



CITINGS

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THALIDOMIDE AND REVLIMID™ ISSUE

The INTERNATIONAL MYELOMA FOUNDATION (IMF) is pleased to introduce the first edition of CITINGS, a quarterly publication featuring the most up-to-date information on research advances and new therapies for the treatment for multiple myeloma. CITINGS will provide physicians and other health care professionals with references and Internet links to the most current U.S. and international journal articles, abstracts, and white papers. Each issue will present articles related to new drugs, either as the focus of the study or as part of the discussion of myeloma treatment.

CITINGS is an evolving publication. In our next issue, we will focus on data presented at the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) meetings. In future editions, we will be highlighting articles of special interest and providing in-depth analysis. We look forward to hearing your comments and suggestions by calling (800) 452-CURE (2873) or clicking on www.myeloma.org.

--Susie Novis, President, IMF

 **Clinical pharmacokinetics of thalidomide** Teo SK, Colburn WA, Tracewell WG, Kook KA, Stirling DI, Jaworsky MS, Scheffler MA, Thomas SD, Laskin OL.

Clinical Pharmacokinetics [2004;43(5):311-27]



<http://www.ingenta.com/isis/searching/ExpandTOC/ingenta;jsessionid=naaox2eae6qm.crescent?issue=pubinfobike://adis/cpk/2004/00000043/00000005&index=4>

This article examines the pharmacokinetics of thalidomide. Thalidomide is minimally metabolised by the liver, but is spontaneously hydrolysed into numerous renally excreted products. More than 90% of the absorbed drug is excreted in the urine and feces within 48 hours.

 **Treatment of multiple myeloma** Barlogie B, Shaughnessy J, Tricot G, Jacobson J, Zangari M, Anaissie E, Walker R, Crowley J.

Blood [Jan 1, 2004;103(1):20-32]



<http://www.bloodjournal.org/cgi/content/full/103/1/20>

This study found that among the prognostic factors evaluated, cytogenetic abnormalities (CAs), which are present in one third of patients with newly diagnosed disease, identify a particularly poor prognosis subgroup with a median survival not exceeding 2 to 3 years. By contrast, in the absence of CAs, 4-year survival rates of 80% to 90% can be obtained with tandem autotransplantations. The study concluded that fundamental and clinical research should, therefore, focus on the molecular and biologic mechanisms of treatment failure in the high-risk subgroup.

 ***Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma*** Hurt EM, Wiestner A, Rosenwald A, Shaffer AL, Campo E, Grogan T, Bergsagel PL, Kuehl WM, Staudt LM. *Cancer Cell* [February 23, 2004;Vol. 5, No. 2:191-200]



<http://www.cancer.org/content/article/abstract?uid=PIIS1535610804000194&highlight=c-maf>

This study found that overexpression of the c-maf oncogene promotes multiple myeloma proliferation, whereas c-maf inhibition blocks tumor formation. The authors conclude that one of the four recurrent translocations in multiple myeloma cells (t(14;16)) deregulates the c-maf gene but the functional consequences of this translocation remain unclear.

 ***A Phase I study of oral CC-5013 (lenalidomide, Revlimid), a thalidomide derivative, in patients with refractory metastatic cancer*** Tohnya TM, Ng SS, Dahut WL, Wright JJ, Arlen PM, Gulley JL, Parker C, Zeldis J, Figg WD.

Clinical Prostate Cancer [March 2004;2(4):241-3]



<http://www.electronicpc.com/journalEZ/detail.cfm?code=39560050020410>

The primary study objectives of this current trial are to determine the maximum tolerated dose of CC-5013 in patients with metastatic cancer that is refractory to therapy of proven efficacy, to characterize the pharmacokinetic and side effect profiles of CC-5013 in patients, and to define the dose-limiting toxicity.

 ***The promise of thalidomide: evolving indications*** Joglekar S, Levin M.

Drugs Today (Barc) [March 2004;40(3):197-204]



http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15148528

This review focuses on thalidomide's mechanisms of action, biochemistry, and pharmacokinetics, and its use in erythema nodosum leprosum as well as multiple myeloma, graft versus host disease, and renal cell carcinoma.

 ***Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers*** Bartlett JB, Michael A, Clarke IA, Dredge K, Nicholson S, Kristeleit H, Polychronis A, Pandha H, Muller GW, Stirling DI, Zeldis J, Dalglish AG.

British Journal of Cancer [March 8, 2004;90(5):955-61]



http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14997189

This study demonstrates the safety and tolerability, and suggests the clinical activity of CC-5013 in the treatment of refractory malignant melanoma. Furthermore, this is the first report demonstrating T-cell stimulatory activity of this class of compound in patients with advanced cancer.

 ***Multiple myeloma*** Sirohi B, Powles R.

Lancet [March 13, 2004;363(9412):875-87]



<http://www.sciencedirect.com/science>

This article looks at the ways in which myeloma treatment has changed in the past decade. The authors conclude that biological treatments such as thalidomide, CC-5013, and bortezomib, which target the myeloma cell and the bone-marrow microenvironment, will hold the key to future success.

