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Thalidomide and Revlimid® Issue

The International Myeloma Foundation *(IMF) is pleased to present our third edition of CITINGS for 2009. 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 – 3rd Quarter, 2009

Bortezomib in combination with pegylated liposomal doxorubicin and thalidomide is an effective steroid independent salvage regimen for patients with relapsed or refractory multiple myeloma: results of a phase II clinical trial.

Chanan-Khan A, Miller KC, Musial L, Padmanabhan S, Yu J, Ailawadhi S, Sher T, Mohr A, Bernstein ZP, Barcos M, Patel M, Iancu D, Lee K, Czuczman MS.

Leuk Lymphoma. 2009 May 22:1-6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19479618?ordinalpos=31&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This phase II trial investigates the efficacy of a steroid-free combination including bortezomib, pegylated liposomal doxorubicin and thalidomide (VDT regimen) and observes that VDT is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Novel agents have demonstrated enhanced efficacy when combined with other antimyeloma agents especially dexamethasone. The steroid doses employed in myeloma regimens are often poorly tolerated. Therefore, in a phase II clinical trial we investigated the efficacy of a steroid-free combination including bortezomib, pegylated liposomal doxorubicin and thalidomide (VDT regimen). Twenty-three patients with relapsed or refractory myeloma or other plasma cell cancers were treated with the VDT regimen. Patient had a median of five prior therapies and 65.2% were refractory to their last regimen. The overall response rates were 55.5% and 22%, respectively. The median progression free survival was 10.9 months (95% CI: 7.3-15.8) and the median overall survival was 15.7 months (95% CI: 9.1-not reached). Fatigue and sensory neuropathy were the most common side effects noted. We observe that VDT is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma.

Richardson P, Jagannath S, Hussein M, Berenson J, Singhal S, Irwin D, Williams SF, Bensinger W, Badros AZ, Vescio R, Kenvin L, Yu Z, Olesnyckyj M, Zeldis J, Knight R, Anderson KC.

Blood. 2009 May 26. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19471019?ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the efficacy and safety of lenalidomide monotherapy in patients with relapsed and refractory myeloma, with data that support treatment with single-agent lenalidomide, as well as support for its use in steroid-sparing combination approaches.

Lenalidomide plus dexamethasone is effective for the treatment of relapsed and refractory multiple myeloma (MM); however, toxicities from dexamethasone can be dose-limiting. We evaluated the efficacy and safety of lenalidomide monotherapy in patients with relapsed and refractory MM. Patients (n = 222) received lenalidomide 30 mg/day once-daily (days 1 - 21 every 28 days) until disease progression or intolerance. Response, progression-free survival (PFS), overall survival (OS), time-to-progression (TTP), and safety were assessed. Overall, 67% of patients had received >/= 3 prior treatment regimens. Partial response or better was reported in 26% of patients and minimal response or better was reported in 44%. There was no difference between patients who had received </= 2 versus >/= 3 prior treatment regimens (45% vs 44%, respectively). Median values for TTP, PFS and OS were 5.2, 4.9 and 23.2 months, respectively. The most common grade 3 or 4 adverse events were neutropenia (60%), thrombocytopenia (39%) and anemia (20%), which proved manageable with dose reduction and supportive care. Grade 3 or 4 febrile neutropenia was noted in 4% of patients. Lenalidomide monotherapy has acceptable toxicities and is active in relapsed and refractory MM patients. These data support treatment with single-agent lenalidomide, as well as its use in steroid-sparing combination approaches.

Genetic variants in XRRC5 may predict development of venous thrombotic events in myeloma patients on thalidomide.

Tewari P, Kenny E, Staines A, Chanock S, Browne P, Lawler M.

Blood. 2009 May 28;113(22):5691-2.

http://www.ncbi.nlm.nih.gov/pubmed/19478055?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: *Blood.* 2008 Dec 15;112(13):4924-34.

First-line thalidomide-dexamethasone therapy in preparation for auto-SCT in young patients (<61 years) with symptomatic multiple myeloma.

Abdelkefi A, Torjman L, Ben Romdhane N, Ladeb S, El Omri H, Ben Othman T, Elloumi M, Bellaj H, Lakhal A, Jeddi R, Aissaouï L, Saad A, Hsaïri M, Boukef K, Dellagi K, Ben Abdeladhim A; Tunisian Multiple Myeloma Study Group.

Bone Marrow Transplant. 2009 Jun;43(11):893.

http://www.ncbi.nlm.nih.gov/pubmed/19513083?ordinalpos=31&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG).

Kastritis E, Zervas K, Symeonidis A, Terpos E, Delimbassi S, Anagnostopoulos N, Michali E, Zomas A, Katodritou E, Gika D, Pouli A, Christoulas D, Roussou M, Kartasis Z, Economopoulos T, Dimopoulos MA.

Leukemia. 2009 Jun;23(6):1152-7. [Epub 2009 Feb 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19225533?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors compare the outcome of 1,376 unselected patients with symptomatic myeloma, who started treatment before or after the introduction of thalidomide. The median overall survival in patients who started treatment after the introduction of novel agents increased by 12 months.

When the novel agents thalidomide, bortezomib and lenalidomide are administered to patients with myeloma in the context of clinical trials, they are associated with a significant improvement in response, progression-free survival and in some studies, overall survival (OS); however, their effect on the outcome of unselected myeloma patients has not been fully assessed. We compared the outcome of 1376 unselected patients with symptomatic myeloma, who started treatment before or after the introduction of thalidomide. The median OS in patients who started treatment after the introduction of novel agents increased by 12 months (48 vs 36 months, P<0.001). This improvement was more pronounced in patients < or =70 years (from 39 to 74 months, P<0.001), but less evident in patients >70 years (from 26

to 33 months, P=0.27). In patients treated after the introduction of novel agents, the international staging system (ISS) could discriminate three groups with significantly different outcomes (5-year survival for ISS stage I, II and III was 66, 45 and 18%, respectively, P<0.001). ISS was also valid in patients who actually received upfront treatment with novel drugs (4-year survival rate was 85, 61 and 26% for ISS stage I, II and III patients, P=0.001).

Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma.

Stadtmauer EA, Weber DM, Niesvizky R, Belch A, Prince MH, San Miguel JF, Facon T, Olesnyckyj M, Yu Z, Zeldis JB, Knight RD, Dimopoulos MA.

Eur J Haematol. 2009 Jun;82(6):426-32. [Epub 2009 Mar 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19302559?ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This subset analysis of data from two phase III studies in patients with relapsed or refractory myeloma evaluates the benefit of initiating lenalidomide plus dexamethasone at first relapse, finding that the combination is both effective and tolerable for second-line myeloma therapy, with the greatest benefit occurring with earlier use.

This subset analysis of data from two phase III studies in patients with relapsed or refractory multiple myeloma (MM) evaluated the benefit of initiating lenalidomide plus dexamethasone at first relapse. Multivariate analysis showed that fewer prior therapies, along with beta(2)-microglobulin (< or = 2.5 mg/L), predicted a better time to progression (TTP; study end-point) with lenalidomide plus dexamethasone treatment. Patients with one prior therapy showed a significant improvement in benefit after first relapse compared with those who received two or more therapies. Patients with one prior therapy had significantly prolonged median TTP (17.1 vs. 10.6 months; P = 0.026) and progression-free survival (14.1 vs. 9.5 months, P = 0.047) compared with patients treated in later lines. Overall response rates were higher (66.9% vs. 56.8%, P = 0.06), and the complete response plus very good partial response rate was significantly higher in first relapse (39.8% vs. 27.7%, P = 0.025). Importantly, overall survival was significantly prolonged for patients treated with lenalidomide plus dexamethasone with one prior therapy, compared with patients treated later in salvage (median of 42.0 vs. 35.8 months, P = 0.041), with no differences in toxicity, dose reductions, or discontinuations despite longer treatment. Therefore, lenalidomide plus dexamethasone is both effective and tolerable for second-line MM therapy and the data suggest that the greatest benefit occurs with earlier use.

The many lives of thalidomide.

Patel MP, Chanan-Khan AA.

Leuk Lymphoma. 2009 Jun;50(6):861-2.

http://www.ncbi.nlm.nih.gov/pubmed/19479617?ordinalpos=36&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: ***Leuk Lymphoma.*** **2009 Apr;50(4):588-92.**

Phase I study of oral lenalidomide in patients with refractory metastatic cancer.

Dahut WL, Aragon-Ching JB, Woo S, Tohnya TM, Gulley JL, Arlen PM, Wright JJ, Ventiz J, Figg WD.

J Clin Pharmacol. 2009 Jun;49(6):650-60.

http://www.ncbi.nlm.nih.gov/pubmed/19451403?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to determine the maximum tolerated dose and to characterize the side effect profile and pharmacokinetics of lenalidomide in patients with advanced refractory solid tumors. They find lenalidomide is well tolerated up to a 35-mg/d intermittent dosing schedule at doses higher than previously indicated for hematologic malignancies, with most frequent grade 1 and 2 toxicities including fatigue, nausea, pruritus/rash, neutropenia, and neuropathy.

Objectives of this study were to determine the maximum tolerated dose and to characterize the side effect profile and pharmacokinetics of lenalidomide in patients with advanced refractory solid tumors. Patients were treated on a modified Fibronacci dose escalation scheme with an oral daily dose of lenalidomide. A total of 45 patients with 8 different tumor types were accrued. Doses administered included 5, 10, and 20 mg continuous daily doses, every 28 days (n = 15), later modified to intermittent doses of 15, 20, 25, 30, 35, and 40 mg, with a 21 days-on and 7 days-off schedule, due to observed side effects. Lenalidomide exhibited a linear pharmacokinetics over a wide range of doses with the mean half-life of 3.9 hours. The renal function affected lenalidomide clearance, resulting in 50% reduction in patients with mild renal impairment compared with patients with normal function (CL/F = 243 mL/min). Stable disease was documented in 12 of 44 evaluable patients, of whom 9 patients had prostate cancer. Most frequent grade 1 and 2 toxicities included fatigue, nausea, pruritus/rash, neutropenia, and neuropathy. Grade 3/4 events were predominantly hematologic. Lenalidomide was well tolerated up to a 35-mg/d intermittent dosing schedule at doses higher than previously indicated for hematologic malignancies.

