



CITINGS

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Thalidomide and Revlimid® Issue

The International Myeloma Foundation (IMF) is pleased to present our third edition of *CITINGS* for 2006. This quarterly publication features citations to the most up-to-date studies on myeloma treatment. In this issue, we focus on thalidomide and Revlimid for the treatment of multiple myeloma. Inside you will find references to the latest published journal articles on both thalidomide and Revlimid from the third quarter of this year.

It is our hope that *CITINGS* will help keep you abreast of the latest developments in myeloma treatment. As always, we welcome your feedback; you may contact the IMF at (800) 452-CURE (2873) or at our website www.myeloma.org.

– Susie Novis, President, IMF

Thalidomide/Revlimid Publications June–September, 2006

Anti-fibrotic effects of thalidomide on hepatic stellate cells and dimethylnitrosamine-intoxicated rats.

Chong LW, Hsu YC, Chiu YT, Yang KC, Huang YT.

J Biomed Sci. 2006 May;13(3):403-18. Epub 2006 Apr 8.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16604421&query_hl=1&itool=pubmed_DocSum

Tumor necrosis factor-alpha (TNF-alpha) plays a central role in cellular necrosis, apoptosis, organ failure, tissue damage, inflammation and fibrosis. These processes, occurring in liver injury, may lead to cirrhosis. Thalidomide, alpha-N-phthalidoglutarimide, C(13)H(10)N(2)(4), has been shown to have immunomodulatory and anti-inflammatory properties, possibly mediated through its anti-TNF-alpha effect. In this study, we investigated the in vitro and in vivo effects of thalidomide on hepatic fibrosis. A cell line of rat hepatic stellate cells (HSC-T6) was stimulated with transforming growth factor-beta1 (TGF-beta1) or TNF-alpha. The inhibitory effects of thalidomide on the NFkappaB signaling cascade and fibrosis markers including alpha-smooth muscle actin (alpha-SMA) and collagen, were assessed. An in vivo therapeutic study was conducted in dimethylnitrosamine (DMN)-treated rats, which were randomly assigned to 1 of 4 groups: vehicle (0.7% carboxyl methyl cellulose, CMC), thalidomide (40 mg/kg), thalidomide (200 mg/kg), or silymarin (50 mg/kg), each given by gavage twice daily for 3 weeks starting after 1 week of DMN administration. Thalidomide (100-800 nM) concentration-dependently inhibited NFkappaB transcriptional activity induced by TNF-alpha, including IKKalpha expression and IkbppaBalpha phosphorylation in HSC-T6 cells. In addition, thalidomide also suppressed TGF-beta1-induced alpha-SMA expression and collagen deposition in HSC-T6 cells. Fibrosis scores of livers from DMN-treated rats receiving high dose of thalidomide (0.89 +/- 0.20) were significantly reduced in comparison with those of DMN-treated rats receiving vehicle (1.56 +/- 0.18). Hepatic collagen contents of DMN rats were also significantly reduced by either thalidomide or silymarin treatment. Immunohistochemical double staining results showed that alpha-SMA- and NFkappaB-positive cells were decreased in the livers from DMN rats receiving either thalidomide or silymarin treatment. In addition, real-time PCR analysis indicated that hepatic mRNA expressions of TGF-beta1,

alpha-SMA, collagen 1alpha2, TNF-alpha and iNOS genes were attenuated by thalidomide treatment. In conclusion, our results showed that thalidomide inhibited activation of HSC-T6 cells by TNF-alpha and ameliorated liver fibrosis in DMN-intoxicated rats.

This study investigates the *in vitro* and *in vivo* effects of thalidomide on hepatic fibrosis. Its results show that thalidomide inhibited activation of HSC-T6 cells by TNF-alpha and ameliorated liver fibrosis in DMN-intoxicated rats.

Clinical implications of chromosomal abnormalities in multiple myeloma.

Terpos E, Eleutherakis-Papaiakovou V, Dimopoulos MA.

Leuk Lymphoma. 2006 May;47(5):803-14.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16753864&query_hl=1&itool=pubmed_DocSum

The adverse prognostic role of cytogenetic abnormalities has recently been established in plasma cell dyscrasias. Modern techniques such as fluorescence in situ hybridization and comparative genomic hybridization have revealed a higher incidence of cytogenetic abnormalities in patients with multiple myeloma (MM) compared to conventional cytogenetics. Hypodiploidy and chromosome 13 abnormalities are found in more than 50% of myeloma patients, representing well known factors with adverse prognosis. Rearrangements involving the switch regions of immunoglobulin heavy chain (IgH) gene at 14q32 with various partner genes represent the most common structural abnormalities, having an incidence of 70% in MM. Structural abnormalities of chromosomes 17 and 8 involving the p53 and c-myc genes are considered to be less frequent events, but carry a poor prognosis. New therapeutic approaches such as non-myeloablative allotransplantation and modern therapeutic agents (thalidomide, lenalidomide, and bortezomib) and their combinations give promise for an improved therapeutic management of patients with MM. The detection of t(4;14), t(14;16), deletion of chromosome 13 on metaphase analysis, or deletion of p53 by FISH will define high-risk prognostic groups that are not generally controlled with high-dose melphalan and autologous stem cell transplantation (ASCT), and should therefore be treated with more investigational therapies. Alternatively, eligible patients who do not have these poor risk factors are more likely to benefit from a high-dose, melphalan-based, regimen followed by ASCT.

The authors discuss the adverse prognostic role of cytogenetic abnormalities that has recently been established in plasma cell dyscrasias and new therapeutic approaches such as non-myeloablative allotransplantation and modern therapeutic agents, and their combinations, which give promise for an improved therapeutic management of patients with myeloma.

Intermediate-dose melphalan (100 mg/m²)/bortezomib/thalidomide/dexamethasone and stem cell support in patients with refractory or relapsed myeloma.

Palumbo A, Avonto I, Bruno B, Falcone A, Scalzulli PR, Ambrosini MT, Bringhen S, Gay F, Rus C, Cavallo F, Falco P, Massaia M, Musto P, Boccadoro M.

Clin Lymphoma Myeloma. 2006 May;6(6):475-7.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16796778&query_hl=1&itool=pubmed_DocSum

BACKGROUND: Bortezomib and thalidomide have shown synergy with melphalan and dexamethasone. We used this 4-drug combination as conditioning before autologous hematopoietic cell infusions. **PATIENTS AND METHODS:** Twenty-six patients with advanced-stage myeloma were treated with melphalan 50 mg/m² and bortezomib 1.3 mg/m² on days -6 and -3 in association with thalidomide 200 mg and dexamethasone 20 mg on days -6 through -3, followed by hematopoietic cell support on day 0. **RESULTS:** Nonhematologic toxicities included pneumonia, febrile neutropenia, and peripheral neuropathy. All patients had undergone autologous transplantation at diagnosis, and 13 patients (50%) underwent an additional transplantation at relapse. Responses occurred in 17 of 26 patients (65%), including 1 complete remission, 3 near complete remissions (12%), and 2 very good partial remissions (8%). Response rate was higher than that induced by the previous line of treatment in 12 patients (46%). **CONCLUSION:** Melphalan/bortezomib/thalidomide/dexamethasone showed encouraging antimyeloma activity in patients with advanced-stage myeloma.

This study concludes that melphalan/bortezomib/thalidomide/dexamethasone shows encouraging antimyeloma activity in patients with advanced-stage myeloma.

 ***A multicenter retrospective analysis of adverse events in Korean patients using bortezomib for multiple myeloma.***

Bang SM, Lee JH, Yoon SS, Park S, Min CK, Kim CC, Suh C, Sohn SK, Min YH, Lee JJ, Kim K, Seong CM, Yoon HJ, Cho KS, Jo DY, Lee KH, Lee NR, Kim CS, Korean Multiple Myeloma Working Party.

Int J Hematol. 2006 May;83(4):309-13.



http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16757429&query_hl=1&itool=pubmed_DocSum

The proteasome inhibitor bortezomib has demonstrated clinical activity in patients with multiple myeloma (MM). Adverse events, including thrombocytopenia and peripheral neuropathy, have affected 30% to 60% of patients overall, and interrupted therapy in 10% to 20%. No prior toxicity data are available for Asian patients who have used bortezomib for MM. We used National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, to review the clinical records of patients with an MM diagnosis from 25 centers in Korea. The included patients were treated with bortezomib alone or in combination with other agents, including thalidomide. Ninety-five MM patients were treated. The patients had a median age of 60 years (range, 42-77 years). The median number of previous treatments was 3 (range, 0-10), and 39% of the patients had been treated with 4 or more major classes of agents, including thalidomide (67%), and autologous stem cell transplantation (51%). Regimens included bortezomib only in 38 patients (40%), bortezomib plus dexamethasone in 34 patients (36%), and bortezomib plus a thalidomide-containing regimen in 23 patients (24%). The analysis of patient response to therapy revealed a complete response (CR) or a near-CR in 31 patients (33%) and a partial response in 30 patients (32%), for an objective response rate of 65% in 93 patients. The most common adverse events reported were thrombocytopenia (47%), sensory neuropathy (42%), anemia (31%), and leukopenia (31%). Thirteen patients (14%) stopped therapy because of adverse events (neuropathy, 8; infection, 4; diarrhea, 1). Neuropathy greater than grade 2 was more frequent in patients who received 4 or more prior therapy regimens (17/37) than in those who received 3 or fewer (14/58). In addition, therapy including thalidomide was significantly correlated with neuropathy of grades 1 to 3 ($P = .001$). We identified 6 therapy-related deaths (6%) within 20 days after the last dose of bortezomib. The causes of death were infection in 3 patients, disease progression in 2 patients, and suicide in 1 patient. The incidences of thrombocytopenia and neurotoxicity were similar; however, gastrointestinal toxicities were relatively low in Korean patients compared with those reported in Western studies. Significant neuropathy was associated with the number of prior regimens and combination with thalidomide. These findings provide useful information for clinicians and patients using bortezomib.

Bortezomib has demonstrated clinical activity in patients with multiple myeloma (MM), but no prior toxicity data are available for Asian patients who have used bortezomib for MM. In this study, 95 MM patients were treated. With a median age of 60 years, and a median number of previous treatments of 3, 39% of the patients had been treated with 4 or more major classes of agents, including thalidomide (67%), and autologous stem cell transplantation (51%). Regimens included bortezomib only, bortezomib plus dexamethasone, and bortezomib plus a thalidomide-containing regimen. The authors identified 6 therapy-related deaths (6%) within 20 days after the last dose of bortezomib. The causes of death were infection in 3 patients, disease progression in 2 patients, and suicide in 1 patient. As compared to Western studies, the incidences of thrombocytopenia and neurotoxicity were similar; however, gastrointestinal toxicities were relatively low in comparison. Significant neuropathy was associated with the number of prior regimens and combination with thalidomide.

