CITINGS

Published by the International Myeloma Foundation | Special Edition: ASCO 2008 | Q2/2008

Thalidomide and Revlimid® Issue

The International Myeloma Foundation *(IMF) presents this special edition of CITINGS, our premiere publication featuring the most up-to-date information on myeloma treatment, focused on thalidomide and Revlimid. This special edition corresponds with the 2008 annual meeting of the American Society of Clinical Oncology (ASCO). In this CITINGS, we have highlighted selected thalidomide and Revlimid data presentations from the ASCO meeting. We also provide references to the latest published journal articles on both thalidomide and Revlimid from the second 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

American Society of Clinical Oncology Presentations 2008

Saturday May 31st

Estimating direct costs of care for patients with relapsed or refractory multiple myeloma in French hospitals.

X. Armoiry, F. Fagnani, L. Benboubker, T. Facon, J. Fermand, C. Hulin, P. Moreau, G. Aulagner

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8596)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8596 **Session Type: General Poster**

Poster No: 53H

Time: 8:00 AM - 12:00 PM **Location: S Hall A1**

This study aims to describe the pattern of usual care of relapsed or refractory MM (RRMM) and to evaluate the fraction of total treatment cost attributable to novel agents, concluding that the actual medical cost of RRMM is substantial (73,000 euros per patient) mainly due to the cost of novel agents, although these drugs have contributed to prolonged survival.

Background: Costly new drugs (bortezomib, lenalidomide) have been marketed in the treatment of multiple myeloma (MM) since 2004. This study aimed to describe the pattern of usual care of relapsed or refractory MM (RRMM) in specialized haematological units during this period and to evaluate the fraction of total treatment cost attributable to those drugs. Methods: A chart review study was conducted in 5 French University hospitals on a representative sample of patients treated for a RRMM during the period 2004-2007 (at exclusion of patients enrolled in a clinical trial) and with at least 18 months of follow-up in the centre. Medical resources were recorded (visits, drugs, hospital stays, treatments for grade 3-4 adverse events or complications) and the corresponding costs were estimated in the perspective of the French Sickness Insurance (these patients are fully reimbursed in France for all their medical expenses). Results: The study included 102 patients with RRMM. Mean age at diagnosis was 58.6 years and 52% were men. The average follow-up from diagnosis or

Funded by an educational grant from Celgene Corporation.

the date of first relapse to death or to the latest news was respectively 56.25 and 23.53 months. From first relapse, the average number of lines per patient was 2.75 (1-7) with a significant difference according to age (2.94 for pts<65ys, 2.17 for pts>65; p<0.05). Novel agents were widely used (73 % of 281 lines) and consisted of thalidomide combinations (28%), bortezomib's based regimens (22%), lenalidomide (13%) and bortezomib+thalidomide (10%). The average duration per line was 8.5 months of which 5.9 months on treatment. The average cost per line was 26,510 euros including 17,525 euros for drugs. The total direct costs were estimated at 73,000 euros per patient from the first relapse until death or last follow-up. Considering the third line in terms of duration and costs, lenalidomide-based treatment was similar to bortezomib (7.4 months and 46,724 euros versus 6.93 months and 46,321 euros respectively). Conclusion: The actual medical cost of RRMM is substantial (73,000 euros per patient) mainly due the cost of novel agents but those drugs have contributed to prolong survival.

High incidence of diarrhea in patients on long term therapy with lenalidomide and dexamethasone for multiple myeloma.

L. Simpson, S. V. Rajkumar, A. Dispenzieri, M. Q. Lacy, S. Hayman, V. Roy, K. Stewart, M. A. Gertz, P. R. Greipp, S. Kumar

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8586)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8586 **Session Type: General Poster**

Poster No: 52D

Time: 8:00 AM - 12:00 PM **Location: S Hall A1**

The authors report diarrhea as an unexpected side effect in a significant proportion of newly diagnosed myeloma patients with prolonged lenalidomide-dexamethasone combination therapy. Most of the risk can be attributed to long-term dexamethasone therapy, and most patients respond to conservative treatments with spontaneous resolution at treatment cessation.