Phase II and pharmacokinetic study of thalidomide in Japanese patients with relapsed/refractory multiple myeloma.

Murakami H, Shimizu K, Sawamura M, Suzuki K, Sugiura I, Kosugi H, Shimazaki C, Taniwaki M, Abe M, Takagi T.

Int J Hematol. 2009 Jun;89(5):636-41. [Epub 2009 Apr 28.]

http://www.ncbi.nlm.nih.gov/pubmed/19399582?ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that low-dose thalidomide is an effective and tolerable treatment for Japanese patients with relapsed/refractory myeloma, with leukopenia and neutropenia as the most serious adverse events; the pharmacokinetics are similar to those observed in Caucasian patients.

To obtain approval from the Ministry of Health, Labor and Welfare of Japan, a phase II study was conducted to assess the pharmacokinetics and pharmacodynamics of thalidomide along with its efficacy and safety in Japanese patients with multiple myeloma. Between 2005 and 2006, 42 patients were enrolled, and 37 patients met eligibility criteria. Of the 37 patients, 3 were excluded from efficacy analysis because of short duration of thalidomide administration (<4 weeks). The overall response rate was 35.3% (12/34), including partial response of 14.7% (5/34) and minimal response of 20.6% (7/34). The adverse events observed in high frequency (>40%) were leukopenia, neutropenia, drowsiness, dry mouth, and constipation. Grade 3 neutropenia was observed in nine cases. Peripheral neuropathy and eruption were observed in about one-quarter of the patients. Deep vein thrombosis was not observed. At a single oral dose of thalidomide (100 mg), the C (max) was 1.68 +/- 0.41 microg/ml, T (max) was 4.54 +/- 1.71 h, T (1/2) was 4.86 +/- 0.44 h, and AUC was 15.87 +/- 3.05 microg h/ml. Low-dose thalidomide was an effective and tolerable treatment for Japanese patients with relapsed/refractory myeloma. Leukopenia and neutropenia were the most serious adverse events. The pharmacokinetics was similar to those observed in Caucasian patients.

Thalidomide chemotherapy-induced peripheral neuropathy: actual status and new perspectives with thalidomide analogues derivatives.

Cundari S, Cavaletti G.

Mini Rev Med Chem. 2009 Jun;9(7):760-8.

http://www.ncbi.nlm.nih.gov/pubmed/19519501?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss novel aspects of IMiDs compounds, including lenalidomide.

IMiDs compounds are a class of analogues of thalidomide, with greater immunomodulatory activity and a superior safety profile compared to the parent compound. They show substantial increase in potency and an interesting tolerability profile, primarily due to a decreased incidence of the most severe side effect of thalidomide, i.e. Chemotherapy-Induced Peripheral Neurotoxicity (CIPN). These novel aspects of the IMiDs compounds will be discussed.

Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial.

Abdelkefi A, Ladeb S, Torjman L, Ben Othman T, Lakhal A, Ben Romdhane N, El Omri H, Elloumi M, Belaaj H, Jeddi R, Aissaouï L, Ksouri H, Ben Hassen A, Msadek F, Saad A, Hsaïri M, Boukef K, Amouri A, Louzir H, Dellagi K, Ben Abdeladhim A, on behalf of the Tunisian Multiple Myeloma Study Group.

Blood. 2009 Jun 11;113(24):6265.

http://www.ncbi.nlm.nih.gov/pubmed/19520824?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Multiple myeloma.

Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC.

Lancet. 2009 Jun 19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19541364?ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss the characteristics of myeloma and how thalidomide and lenalidomide target both myeloma cells and the bone marrow microenvironment—creating a treatment framework that promises improved outcomes not only for myeloma patients but also those with other hematological malignancies and solid tumors.

Multiple myeloma is characterised by clonal proliferation of malignant plasma cells, and mounting evidence indicates that the bone marrow microenvironment of tumour cells has a pivotal role in myeloma pathogenesis. This knowledge has already expanded treatment options for patients with multiple myeloma. Prototypic drugs thalidomide, bortezomib, and lenalidomide have each been approved for

the treatment of this disease by targeting both multiple myeloma cells and the bone marrow microenvironment. Although benefit was first shown in relapsed and refractory disease, improved overall response, duration of response, and progression-free and overall survival can be achieved when these drugs are part of first-line regimens. This treatment framework promises to improve outcome not only for patients with multiple myeloma, but also with other haematological malignancies and solid tumours.

Phase II Study of Thalidomide Plus Dexamethasone Induction Followed by Tandem Melphalan-Based Autotransplantation and Thalidomide-Plus-Prednisone Maintenance for Untreated Multiple Myeloma: A Southwest Oncology Group Trial (S0204).

Hussein MA, Bolejack V, Zonder JA, Durie BG, Jakubowiak AJ, Crowley JJ, Barlogie B.

J Clin Oncol. 2009 Jun 22. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19546405?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In this phase II trial, newly diagnosed myeloma patients receive thalidomide-dexamethasone induction, tandem melphalan-based tandem transplantation, and thalidomide-prednisone maintenance. The authors find that survival outcomes are superior for International Staging System stage 1 disease, when lactate dehydrogenase levels are normal and a second transplantation is applied in a timely fashion.

PURPOSE: Thalidomide-dexamethasone (THAL-DEX) is standard induction therapy for multiple myeloma (MM). Tandem melphalan-based transplantations have yielded superior results to single transplantations. Phase II trial S0204 was designed to improve survival results reported for the predecessor, phase III trial S9321 by 50%. PATIENTS AND METHODS: Newly diagnosed patients with MM were eligible for S0204 with THAL-DEX induction, tandem melphalan-based tandem transplantation, and THAL-prednisone maintenance. RESULTS: Of 143 eligible patients, 142 started induction, 73% completed first transplantation, 58% completed second transplantation, and 56% started maintenance. The quantity of stem cells required for two transplantations was reached in 88% of 111 patients undergoing collection, 74% of whom completed both transplantations. Partial response, very good partial remission, and complete response were documented after 12 months of maintenance therapy in 87%, 72%, and 22% of patients, respectively. During a median follow-up time of 37 months, 4-year estimates of event-free and overall survival were 50% and 64%, respectively. Survival outcomes were superior for International Staging System (ISS) stage 1 disease, when lactate dehydrogenase (LDH) levels were normal and a second transplantation was applied in a timely fashion. CONCLUSION: Both overall survival (P = .0002) and event-free survival (P < .0001) were significantly improved with S0204 compared with S9321 when 121 and 363 patients, respectively, were matched on ISS stage and LDH.

Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide, lenalidomide or bortezomib- containing regimens.

Kumar S, Giralt S, Stadtmauer EA, Harousseau JL, Palumbo A, Bensinger W, Comenzo RL, Lentzsch S, Munshi N, Niesvizky R, San Miguel J, Ludwig H, Bergsagel L, Blade J, Lonial S, Anderson KC, Tosi P, Sonneveld P, Sezer O, Vesole D, Cavo M, Einsele H, Richardson PG, Durie BG, Rajkumar SV.

Blood. 2009 Jun 26. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19561323?ordinalpos=19&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

With increasing use of the novel agents (such as thalidomide and lenalidomide) in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. The authors recommend early mobilization of stem cells, preferable with in the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

The past decade has witnessed a paradigm shift in the initial treatment of multiple myeloma with the introduction of novel agents such as thalidomide, lenalidomide and bortezomib, leading to improved outcomes. High dose therapy and autologous stem cell transplantation remains an important therapeutic option for patients with multiple myeloma eligible for the procedure. Prior to the advent of the novel agents, patients underwent stem cell collection prior to significant alkylating agent exposure, given their potential deleterious effect on stem cell collection. With increasing use of the novel agents in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. An expert panel of the International Myeloma Working Group was convened to examine the implications of these therapies on stem collection in patients with myeloma and to develop recommendations for addressing these issues. Here we summarize the currently available data and present our perspective on the problem and potential options to overcome this problem. Specifically, we recommend early mobilization of stem cells, preferable with in the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

Bortezomib in combination with pegylated liposomal doxorubicin and thalidomide is an effective steroid independent salvage regimen for patients with relapsed or refractory multiple myeloma: results of a phase II clinical trial.

Chanan-Khan A, Miller KC, Musial L, Padmanabhan S, Yu J, Ailawadhi S, Sher T, Mohr A, Bernstein ZP, Barcos M, Patel M, Iancu D, Lee K, Czuczman MS.

Leuk Lymphoma. 2009 Jul;50(7):1096-101.

http://www.ncbi.nlm.nih.gov/pubmed/19479618?ordinalpos=58&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In this study, the authors observe that a combination of bortezomib, pegylated liposomal doxorubicin and thalidomide is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Novel agents have demonstrated enhanced efficacy when combined with other antimyeloma agents especially dexamethasone. The steroid doses employed in myeloma regimens are often poorly tolerated. Therefore, in a phase II clinical trial we investigated the efficacy of a steroid-free combination including bortezomib, pegylated liposomal doxorubicin and thalidomide (VDT regimen). Twenty-three patients with relapsed or refractory myeloma or other plasma cell cancers were treated with the VDT regimen. Patient had a median of five prior therapies and 65.2% were refractory to their last regimen. The overall response rates were 55.5% and 22%, respectively. The median progression free survival was 10.9 months (95% CI: 7.3-15.8) and the median overall survival was 15.7 months (95% CI: 9.1-not reached). Fatigue and sensory neuropathy were the most common side effects noted. We observe that VDT is an effective steroid-free regimen with ability to induce durable remission even in patients with refractory myeloma.