 ***Optimizing the efficacy and safety of bortezomib in relapsed multiple myeloma.***

Richardson P, Jagannath S, Colson K.

Clin Adv Hematol Oncol. 2006 May;4(5):1; discussion 8; suppl 13.



http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16830422&query_hl=1&itool=pubmed_DocSum

Bortezomib (Velcade, Millennium) is the first proteasome inhibitor to be used in clinical practice and is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy. Bortezomib inhibits the intracellular degradation of proteins necessary for normal cell cycling and function. This, in turn, results in cell-cycle arrest and apoptosis. Bortezomib has shown significant activity in trials of patients with relapsed or refractory multiple myeloma; approximately one third of patients have shown significant improvement with bortezomib monotherapy in phase II and III clinical trials. Early phase trials are also evaluating bortezomib in combination with other agents used in the treatment of multiple myeloma, including melphalan, prednisone, thalidomide, and lenalidomide. Preliminary data suggest that bortezomib may act synergistically with some agents, and improves response rates. Bortezomib is generally well tolerated, but common side effects include peripheral neuropathy and thrombocytopenia. Studies are underway to explore different dosing strategies as well as ways

to maximize patient benefit while reducing toxicity. This review will discuss what is known thus far about the efficacy and safety profile of bortezomib, ways for optimizing treatment with bortezomib, and strategies for managing side effects and enhancing quality of life.

The authors discuss what is known thus far about the efficacy and safety profile of bortezomib, ways for optimizing treatment, evaluations of bortezomib in combination with other agents, including thalidomide, and strategies for managing side effects and enhancing quality of life.

Reversible paraparesis in multiple myeloma with renal failure.

Terrier B, Joly D, Ghez D, Knebelmann B, Fakhouri F, Hummel A.

Nephrol Dial Transplant. 2006 May;21(5):1439-40. [Epub 2006 Mar 6.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16520348&query_hl=1&itool=pubmed_DocSum

No abstract provided.

Thalidomide does not interact with P-glycoprotein.

Zimmermann C, Gutmann H, Drewe J.

Cancer Chemother Pharmacol. 2006 May;57(5):599-606. Epub 2005 Sep 1.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16136308&query_hl=1&itool=pubmed_DocSum

BACKGROUND: There is growing clinical interest in thalidomide for the treatment of various disorders due to its anti-inflammatory, immunomodulatory, and anti-angiogenic properties. In numerous clinical trials thalidomide is used as an adjunct to standard therapy. Therefore, clinicians should be aware of all possible drug-drug interactions that might occur with this drug. P-glycoprotein (P-gp), a drug efflux transporter that is expressed in many tissues, is the cause of several drug-drug interactions. P-gp induction or inhibition can lead to ineffective therapy or side-effects. In this study, we investigated thalidomide's potential to cause drug-drug interactions on the level of P-gp. **METHODS:** LS180 cells were incubated with thalidomide for 72 h in order to determine P-gp induction using real-time RT-PCR. A human leukaemia cell line over-expressing MDR1 (CCRF-CEM/MDR1) was used to measure uptake of rhodamine 123, a P-gp substrate, in the presence of thalidomide. Dose-dependent and bi-directional transport of thalidomide through Caco-2 cell monolayers was performed to assess site-directed permeability. Transport rates were determined using HPLC including chiral separation of the thalidomide enantiomers. **RESULTS:** Thalidomide did not induce P-gp expression in LS180 cells. The uptake of rhodamine 123 in CCRF cells over-expressing MDR1 was not influenced by co-incubation with thalidomide. The transport through Caco-2 monolayers was linear and the permeability was similar for both directions. No differences between the thalidomide enantiomers were observed. **CONCLUSIONS:** Our study indicates that thalidomide is neither a substrate, nor an inhibitor or an inducer of P-gp. Therefore, P-gp-related drug-drug interactions with thalidomide are not likely.

There is growing clinical interest in thalidomide for the treatment of various disorders due to its anti-inflammatory, immunomodulatory, and anti-angiogenic properties. In numerous clinical trials thalidomide is used as an adjunct to standard therapy. Therefore, clinicians should be aware of all possible drug-drug interactions that might occur with this drug. P-glycoprotein (P-gp), a drug efflux transporter that is expressed in many tissues, is the cause of several drug-drug interactions. This study indicates that thalidomide is neither a substrate, nor an inhibitor or an inducer of P-gp and, therefore, P-gp-related drug-drug interactions with thalidomide are not likely.

Anti-nociceptive effect of thalidomide on zymosan-induced experimental articular incapacitation.

Vale ML, Cunha FQ, Brito GA, Benevides VM, Ferreira SH, Poole S, Ribeiro RA.

Eur J Pharmacol. 2006 May 1;536(3):309-17. Epub 2006 Mar 10.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16597438&query_hl=1&itool=pubmed_DocSum

The anti-nociceptive effect of thalidomide on zymosan-induced articular knee joint incapacitation in rats was investigated. Thalidomide (5-45 mg/kg), given 30 min before but not 2 h after the intra-articular injection of zymosan, inhibited the nociceptive response in a dose-dependent manner. Furthermore, thalidomide pretreatment significantly reduced the

concentration of tumor necrosis factor-alpha (TNF-alpha, -68.4%) in the exudate of zymosan-injected joints, but not those of interleukin-1beta, interleukin-6, CINC-1 or interleukin-10. The expression of TNF-alpha, determined by immunohistochemical staining, in synovial tissues obtained from articular joints injected with zymosan was also inhibited by thalidomide pretreatment. The anti-nociceptive effect of thalidomide was not reversed by the co-administration of an opioid receptor antagonist, naloxone, suggesting that endogenous opioids do not mediate the anti-nociceptive effect of thalidomide in this model. In conclusion, the anti-nociceptive activity of thalidomide in zymosan-induced articular incapacitation is associated with the inhibition of TNF-alpha by resident synovial cells.

The authors investigate the anti-nociceptive effect of thalidomide on zymosan-induced articular knee joint incapacitation in rats, and conclude that anti-nociceptive activity of thalidomide in zymosan-induced articular incapacitation is associated with the inhibition of TNF-alpha by resident synovial cells.

Thalidomide therapy for myelofibrosis with myeloid metaplasia.

Thomas DA, Giles FJ, Albitar M, Cortes JE, Verstovsek S, Faderl S, O'Brien SM, Garcia-Manero G, Keating MJ, Pierce S, Zeldis J, Kantarjian HM.

Cancer. 2006 May 1;106(9):1974-84.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16583431&query_hl=1&itool=pubmed_DocSum

BACKGROUND: Thalidomide is a putative antiangiogenesis agent with activity in several hematologic malignancies. **METHODS:** Forty-four patients who had myelofibrosis with myeloid metaplasia received treatment with thalidomide in a Phase II clinical trial at a dose of 200 mg daily with escalation by 200 mg weekly until the best tolerated dose (maximum, 800 mg) was reached. **RESULTS:** Seventeen of 41 evaluable patients (41%) who received treatment for at least 15 days had a response. A complete response (without reversal of bone marrow fibrosis) was achieved in 4 patients (10%), a partial response was achieved in 4 patients (10%), and hematologic improvements in anemia, thrombopenia, and/or splenomegaly were observed in 9 patients (21%). Improvements in anemia occurred in 7 of 35 patients (20%) with hemoglobin levels <10.0 g/dL, and improvements in thrombopenia occurred in 5 of 24 patients (21%) with platelet counts <100 x 10(9)/L. Five of 24 patients (21%) became transfusion-independent. Major or minor regression of splenomegaly was noted in 9 of 29 evaluable patients (31%), and complete regression was noted in 5 patients. Responders had a lower baseline median vascular endothelial growth factor levels (77.9 pg/mL vs. 97.7 pg/mL; P <.01) and higher median basis fibroblast growth factor levels (60.8 pg/mL vs. 37.4 pg/mL; P <.01) compared with nonresponders. Nine patients (22%) had deterioration that was attributed to thalidomide (resolved after withdrawal) with either progressive cytopenias or excessive proliferation. Two patients developed Grade 3 neutropenia with recovery and resumed therapy with dose reductions, and both later achieved a complete response. Dose-related toxicities included fatigue (50%), constipation (48%), rash or pruritis (37%), sedation (35%), peripheral edema (29%), tremors (23%), peripheral neuropathy (22%), and orthostasis (16%). **CONCLUSIONS:** Thalidomide warrants further evaluation in patients with MMM, particularly in combination regimens, along with the investigation of newer analogs.

This study concludes that thalidomide warrants further evaluation in patients with myelofibrosis with myeloid metaplasia, particularly in combination regimens, along with the investigation of newer analogs.

Thalidomide and celecoxib as potential modulators of irinotecan's activity in cancer patients.

Villalona-Calero M, Schaaf L, Phillips G, Otterson G, Panico K, Duan W, Kleiber B, Shah M, Young D, Wu WH, Kuhn J.

Cancer Chemother Pharmacol. 2006 May 1; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16685529&query_hl=1&itool=pubmed_DocSum

Purpose: Nuclear factor-kappaB (NF-kappaB) activation induces resistance to irinotecan. Preclinically, thalidomide and COX-2 inhibitors reduce NF-kappaB activation. We tested the feasibility of combining irinotecan with thalidomide and thalidomide/celecoxib in patients with refractory malignancies. **Patients/methods:** The study was conducted in two parts. First, the optimal dose of thalidomide (400 or 200 mg daily) in combination with irinotecan 125 mg/m(2) days 1 and 8 every 3 weeks was determined. In the second part, celecoxib 400 mg twice-daily was added to irinotecan/thalidomide. Pharmacokinetics of irinotecan and thalidomide alone or concurrently were evaluated. Tumor necrosis factor alpha, beta-fibroblast growth factor, and NF-kappaB activation were measured in blood mononuclear cells (PBMC). No CYP450 enzyme inducers/inhibitors were allowed. **Results:** Thirty-six patients were enrolled: Eleven received thalidomide 400 mg, 13 thalidomide 200 mg and 12 thalidomide 400 mg and celecoxib, with irinotecan. For the two-drug combination, there was a higher rate of moderate/severe diarrhea/myelosuppression with thalidomide 200 mg. Thus thalidomide 400 mg was combined with celecoxib. The triple

combination resulted in similar toxicity as the doublet with the lower thalidomide dose. Concurrent administration of irinotecan/thalidomide did not influence pharmacokinetics. Anti-tumor responses occurred in two patients and prolonged stabilization in eight others. NF-kappaB activation increased over time. Patients experiencing tumor response or prolonged stabilization had lower NF-kappaB activation, albeit not statistically significant ($P = 0.124$). Conclusions: The combination of thalidomide/irinotecan is safe and devoid of PK interactions. Thalidomide 400 mg appeared more suitable for combination, whereas the addition of celecoxib did not improve tolerability. Tumor-specific studies in patients with lesser prior treatment will be necessary to establish the therapeutic impact of the combinations.

