectively only (currently) when drugs are combined. For example, Rapamycin and CC-5013, in contrast to the cytostatic effects observed by rapamycin alone, induces apoptosis at doses well below those pharmacologically achievable in vivo.

The pathophysiologic role of VEGF in hematologic malignancies: therapeutic implications.
Podar K, Anderson KC
Blood, 2005 February 15, 105 (4); 1383-1395.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15471951
It has previously been shown that VEGF triggers growth, survival, and migration of leukemia and multiple myeloma cells; plays a pivotal role in hematopoiesis; inhibits maturation of dendritic cells; and increases osteoclastic bone-resorbing activity as well as osteoclast chemotaxis. The authors argue that Revlimid should be used to target the biochemical pathways involved.

Cyclooxygenase-2 (COX-2) is frequently expressed in multiple myeloma and is an independent predictor of poor outcome.
Ladetto M, Vallet S, Trojan A, Boccadoro M, *et al.*
Blood, Feb 2005; 10.1182/blood-2004-11-4201.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15731178
COX-2 is an inflammation-associated enzyme involved in the pathogenesis of many solid tumors, but little is known about its presence and role in hematological neoplasms. Multiple myeloma is known to involve a deregulated cytokine network with secretion of inflammatory mediators. The authors showed that COX-2 positivity was associated with a poor outcome in terms of progression-free (18 vs. 36; months, $p<0.001$) and overall survival (28 vs. 52 months, $p<0.05$). Real-time PCR showed COX-2 mRNA over-expression. IC and cell separation studies demonstrated COX-2 expression to be restricted to malignant plasma cells. Therapeutic approaches including drugs such as Revlimid may be effective in this setting.

Interfering with amyloidosis.
Seldin DC
Blood, 2004 December 1; 104(12): 3419-3420.
http://www.bloodjournal.org/cgi/content/full/104/12/3419-a?maxtoshow=&HITS=&hits=&RESULTFORMAT=&fulltext=revlimid&andorexactfulltext=and&searchid=1112084679501_1618&stored_search=&FIRSTINDEX=0&sortspec=date&resourcetype=1
Patients diagnosed with AL amyloidosis have a worse prognosis than patients with multiple myeloma. With traditional oral melphalan and prednisone chemotherapy, hematologic responses are difficult to document, and amelioration of the end-organ damage is not frequently observed. Fortunately clinical trials involving dugs such as Revlimid and Velcade are currently underway, provide new hope for patients with this morbid plasma cell disease. With the results of these studies in hand, one will be able to design new trials that will compare effective regimens against each other; treatment has the potential to improve dramatically.

Thalidomide-derived immunomodulatory drugs as therapeutic agents.
Galustian C, Labarthe MC, Bartlett JB, Dalgleish AG
Expert Opin Biol Ther. 2004 Dec; 4(12):1963-70.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15571458
The authors argue that the key to the therapeutic potential of IMiDs lies in the fact that the drugs have multiple mechanisms of action, which may produce both anti-inflammatory and anti-tumor effects. These effects are probably contextual, depending both on the cell type and the stimulus involved. Mechanisms associated with IMiD activity include TNF-alpha-inhibitory, T cell costimulatory and antiangiogenic activities. Studies of the mechanisms of action of these drugs are ongoing and will facilitate the continued development of this class of compound in a number of diseases.

Circulating endothelial progenitor cells in multiple myeloma: implications and significance.
Zhang H, Vakil V, Braunstein M, *et al.*
Blood First Edition Paper, prepublished online December 23, 2004; DOI 10.1182/blood-2004-06-2101.
http://www.bloodjournal.org/cgi/content/abstract/2004-06-2101v1?maxtoshow=&HITS=&hits=&RESULTFORMAT=&fulltext=cc5013&andorexactfulltext=and&searchid=1112084339843_1416&stored_search=&FIRSTINDEX=0&sortspec=date&resourcetype=1
This study sought to characterize circulating endothelial cells (CECs) and their relation to disease activity and therapeutic response in thirty-one consecutive myeloma patients. Co-expression of vascular endothelial growth factor receptor-2 (KDR) and CD133 characterized endothelial progenitor cells (EPCs) in myeloma, and KDR mRNA elevations correlated with M protein levels. In vitro exposure of endothelial cells (ECs) to thalidomide or its derivative CC-5013 inhibited gene expression of the receptors for transforming growth factor and thrombin.

In vitro and in vivo activity of atiprimod (N-N-diethl-8,8-dipropyl-2-azaspiro [4.5] decane-2-propanamine) inhibits human multiple myeloma cell growth in the bone marrow milieu.
Hamasaki M, Hideshima T, Tassone P, Neri P, *et al.*
Blood First Edition Paper, prepublished online February 10, 2005; DOI 10.1182/blood-2004-09-3794.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15705788
Atiprimod is an orally-bioavailable cationic amphiphilic compound which significantly inhibits production of interleukin (IL)-6 and inflammation in rat arthritis and autoimmune animal models. Importantly, Atiprimod inhibits both IL-6 and vascular endothelial growth factor (VEGF) secretion in bone marrow stromal cells (BMSCs) triggered by myeloma cell binding, and also inhibits angiogenesis on human umbilical vein cells (HUVEC). This study provides a framework for future clinical trials including those with Revlimid and other anti-angiogenesis drugs.

Clinical Trials Update

Phase III Special Protocol Assessment (SPA) Trials Exceed Pre-Specified Interim Efficacy Endpoint

An Independent Data Monitoring Board has advised Celgene to unblind two Phase III clinical trials of Revlimid (lenalidomide) in patients with relapsed or refractory myeloma involving over 700 patients. The trial design included a primary endpoint of time to disease progression calculated as the time from randomization to the first documentation of progressive disease based on Blade myeloma response criteria.

- The trials overwhelmingly showed a delay in time to disease progression for patients receiving Revlimid compared to original projections

- The preliminary safety profile was favorable

- Plans are under way to offer expanded access to Revlimid for patients with previously treated myeloma (subject to appropriate regulatory approval)

Other current trials include:

- **SWOG-S0232 (NCT00064038)** - Phase III Double-Blinded Placebo Controlled Phase III Trial Comparing Dexamethasone (DEX) to the Combination of DEX + CC-5013 in Patients with Newly Diagnosed Multiple Myeloma

- **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

- **UARK 2003-35** - Study of Bortezomib and Revlimid™ for Patients Relapsing or Progressing on Total Therapy II

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

- **BUMC-2004-009** - Phase II Study of CC-5013 With or Without Dexamethasone in Patients With Primary Systemic (AL) Amyloidosis

- Phase II study of Biaxin, Revlimid, and Dexamethasone in patients with newly-diagnosed multiple myeloma.

- Phase I Study of Velcade with Revlimid in Relapsed and Refractory MM: The RevVel Study