Expanded safety experience with lenalidomide plus dexamethasone in relapsed or refractory multiple myeloma.

Chen C, Reece DE, Siegel D, Niesvizky R, Boccia RV, Stadtmauer EA, Abonour R, Richardson P, Matous J, Kumar S, Bahlis NJ, Alsina M, Vescio R, Coutre SE, Pietronigro D, Knight RD, Zeldis JB, Rajkumar V.

Br J Haematol. 2009 Jul;146(2):164-70. [Epub 2009 May 26.]

http://www.ncbi.nlm.nih.gov/pubmed/19545290?ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report on an expanded access program that was designed to provide lenalidomide to patients likely to benefit and to obtain additional safety information. Safety data confirmed known adverse events of lenalidomide plus dexamethasone therapy in patients with relapsed/refractory myeloma.

Lenalidomide gained Food and Drug Administration (FDA) approval for treatment of patients with relapsed or refractory multiple myeloma (MM) in combination with dexamethasone in June 2006. In April 2005, the FDA and patient advocacy groups requested an expanded access programme to both provide lenalidomide to patients likely to benefit and obtain additional safety information. Relapsed/refractory MM patients received lenalidomide 25 mg/d (days 1-21) and dexamethasone 40 mg/d (days 1-4, 9-12, and 17-20 of cycles 1-4; days 1-4 only from cycle 5 onwards), in 4-week cycles until disease progression, study drug discontinuation, or lenalidomide approval. Of the 1438 patients enrolled, approximately 60% were male, median age was 64 years, and 61.7% had Durie-Salmon stage III disease. Median time on study was 15.4 weeks (range: 0.1-49.1) and median dose was 25 mg. The most common adverse events (AEs) were haematological (49%), gastrointestinal (59%), and fatigue (55%). The most common grade > or =3 AEs were haematological (45%), fatigue (10%), and pneumonia (7%). The most common serious AEs were pneumonia (8%), pyrexia (4%), and deep-vein thrombosis (3%). Primary cause of death was disease progression (10%). Safety data confirmed known AEs of lenalidomide plus dexamethasone therapy in patients with relapsed/refractory MM.

Hypercoagulable states in patients with multiple myeloma can affect the thalidomide-associated venous thromboembolism.

Talamo GP, Ibrahim S, Claxton D, Tricot GJ, Fink LM, Zangari M.

Blood Coagul Fibrinolysis. 2009 Jul;20(5):337-9.

http://www.ncbi.nlm.nih.gov/pubmed/19367157?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The results of this retrospective study suggest that myeloma patients with thromboembolic complications during treatment with thalidomide have a frequent concomitant underlying thrombophilic state.

The therapeutic use of thalidomide in patients with multiple myeloma is often complicated by the development of venous thromboembolism. The objective of the present study was to identify hypercoagulable states associated with development of venous thromboembolism in thalidomide-treated multiple myeloma patients. We screened 49 consecutive multiple myeloma patients treated with thalidomide at baseline for hypercoagulability. With a median follow-up of 11 months, 10 of 49 multiple myeloma patients developed a thrombotic episode. Laboratory assays revealed an underlying abnormality in nine of the 10 patients; hypercoagulable screenings were normal in 36

of the 39 patients who did not develop venous thromboembolism (P < 0.0001). Our retrospective study results suggest that the multiple myeloma patients with thromboembolic complications during treatment with thalidomide have a frequent concomitant underlying thrombophilic state.

Lenalidomide for the treatment of relapsed multiple myeloma.

Gajraj E, Chung H, Boysen M, Barnett DB, Longson C.

Lancet Oncol. 2009 Jul;10(7):647-8.

http://www.ncbi.nlm.nih.gov/pubmed/19585686?ordinalpos=57&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Post-transplant immunotherapy with donor-lymphocyte infusion and novel agents to upgrade partial into complete and molecular remission in allografted patients with multiple myeloma.

Kröger N, Badbaran A, Lioznov M, Schwarz S, Zeschke S, Hildebrand Y, Ayuk F, Atanackovic D, Schilling G, Zabelina T, Bacher U, Klyuchnikov E, Shimoni A, Nagler A, Corradini P, Fehse B, Zander A.

Exp Hematol. 2009 Jul;37(7):791-8. [Epub 2009 May 31.]

http://www.ncbi.nlm.nih.gov/pubmed/19487069?ordinalpos=54&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to investigate post-transplant immunotherapy with escalating donor-lymphocyte infusions and novel agents (including thalidomide and lenalidomide) to target complete remission. Their findings demonstrate the clinical relevance of posttransplantation therapies to upgrade remission, and of remission's depth for long-term survival in myeloma patients.

OBJECTIVE: To investigate post-transplant immunotherapy with escalating donor-lymphocyte infusions (DLI) and novel agents (thalidomide, bortezomib, and lenalidomide) to target complete remission (CR). MATERIALS AND METHODS: Thirty-two patients with multiple myeloma who achieved only partial remission after allogeneic stem cell transplantation were treated with DLI. If no CR was achieved, one of the novel agents was added to target CR. RESULTS: CR defined either by European Group for Blood and Marrow Transplantation criteria, flow cytometry, or molecular methods as assessed by patient-specific immunoglobulin H-polymerase chain reaction or plasma cell chimerism polymerase chain reaction was accomplished in 59%, 63%, and 50% of patients, respectively. Achievement of CR resulted in improved 5-year progressive-free and overall survival, according to European Group for Blood and Marrow Transplantation criteria (53% vs 35%; p=0.03 and 90% vs 62%; p=0.06), flow cytometry (74% vs 15%; p=0.001 and 100% vs 52%; p=0.1), or molecular methods (84% vs 38%; p=0.001 and 100% vs 71%; p=0.03). CONCLUSIONS: Our finding demonstrates the clinical relevance of posttransplantation therapies to upgrade remission, and of remission's depth for long-term survival in myeloma patients.

Thalidomide treatment down-regulates SDF-1alpha and CXCR4 expression in multiple myeloma patients.

Oliveira AM, Maria DA, Metzger M, Linardi C, Giorgi RR, Moura F, Martinez GA, Bydlowski SP, Novak EM.

Leuk Res. 2009 Jul;33(7):970-3. [Epub 2008 Oct 30.]

http://www.ncbi.nlm.nih.gov/pubmed/18976811?ordinalpos=60&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' findings indicate that thalidomide therapy induces down-regulation of CXCR4 and its ligand SDF-1alpha in multiple myeloma.

The chemokine stromal-derived factor-1alpha (SDF-1alpha) and its receptor CXCR4 are critically involved in directional migration and homing of plasma cells in multiple myeloma. Here, we show that the expression of SDF-1alpha and CXCR4 was significantly down-regulated in patients treated with thalidomide (n=10) as compared to newly diagnosed MM patients (n=31) and MM patients treated with other drugs (n=38). SDF-1 alpha and CXCR4 expression was also significantly decreased in a RPMI 8226 cell line treated with 10 and 20micromol/L of thalidomide. Our findings indicate that thalidomide therapy induces down-regulation of CXCR4 and its ligand SDF-1alpha in multiple myeloma.

Re: Tandem vs single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis.

Giralt S, Vesole DH, Somlo G, Krishnan A, Stadtmauer E, Mccarthy P, Pasquini MC; Blood and Marrow Transplant Clinical Trials Network Multiple Myeloma Working Group.

J Natl Cancer Inst. 2009 Jul 1;101(13):964; author reply 966-7. [Epub 2009 Jun 17.]

http://www.ncbi.nlm.nih.gov/pubmed/19535777?ordinalpos=56&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: *J Natl Cancer Inst.* 2009 Jan 21;101(2):100-6.

Lenalidomide as salvage therapy after allo-SCT for multiple myeloma is effective and leads to an increase of activated NK (NKp44(+)) and T (HLA-DR(+)) cells.

Lioznov M, El-Cheikh J Jr, Hoffmann F, Hildebrandt Y, Ayuk F, Wolschke C, Atanackovic D, Schilling G, Badbaran A, Bacher U, Fehse B, Zander AR, Blaise D, Mohty M, Kröger N.

Bone Marrow Transplant. 2009 Jul 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19584825?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors investigate efficacy and toxicity of lenalidomide in 24 heavily pretreated myeloma patients with a median age of 59 years and relapse after allo-SCT. In their study, response is achieved in 66% of patients, and they find that immunomonitoring after lenalidomide shows significant increase of activated NK (NKp44(+)) and T (HLA-DR(+)) cells, as well as regulatory T cells (CD4(+), CD25(+), CD127(lo)), supporting an immunomodulating anti-myeloma effect of lenalidomide.

We investigated efficacy and toxicity of lenalidomide in 24 heavily pretreated myeloma patients with a median age of 59 years (range: 37-70) and relapse after allo-SCT. Lenalidomide was given at a dose of 15 mg (n=4), or 25 mg (n=20), orally once daily on day 1 to day 1 every 28 days, with (n=20) or without (n=4) DHAP. The median number of lenalidomide cycles was five (range: 2-17). Major side effects were leukopenia (grade 4: 4%, grade 3: 21% and grade 2: 17%) and thrombocytopenia (grade 3: 17% and grade 2: 29%); infectious complications were observed in 50%. Non-hematological toxicity consisted of muscle cramps (n=9), fatigue (n=5) and constipation (n=2). Mild grade I-II GVHD was seen in three patients. Response was achieved in 66%: CR in 8%, VGPR in 8%, PR in 50% and SD in 13%. The median time to progression was 9.7 months (95% confidence interval (CI): 7.5-11.9), and median OS was 19.9 months (95% CI: 17.3-22.5). Immunomonitoring after lenalidomide showed significant increase of activated NK (NKp44(+)) and T (HLA-DR(+)) cells, as well as regulatory T cells (CD4(+), CD25(+), CD127(lo)), supporting an immunomodulating anti-myeloma effect of lenalidomide.