Nuclear factor-kappaB (NF-kappaB) activation induces resistance to irinotecan. Preclinically, thalidomide and COX-2 inhibitors reduce NF-kappaB activation. The authors test the feasibility of combining irinotecan with thalidomide and thalidomide/celecoxib in patients with refractory malignancies and find that the combination of thalidomide/irinotecan is safe and devoid of PK interactions.

Lenalidomide and venous thrombosis in multiple myeloma.

Knight R, DeLap RJ, Zeldis JB.

N Engl J Med. 2006 May 11;354(19):2079-80.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16687729&query_hl=1&itool=pubmed_DocSum

No abstract.

Lenalidomide and venous thrombosis in multiple myeloma.

Rajkumar SV, Blood E.

N Engl J Med. 2006 May 11;354(19):2079-80.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16696148&query_hl=1&itool=pubmed_DocSum

No abstract.

Frequent gain of chromosome band 1q21 in plasma cell dyscrasias detected by fluorescence in situ hybridization: Incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem cell transplantation.

Hanamura I, Stewart JP, Huang Y, Zhan F, Santra M, Sawyer JR, Hollmig K, Zangarri M, Pineda-Roman M, van Rhee F, Cavall F, Burington B, Crowley J, Tricot G, Barlogie B, Shaughnessy Jr JD.

Blood. 2006 May 16; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16705089&query_hl=1&itool=pubmed_DocSum

Using fluorescence in situ hybridization we investigated amplification of chromosome band 1q21 (Amp1q21) in over 500 untreated patients with monoclonal gammopathy of undetermined significance (MGUS, n=14), smoldering multiple myeloma (SMM, n=31) and newly diagnosed MM (n=479) as well as 45 relapsed MM. The frequency of Amp1q21 was 0% in MGUS, 45% in SMM, 43% in newly diagnosed MM and 72% in relapsed MM (newly diagnosed vs. relapsed MM, $P<0.0001$). Amp1q21 was detected in 10 of 12 patients who evolved to active MM compared to 4 of 19 who remained SMM ($P<0.001$). Newly diagnosed MM with Amp1q21 had inferior 5-year event-free/overall survival compared with those lacking Amp1q21 (38%/52% vs. 62%/78%, both, $P<0.0001$). Thalidomide improved 5-year EFS in patients lacking Amp1q21 but not in those with Amp1q21, $P=0.0044$). Multivariate analysis including other major predictors revealed that Amp1q21 was an independent poor prognostic factor. Relapsed patients who had Amp1q21 at relapse had inferior 5-year post-relapse survival compared with those lacking Amp1q21 at relapse (15% vs. 53%, $P=0.0271$). The proportion of cells with Amp1q21 and the copy number of 1q21 tended to increase at relapse compared with diagnosis. Our data suggest that Amp1q21 is associated with both disease progression and poor prognosis.

Using fluorescence in situ hybridization the authors investigate amplification of chromosome band 1q21 (Amp1q21) in over 500 untreated patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma, and newly diagnosed multiple myeloma (MM), as well as relapsed MM. The authors found that the proportion of cells with

Amp1q21 and the copy number of 1q21 tended to increase at relapse compared with diagnosis, and their data suggest that Amp1q21 is associated with both disease progression and poor prognosis.

 ***Thalidomide radiosensitization of normal murine hematopoietic but not squamous cell carcinoma or multiple myeloma tumor cell lines.***

Epperly MW, Greenberger EE, Franicola D, Jacobs S, Greenberger JS.

In Vivo. 2006 May-Jun;20(3):333-9.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16724666&query_hl=1&itool=pubmed_DocSum

BACKGROUND: Thalidomide (TL), due to its antiangiogenic effects, has been postulated to be a potential radiosensitizer of multiple myeloma and squamous tumors in vivo. MATERIALS AND METHODS: To determine whether TL was a radiosensitizer, 32D cl 3 cells (hematopoietic progenitor) as well as SCC-VII (squamous cell carcinoma), OPM1 or OPM2 (multiple myeloma) tumor cells were irradiated to doses ranging from 0 to 8 Gy and then plated in 0, 50 or 150 microM TL in each of three protocols: i) 1 hour before irradiation; ii) 1 hour before irradiation and also in medium following irradiation; or iii) placed in TL containing medium following irradiation. RESULTS: Using 150 microM TL (which did not stimulate cell growth) the 32D cl 3 cells had increased radiation sensitivity compared to the control irradiated cells. In contrast, the SCC-VII, OPM1 or OPM2 cells showed no detectable radiosensitization when incubated in TL before, during or after irradiation compared to the control irradiated cells. CONCLUSION: These results demonstrated that TL may be a selective radiosensitizer.

Thalidomide, due to its antiangiogenic effects, has been postulated to be a potential radiosensitizer of multiple myeloma and squamous tumors in vivo. Based upon the results of this study, the authors conclude that thalidomide may be a selective radiosensitizer.

 ***Combination chemotherapy with cyclophosphamide, thalidomide and dexamethasone for patients with refractory, newly diagnosed or relapsed myeloma.***

Sidra G, Williams CD, Russell NH, Zaman S, Myers B, Byrne JL.

Haematologica. 2006 Jun;91(6):862-3.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16769594&query_hl=1&itool=pubmed_DocSum

We evaluated the combination of thalidomide, pulsed dexamethasone and weekly cyclophosphamide (CTD) for the treatment of patients with newly diagnosed, relapsed or VAD-refractory multiple myeloma. We found that this combination was highly effective in inducing responses in all treatment groups with an overall response rate of 83.8%. CTD was well tolerated and did not impair stem cell mobilization.

The authors evaluate the combination of thalidomide, pulsed dexamethasone and weekly cyclophosphamide (CTD) for the treatment of patients with newly diagnosed, relapsed or VAD-refractory multiple myeloma and find that this combination is highly effective in inducing responses in all treatment groups with an overall response rate of 83.8%. CTD was well tolerated and did not impair stem cell mobilization.

 ***Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis.***

Ikhlaque N, Seshadri V, Kathula S, Baumann MA.

Am J Hematol. 2006 Jun;81(6):420-2.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16680743&query_hl=1&itool=pubmed_DocSum

BACKGROUND: Deep venous thrombosis (DVT) is a common complication of thalidomide treatment. There is little information to guide clinicians in selecting effective preventive treatments and physician practice varies. We sought to determine whether prophylactic anticoagulation with warfarin prevents DVT related to thalidomide treatment. METHODS: We reviewed the records of 131 patients receiving thalidomide for a variety of indications. Fifty-five patients were prescribed warfarin with the intent of preventing DVT. Thirty-seven patients received warfarin at a dose of 1-2 mg per day (low dose) and 18 received a dose intended to raise the INR to 2-3 (high dose). RESULTS: Twenty-one of the 131 patients developed venous thrombosis during thalidomide treatment. Eighteen of the 76 patients (23.7%) who were not prescribed prophylactic anticoagulation developed

DVT compared to 3 of the 55 patients (5.5%) who were prescribed any dose of prophylactic warfarin ($P = 0.010$). Only 1 of the 37 patients who received low-dose warfarin developed DVT ($P = 0.011$). Bleeding complications occurred in 4 patients, all of whom were receiving high-dose warfarin. **CONCLUSION:** Prophylactic anticoagulation with warfarin reduces the risk of thrombosis during thalidomide treatment. Low-dose warfarin may be as effective as higher dose treatment and may result in fewer bleeding complications.

Deep venous thrombosis (DVT) is a common complication of thalidomide treatment. There is little information to guide clinicians in selecting effective preventive treatments and physician practice varies. The authors seek to determine whether prophylactic anticoagulation with warfarin prevents DVT related to thalidomide treatment. They conclude that prophylactic anticoagulation with warfarin reduces the risk of thrombosis during thalidomide treatment and that low-dose warfarin may be as effective as higher dose treatment and may result in fewer bleeding complications.

Thromboembolism risk reduction in multiple myeloma patients treated with immunomodulatory drug combinations.

Hussein MA.

Thromb Haemost. 2006 Jun;95(6):924-30.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16732369&query_hl=1&itool=pubmed_DocSum

Deep vein thrombosis and its lethal complication pulmonary embolism are manifestations of venous thromboembolism (VTE), which is typically associated with cancer and recent major surgery. Certain solid tumors and hematologic malignancies impose an inherently elevated risk of VTE that is compounded by chemotherapy and other risk factors. Multiple myeloma (MM) and other plasma cell dyscrasias are thrombogenic as a consequence of their multiple hemostatic effects, including elevated interleukin-6 levels, pro-coagulant antibody formation, paraprotein interference with fibrin structure, activated protein C resistance, and endothelial damage. The oral immunomodulatory drugs thalidomide and lenalidomide have produced major therapeutic responses in patients with MM when used in combination with oral steroids and chemotherapy, but a high incidence of VTE has been reported. Various VTE prophylaxis strategies with thalidomide- and lenalidomide-containing combinations have been investigated in clinical studies. This review discusses emerging results on the use of VTE prophylaxis to minimize VTE risks associated with MM treatment regimens containing thalidomide and lenalidomide.

The authors discuss emerging results on the use of venous thromboembolism (VTE) prophylaxis to minimize VTE risks associated with myeloma treatment regimens containing thalidomide and lenalidomide.

The use of thalidomide in myeloma therapy as an effective anticancer drug.

Sze DM, Brown R, Yang S, Ho PJ, Gibson J, Joshua D.

Curr Cancer Drug Targets. 2006 Jun;6(4):325-31.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16848723&query_hl=1&itool=pubmed_DocSum

Thalidomide and its immunomodulatory derivatives have provided the most significant advance in the therapy of myeloma since the introduction of high dose chemotherapy followed by stem cell transplantation nearly 20 years ago. The mechanism of action of thalidomide is complex and involves many aspects of malignant plasma cell growth and bone marrow stromal cell microenvironment interaction. Thalidomide was first used because of its anti-angiogenic properties, however it is the immunomodulatory actions that involve increasing host tumour-specific immunosurveillance by both T cell and natural killer cells which may be the most important mode of action.