-  ***Low-dose thalidomide for multiple myeloma: interim analysis of a compassionate use program*** Steurer M, Spizzo G, Mitterer M, Gastl G.
Onkologie [April 2004;27(2):150-4]
 <http://www.ncbi.nlm.nih.gov/80/entrez/utills/lofref.fcgi?PrId=3030&uid=15138347&db=PubMed&url=http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=ONK2004027002150>
The authors conclude that low-dose thalidomide (50-100 mg/day) alone or in combination is a safe, well-tolerated and effective form of therapy for patients with myeloma at various stages of disease.
-  ***Early response predicts thalidomide efficiency in patients with advanced multiple myeloma*** Waage A, Gimsing P, Juliusson G, Turesson I, Gulbrandsen N, Eriksson T, Hjorth M, Nielsen JL, Lenhof S, Westin J, Wisløff F for the Nordic Myeloma Study Group.
British Journal of Haematology [April 2004;Vol. 125, Issue 2:149]
 <http://www.blackwell-synergy.com/openurl?genre=article&sid=nlm:pubmed&issn=0007-1048&date=2004&volume=125&issue=2&spage=149>
Sixty-five patients who were primary or secondary refractory to melphalan/prednisone or other chemotherapy, or relapsed within 6 months after high-dose chemotherapy with stem cell support, were given thalidomide at a dose of 200 mg/d escalating to 800 mg. The patients were followed for a median of 2 years and 22 weeks. The study found no relationship between thalidomide concentration and effect after 12 weeks.
-  ***A low serum level of soluble tumor necrosis factor receptor p55 predicts response to thalidomide in advanced multiple myeloma*** Brenne AT, Romstad LH, Gimsing P, Juliusson G, Turesson I, Romundstad P, Borset M, Sundan A, Waage A.
Haematologica [May 2004; 89(5):552-6]
 <http://www.haematologica.org/journal/2004/5/552/>
The authors conclude that soluble TNFR p55 is an adverse prognostic factor in myeloma patients with relapsed or refractory disease treated with thalidomide. Patients with a low pre-treatment level of this receptor have a better response rate and a longer overall survival.
-  ***Tumor angiogenesis in the bone marrow of multiple myeloma patients and its alteration by thalidomide treatment*** Du W, Hattori Y, Hashiguchi A, Kondoh K, Hozumi N, Ikeda Y, Sakamoto M, Hata J, Yamada T.
Pathology International [May 2004;Volume 54 Issue 5:285]
 <http://www.blackwell-synergy.com/openurl?genre=article&sid=nlm:pubmed&issn=1320-5463&date=2004&volume=54&issue=5&spage=285>
This study found that thalidomide seems to be effective in the treatment of multiple myeloma through the impairment of angiogenesis by decreasing FGF-2 and VEGF production. This is the first report on pathological evidence in the bone marrow of MM before and after thalidomide treatment, in Japan.
-  ***Benefit and timing of second transplantations in multiple myeloma: clinical findings and methodological limitations in a European Group for Blood and Marrow Transplantation registry study*** Morris C, Iacobelli S, Brand R, Bjorkstrand B, Drake M, Niederwieser D, Gahrton G.
Journal of Clinical Oncology [May 1, 2004;Vol 22, No. 9:1674-1681]
 <http://www.jco.org/cgi/content/abstract/22/9/1674>
This study concluded that to improve survival of tandem autologous transplantation in multiple myeloma, the second transplantation should preferably be performed before relapse and within 6 to 12 months of the first transplantation.

-  ***Magnitude of response with myeloma frontline therapy does not predict outcome: importance of time to progression in Southwest Oncology Group chemotherapy trials***
Durie BGM, Jacobson J, Barlogie B, Crowley J.
Journal of Clinical Oncology [May 15, 2004;Vol 22, No. 10:1857-1863]
 <http://www.jco.org/cgi/content/abstract/22/10/1857>
The authors conclude that the magnitude of response, as a single variable, does not predict survival duration. Patients with response and stable disease have equivalent outcome. Only patients with progressive disease have a poorer outcome. The best indicator of survival is time to first progression.
-  ***Response to thalidomide in multiple myeloma: impact of angiogenic factors*** Rosinol L, Cibeira MT, Segarra M, Cid MC, Filella X, Aymerich M, Rozman M, Arenillas L, Esteve J, Blade J, Montserrat E.
Cytokine [May 21,2004;26(4):145-8]
 http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15149630
The authors state that although extramedullary plasmacytomas (EMP) have a high vascularization, the response of these patients to thalidomide is controversial. Thirty-eight patients with refractory/relapsed MM were treated with thalidomide. Eleven patients had EMP when therapy was initiated. The study found that the serum levels of FGF-2 and IL-6 did not correlate with response to treatment or presence of EMP.
-  ***Common and rare side-effects of low-dose thalidomide in multiple myeloma: focus on the dose-minimizing peripheral neuropathy***
Offidani M, Corvatta L, Marconi M, Malerba L, Mele A, Olivieri A, Brunori M, Catarini M, Candela M, Capelli D, Montanari M, Rupoli S, Leoni P.
European Journal of Haematology [June 2004;72(6):403-9]
 http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15128418
This study investigated the common and rare side effects, especially analyzing peripheral neuropathy, in order to optimize the thalidomide dose for minimizing this side effect. In patients with advanced multiple myeloma, the authors found that a thalidomide daily dose of 150 mg minimizes peripheral neuropathy without jeopardizing response and survival.