Multiple myeloma: management of adverse events.

Gay F, Palumbo A.

Med Oncol. 2009 Jul 7. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19582597?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors focus on frequency and management of main adverse events in newly diagnosed and relapsed myeloma patients and provide guidelines for dose reductions and supportive therapy, including with lenalidomide.

The combination of conventional chemotherapy or dexamethasone with new drugs, such as immunomodulatory agents and proteasome inhibitors, has substantially changed the treatment paradigm of myeloma patients. New drugs have been incorporated in pre-transplant induction regimens and post-transplant consolidation and maintenance strategies for young patients; in elderly patients, standard melphalan and prednisone (MP) plus thalidomide or plus bortezomib are now considered standards of care, and ongoing trials are assessing if lenalidomide plus standard MP or plus low-dose dexamethasone may be other options. The efficacy of these drugs needs to be balanced against their toxicity. Different drugs have a different toxicity profile. The choice for the best treatment strategy for every single patient should be based on results of scientific randomized studies but tailored to account for patient's biological age, comorbidities, and the expected toxicity profile of different regimens. Prompt dose reduction and accurate management of treatment-related toxicity can greatly reduce early discontinuation rate and significantly improve treatment efficacy. This chapter will focus on frequency and management of main adverse events in newly diagnosed and relapsed myeloma patients and will provide guidelines for dose reductions and supportive therapy.

Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone.

Kapoor P, Kumar S, Fonseca R, Lacy MQ, Witzig TE, Hayman SR, Dispenzieri A, Buadi F, Bergsagel PL, Gertz MA, Dalton RJ, Mikhael JR, Dingli D, Reeder CB, Lust JA, Russell SJ, Roy V, Zeldenrust SR, Stewart AK, Kyle RA, Greipp PR, Rajkumar SV.

Blood. 2009 Jul 16;114(3):518-21. [Epub 2009 Mar 26.]

http://www.ncbi.nlm.nih.gov/pubmed/19324902?ordinalpos=18&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors study the outcome after initial therapy with lenalidomide-dexamethasone among 100 newly diagnosed patients, risk-stratified by genetic abnormalities and plasma cell labeling index. They conclude that high-risk patients achieve less durable responses with lenalidomide-dexamethasone compared with standard-risk patients, with no significant differences in overall survival are apparent.

The outcome of patients with multiple myeloma is dictated primarily by cytogenetic abnormalities and proliferative capacity of plasma cells. We studied the outcome after initial therapy with lenalidomide-dexamethasone among 100 newly diagnosed patients, risk-stratified by genetic abnormalities and plasma cell labeling index. A total of 16% had high-risk multiple myeloma, defined by the presence of hypodiploidy, del(13q) by metaphase cytogenetics, del(17p), IgH translocations [t(4;14), or t(14;16)] or plasma cell labeling index more

than or equal to 3%. Response rates were 81% vs 89% in the high-risk and standard-risk groups, respectively. The median progression-free survival was shorter in the high-risk group (18.5 vs 36.5 months, P < .001), but overall survival was comparable. Because of unavailability of all tests for every patient, we separately analyzed 55 stringently classified patients, and the results were similar. In conclusion, high-risk patients achieve less durable responses with lenalidomide-dexamethasone compared with standard-risk patients; no significant differences in overall survival are apparent so far. These results need confirmation in larger, prospectively designed studies.

Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13.

Reece D, Song KW, Fu T, Roland B, Chang H, Horsman DE, Mansoor A, Chen C, Masih-Khan E, Trieu Y, Bruyere H, Stewart DA, Bahlis NJ.

Blood. 2009 Jul 16;114(3):522-5. [Epub 2009 Mar 30.]

http://www.ncbi.nlm.nih.gov/pubmed/19332768?ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors investigate the effects of the most common unfavorable cytogenetic abnormalities in myeloma patients treated with the combination of lenalidomide and dexamethasone. They find that patients with either del(13q) or t(4;14) experience a median time to progression and overall survival comparable with those without these cytogenetic abnormalities, but patients with del(17p13) have a significantly worse outcome.

Although the combination of lenalidomide and dexamethasone is effective therapy for patients with relapsed/refractory multiple myeloma, the influence of high-risk cytogenetic abnormalities on outcomes is unknown. This subanalysis of a large, open-label study investigated the effects of the most common unfavorable cytogenetic abnormalities detected by fluorescence in situ hybridization, del(13q), t(4;14), and del(17p13), in 130 evaluable patients treated with this regimen. Whereas patients with either del(13q) or t(4;14) experienced a median time to progression and overall survival comparable with those without these cytogenetic abnormalities, patients with del(17p13) had a significantly worse outcome, with a median time to progression of 2.22 months (hazard ratio, 2.82; P < .001) and median overall survival of 4.67 months (hazard ratio, 3.23; P < .001). Improved therapeutic strategies are required for this subgroup of patients.

Prognostic significance of apoptotic index in multiple myeloma patients treated by conventional therapy and novel agents, thalidomide and bortezomib.

Jiri M, Vlastimil S, Jaroslav B, Marketa Z, Tomas P, Marta O, Katerina L.

Eur J Haematol. 2009 Jul 18. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19624720?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to assess the outcome of the measurement of apoptotic index in myeloma patients treated by conventional chemotherapy and novel drugs (including thalidomide). Their results suggest the use of apoptotic index by flow cytometry measurement as a fast and accessible method for prognostic stratification of myeloma patients in routine practice.

ABSTRACT Objective: To assess the outcome of the measurement of apoptotic index in myeloma patients treated by conventional chemotherapy and novel drugs with biological mechanism of action, thalidomide and bortezomib. Patients and methods: In a cohort of 189 patients with newly diagnosed multiple myeloma (MM) from November 1997 through February 2008, we assessed the prognostic significance of plasma cell apoptotic index (PC-AI) using annexin-V. The whole group was subsequently divided according to treatment approach (conventional chemotherapy only vs inclusion of novel drugs, thalidomide and bortezomib), and curves of overall survival were constructed. Results: In the whole group (n = 189), low levels of PC-AI < 4.5% significantly separated patients with unfavorable prognosis (median OS 16 vs 38 months, p = 0.004). In patients treated with conventional chemotherapy only (n = 139) the results were similar (median OS 10 vs 25 months, p = 0.02), and the apoptotic index maintained its significance even within the group of 50 patients treated also with novel drugs (median OS 30 vs 54 months, p = 0.027). PC-AI was found to be independent both on Durie-Salmon staging system (D-S) and the International Prognostic Index (IPI). Conclusion: Presented results suggest the use of apoptotic index by flow cytometry measurement as a fast and accessible method for prognostic stratification of myeloma patients in routine practice.

Phase II study of thalidomide plus dexamethasone induction followed by tandem melphalan-based autotransplantation and thalidomide-plus-prednisone maintenance for untreated multiple myeloma: a southwest oncology group trial (S0204).

Hussein MA, Bolejack V, Zonder JA, Durie BG, Jakubowiak AJ, Crowley JJ, Barlogie B.

J Clin Oncol. 2009 Jul 20;27(21):3510-7. [Epub 2009 Jun 22.]

http://www.ncbi.nlm.nih.gov/pubmed/19546405?ordinalpos=36&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This phase II trial was designed to improve survival results reported for its predecessor phase III trial. The authors find that both overall survival and event-free survival were significantly improved with this thalidomide-dexamethasone induction, tandem melphalan-based tandem transplantation, and thalidomide-prednisone maintenance.

PURPOSE Thalidomide-dexamethasone (THAL-DEX) is standard induction therapy for multiple myeloma (MM). Tandem melphalan-based transplantations have yielded superior results to single transplantations. Phase II trial S0204 was designed to improve survival results reported for the predecessor, phase III trial S9321 by 50%. PATIENTS AND METHODS Newly diagnosed patients with MM were eligible for S0204 with THAL-DEX induction, tandem melphalan-based tandem transplantation, and THAL-prednisone maintenance. Results Of 143 eligible patients, 142 started induction, 73% completed first transplantation, 58% completed second transplantation, and 56% started maintenance. The quantity of stem cells required for two transplantations was reached in 88% of 111 patients undergoing collection, 74% of whom completed both transplantations. Partial response, very good partial remission, and complete response were documented after 12 months of maintenance therapy in 87%, 72%, and 22% of patients, respectively. During a median follow-up time of 37 months, 4-year estimates of event-free and overall survival were 50% and 64%, respectively. Survival outcomes were superior for International Staging System (ISS) stage 1 disease, when lactate dehydrogenase (LDH) levels were normal and a second transplantation was applied in a timely fashion. CONCLUSION Both overall survival (P = .0002) and event-free survival (P < .0001) were significantly improved with S0204 compared with S9321 when 121 and 363 patients, respectively, were matched on ISS stage and LDH.

Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma.

Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, Petrucci MT, Yu Z, Olesnyckyj M, Zeldis JB, Knight RD, Weber DM.

Leukemia. 2009 Jul 23. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19626046?ordinalpos=15&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors present a pooled update of two large, multicenter placebo-controlled randomized phase III trials of patients with relapsed/refractory myeloma, with data that confirm the significant response and survival benefit with lenalidomide and dexamethasone.