The authors discuss how thalidomide and its immunomodulatory derivatives have provided the most significant advance in the therapy of myeloma since the introduction of high dose chemotherapy followed by stem cell transplantation nearly 20 years ago.

 ***Importance of the stress kinase p38alpha in mediating the direct cytotoxic effects of the thalidomide analogue, CPS49, in cancer cells and endothelial cells.***

Warfel NA, Lepper ER, Zhang C, Figg WD, Dennis PA.

Clin Cancer Res. 2006 Jun 1;12(11 Pt 1):3502-9.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16740776&query_hl=1&itool=pubmed_DocSum

PURPOSE: Thalidomide has gained renewed interest as a cancer therapeutic due to its potential antiangiogenic effects. The thalidomide analogues CPS11 and CPS49 are active in preclinical angiogenesis assays and xenograft model systems, but the biochemical basis for these observations is unclear. **EXPERIMENTAL DESIGN:** To address this question, we assessed the toxicity of these thalidomide analogues in cancer cells, endothelial cells, and genetically modified cells using assays that measure apoptotic and nonapoptotic cell death. Phosphospecific and native antibodies were used in immunoblotting and immunohistochemical experiments to assess the activation states of kinases that control cellular survival in vitro and in vivo. **RESULTS:** CPS49 predominantly induced nonapoptotic cell death in lung cancer cells, prostate cancer cells, and endothelial cells in a dose-dependent manner, whereas CPS11 was not cytotoxic. CPS49 did not inhibit kinases that promote survival, such as Akt or extracellular signal-regulated kinase, but rather rapidly activated the stress kinase p38 pathway in both cancer cells and endothelial cells. CPS49 activated p38 in tumor xenografts. Using p38alpha^{-/-} cells or an inhibitor of p38, we show that the presence and activation of p38alpha is important for cytotoxicity in all cell types examined. **CONCLUSIONS:** Our studies identify a unifying mechanism of action for cytotoxicity of the tetrafluorinated thalidomide analogue, CPS49, and suggest that activation of p38 could serve as a biomarker in clinical trials with CPS49.

Thalidomide has gained renewed interest as a cancer therapeutic due to its potential antiangiogenic effects. The thalidomide analogues CPS11 and CPS49 are active in preclinical angiogenesis assays and xenograft model systems, but the biochemical basis for these observations is unclear. This study identifies a unifying mechanism of action for cytotoxicity of the tetrafluorinated thalidomide analogue, CPS49, and suggests that activation of p38 could serve as a biomarker in clinical trials with CPS49.

 ***Thalidomide for multiple myeloma.***

Folkman J, Rogers MS.

N Engl J Med. 2006 Jun 1;354(22):2389-90; *author reply* 2389-90.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16738279&query_hl=1&itool=pubmed_DocSum

Comment on: *N Engl J Med.* 2006 Mar 9;354(10):1021-30.

 ***Thalidomide, dexamethasone and pegylated liposomal doxorubicin (ThaDD) for newly diagnosed multiple myeloma patients over 65 years.***

Offidani M, Corvatta L, Piersantelli MN, Visani G, Alesiani F, Brunori M, Galieni P, Catarini M, Burattini M, Centurioni R, Ferranti M, Rupoli S, Scortechini AR, Giuliodori L, Candela M, Capelli D, Montanari M, Olivieri A, Poloni A, Polloni C, Marconi M, Leoni P.

Blood. 2006 Jun 8; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16763209&query_hl=1&itool=pubmed_DocSum

We present the results of a phase II study using thalidomide, dexamethasone and pegylated liposomal doxorubicin (ThaDD) in the treatment of 50 newly diagnosed multiple myeloma patients over 65 years. Thalidomide was administered orally 100 mg at bedtime continuously, dexamethasone orally 40 mg days 1-4 and 9-12 and pegylated liposomal doxorubicin intravenously 40 mg/m² on day 1 over the 28-days cycle. Response was assessed according to the EBMT criteria. Seventeen (34%) patients achieved CR, 7 (14%) nCR, 5 (10%) VGPR, 15 (30%) PR and 5 (10%) MR resulting in an ORR of 98%. Only one patient (2%) presented progressive disease. Time to progression (TTP), event-free survival (EFS) and overall survival (OS) projected at 3 years were 60%, 57% and 74% respectively, and these parameters were significantly higher in those patients achieving a response \geq VGPR versus those who did not. Grade 3-4 nonhematologic adverse events were constipation (10%), fatigue (6%), tremors (4%), mucositis (4%) and palmar-plantar erythro-dysesthesia (2%). Grade 3-4 neutropenia occurred in 12% of patients. Grade

3-4 infections and thrombo-embolic accidents were observed in 22% and 14% of patients, respectively. In the treatment of elderly patients with newly diagnosed multiple myeloma, ThaDD is a very effective regimen with manageable toxicity.

The authors present the results of a phase II study using thalidomide, dexamethasone and pegylated liposomal doxorubicin (ThaDD) in the treatment of 50 newly diagnosed multiple myeloma (MM) patients over 65 years of age. They conclude that in the treatment of elderly patients with newly diagnosed MM, ThaDD is a very effective regimen with manageable toxicity.

Thalidomide in elderly patients with multiple myeloma.

Kusumi E, Matsumura T, Yuji K, Tanaka Y, Kami M.

Lancet. 2006 Jun 17;367(9527):1977; author reply 1977-8.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16782479&query_hl=1&itool=pubmed_DocSum

Comment on: *Lancet.* 2006 Mar 11;367(9513):825-31.

Thalidomide and dexamethasone for newly diagnosed multiple myeloma: is this really the standard of care?

Nabhan C, Bitran JD.

J Clin Oncol. 2006 Jun 20;24(18):2967-8; author reply 2968-9.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16782938&query_hl=1&itool=pubmed_DocSum

Comment on: *J Clin Oncol.* 2006 Jan 20;24(3):334-6 and *J Clin Oncol.* 2006 Jan 20;24(3):431-6.

Extramedullary disease and targeted therapies for hematological malignancies – is the association real?

Raanani P, Shpilberg O, Ben-Bassat I.

Ann Oncol. 2006 Jun 21; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16790518&query_hl=1&itool=pubmed_DocSum

During the past years targeted therapies have gained a major role in the treatment of cancer patients, including those with hematological malignancies. Extramedullary involvement is a rare manifestation of acute and chronic leukemias and of multiple myeloma. Nevertheless, with the expanding use of targeted treatments there is an impression that the incidence of extramedullary relapses is increasing. We reviewed the reports on this phenomenon in patients treated with all-trans-retinoic acid and arsenic trioxide for acute promyelocytic leukemia, thalidomide and bortezomib for multiple myeloma and imatinib for chronic myeloid leukemia. The pathogenetic mechanisms suggested are: life prolongation by these treatments allowing for disease progression arising from dormant cells; poor penetration of the drugs to sanctuary sites like the central nervous system; the requirement of some of these drugs, especially thalidomide, for the marrow microenvironment to exert their action; and finally, a possible active role for some of the drugs, like all-trans-retinoic acid. Since the use of these targeted therapies is expanding we should be aware of this association.

During the past years targeted therapies have gained a major role in the treatment of cancer patients, including those with hematological malignancies. Extramedullary involvement is a rare manifestation of acute and chronic leukemias and of multiple myeloma (MM). Nevertheless, with the expanding use of targeted treatments there is an impression that the incidence of extramedullary relapses is increasing. The authors review the reports on this phenomenon, including in patients treated with thalidomide and bortezomib for MM.

 ***Deep vein thrombosis and pulmonary embolism in a patient with multiple myeloma treated with thalidomide and dexamethasone [Article in Japanese].***

Miyazawa Y, Irisawa H, Uchiumi H, Saitoh T, Handa H, Matsushima T, Tsukamoto N, Karasawa M, Murakami H, Nojima Y. *Rinsho Ketsueki [The Japanese Journal of Clinical Hematology]* 2006 Jul;47(7):656-60.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16910577&query_hl=1&itool=pubmed_DocSum

A 51-year-old man visited our hospital because of fever in 2003. With the discovery of the presence of a chest wall tumor, pleural effusion and M-protein, and increased plasma cells in the bone marrow, a diagnosis of multiple myeloma was established. Since the effect of combination chemotherapy followed by tandem auto-PBSCT lasted only one year, thalidomide and dexamethasone administration was started in November 2004. However, three months later, his lower limbs became swollen. Elevation of fibrin degradation product (FDP) and computed tomography findings suggested deep vein thrombosis and pulmonary embolism. With heparin and warfarin, these thromboses disappeared. Furthermore, chemotherapy strategies in addition to thalidomide were safely performed with anti-coagulation therapy. As thalidomide has become an accepted component in therapeutic strategies for multiple myeloma, careful attention must be paid to the prevention of thrombosis.

The authors note that as thalidomide has become an accepted component in therapeutic strategies for multiple myeloma, careful attention must be paid to the prevention of thrombosis.

Emerging role of novel combinations for induction therapy in multiple myeloma.

Voorhees PM, Orlowski RZ.

Clin Lymphoma Myeloma. 2006 Jul;7(1):33-41.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16879768&query_hl=1&itool=pubmed_DocSum

Although multiple myeloma (MM) remains an incurable disease, there has been a concerted effort toward understanding its molecular pathogenesis, which has paved the way for the development of highly effective, novel therapeutic agents such as the immunomodulatory agents thalidomide and lenalidomide, and the proteasome inhibitor bortezomib. A better understanding of the molecular basis of chemotherapy resistance and the molecular sequelae of conventional cytotoxic and novel agents on MM cells and the bone marrow microenvironment has afforded the opportunity to study novel, rationally designed combination therapies in the clinic. These regimens have shown impressive activity in relapsed/refractory MM, and recent work has demonstrated unprecedented response rates in the first-line setting rivaling those seen with autologous stem cell transplantation. Recently presented results of 2 phase III clinical trials comparing melphalan/prednisone (MP) with MP and thalidomide (MP-Thal) in older patients with newly diagnosed MM have demonstrated superior progression-free survival and overall survival rates with MP-Thal, thus providing the first evidence that the improved response rates to these novel combination regimens will translate into better patient outcomes. Herein we review the early promising clinical activity of these regimens in patients with newly diagnosed MM.

The authors review the early promising clinical activity of a regimen of melphalan/prednisone with thalidomide in the treatment of newly diagnosed myeloma patients.

 ***Lenalidomide inhibits proliferation of Namalwa CSN.70 cells and interferes with Gab1 phosphorylation and adaptor protein complex assembly.***

Gandhi AK, Kang J, Naziruddin S, Parton A, Schafer PH, Stirling DI.

Leuk Res. 2006 Jul;30(7):849-58. [Epub 2006 Feb 21.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16494942&query_hl=8&itool=pubmed_DocSum

Lenalidomide (Revlimid, CC-5013) belongs to a line of compounds known as immunomodulatory drugs (IMiDs) that are under clinical investigation in hematopoietic and solid tumor cancers. Lenalidomide efficacy has been reported in clinical trials of multiple myeloma and myelodysplastic syndromes (MDS), particularly in MDS patients with a del 5q cytogenetic abnormality, with or without other cytogenetic abnormalities. Here we report that lenalidomide inhibits proliferation of chromosome 5 deleted hematopoietic tumor cell lines in vitro, whether from the B cell, T cell, or myeloid lineage. There was diversity in the responses of the various cell lines to lenalidomide, with one undergoing cell cycle arrest, and others undergoing apoptosis. In

the most lenalidomide-sensitive chromosome 5 deleted cell line, Namalwa CSN.70, the compound induced G0/G1 cell cycle arrest, inhibited Akt and Gab1 phosphorylation, and inhibited the ability of Gab1 to associate with a receptor tyrosine kinase. Lenalidomide also enhanced AP-1 transcriptional activity in Namalwa, but not in the other cell lines tested. These studies provide evidence for the mechanism of action of lenalidomide in chromosome 5 deleted hematopoietic tumors in vitro, and may provide a better understanding of the drug's activity in clinical applications.

The studies of these authors provide evidence for the mechanism of action of lenalidomide in chromosome 5 deleted hematopoietic tumors in vitro, and may provide a better understanding of the drug's activity in clinical applications.

 ***Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma.***

Hussein MA, Baz R, Srkalovic G, Agrawal N, Suppiah R, Hsi E, Andresen S, Karam MA, Reed J, Faiman B, Kelly M, Walker E. *Mayo Clin Proc.* 2006 Jul;81(7):889-95.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16835968&query_hl=1&itool=pubmed_DocSum

OBJECTIVE: To evaluate the efficacy and safety of adding thalidomide to the pegylated liposomal doxorubicin, vincristine, and decreased-frequency dexamethasone (DVd) regimen for multiple myeloma. **PATIENTS AND METHODS:** Patients newly diagnosed as having active multiple myeloma and those with relapsed-refractory disease were studied between August 2001 and October 2003. Patients received DVd as previously described. Thalidomide was given at 50 mg/d orally and the dose increased slowly to a maximum of 400 mg/d. At the time of best response, patients received maintenance prednisone, 50 mg orally every other day, and daily thalidomide at the maximum tolerated dose for each patient. The primary end point was the rate of complete responses plus very good partial responses as defined by the European Group for Blood and Marrow Transplantation criteria and the Intergroupe Francais du Myelome, respectively. **RESULTS:** Of 102 eligible patients, 53 were newly diagnosed as having multiple myeloma, and 49 had been previously treated for multiple myeloma. The complete response plus very good partial response rate was 49% and 45%, with an overall response rate of 87% and 90% for patients with newly diagnosed and previously treated multiple myeloma, respectively. Furthermore, better responses were associated with improved progression-free and overall survival. The most common grade 3 and 4 adverse events were thromboembolic events (25%), peripheral neuropathy (22%), and neutropenia (14%). **CONCLUSIONS:** The addition of thalidomide to the DVd regimen significantly improves the response rate and quality of responses compared with the DVd regimen alone. This improvement is associated with longer progression-free and overall survival. The rate of observed quality responses is comparable to responses seen with high-dose therapy.

The authors evaluate the efficacy and safety of adding thalidomide to the pegylated liposomal doxorubicin, vincristine, and decreased-frequency dexamethasone (DVd) regimen for multiple myeloma, and conclude that the addition of thalidomide to the DVd regimen significantly improves the response rate and quality of responses compared with the DVd regimen alone.

 ***Proteasome inhibition in multiple myeloma.***

Kropff M, Bisping G, Wenning D, Berdel WE, Kienast J. *Eur J Cancer.* 2006 Jul;42(11):1623-39. [Epub 2006 Jul 3.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16820291&query_hl=1&itool=pubmed_DocSum

The ubiquitin-proteasome pathway is the major cellular degradative system for various proteins critical for proliferation, survival and homing of myeloma cells. Bortezomib is the first specific and reversible proteasome inhibitor for clinical application in humans. Phase I studies have defined the maximum tolerated dose and suggested activity against multiple myeloma. From single agent phase II studies, a rate of at least partial responses ranging from 27% for relapsed and refractory to 38% for second-line patients was derived. In comparison with pulsed dexamethasone, bortezomib enabled a higher response rate, a longer time to myeloma progression and a longer survival for patients after one to three prior lines of therapy. Preclinical and clinical phase I studies as well as initial phase II studies combining bortezomib with conventional chemotherapy or thalidomide support the assumption that bortezomib sensitizes myeloma cells to these drugs resulting in additive or synergistic activity.

The authors highlight that preclinical and clinical phase I studies, as well as initial phase II studies, combining bortezomib with conventional chemotherapy or thalidomide support the assumption that bortezomib sensitizes myeloma cells to these drugs resulting in additive or synergistic activity.

The role of thalidomide in multiple myeloma.

Schwab C, Jagannath S.

Clin Lymphoma Myeloma. 2006 Jul;7(1):26-9.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16879766&query_hl=1&itool=pubmed_DocSum

Thalidomide has been demonstrated to be active as a first-line and salvage therapy in patients with multiple myeloma. Numerous studies over the past 8 years have shown it to induce high response rates and improve event-free survival in newly diagnosed patients as well as those with relapsed/refractory disease. Recent randomized clinical trials have demonstrated that thalidomide-based regimens are superior to conventional treatments in terms of response rates and event-free survival. However, few trials have demonstrated a survival benefit with thalidomide, indicating the need for further trials. This review will focus on recent trials of thalidomide in relapsed/refractory and newly diagnosed multiple myeloma and address some of the common adverse events associated with thalidomide treatment.

This review focuses on recent trials of thalidomide in relapsed/refractory and newly diagnosed multiple myeloma and addresses some of the common adverse events associated with thalidomide treatment.

The role of the bone microenvironment in the pathophysiology and therapeutic management of multiple myeloma: Interplay of growth factors, their receptors and stromal interactions.

Mitsiades CS, Mitsiades NS, Munshi NC, Richardson PG, Anderson KC.

Eur J Cancer. 2006 Jul;42(11):1564-73. [Epub 2006 Jun 9.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16765041&query_hl=1&itool=pubmed_DocSum

The close relationship between the biological behaviour of malignant cells and the local microenvironment where they reside is a feature of diverse neoplasias. Multiple myeloma (MM) is considered a main disease model for the study of such interactions and the mechanisms that can lead to bone-related clinical complications, as well as the role of these interactions in attenuating the activity of conventional anti-MM therapeutics, such as dexamethasone and cytotoxic chemotherapeutics. This review focuses on recent progress in the study of interactions of MM cells with their local microenvironment. Major emphasis is placed on how bone marrow stromal cells (BMSCs) and other normal constituents of the bone marrow milieu promote, through cell adhesion- and cytokine-mediated mechanisms, the ability of MM cells to resist conventional anti-MM therapies. The review also addresses ongoing research into these mechanisms, which has already provided several new molecular targets and corresponding therapeutic strategies, such as the proteasome inhibitor bortezomib and thalidomide derivatives (e.g. lenalidomide), for the management of myeloma.

This review focuses on recent progress in the study of interactions of multiple myeloma cells with their local microenvironment, including ongoing research into cell adhesion- and cytokine-mediated mechanisms, which have already provided several new molecular targets and corresponding therapeutic strategies, such as the proteasome inhibitor bortezomib and thalidomide derivatives (e.g. lenalidomide), for the management of myeloma.

State of the art therapy in multiple myeloma and future perspectives.

Denz U, Haas PS, Wasch R, Einsele H, Engelhardt M.

Eur J Cancer. 2006 Jul;42(11):1591-600. [Epub 2006 Jul 3.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16815703&query_hl=1&itool=pubmed_DocSum

Treatment for multiple myeloma (MM) has changed beyond recognition in the past decades. While until the early 1980s, MM caused a slow progressive decline in quality of life until death after about two years, today's patients can expect a 50% chance of achieving a complete remission, a median survival time of five years and a 20% chance of surviving longer than ten years. State of the art therapy comprises: evidence-based supportive care; highly effective and well tolerated chemotherapeutic regimens; and for patients qualifying for intensive high-dose conditioning, autologous haematopoietic stem cell transplantation (HSCT) is an option. Maintenance therapy has become increasingly important since a majority of patients is able to achieve a good remission after front-line therapy which is aimed to be preserved as long as possible. In addition, improved understanding of the disease biology has led to the development of novel biological treatment agents, such as thalidomide, bortezomib and others, targeted at

cellular mechanisms and interactions, e.g. with the bone marrow microenvironment. These strategies are incrementally integrated into modern MM care. This review considers recent clinical advancements in anti-myeloma strategies and provides an overview of the state of the art management of MM patients.

This review considers recent clinical advancements in anti-myeloma strategies and provides an overview of the state of the art management of myeloma patients, including the development of novel biological treatment agents, such as thalidomide, bortezomib and others, targeted at cellular mechanisms and interactions, e.g. with the bone marrow microenvironment.

Thalidomide and lenalidomide in the treatment of multiple myeloma.

Kumar S, Rajkumar SV.

Eur J Cancer. 2006 Jul;42(11):1612-22. [Epub 2006 Jun 5.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16750621&query_hl=1&itool=pubmed_DocSum

Although multiple myeloma (MM) is incurable with currently available treatments, the introduction of thalidomide and the development of safer and more active thalidomide analogues represent a major advance in the therapy of this disease. Thalidomide, initially introduced for treatment of MM because of its anti-angiogenic properties, has shown remarkable activity alone and in combination with other drugs in patients across all stages of the disease. Given the potential for teratogenicity with thalidomide and the non-haematologic toxicities of the drug, several analogues referred to as “immunomodulatory drugs” (IMiDs) were developed with the intent of enhancing the immunomodulatory effect while minimizing the teratogenic risk. Lenalidomide (CC-5013) and Actimid (CC-4047) are the first such analogues to undergo clinical testing. Lenalidomide has shown impressive activity in relapsed refractory myeloma as well as newly diagnosed disease. The precise mechanism of anti-MM activity of thalidomide and the IMiDs is not clear, but studies suggest that several other mechanisms besides anti-angiogenic effects may play a role. In this paper we review the development, pharmacology, mechanism of action, pre-clinical and clinical efficacy, and the current status of thalidomide and the IMiDs in the treatment of MM.