We present a pooled update of two large, multicenter MM-009 and MM-010 placebo-controlled randomized phase III trials that included 704 patients and assessed lenalidomide plus dexamethasone versus dexamethasone plus placebo in patients with relapsed/refractory multiple myeloma (MM). Patients in both studies were randomized to receive 25 mg daily oral lenalidomide or identical placebo, plus 40 mg oral dexamethasone. In this pooled analysis, using data up to unblinding (June 2005 for MM-009 and August 2005 for MM-010), treatment with lenalidomide plus dexamethasone significantly improved overall response (60.6 vs 21.9%, P<0.001), complete response rate (15.0 vs 2.0%, P<0.001), time to progression (median of 13.4 vs 4.6 months, P<0.001) and duration of response (median of 15.8 months vs 7 months, P<0.001) compared with dexamethasone-placebo. At a median follow-up of 48 months for surviving patients, using data up to July 2008, a significant benefit in overall survival (median of 38.0 vs 31.6 months, P=0.045) was retained despite 47.6% of patients who were randomized to dexamethasone-placebo receiving lenalidomide-based treatment after disease progression or study unblinding. Low beta(2)-microglobulin and low bone marrow plasmacytosis were associated with longer survival. In conclusion, these data confirm the significant response and survival benefit with lenalidomide and dexamethasone.

Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma.

Richardson P, Jagannath S, Hussein M, Berenson J, Singhal S, Irwin D, Williams SF, Bensinger W, Badros AZ, Vescio R, Kenvin L, Yu Z, Olesnyckyj M, Zeldis J, Knight R, Anderson KC.

Blood. 2009 Jul 23;114(4):772-8. [Epub 2009 May 26.]

http://www.ncbi.nlm.nih.gov/pubmed/19471019?ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the efficacy and safety of lenalidomide monotherapy in patients with relapsed and refractory myeloma, finding that the data supports treatment with single-agent lenalidomide in addition to its use in steroid-sparing combination approaches.

Lenalidomide plus dexamethasone is effective for the treatment of relapsed and refractory multiple myeloma (MM); however, toxicities from dexamethasone can be dose limiting. We evaluated the efficacy and safety of lenalidomide monotherapy in patients with relapsed and refractory MM. Patients (N = 222) received lenalidomide 30 mg/day once daily (days 1-21 every 28 days) until disease progression or

intolerance. Response, progression-free survival (PFS), overall survival (OS), time to progression (TTP), and safety were assessed. Overall, 67% of patients had received 3 or more prior treatment regimens. Partial response or better was reported in 26% of patients, with minimal response 18%. There was no difference between patients who had received 2 or fewer versus 3 or more prior treatment regimens (45% vs 44%, respectively). Median values for TTP, PFS, and OS were 5.2, 4.9, and 23.2 months, respectively. The most common grade 3 or 4 adverse events were neutropenia (60%), thrombocytopenia (39%), and anemia (20%), which proved manageable with dose reduction. Grade 3 or 4 febrile neutropenia occurred in 4% of patients. Lenalidomide monotherapy is active in relapsed and refractory MM with acceptable toxicities. These data support treatment with single-agent lenalidomide, as well as its use in steroid-sparing combination approaches.

Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients.

Varettoni M, Corso A, Pica G, Mangiacavalli S, Pascutto C, Lazzarino M.

Ann Oncol. 2009 Jul 24. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19633044?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors investigate the incidence of extramedullary (EM) disease, its relationship with prior exposure to high-dose therapy (HDT) or novel agents (including thalidomide and lenalidomide), and its prognostic impact on myeloma patients. They find HDT and novel agents seem not to increase the risk of EM disease.

BACKGROUND: There are few data on the incidence and prognosis of extramedullary (EM) multiple myeloma (MM). There are concerns about a possible increase of EM relapses with the expanding use of high-dose therapy (HDT) and biological agents. PATIENTS AND METHODS: The incidence of EM disease, its relationship with prior exposure to HDT or novel agents, and its prognostic impact were analyzed in 1003 MM patients. Based on the different therapies available, three periods were considered: 1971-1993, conventional-dose chemotherapy; 1994-1999, HDT for younger patients; and 2000-2007, introduction of novel agents. RESULTS: Overall, 13% of patients had EM disease, 7% at diagnosis and 6% later. In the 2000-2007 period, there was a significant increase of EM involvement, at diagnosis ($P = 0.02$) and during follow-up ($P = 0.03$). The risk of EM spread was not significantly increased after HDT [hazard ratio (HR 0.6)], bortezomib (HR 1.62), or thalidomide/lenalidomide (HR 1.07). EM disease was associated with shorter overall (HR 3.26, $P < 0.0001$) and progression-free (HR 1.46, $P = 0.04$) survival. CONCLUSIONS: The incidence of EM disease has increased, probably due to the availability of more sensitive imaging techniques and the prolongation of patients' survival. HDT or novel agents seem not to increase the risk of EM disease. EM involvement confers a poor prognosis.

Multiple myeloma.

Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC.

Lancet. 2009 Jul 25;374(9686):324-39. [Epub 2009 Jun 21.]

http://www.ncbi.nlm.nih.gov/pubmed/19541364?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss the nature of myeloma and treatment drugs, including thalidomide and lenalidomide, as a framework that promises to improve outcome not only for myeloma patients but also those with other hematological malignancies and solid tumors.

Multiple myeloma is characterised by clonal proliferation of malignant plasma cells, and mounting evidence indicates that the bone marrow microenvironment of tumour cells has a pivotal role in myeloma pathogenesis. This knowledge has already expanded treatment options for patients with multiple myeloma. Prototypic drugs thalidomide, bortezomib, and lenalidomide have each been approved for the treatment of this disease by targeting both multiple myeloma cells and the bone marrow microenvironment. Although benefit was first shown in relapsed and refractory disease, improved overall response, duration of response, and progression-free and overall survival can be achieved when these drugs are part of first-line regimens. This treatment framework promises to improve outcome not only for patients with multiple myeloma, but also with other haematological malignancies and solid tumours.

Differential activities of thalidomide and isoprenoid biosynthetic pathway inhibitors in multiple myeloma cells.

Holstein SA, Tong H, Hohl RJ.

Leuk Res. 2009 Jul 29. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19646757?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors evaluate the interactions between thalidomide and the isoprenoid biosynthetic pathway (IBP) inhibitors in myeloma cells, with findings that provide a mechanism for the differential sensitivity of myeloma cells to pharmacologic manipulation of the IBP.

Thalidomide has emerged as an effective agent for treating multiple myeloma; however the precise mechanism of action remains unknown. Agents known to target the isoprenoid biosynthetic pathway (IBP) can have cytotoxic effects in myeloma cells. The interactions between thalidomide and IBP inhibitors in human multiple myeloma cells were evaluated. Enhanced cytotoxicity and induction

of apoptosis were observed in RPMI-8226 cells. Examination of intracellular levels of farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) revealed a wide variance in basal levels and response to IBP inhibitors. These findings provide a mechanism for the differential sensitivity of myeloma cells to pharmacologic manipulation of the IBP.

Antiangiogenic drugs: insights into drug development from endostatin, avastin and thalidomide.

Holaday JW, Berkowitz BA.

Mol Interv. 2009 Aug;9(4):157-66.

http://www.ncbi.nlm.nih.gov/pubmed/19720747?ordinalpos=68&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Arterial thrombosis with immunomodulatory derivatives in the treatment of multiple myeloma: a single-center case series and review of the literature.

Martin MG, Vij R.

Clin Lymphoma Myeloma. 2009 Aug;9(4):320-3.

http://www.ncbi.nlm.nih.gov/pubmed/19717384?ordinalpos=56&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors describe five unusual arterial thromboses in patients with myeloma shortly after beginning thalidomide-based therapies.

Although the increased risk of venous thrombotic events with thalidomide in multiple myeloma (MM) has been well described, an association with an increased risk of arterial events is less well appreciated. We describe 5 unusual arterial thromboses in patients with MM shortly after beginning thalidomide-based therapies. The cases are remarkable for a paucity of risk factors and short latency. We also review the literature on arterial thromboembolic events in patients taking thalidomide. Care should be taken in future trials to document arterial events with both thalidomide and lenalidomide.

Effect of Thalidomide Combined with Dexamethasone on Multiple Myeloma KM3 Cells. [Article in Chinese]

He B, Zhang Y, Zhou W, Gao N, Gao B, Gu J, Li JY.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2009 Aug;17(4):903-7.

http://www.ncbi.nlm.nih.gov/pubmed/19698226?ordinalpos=70&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors conclude that thalidomide combined with dexamethasone shows synergistic inhibitory effect on myeloma KM3 cells, most likely through down-regulating the expression of IL-6, TNF-alpha and survivin, and up-regulating the expression of ES in KM3 cells.

The purpose of this study was to investigate the effect of thalidomide (THD) combined with dexamethasone (Dx) on multiple myeloma KM3 cells and its mechanism. The effect of the different concentrations and treatment time of THD or THD + Dx on KM3 cells was assayed by cytotoxicity test (MTT mothod), the inhibitory ratio of THD or THD + Dx on the KM3 cell growth was detected for choosing the best intervention condition. The expression levels of IL-6, TNF-alpha, VEGF, ES, survivin in supernatant of cells treated with best intervention condition were measured by indirect ELISA. The results indicated that an enhancement of cell growth inhibition was observed in treated KM3 cells along with increasing of drug concentrations and prolonging of treatment times, at the same time the THD combined with Dx could significantly inhibit the KM3 cell growth. The combination of THD in concentration of 80 or 100 microg/ml with Dx in concentration of 4 microg/ml decreased the expression of IL-6, TNF-alpha and survivin, increased the expression of ES, while no influence on VEGF expression was found. It is concluded that THD combined with Dx shows the synergistic inhibitory effect on KM3 cells, they bring the effect resistant to multiple myeloma probably through down-regulating the expression of IL-6, TNF-alpha and survivin, and up-regulating the expression of ES in KM3 cell.

Extramedullary (EMP) relapse in unusual locations in multiple myeloma: Is there an association with precedent thalidomide administration and a correlation of special biological features with treatment and outcome?