The authors review the development, pharmacology, mechanism of action, pre-clinical and clinical efficacy, and the current status of thalidomide and its analogues in the treatment of multiple myeloma.

Thalidomide-induced severe hepatotoxicity.

Hanje AJ, Shamp JL, Thomas FB, Meis GM.

Pharmacotherapy. 2006 Jul;26(7):1018-22.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16803426&query_hl=1&itool=pubmed_DocSum

Thalidomide is a relatively safe and efficacious form of therapy in the treatment of advanced, refractory multiple myeloma. Hepatotoxicity is listed as an extremely rare adverse effect associated with its use. We describe a 76-year-old woman with multiple myeloma who was treated with dexamethasone and thalidomide. By week 6 of therapy, she had developed acute increases in her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels to more than 50 times the upper limit of normal. Her liver function test results had been within the normal ranges before and immediately after the start of therapy, and the patient had no known history of underlying liver disease. A liver biopsy specimen demonstrated evidence of acute injury with chronic changes of underlying steatosis and bridging fibrosis due to previously undiagnosed nonalcoholic steatohepatitis. Immediately after discontinuing thalidomide, her liver function test results began trending downward. Seven days later, her AST and ALT levels had improved to 86 and 165 U/L, respectively. This case and a limited number of other reports demonstrate severe hepatotoxicity as a rare but potentially serious adverse effect of thalidomide therapy. With the expanding use of thalidomide as a therapeutic agent, clinicians must recognize severe hepatotoxicity as a potential complication. Whether patients with preexisting liver disease are at increased risk when receiving thalidomide remains to be seen.

Hepatotoxicity is listed as an extremely rare adverse effect associated with use of thalidomide. The authors describe a 76-year-old woman with multiple myeloma who was treated with dexamethasone and thalidomide. This case and a limited number of other reports demonstrate severe hepatotoxicity as a rare but potentially serious adverse effect of thalidomide therapy. With the expanding use of thalidomide as a therapeutic agent, the authors conclude that clinicians must recognize severe hepatotoxicity as a potential complication.

 ***An update: Health economics of managing multiple myeloma.***

Moeremans K, Annemans L.

Eur J Cancer. 2006 Jul;42(11):1684-91. [Epub 2006 Jun 16.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16781867&query_hl=1&itool=pubmed_DocSum

Based on Medline search, a summary is provided of recent health economic evidence in published literature relating to the management of multiple myeloma. The following major components of current multiple myeloma treatments are discussed: induction chemotherapy, high-dose chemotherapy supported by autologous peripheral stem cell transplantation (ASCT), long-term biphosphonates therapy to prevent skeletal events and recent advances for the treatment of relapsed or refractory multiple myeloma and under evaluation in primary treatment (thalidomide and bortezomib). Our study shows that there still appears to be a need for health economic information to confirm the cost-effectiveness of stem cell support versus high-dose chemotherapy without stem cell support, as well as to assess optimal biphosphonate treatment regimens. There is also a clear need for peer reviewed economic evaluations of novel therapies such as thalidomide and Bortezomib in the treatment of multiple myeloma at different stages of the disease.

The authors conclude that there is a clear need for peer reviewed economic evaluations of novel therapies such as thalidomide and bortezomib in the treatment of multiple myeloma at different stages of the disease.

 ***Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis.***

Zonder JA, Barlogie B, Durie BG, McCoy J, Crowley J, Hussein MA.

Blood. 2006 Jul 1;108(1):403; author reply 404.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16790586&query_hl=8&itool=pubmed_DocSum

No abstract.

 ***Development of new CoMFA and CoMSIA 3D-QSAR models for anti-inflammatory phthalimide-containing TNFalpha modulators.***

Avila CM, Romeiro NC, Sperandio da Silva GM, Sant'anna CM, Barreiro EJ, Fraga CA.

Bioorg Med Chem. 2006 Jul 13; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16843662&query_hl=1&itool=pubmed_DocSum

In the present study, we describe a new 3D-QSAR analysis of 42 previously reported thalidomide analogues, with the ability to modulate the pro-inflammatory cytokine TNFalpha, by using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Three statistically significant models were obtained. The best resulting CoMFA and CoMSIA models have conventional $r(2)$ values of 0.996 and 0.983, respectively. The cross-validated $q(2)$ values are 0.869 and 0.868, respectively. The analysis of CoMFA and CoMSIA contour maps provided insight into the possible sites for structural modification of the thalidomide analogues for better activity and reduced toxicity.

The authors describe a new 3D-QSAR analysis of 42 previously reported thalidomide analogues, with the ability to modulate the pro-inflammatory cytokine TNFalpha, by using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Three statistically significant models were obtained.

Enhancement of ligand-dependent activation of human natural killer T cells by lenalidomide: therapeutic implications.

Chang DH, Liu N, Klimek V, Hassoun H, Mazumder A, Nimer SD, Jagannath S, Dhodapkar MV.

Blood. 2006 Jul 15;108(2):618-21. [Epub 2006 Mar 28.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16569772&query_hl=1&itool=pubmed_DocSum

Natural killer T (NKT) cells are CD1d-restricted glycolipid reactive innate lymphocytes that play an important role in protection from pathogens and tumors. Pharmacologic approaches to enhance NKT cell function will facilitate specific NKT targeting in the clinic. Here we show that lenalidomide (LEN), a novel thalidomide (Thal) analog, enhances antigen-specific expansion of NKT cells in response to the NKT ligand alpha-galactosylceramide (alpha-GalCer) in both healthy donors and patients with myeloma. NKT cells activated in the presence of LEN have greater ability to secrete interferon-gamma. Antigen-dependent activation of NKT cells was greater in the presence of dexamethasone (DEX) plus LEN than with DEX alone. Therapy with LEN/Thal also led to an increase in NKT cells in vivo in patients with myeloma and del5q myelodysplastic syndrome. Together these data demonstrate that LEN and its analogues enhance CD1d-mediated presentation of glycolipid antigens and support combining these agents with NKT targeted approaches for protection against tumors.

The authors demonstrate that lenalidomide, a novel thalidomide analog, and its analogues enhance CD1d-mediated presentation of glycolipid antigens, and support combining these agents with NKT targeted approaches for protection against tumors.

A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma.

Richardson PG, Blood E, Mitsiades CS, Jagannath S, Zeldenrust SR, Alsina M, Schlossman RL, Rajkumar SV, Desikan KR, Hideshima T, Munshi NC, Kelly-Colson K, Doss D, McKenney ML, Gorelik S, Warren D, Freeman A, Rich R, Wu A, Olesnyckyj M, Wride K, Dalton WS, Zeldis J, Knight R, Weller E, Anderson KC.

Blood. 2006 Jul 18; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16840727&query_hl=8&itool=pubmed_DocSum

This multi-center, open-label, randomized phase 2 study evaluated 2 dose regimens of lenalidomide for relapsed, refractory myeloma. Seventy patients were randomized to receive either 30 mg once-daily or 15 mg twice-daily oral lenalidomide for 21 of every 28-day cycle. Patients with progressive or stable disease after two cycles received dexamethasone. Analysis of the first 70 patients showed increased grade 3-4 myelosuppression in patients receiving 15 mg twice-daily (41% versus 13%, p=0.03). An additional 32 patients received 30 mg once-daily. Responses were evaluated according to EBMT criteria. Overall response rate (complete, partial or minor) to lenalidomide alone was 25% (24% for once-daily and 28% for twice-daily lenalidomide, respectively). Median overall survival in 30 mg once-daily and twice-daily groups was 31 and 27 months. Median progression-free survival was 7.7 months on once-daily vs 3.9 months on twice-daily lenalidomide (p=0.2). Dexamethasone was added in 68 patients and 29% responded. Time to first occurrence of grade 3-4 myelosuppression was shorter in the twice-daily group (1.8 vs 5.5 months, p=0.05). Significant peripheral neuropathy and deep vein thrombosis each occurred in only 3%. Lenalidomide is active and well tolerated in relapsed, refractory myeloma. The 30 mg once-daily regimen provides the basis for future studies as monotherapy and with dexamethasone.

This multi-center, open-label, randomized phase 2 study evaluates 2 dose regimens of lenalidomide for relapsed, refractory myeloma. The authors conclude that lenalidomide is active and well tolerated in relapsed, refractory myeloma, and the 30 mg once-daily regimen provides the basis for future studies as monotherapy and with dexamethasone.

Maintenance therapy with thalidomide improves survival in multiple myeloma patients.

Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, Yakoub Agha I, Bourhis JH, Garderet L, Pegourie B, Dumontet C, Renaud M, Voillat L, Berthou C, Marit G, Monconduit M, Caillot D, Grobois B, Avet-Loiseau H, Moreau P, Facon T.

Blood. 2006 Jul 27; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16873668&query_hl=1&itool=pubmed_DocSum

Newer chemotherapeutic protocols as well as high dose chemotherapy have increased the response rate in myeloma. However, these treatments are not curative. Effective maintenance strategies are now required to prolong the duration of response. We conducted a randomized trial of maintenance treatment with thalidomide and pamidronate. Two months after high dose therapy, 597 patients under the age of 65 years were randomly assigned to receive no maintenance (arm A), pamidronate (arm B), or pamidronate plus thalidomide (arm C). A complete or very good partial response was achieved by 55% of patients in arm A, 57% in arm B, and 67% in arm C (P=0.03). The 3-year post-randomization probability of event-free-survival was 36% in arm A, 37% in arm B, and 52% in arm C (P<0.009). The 4-year post-diagnosis probability of survival was 77% in arm A, 74% in arm B, and 87% in arm C (P<0.04). The proportion of patients who had skeletal events was 24% in arm A, 21% in arm B, and 18% in arm C (P=0.4). Thalidomide is an effective maintenance therapy in patients with multiple myeloma. Maintenance treatment with pamidronate does not decrease the incidence of bone events.

Newer chemotherapeutic protocols as well as high dose chemotherapy have increased the response rate in myeloma. However, these treatments are not curative. Effective maintenance strategies are now required to prolong the duration of response. The authors conduct a randomized trial of maintenance treatment with thalidomide and pamidronate and find that thalidomide is an effective maintenance therapy in patients with myeloma but maintenance treatment with pamidronate does not decrease the incidence of bone events.

Multiple myeloma in end-stage renal disease.

Penfield JG.