Katodritou E, Gastari V, Verrou E, Hadjiaggelidou C, Varthaliti M, Georgiadou S, Laschos K, Xirou P, Yiannaki E, Constantinou N, Markala D, Zervas K.

Leuk Res. 2009 Aug;33(8):1137-40. [Epub 2009 Feb 27.]

http://www.ncbi.nlm.nih.gov/pubmed/19250676?ordinalpos=66&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report nine cases of extramedullary relapse of myeloma, presented in unusual locations, seven of which had previously been treated with thalidomide-containing regimens.

Extramedullary relapse constitutes an uncommon manifestation of multiple myeloma (MM), characterized by highly malignant histology, special biological features, resistance to treatment and poor outcome. Its incidence has been increased during the last years, probably due

to the introduction of novel strategies in the management of MM, including intensified treatment and immunomodulatory drugs. Here we report nine cases of extramedullary relapse of MM, presented in unusual locations, seven of which had previously been treated with thalidomide-containing regimens (TCR). Our aim was to explore the morphological, immunophenotypical, molecular and laboratory characteristics accompanying EMP-relapse and seek possible correlations with treatment and clinical outcome.

Maintenance treatment of multiple myeloma-review. [Article in Chinese]

Su JY, Li X.

Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2009 Aug;17(4):1111-7.

http://www.ncbi.nlm.nih.gov/pubmed/19698272?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This article summarizes the current progress in the maintenance treatments for myeloma, including the use of thalidomide.

Chemotherapy with traditional standard dose or autologous stem cell transplantation (ASCT) after chemotherapy with high dose have some remission effect for multiple myeloma, but relapse still exists. The maintenance treatment would prolonged the remission stage. These treatments included the use of alkylating agent, interferon, corticosteroids, thalidomide and so on. Every maintenance treatment has some advantages and some side effects. The truly effective maintenance treatment would not only minimize the harm of the disease, but also would prolong the overall survival, progression-free survival and the event-free survival. This article summarizes the current progress in the maintenance treatments for multiple myeloma.

Remission induction with lenalidomide alone in a patient with previously untreated plasmablastic myeloma: a case report.

Sher T, Miller KC, Lee K, Chanan-Khan A.

Clin Lymphoma Myeloma. 2009 Aug;9(4):328-30.

http://www.ncbi.nlm.nih.gov/pubmed/19717386?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors present the first description of a plasmablastic variety of myeloma successfully treated with lenalidomide alone.

Multiple myeloma patients with plasmablastic morphology of tumor cells and extramedullary presentation of disease often have an aggressive clinical course and resistance to chemotherapy. We describe a case of an elderly patient who presented with extramedullary, IgA-lambda-secreting multiple myeloma with plasmablastic features who demonstrated impressive clinical response to single-agent lenalidomide. This is the first description of a plasmablastic variety of multiple myeloma successfully treated with lenalidomide alone.

Treatment of multiple myeloma: a comprehensive review.

Kyle RA, Rajkumar SV.

Clin Lymphoma Myeloma. 2009 Aug;9(4):278-88.

http://www.ncbi.nlm.nih.gov/pubmed/19717377?ordinalpos=57&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This comprehensive review of myeloma treatment strategies includes use of novel therapies, including thalidomide and lenalidomide.

Multiple myeloma (MM) is a neoplastic plasma cell disorder that results in end-organ damage (hypercalcemia, renal insufficiency, anemia, or skeletal lesions). Patients should not be treated unless they have symptomatic (end-organ damage) MM. They should be classified as having high-risk or standard-risk disease. Patients are classified as high risk in the presence of hypodiploidy or deletion of chromosome 13 (del[13]) with conventional cytogenetics, the presence of t(4:14), t(14;16), t(14;20) translocations or del(17p) with fluorescence in situ hybridization. High-risk disease accounts for about 25% of patients with symptomatic MM. If the patient is deemed eligible for autologous stem cell transplantation (ASCT), 3 or 4 cycles of lenalidomide and low-dose dexamethasone, or bortezomib and dexamethasone, or thalidomide and dexamethasone are reasonable choices. Stem cells should then be collected and one may proceed with an ASCT. If the patient has a complete response or a very good partial response (VGPR), the patient may be followed without maintenance therapy. If the patient has a less than VGPR, a second ASCT is encouraged. If the patient is in the high-risk group, a bortezomib-containing regimen to maximum response followed by 2 additional cycles of therapy is a reasonable approach. Lenalidomide and low-dose dexamethasone is another option for maintenance until progression. If the patient is considered ineligible for an ASCT, then melphalan, prednisone, and thalidomide is suggested for the standard-risk patient, and melphalan, prednisone, and bortezomib (MPV) for the high-risk patient. Treatment of relapsed or refractory MM is covered. The novel therapies-thalidomide, bortezomib, and lenalidomide-have resulted in improved survival rates. The complications of MM are also described. Multiple myeloma is a plasma cell neoplasm that is characterized by a single clone of plasma cells producing a monoclonal protein (M-protein). The malignant proliferation of plasma cells produces skeletal destruction that leads to bone pain and pathologic fractures. The M-protein might lead to renal failure, hyperviscosity syndrome, or through the suppression of uninvolved immunoglobulins, recurrent infections. Anemia and hypercalcemia are common complications.

Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial.

Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, Dib M, Guillerm G, Salles B, Eschard JP, Lenain P, Casassus P, Azaïs I, Decaux O, Garderet L, Mathiot C, Fontan J, Lafon I, Virion JM, Moreau P.

J Clin Oncol. 2009 Aug 1;27(22):3664-70. [Epub 2009 May 18.]

http://www.ncbi.nlm.nih.gov/pubmed/19451428?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This randomized, placebo-controlled, phase III trial investigates the efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed myeloma and confirms the superiority of this combination over melphalan and prednisone alone for this patient group.

PURPOSE: Until recently, melphalan and prednisone were the standards of care in elderly patients with multiple myeloma. The addition of thalidomide to this combination demonstrated a survival benefit for patients age 65 to 75 years. This randomized, placebo-controlled, phase III trial investigated the efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed myeloma. PATIENTS AND METHODS: Between April 2002 and December 2006, 232 previously untreated patients with myeloma, age 75 years or older, were enrolled and 229 were randomly assigned to treatment. All patients received melphalan (0.2 mg/kg/d) plus prednisone (2 mg/kg/d) for 12 courses (day 1 to 4) every 6 weeks. Patients were randomly assigned to receive 100 mg/d of oral thalidomide (n = 113) or placebo (n = 116), continuously for 72 weeks. The primary end point was overall survival. RESULTS: After a median follow-up of 47.5 months, overall survival was significantly longer in patients who received melphalan and prednisone plus thalidomide compared with those who received melphalan and prednisone plus placebo (median, 44.0 v 29.1 months; P = .028). Progression-free survival was significantly prolonged in the melphalan and prednisone plus thalidomide group (median, 24.1 v 18.5 months; P = .001). Two adverse events were significantly increased in the melphalan and prednisone plus thalidomide group: grade 2 to 4 peripheral neuropathy (20% v 5% in the melphalan and prednisone plus placebo group; P < .001) and grade 3 to 4 neutropenia (23% v 9%; P = .003). CONCLUSION: This trial confirms the superiority of the combination melphalan and prednisone plus thalidomide over melphalan and prednisone alone for prolonging survival in very elderly patients with newly diagnosed myeloma. Toxicity was acceptable.

Constitutive down-regulation of Osterix in osteoblasts from myeloma patients: In vitro effect of Bortezomib and Lenalidomide.

De Matteo M, Brunetti AE, Maiorano E, Cafforio P, Dammacco F, Silvestris F.

Leuk Res. 2009 Aug 3. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19656567?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' findings provide additional evidence suggesting that, at least in vitro, lenalidomide is ineffective in the promotion of osteoblast maturation.

Bortezomib and Lenalidomide have been shown to be effective in the control of multiple myeloma (MM) progression. We have investigated their role in the in vitro expression of Osterix by primary osteoblast cultures from MM patients and found that Osterix RNA was constitutively down-regulated in these cells. Treatment of osteoblasts with Bortezomib resulted in an increase of Osterix RNA and in enhanced activity of both BMP-2 and Runx2. Instead, Lenalidomide was unable to modify Osterix transcription. These findings provide additional evidence suggesting that, at least in vitro, Bortezomib promotes the osteoblast maturation whereas Lenalidomide is ineffective.

Mechanism of action of lenalidomide in hematological malignancies.

Kotla V, Goel S, Nischal S, Heuck C, Vivek K, Das B, Verma A.

J Hematol Oncol. 2009 Aug 12;2:36.

http://www.ncbi.nlm.nih.gov/pubmed/19674465?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Even though the exact molecular targets of lenalidomide are not well known, the authors discuss how its activity across a spectrum of neoplastic conditions highlights the possibility of multiple target sites of action.

ABSTRACT: Immunomodulatory drugs lenalidomide and pomalidomide are synthetic compounds derived by modifying the chemical structure of thalidomide to improve its potency and reduce its side effects. Lenalidomide is a 4-amino-glutamyl analogue of thalidomide that lacks the neurologic side effects of sedation and neuropathy and has emerged as a drug with activity against various hematological and solid malignancies. It is approved by FDA for clinical use in myelodysplastic syndromes with deletion of chromosome 5q and multiple myeloma. Lenalidomide has been shown to be an immunomodulator, affecting both cellular and humoral limbs of the immune system. It has also been shown to have anti-angiogenic properties. Newer studies demonstrate its effects on signal transduction that can partly explain its selective efficacy in subsets of MDS. Even though the exact molecular targets of lenalidomide are not well known, its activity across a spectrum of neoplastic conditions highlights the possibility of multiple target sites of action.

Reversal of dialysis-dependent renal failure in patients with advanced multiple myeloma: single institutional experiences over 8 years.

Matsue K, Fujiwara H, Iwama KI, Kimura SI, Yamakura M, Takeuchi M.

Ann Hematol. 2009 Aug 20. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19693498?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors study the impact on the reversibility of high-dose dexamethasone and/or thalidomide-containing regimen in 12 newly diagnosed myeloma patients and find that dialysis-dependent renal failure is reversible in most myeloma patients, even if the patient is in advanced age.

Acute renal failure in patients with multiple myeloma (MM) requiring dialysis is a serious complication and is associated with extremely poor survival. In addition, its treatment included high-dose dexamethasone and/or thalidomide-containing regimens on the reversibility of renal function, which has not been adequately evaluated previously. We studied the impact on the reversibility of high-dose dexamethasone and/or thalidomide-containing regimen in 12 newly diagnosed MM patients (median 74 years, range; 63-85 years) who required dialysis at Kameda General Hospital from 2001 to 2008. There were seven light chain only myelomas, three IgD myelomas, and two IgG myelomas. Ten patients initially received high-dose dexamethasone-based treatment and two received thalidomide-based treatment, with modifications. Complete (CR) and partial responses (PR) were obtained in three and five patients, respectively. Dialysis independency was achieved in all eight patients (67%) who achieved better than PR, with a median duration of 2.0 months. Six of the ten patients who received high-dose dexamethasone-containing regimen and all of the two patients received thalidomide-containing regimen became dialysis-independent. A high concentration of serum-free light chain was detected in all patients examined, before the start of anti-myeloma treatment, and this was associated with the presence of advanced renal failure. Improved renal function was preceded by a significant decrease in serum-free light chain in patients who achieved dialysis independence. These results suggest that dialysis-dependent renal failure is reversible by dexamethasone- or thalidomide-based treatments in most patients with MM, even if the patient is in advanced age, and that serum-free light chain monitoring might be useful for predicting improvements in renal function.

Thrombotic Events in Cancer Patients Receiving Antiangiogenesis Agents.

Zangari M, Fink LM, Elice F, Zhan F, Adcock DM, Tricot GJ.

J Clin Oncol. 2009 Aug 24. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19704059?ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In this overview, the authors discuss specific drug-associated hemostatic complications, the already known pathogenetic mechanisms involved, and the effect of varying antithrombotic strategies of agents including thalidomide and lenalidomide.

Tumor-associated neoangiogenesis has recently become a suitable target for antineoplastic drug development. In this overview, we discuss specific drug-associated hemostatic complications, the already known pathogenetic mechanisms involved, and the effect of varying antithrombotic strategies. Multiple agents with angiogenic inhibitory capacity (thalidomide, lenalidomide, bevacizumab, sunitinib, sorafenib, and sirolimus) have obtained US Food and Drug Administration approval, and many others have entered clinical trials. Arterial and venous thromboembolism and hemorrhage have emerged as significant toxicities associated with the use of angiogenesis inhibitors. We present a detailed analysis of the literature on thrombotic complication of antiangiogenic drugs. Close attention to hemostatic complications during antiangiogenic treatment is warranted. Further studies are required to better understand the pathophysiologic mechanisms involved and to define a safe prophylactic strategy.

Low incidence of clinically apparent thromboembolism in Korean patients with multiple myeloma treated with thalidomide.

Koh Y, Bang SM, Lee JH, Yoon HJ, Do YR, Ryoo HM, Lee N, Kim SJ, Kim K, Yoon SS, Won JH, Mun YC, Lee MH, Rhee KH, Kim HJ, Eom H, Kim MK, Shin HC; Korean Multiple Myeloma Working Party.

Ann Hematol. 2009 Aug 25. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19705118?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors study Korean myeloma patients treated with thalidomide to determine the frequency of thromboembolic events (TE) and associated risk factors and find the frequency of TE is low as compared to Caucasian patient populations.

The frequency of thromboembolic events (TE) in Caucasian patients with multiple myeloma (MM) receiving thalidomide as the initial treatment has been reported to be 10-58% without prophylactic anticoagulation. Korean MM patients treated with thalidomide were studied to determine the frequency of TE and associated risk factors. A retrospective medical record review of the Korean MM registry from 25 centers in Korea between 2003 and 2007 was performed. We assessed the incidence of arterial and venous TE and the associated clinical parameters. Three hundred and sixty MM patients (median age 61 years, range 32-88 years) received thalidomide treatment. Fourteen patients (3.9%) developed TE: 12 had venous and two had arterial locations. The sites for the venous TE included lungs (seven),

lower extremities (four), upper extremities (one), and neck (one). Arterial TE developed in cerebral and peripheral arteries each. No single clinical parameter such as prerequisite for the metabolic syndrome, disease status, and treatment regimen were predictive for the development of TE. The frequency of TE in patients who received thalidomide as initial therapy (7/155) was not different from those who received thalidomide for progressive or relapsed disease (7/205, p = 0.592). The frequency of TE during thalidomide treatment in Korean patients with MM was low. No significant clinical factor was found to be a risk factor. The subgroup requiring thromboprophylaxis among the Korean patients with MM, receiving thalidomide, needs to be clarified.

Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens.

Kumar S, Giralt S, Stadtmauer EA, Harousseau JL, Palumbo A, Bensinger W, Comenzo RL, Lentzsch S, Munshi N, Niesvizky R, San Miguel J, Ludwig H, Bergsagel L, Blade J, Lonial S, Anderson KC, Tosi P, Sonneveld P, Sezer O, Vesole D, Cavo M, Einsele H, Richardson PG, Durie BG, Rajkumar SV; International Myeloma Working Group.

Blood. 2009 Aug 27;114(9):1729-35. [Epub 2009 Jun 26.]

http://www.ncbi.nlm.nih.gov/pubmed/19561323?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

An expert panel examines the implications of therapies (including thalidomide and lenalidomide) on stem collection in patients with myeloma and to develops recommendations for addressing their impact on the ability to collect stem cells, ultimately recommending early mobilization of stem cells, preferably within the first four cycles of initial therapy.

The past decade has witnessed a paradigm shift in the initial treatment of multiple myeloma with the introduction of novel agents such as thalidomide, lenalidomide, and bortezomib, leading to improved outcomes. High-dose therapy and autologous stem cell transplantation remains an important therapeutic option for patients with multiple myeloma eligible for the procedure. Before the advent of the novel agents, patients underwent stem cell collection prior to significant alkylating agent exposure, given its potential deleterious effect on stem cell collection. With increasing use of the novel agents in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. An expert panel of the International Myeloma Working Group (IMWG) was convened to examine the implications of these therapies on stem collection in patients with myeloma and to develop recommendations for addressing these issues. Here we summarize the currently available data and present our perspective on the problem and potential options to overcome this problem. Specifically, we recommend early mobilization of stem cells, preferably within the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

Short-Term Thalidomide Incorporated Into Double Autologous Stem-Cell Transplantation Improves Outcomes in Comparison With Double Autotransplantation for Multiple Myeloma.

Cavo M, Di Raimondo F, Zamagni E, Patriarca F, Tacchetti P, Casulli AF, Volpe S, Perrone G, Ledda A, Ceccolini M, Califano C, Bigazzi C, Offidani M, Stefani P, Ballerini F, Fiacchini M, de Vivo A, Brioli A, Tosi P, Baccarani M.

J Clin Oncol. 2009 Aug 31. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19720903?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors assess the potential benefits with thalidomide incorporated into double autologous stem-cell transplantation for younger patients with newly diagnosed myeloma and find that the addition of first-line thalidomide improves clinical outcomes.

PURPOSE: To assess potential benefits with thalidomide incorporated into double autologous stem-cell transplantation (ASCT) for younger patients with newly diagnosed multiple myeloma (MM). PATIENTS AND METHODS: One hundred thirty-five patients who received thalidomide from induction until the second ASCT were retrospectively analyzed in comparison with an equal number of pair mates treated with double ASCT not including thalidomide. RESULTS: On an intention-to-treat basis, the addition of thalidomide to double ASCT effected a significant improvement in the rate (68% v 49%; P = .001) and duration (62% v 33% at 4 years; P < .001) of at least very good partial response (VGPR), time to progression (TTP; 61% v 41% at 4 years; P < .001) and progression-free survival (PFS; 51% v 31% at 4 years; P = .001). A trend was also noted for extended overall survival (OS) among thalidomide-treated patients (69% at 5 years v 53% for the control group), although the difference between the two groups was not statistically significant (P = .07). Benefits with thalidomide in increasing the rate of VGPR or better response, TTP, and PFS were confirmed in a multivariate analysis. Median OS after relapse was 24 months for patients receiving thalidomide added to double ASCT and 25 months for the control group. Overall, 17% of patients discontinued thalidomide, including 8% because of drug-related adverse events. CONCLUSION: In comparison with double ASCT, the addition of first-line thalidomide to double ASCT improved clinical outcomes. Short-term thalidomide was generally well tolerated and had no adverse impact on postrelapse survival.

Initial therapy in multiple myeloma: investigating the new treatment paradigm.

Kettle JK, Finkbiner KL, Klenke SE, Baker RD, Henry DW, Williams CB.

J Oncol Pharm Pract. 2009 Sep;15(3):131-41. [Epub 2009 Mar 10.]

http://www.ncbi.nlm.nih.gov/pubmed/19276138?ordinalpos=31&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss the development of three novel chemotherapeutic agents—thalidomide, lenalidomide, and bortezomib— that has resulted in a fundamental shift in the management of myeloma.