Semin Dial. 2006 Jul-Aug;19(4):329-34.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16893412&query_hl=1&itool=pubmed_DocSum

Multiple myeloma is a common cause of chronic kidney disease (CKD). Patients with myeloma-related kidney disease but low levels of serum monoclonal proteins can be diagnosed with symptomatic myeloma in a simplified diagnostic classification. The presence and type of renal disease in myeloma is dependent on the light chain secreted. Treatment has recently changed and now includes the use of thalidomide and bisphosphonates. Thalidomide can cause hyperkalemia and bisphosphonates can cause renal failure in patients with CKD. Their use is not contraindicated, but they should be used with caution. High-dose melphalan with an autologous stem cell transplant is now the standard of care and should not be withheld from patients with CKD, even those on dialysis. This treatment can improve the renal disease, and this is more likely if treatment is started early. In patients with persistent dialysis dependence, renal transplantation can be performed if the patient has a complete remission.

The author discusses multiple myeloma (MM) as a common cause of chronic kidney disease (CKD). Patients with myeloma-related kidney disease but low levels of serum monoclonal proteins can be diagnosed with symptomatic myeloma in a simplified diagnostic classification. The presence and type of renal disease in MM is dependent on the light chain secreted. Treatment has recently changed and now includes the use of thalidomide and bisphosphonates. Thalidomide can cause hyperkalemia and bisphosphonates can cause renal failure in patients with CKD. Their use is not contraindicated, but they should be used with caution.

 ***Advances in oral therapy in the treatment of multiple myeloma.***

Doss DS.

Clin J Oncol Nurs. 2006 Aug;10(4):514-20.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16927905&query_hl=1&itool=pubmed_DocSum

Conventional IV chemotherapy regimens used for induction chemotherapy or salvage therapy in the treatment of multiple myeloma (MM) are cumbersome, with a negative impact on patient quality of life. A number of new oral drugs, including immunomodulatory agents such as thalidomide and lenalidomide, have demonstrated potent antimyeloma activity in relapsed and refractory as well as newly diagnosed MM. Clinically, response rates of 56%-72% have been reported with the combination of thalidomide and dexamethasone in patients with newly diagnosed disease; however, the combination is associated with a higher incidence of side effects, including constipation, somnolence, peripheral neuropathy, and thromboembolic complications. In contrast, preliminary safety and efficacy data from clinical studies of lenalidomide show promise. Response rates as high as 83% have been reported in patients with newly diagnosed MM, and the most common adverse event is manageable myelosuppression, which is reversible with dose reduction. Lenalidomide has different toxicities than thalidomide, exhibiting greater myelosuppression but virtually no constipation, somnolence, or peripheral neuropathy. Oncology nurses play a key role in monitoring patients for side effects and pain control and educating them about emerging treatment options. This article reviews the nursing experience with oral agents in the treatment of MM.

A number of new oral drugs, including immunomodulatory agents such as thalidomide and lenalidomide, have demonstrated potent antimyeloma activity in relapsed and refractory as well as newly diagnosed multiple myeloma (MM). Oncology nurses play a key role in monitoring patients for side effects and pain control and educating them about emerging treatment options. This article reviews the nursing experience with oral agents in the treatment of MM.

 ***Enoxaparin or aspirin for the prevention of recurrent thromboembolism in newly diagnosed myeloma patients treated with melphalan and prednisone plus thalidomide or lenalidomide.***

Palumbo A, Rus C, Zeldis JB, Rodeghiero F, Boccadoro M; The Italian Multiple Myeloma Network, Gimema.

J Thromb Haemost. 2006 Aug;4(8):1842-5.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16879233&query_hl=1&itool=pubmed_DocSum

No abstract.

 ***Lenalidomide in multiple myeloma.***

Richardson PG, Mitsiades C, Hideshima T, Anderson KC.

Expert Rev Anticancer Ther. 2006 Aug;6(8):1165-73.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16925483&query_hl=1&itool=pubmed_DocSum

Current therapies for multiple myeloma include steroids, alkylating agents and high-dose chemotherapy with autologous stem cell transplant. These approaches are typically associated with initially good response rates, but they ultimately fail as a result of disease progression. New therapies that overcome resistance, lower toxicity and maintain remission are needed. Recent advances in the treatment of multiple myeloma include bortezomib and thalidomide. Lenalidomide (Revlimid) is an immunomodulatory drug that has undergone rapid clinical development in multiple myeloma and was recently approved by the US FDA for use in patients with relapsed disease. Clinical trials demonstrate that lenalidomide, particularly in combination with dexamethasone, produces durable clinical responses in patients with relapsed and refractory disease and is generally well tolerated, with manageable toxicities. This review summarizes the profile of lenalidomide and the current evidence for its efficacy in multiple myeloma.

This review summarizes the profile of lenalidomide (Revlimid) and the current evidence for its efficacy in multiple myeloma.

 ***Neutrophilic dermatosis (sweet syndrome) of the hands associated with lenalidomide.***

Hoverson AR, Davis MD, Weenig RH, Wolanskyj AP.

Arch Dermatol. 2006 Aug;142(8):1070-1.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16924066&query_hl=9&itool=pubmed_DocSum

No abstract.

 ***Thalidomide metabolism and hydrolysis: mechanisms and implications.***

Lepper ER, Smith NF, Cox MC, Scripture CD, Figg WD.

Curr Drug Metab. 2006 Aug;7(6):677-85.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16918319&query_hl=1&itool=pubmed_DocSum

Despite its controversial past, thalidomide is currently under investigation for the treatment of several disease types, ranging from inflammatory conditions to cancer. The mechanism of action of thalidomide is complex and not yet fully understood, but there is some evidence to suggest that metabolism may play a role. Consequently, there has been a considerable effort to characterize the metabolism of thalidomide in recent years. Thalidomide undergoes biotransformation by non-enzymatic hydrolysis and enzyme-mediated hydroxylation to form a multitude of metabolites. Metabolite identification and reaction phenotyping studies have been performed and will be discussed in this review in addition to interspecies differences in thalidomide metabolism.

The mechanism of action of thalidomide is complex and not yet fully understood, but there is some evidence to suggest that metabolism may play a role. The authors discuss the metabolite identification and reaction phenotyping studies that have been performed, in addition to interspecies differences in thalidomide metabolism.

 ***Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients.***

Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, Krikelis D, Terpos E.

Br J Haematol. 2006 Aug 1; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16889620&query_hl=1&itool=pubmed_DocSum

The incidence, characteristics and risk factors for the development of osteonecrosis of the jaw (ONJ) were evaluated among 303 myeloma patients. Only patients who received bisphosphonates developed ONJ (28/254; 11%). Zoledronic acid produced 9.5-fold greater risk for developing ONJ than pamidronate alone ($P = 0.042$) and 4.5-fold greater risk than subsequent use of pamidronate + zoledronic acid ($P = 0.018$). Use of thalidomide and number of bisphosphonate infusions also increased the risk for ONJ by 2.4-fold ($P = 0.043$), and 4.9-fold respectively ($P = 0.012$). ONJ developed earlier among patients receiving zoledronic acid. Our data indicates that administration of zoledronic acid for more than 2 years or in combination with thalidomide requires caution in myeloma.

The incidence, characteristics and risk factors for the development of osteonecrosis of the jaw (ONJ) are evaluated among 303 myeloma patients. The authors find that only patients who received bisphosphonates developed ONJ (28/254; 11%), and that data indicates that administration of zoledronic acid for more than 2 years or in combination with thalidomide requires caution in myeloma.

 ***Toxicity profile of the immunomodulatory thalidomide analogue, lenalidomide: Phase I clinical trial of three dosing schedules in patients with solid malignancies.***

Sharma RA, Steward WP, Daines CA, Knight RD, O'byrne KJ, Dalglish AG.

Eur J Cancer. 2006 Aug 7; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16899362&query_hl=1&itool=pubmed_DocSum

Thalidomide is an anti-angiogenic agent currently used to treat patients with malignant cachexia or multiple myeloma. Lenalidomide (CC-5013) is an immunomodulatory thalidomide analogue licensed in the United States of America (USA) for the treatment of a subtype of myelodysplastic syndrome. This two-centre, open-label phase I study evaluated dose-limiting toxicities in 55 patients with malignant solid tumours refractory to standard chemotherapies. Lenalidomide capsules were consumed once daily for 12 weeks according to one of the following three schedules: (I) 25mg daily for the first 7 d, the daily dose increased by 25mg each week up to a maximum daily dose of 150mg; (II) 25mg daily for 21 d followed by a 7-d rest period, the 4-week cycle repeated for 3 cycles; (III) 10mg daily continuously. Twenty-six patients completed the study period. Two patients experienced a grade 3 hypersensitivity rash. Four patients in cohort I and 4 patients in cohort II suffered grade 3 or 4 neutropaenia. In 2 patients with predisposing medical factors, grade 3 cardiac dysrhythmia was recorded. Grade 1 neurotoxicity was detected in 6 patients. One complete and two partial radiological responses were measured by computed tomography scanning; 8 patients had stable disease after 12 weeks of treatment. Fifteen patients remained on treatment as named patients; 1 with metastatic melanoma remains in clinical remission 3.5 years from trial entry. This study indicates the tolerability and potential clinical efficacy of lenalidomide in patients with advanced solid tumours who have previously received multi-modality treatment. Depending on the extent of myelosuppressive pre-treatment, dose schedules (II) or (III) are advocated for large-scale trials of long-term administration.

This study indicates the tolerability and potential clinical efficacy of lenalidomide in patients with advanced solid tumours who have previously received multi-modality treatment.

 ***Acquired activated protein C resistance and thrombosis in multiple myeloma patients.***

Jimenez VH 1st, Dominguez VJ 1st.

Thromb J. 2006 Aug 21;4(1):11. [Epub ahead of print.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16923190&query_hl=1&itool=pubmed_DocSum

ABSTRACT: Background An increased incidence of deep venous thrombosis (DVT) has been described in multiple myeloma (MM). A recently described mechanism of hypercoagulability in cancer patients including MM patients is acquired activated protein C resistance (APC-R). The purpose of the present study was to examine the association between the combination of thalidomide plus chemotherapy and DVT development in a cohort of patients with newly diagnosed multiple myeloma. We also evaluated the association between acquired activated protein C resistance and DVT. Methods Patients with newly diagnosed and symptomatic MM (untreated or with one cycle of preceding chemotherapy) were evaluated. The present study is a prospective, descriptive, longitudinal and observational one. The coagulations tests were performed including: prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen, anticardiolipin antibodies, lupus anticoagulant, antithrombin, protein C and protein S activities, factor VIII, activated protein C (APC) resistance, factor V Leiden, and quantitative D-dimers. Factor V Leiden mutation was detected by analysis of the polymerase chain reaction amplification of genomic DNA. Results Fifty newly diagnosed multiple myeloma patients were included in the study. DVT was developed in 8 patients (16%). Six patients were confirmed to have acquired activated C protein resistance. All of them were tested twice. Four out of 6 patients developed DVT (66%), all of them received thalidomide at a median dose of 200 mg qd. Conclusions APC-R appears to be a transitional condition may be related to myeloma status. Thrombotic complications can affect morbidity and even mortality in these patients. To fully evaluate the potential synergistic anticancer activity of combinations of chemotherapy and thalidomide, effective prophylactic anticoagulation should be implemented in all controlled trials, at least during the first few cycles of treatment.

This study examines the association between the combination of thalidomide plus chemotherapy and deep venous thrombosis development in a cohort of patients with newly diagnosed multiple myeloma. The authors concludes that thrombotic complications can affect morbidity and even mortality in these patients and that to fully evaluate the potential synergistic anticancer activity of combinations of chemotherapy and thalidomide, effective prophylactic anticoagulation should be implemented in all controlled trials, at least during the first few cycles of treatment.

 ***Development of Neuropathy in Patients With Myeloma Treated With Thalidomide: Patterns of Occurrence and the Role of Electrophysiologic Monitoring.***

Mileshkin L, Stark R, Day B, Seymour JF, Zeldis JB, Prince HM.

J Clin Oncol. 2006 Aug 28; [Epub ahead of print].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16940275&query_hl=1&itool=pubmed_DocSum

PURPOSE: Peripheral neuropathy frequently limits the duration of treatment with thalidomide for patients with multiple myeloma. We assessed the time course of occurrence, possible predictive factors, and the utility of serial nerve electrophysiological studies (NES) for detecting onset of neuropathy. **METHODS:** Seventy-five patients with relapsed/refractory myeloma were enrolled onto a multicenter trial of dose-escalating thalidomide with or without interferon. Patients underwent clinical assessment plus NES at baseline and every 3 months. Time to development of neuropathy according to clinical or NES criteria was compared. Patient and treatment-related factors were compared as predictors of neuropathy. **RESULTS:** Thirty-nine percent had some NES abnormalities at baseline. Patients received thalidomide at a median dose-intensity of 373 mg/d. Thirty-one of 75 patients (41%) developed neuropathy during thalidomide treatment; 11 patients (15%) discontinued treatment with thalidomide due to neuropathy. The actuarial incidence of neuropathy increased from 38% at 6 months to 73% at 12 months, with 81% of responding patients developing this complication. Serial NES did not reliably predict the imminent development of clinical neuropathy requiring thalidomide cessation, nor were patient age, sex, or prior therapy predictive. Patients who developed neuropathy had a longer duration of thalidomide exposure (median, 268 v 89 days; $P = .0001$). Cumulative dose or dose-intensity received was not predictive. **CONCLUSION:** The majority of patients will develop peripheral neuropathy given sufficient length of treatment with thalidomide. To minimize the risk of neurotoxicity, therapy should be limited to less than 6 months. Electrophysiologic monitoring provides no clear benefit versus careful clinical evaluation for the development of clinically significant neuropathy.

The authors conclude that a majority of patients will develop peripheral neuropathy given sufficient length of treatment with thalidomide. To minimize the risk of neurotoxicity, therapy should be limited to less than 6 months. Electrophysiologic monitoring provides no clear benefit versus careful clinical evaluation for the development of clinically significant neuropathy.

 ***Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients.***

Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, Krikelis D, Terpos E.

Br J Haematol. 2006 Sep;134(6):620-3. Epub 2006 Aug 1.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16889620&query_hl=1&itool=pubmed_DocSum

The incidence, characteristics and risk factors for the development of osteonecrosis of the jaw (ONJ) were evaluated among 303 myeloma patients. Only patients who received bisphosphonates developed ONJ (28/254; 11%). Zoledronic acid produced 9.5-fold greater risk for developing ONJ than pamidronate alone ($P = 0.042$) and 4.5-fold greater risk than subsequent use of pamidronate + zoledronic acid ($P = 0.018$). Use of thalidomide and number of bisphosphonate infusions also increased the risk for ONJ by 2.4-fold ($P = 0.043$), and 4.9-fold respectively ($P = 0.012$). ONJ developed earlier among patients receiving zoledronic acid. Our data indicates that administration of zoledronic acid for more than 2 years or in combination with thalidomide requires caution in myeloma.

The authors' results indicate that osteonecrosis of the jaw develops earlier among patients receiving zoledronic acid. The administration of zoledronic acid for more than 2 years in combination with thalidomide requires caution in myeloma.

 ***Thalidomide-induced symptomatic third-degree atrioventricular block.***

Hinterseer M, Becker A, Kaab S, Lang N, Nabauer M, Steinbeck G.

Clin Res Cardiol. 2006 Sep;95(9):474-476. Epub 2006 Jun 20.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16773277&query_hl=1&itool=pubmed_DocSum

No abstract.

 ***Toxicity profile of the immunomodulatory thalidomide analogue, lenalidomide: Phase I clinical trial of three dosing schedules in patients with solid malignancies.***

Sharma RA, Steward WP, Daines CA, Knight RD, O'byrne KJ, Dalgleish AG.

Eur J Cancer. 2006 Sep;42(14):2318-25. Epub 2006 Aug 8.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16899362&query_hl=1&itool=pubmed_DocSum

Thalidomide is an anti-angiogenic agent currently used to treat patients with malignant cachexia or multiple myeloma. Lenalidomide (CC-5013) is an immunomodulatory thalidomide analogue licensed in the United States of America (USA) for the treatment of a subtype of myelodysplastic syndrome. This two-centre, open-label phase I study evaluated dose-limiting toxicities in 55 patients with malignant solid tumours refractory to standard chemotherapies. Lenalidomide capsules were consumed once daily for 12 weeks according to one of the following three schedules: (I) 25mg daily for the first 7 d, the daily dose increased by 25mg each week up to a maximum daily dose of 150mg; (II) 25mg daily for 21 d followed by a 7-d rest period, the 4-week cycle repeated for 3 cycles; (III) 10mg daily continuously. Twenty-six patients completed the study period. Two patients experienced a grade 3 hypersensitivity rash. Four patients in cohort I and 4 patients in cohort II suffered grade 3 or 4 neutropaenia. In 2 patients with predisposing medical factors, grade 3 cardiac dysrhythmia was recorded. Grade 1 neurotoxicity was detected in 6 patients. One complete and two partial radiological responses were measured by computed tomography scanning; 8 patients had stable disease after 12 weeks of treatment. Fifteen patients remained on treatment as named patients; 1 with metastatic melanoma remains in clinical remission 3.5 years from trial entry. This study indicates the tolerability and potential clinical efficacy of lenalidomide in patients with advanced solid tumours who have previously received multi-modality treatment. Depending on the extent of myelosuppressive pre-treatment, dose schedules (II) or (III) are advocated for large-scale trials of long-term administration.

This study indicates the tolerability and potential clinical efficacy of lenalidomide in patients with advanced solid tumors who have previously received multi-modality treatment.

 ***Vincristine, doxorubicin, and dexamethasone or thalidomide plus dexamethasone for newly diagnosed patients with multiple myeloma?***

Jimenez-Zepeda VH, Dominguez-Martinez VJ.

Eur J Haematol. 2006 Sep;77(3):239-44. [Epub 2006 Jul 19.]

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16856924&query_hl=1&itool=pubmed_DocSum

Multiple myeloma (MM) is a malignant plasma cell tumor that is distributed at multiple sites within the bone marrow compartments. High-dose dexamethasone regimens [including vincristine, doxorubicin, and dexamethasone (VAD) chemotherapy] induce rapid responses, and have resulted in improved survival for many patients when followed by intensive therapy with autologous stem cell support early in the disease course. However, VAD have several disadvantages including the need for an intravenous indwelling catheter, which predisposes patients to catheter-related sepsis and thrombosis; most of the activity of VAD was from high-dose dexamethasone component. We enrolled all patients who fulfilled entire criteria for MM during the period between January 1997 and December 2005. The present study is a descriptive, retrospective, longitudinal, and observational one. The frequency of response (CR, VGPR/NCR, and PR) in the group of thalidomide and dexamethasone was 84.3% (CR 18.75% VGPR/NCR 18.75%, and PR 46.8%) being higher than VAD, 55% (CR 16%, VGPR/NCR 5%, and PR 34%). P= 0.0005. In summary, we conclude Thal/dex is an effective therapy in newly diagnosed MM inducing objective responses in over 84.3%.

The authors conclude that thalidomide/dexamethasone is an effective therapy in newly diagnosed multiple myeloma, inducing objective responses in over 84.3% of patients studied.

Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation.

Hanamura I, Stewart JP, Huang Y, Zhan F, Santra M, Sawyer JR, Hollmig K, Zangarri M, Pineda-Roman M, van Rhee F, Cavallo F, Burington B, Crowley J, Tricot G, Barlogie B, Shaughnessy JD Jr.

Blood. 2006 Sep 1;108(5):1724-32. Epub 2006 May 16.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16705089&query_hl=1&itool=pubmed_DocSum

Using fluorescence in situ hybridization we investigated amplification of chromosome band 1q21 (Amp1q21) in more than 500 untreated patients with monoclonal gammopathy of undetermined significance (MGUS; n = 14), smoldering multiple myeloma (SMM; n = 31), and newly diagnosed MM (n = 479) as well as 45 with relapsed MM. The frequency of Amp1q21 was 0% in MGUS, 45% in SMM, 43% in newly diagnosed MM, and 72% in relapsed MM (newly diagnosed versus relapsed MM, $P < .001$). Amp1q21 was detected in 10 of 12 patients whose disease evolved to active MM compared with 4 of 19 who remained with SMM ($P < .001$). Patients with newly diagnosed MM with Amp1q21 had inferior 5-year event-free/overall survival compared with those lacking Amp1q21 (38%/52% versus 62%/78%, both $P < .001$). Thalidomide improved 5-year EFS in patients lacking Amp1q21 but not in those with Amp1q21 ($P = .004$). Multivariate analysis including other major predictors revealed that Amp1q21 was an independent poor prognostic factor. Relapsed patients who had Amp1q21 at relapse had inferior 5-year postrelapse survival compared with those lacking Amp1q21 at relapse (15% versus 53%, $P = .027$). The proportion of cells with Amp1q21 and the copy number of 1q21 tended to increase at relapse compared with diagnosis. Our data suggest that Amp1q21 is associated with both disease progression and poor prognosis.

This study suggests that amplification of chromosome band 1q21 (Amp1q21) is associated with both myeloma disease progression and poor prognosis. Thalidomide improved 5-year event-free survival in patients lacking Amp1q21 but not in those with Amp1q21.



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