The development of three novel chemotherapeutic agents - thalidomide, lenalidomide, and bortezomib - has resulted in a fundamental shift in the management of multiple myeloma. Despite this tremendous advancement, the selection of initial treatment must still be made with a degree of uncertainty as a true standard therapy has yet to be established. Although challenging, the relative abundance of therapeutic options, when taken into consideration with unique patient characteristics, creates the potential for individualization of care. For patients eligible for autologous stem cell transplantation, various combinations of novel agents with dexamethasone or traditional chemotherapy have supplanted the previous standard regimen consisting of vincristine, doxorubicin, and dexamethasone. In elderly patients or others that are deemed ineligible for the transplant procedure, the addition of a novel agent to melphalan-prednisone has demonstrated significant improvements in response rates. Due to the immaturity of the available data, it is perhaps best to regard the era of novel agents with a degree of rational enthusiasm, as the ultimate impact on patient care remains undetermined. Although further research is clearly implicated, recent advancements have resulted in significant progress toward obtaining optimum outcomes in a historically challenging disease.

Long-term outcome in relapsed and refractory multiple myeloma treated with thalidomide. Balancing efficacy and side-effects.

Corso A, Zappasodi P, Barbarano L, Petrucci MT, Palumbo A, Caravita T, Mangiacavalli S, Cafro AM, Varettoni M, Gay F, Morra E, Lazzarino M.

Leuk Res. 2009 Sep;33(9):e145-9. [Epub 2009 Apr 16.]

http://www.ncbi.nlm.nih.gov/pubmed/19375164?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

A total of 303 myeloma patients are retrospectively reviewed to evaluate long-term efficacy and toxicity of thalidomide alone or in combination with steroids. The authors conclude that thalidomide produces high response rate in relapsed/refractory myeloma.

A total of 303 MM patients were retrospectively reviewed to evaluate long-term efficacy and toxicity of thalidomide alone or in combination with steroids. Overall response rate was 57% (CR/VGPR 12%). Median TTP, PFS and OS were 13.4 months, 20.6 months, and 26.2 months, respectively. PFS and OS were significantly different according to response ($p<0.0001$), with better outcome in patients achieving CR/VGPR (PFS and OS 35.4 months and 63 months, respectively). PFS and OS of patients achieving SD or PR were overlapping ($p=0.3$). The addition of steroids significantly increased the response rate ($p=0.01$). The most clinically relevant complications were neuropathy (40%), constipation (26%), thromboembolic events (7%). Thalidomide was reduced for toxicity in 68 patients (24%) and permanently discontinued in 36 (12%). In conclusion, thalidomide produces high response rate in relapsed/refractory MM. The best outcome is observed in patients with good quality response, but even patients with suboptimal response may obtain durable survival.

Thalidomide alters nuclear architecture without ABCB1 gene modulation in drug-resistant myeloma cells.

Trussardi-Regnier A, Lavenus S, Gorisse MC, Dufer J.

Int J Oncol. 2009 Sep;35(3):641-7.

http://www.ncbi.nlm.nih.gov/pubmed/19639185?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors analyze the effects of a 24-hour short-term treatment by thalidomide or its active metabolite phthaloyl glutamic acid (PGA) on nuclear chromatin higher-order organization and ABCB1 gene expression in drug-sensitive and drug-resistant 8226 human myeloma cells. Their data suggest that short-term treatments by thalidomide or PGA do not induce any significant change on ABCB1 gene expression, though they modulate chromatin supra-organization in drug-resistant 8226 human myeloma cells.

ABCB1 gene overexpression has been described as an important mechanism for resistance to conventional chemotherapy in multiple myelomas. In the refractory multiple myelomas, other drug regimens have been successfully applied, including thalidomide treatments. Besides its well-documented anti-angiogenic effects, thalidomide therapy could result in a decrease in ABCB1 gene expression. In this study, we analysed the effects of a 24-h short-term treatment by thalidomide or its active metabolite phthaloyl glutamic acid (PGA) on nuclear chromatin higher-order organisation and ABCB1 gene expression in drug-sensitive and drug-resistant 8226 human myeloma cells. As compared to sensitive cells, 8226-Dox40 drug-resistant cells exhibited an increase in chromatin texture condensation and ABCB1 gene overexpression. At this gene promoter level, the -50 and -100 GC boxes displayed an unmethylated profile in drug-sensitive cells whereas drug-resistant cell promoter GC boxes were fully methylated. Thalidomide and PGA induced significant chromatin textural changes

in 8226-Dox40 drug-resistant cells only with neither alteration in ABCB1 gene expression nor methylation profile of its promoter. Conversely thalidomide and PGA induced down-regulation of VEGF gene expression in both drug-sensitive and -resistant myeloma cells. These data suggest that short-term treatments by thalidomide or PGA do not induce any significant change on ABCB1 gene expression though they modulate chromatin supra-organisation in drug-resistant 8226 human myeloma cells.

Myeloma-associated polyneuropathy responding to lenalidomide.

Layzer R, Wolf J.

Neurology. 2009 Sep 8;73(10):812-3.

http://www.ncbi.nlm.nih.gov/pubmed/19738177?ordinalpos=10&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Prognostically significant cytotoxic T cell clones are stimulated after thalidomide therapy in patients with multiple myeloma.

Brown RD, Spencer A, Ho PJ, Kennedy N, Kabani K, Yang S, Sze DM, Aklilu E, Gibson J, Joshua DE.

Leuk Lymphoma. 2009 Sep 10:1-5. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19757299?ordinalpos=18&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that expanded T cell clones are prognostically significant and have an impact on progression after thalidomide therapy in a proportion of myeloma patients.

The expanded T cell clones are associated with a prolonged survival in patients with multiple myeloma. We sought to confirm this prognostic significance in a multicenter patient cohort and investigate the effect of thalidomide on clones and T regulatory cells (T(regs)). Blood was collected from 120 patients enrolled in a Phase III trial of maintenance therapy +/- thalidomide after autologous stem cell transplantation. TCR Vbeta repertoire analysis identified T cell expansions in 48% of patients pre-transplant and 68% after 8-month maintenance. T cell expansions, previously shown to be clonal, were predominantly CD8 + (93%) and all 24 TCR Vbeta families tested were represented. Thalidomide therapy was associated with a significant increase in the incidence of patients with multiple expansions (49%vs. 23%; chi(2) = 6.8; p = 0.01). The presence of expansions regardless of therapy was associated with a significantly longer median progression free survival (PFS) (32.1 vs. 17.6 months; chi(2) = 5.6; p = 0.02) and overall survival (OS) (chi(2) = 3.9; p < 0.05). Median PFS in the thalidomide arm was 50.9 months for patients with expansions and 28.3 months for patients without expansions (chi(2) = 19.4; p = 0.0002). Thalidomide did not appear to modulate T(reg) numbers. Expanded T cell clones are prognostically significant and have an impact on progression after thalidomide therapy in a proportion of patients.

The use of novel agents in the treatment of relapsed and refractory multiple myeloma.

Laubach JP, Mahindra A, Mitsiades CS, Schlossman RL, Munshi NC, Ghobrial IM, Carreau N, Hideshima T, Anderson KC, Richardson PG.

Leukemia. 2009 Sep 10. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19741729?ordinalpos=19&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This review focuses on the role of thalidomide, lenalidomide, and bortezomib in relapsed and refractory myeloma.

Although outcomes for patients with multiple myeloma (MM) have improved over the past decade, the disease remains incurable and even patients who respond well to induction therapy ultimately relapse and require additional treatment. Conventional chemotherapy and high-dose therapy with stem cell transplantation (SCT) have historically been utilized in the management of relapsed MM, but in recent years the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib, have assumed a primary role in this setting. This review focuses on the role of thalidomide, lenalidomide and bortezomib in relapsed and refractory MM, with additional discussion dedicated to emerging drugs in relapsed MM that may prove beneficial to patients with this disease.

Pomalidomide and lenalidomide induce p21 WAF-1 expression in both lymphoma and multiple myeloma through a LSD1-mediated epigenetic mechanism.

Escoubet-Lozach L, Lin IL, Jensen-Pergakes K, Brady HA, Gandhi AK, Schafer PH, Muller GW, Worland PJ, Chan KW, Verhelle D.

Cancer Res. 2009 Sep 15;69(18):7347-56. [Epub 2009 Sep 8.]

http://www.ncbi.nlm.nih.gov/pubmed/19738071?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' results provide new insights on the mechanism of action of pomalidomide and lenalidomide in the regulation of gene transcription, imply possible efficacy in p53 mutated and deleted cancer, and suggest new potential clinical uses as an epigenetic therapy.

Lenalidomide and pomalidomide have both been evaluated clinically for their properties as anticancer agents, with lenalidomide being available commercially. We previously reported that both compounds cause cell cycle arrest in Burkitt's lymphoma and multiple myeloma cell lines by increasing the level of p21(WAF-1) expression. In the present study, we unravel the molecular mechanism responsible for p21(WAF-1) up-regulation using Namalwa cells as a human lymphoma model. We show that the increase of p21(WAF-1) expression is regulated at the transcriptional level through a mechanism independent of p53. Using a combination of approaches, we show that several GC-rich binding transcription factors are involved in pomalidomide-mediated up-regulation of p21(WAF-1). Furthermore, we report that p21(WAF-1) up-regulation is associated with a switch from methylated to acetylated histone H3 on p21(WAF-1) promoter. Interestingly, lysine-specific demethylase-1 (LSD1) silencing reduced both pomalidomide and lenalidomide up-regulation of p21(WAF-1), suggesting that this histone demethylase is involved in the priming of the p21(WAF-1) promoter. Based on our findings, we propose a model in which pomalidomide and lenalidomide modify the chromatin structure of the p21(WAF-1) promoter through demethylation and acetylation of H3K9. This effect, mediated via LSD1, provides GC-rich binding transcription factors better access to DNA, followed by recruitment of RNA polymerase II and transcription activation. Taken together, our results provide new insights on the mechanism of action of pomalidomide and lenalidomide in the regulation of gene transcription, imply possible efficacy in p53 mutated and deleted cancer, and suggest new potential clinical uses as an epigenetic therapy.

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