Background: Several phase II and III trials have demonstrated high response rates and improved survival and excellent tolerability with lenalidomide (Len) and dexamethasone (Len-Dex) in newly diagnosed myeloma (NMM). Therefore many pts continue on therapy for prolonged periods which might be associated with unexpected side effects. Methods: We reviewed the frequency of diarrhea with Lenalidomide in NMM, on two trials utilizing Len-Dex at MAyo. and in MM009/MM010 phase III trials. Toxicity data was prospectively collected using NCI CTCAE v 3.0. Results: Sixty seven NMM pts in Mayo trials and 703 pts in MM 009/010 trials were studied. In Mayo trials, the median duration of follow up and therapy was 28.6 mos and 8.5 mos (range, 1-47 mos) respectively. Eighteen pts (27%) reported diarrhea.Median duration of therapy for patients with diarrhea was 31 mos (range, 9-43) compared to 5 mos (range, 1-47) without diarrhea; ($P < 0.001$). No diarrhea was observed with therapy < 8 mos. Median time to diarrhea onset was 19 mos. One pt had grade 3 persistent diarrhea; all others had grade 1 or 2. One pt with grade 2 diarrhea required dose reduction of Len and one with grade 3 diarrhea required treatment cessation for palliation. Others benefitted from a conservative approach with Imodium as needed. We analyzed MM009/010 trials to estimate baseline diarrhea risk and risk with Len addition. The incidence of diarrhea was 38.8% and 28% in the Len-Dex (n=353) and Dex arm (n=350) respectively(excess risk of 10%). Multivariate logistic regression was done including therapy duration and treatment arm. Only duration of therapy was significant in this analysis ($P<0.001$); treatment with Len-Dex was not significant ($P=0.4$).We examined a cohort of pts in MM009/010 trials receiving 9-15 mos of therapy to further understand the effect of treatment duration. With adjustment for treatment duration, the incidence of diarrhea was identical; 42.3% (Len-Dex) and 42.5% (placebo-Dex). Discussion: We report diarrhea as an unexpected side effect in a significant proportion of patients with prolonged Len-Dex combination therapy. Most of the risk can be attributed to long-term Dex therapy. Most patients respond to conservative treatments with spontaneous resolution at treatment cessation.

Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome wi.

S. V. Rajkumar, S. Jacobus, N. Callander, R. Fonseca, D. Vesole, M. V. Williams, R. Abonour, D. S. Siegel, M. Katz, P. R. Greipp

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8504)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8504 **Session Type: Clinical Science Symposia**

Time: 8:30 AM - 8:45 AM **Location: E Arie Crown Theater**

This study compares lenalidomide (Len) plus high (standard) dose Dex (RD) vs Len plus low dose Dex (Rd) in newly diagnosed myeloma (MM) and concludes that Rd results in superior overall survival (OS) compared to RD. The two-year OS rate was 91% among patients who received primary therapy with Rd, and 94% among patients who received RD/Rd following by stem cell transplantation.

Background: We compared lenalidomide (Len) plus high (standard) dose Dex (RD) vs Len plus low dose Dex (Rd) in newly diagnosed myeloma (MM). Methods: Pts with untreated, symptomatic MM were eligible. Len dose was 25 mg/day PO d 1-21 every 28 days. Pts in the RD arm received high-dose Dex 40 mg d 1-4, 9-12, and 17-20 PO q 28 d; pts in the Rd arm received low dose Dex 40 mg d 1, 8, 15, and 22 PO q 28 d. The primary null hypothesis was that

response rates at 4 mos on the 2 arms are equivalent (difference >15% unacceptable), one-sided 0.10 Type I and 0.05 Type II error rate. All analysis were intent to treat. Results: 445 pts (median age, 65 yrs) were randomized: 223 (RD) and 222 (Rd). 383 were eligible as of Dec 2007. Arms were well balanced. Grade >3 toxicities occurred within 1st 4 cycles in 50% (RD) vs 30% (Rd) respectively, P<0.001. 149 pts reported stem cell harvest attempt; 97% were successful. PR or higher within the first 4 cycles was seen in 82% (RD) vs 70% (Rd), P=0.007 (excluding 14 pts with missing data). CR+VGPR rates were 52% vs 42%, P=0.06 (excluding 9 pts missing data). Overall survival (OS) was significantly superior with Rd, P=0.006; one yr survival 96% (Rd) vs 88% (RD); 2 year OS rates 87% (Rd) vs 75% (RD). We performed a landmark analysis after 4 mos of treatment. Of 421 pts alive at the landmark analysis, 210 went off-study and 211 continued primary therapy with RD/Rd. Of pts who went off study at 4 mos, 108 pts (51%) did not pursue SCT (median age 67); 1 yr OS and 2 yr OS rates were 85% and 70% respectively. The remaining 102 pts (49%) underwent SCT (median age 57); the 1 yr OS and 2 yr OS rates were 99% and 94% respectively. There was no difference in % pts who went to SCT between the 2 arms, 29% (RD) and 31% (Rd). Corresponding 1 yr and 2 yr OS rates among 211 pts (median age 67) who continued on primary therapy beyond 4 mos were: RD (n=91) 96% and 80% respectively, and Rd (n=120) 99% and 91% respectively. Conclusions: Rd results in superior OS compared to RD. In a landmark analysis, the two year OS rate was 91% among pts who received primary therapy with Rd, and 94% among pts who received RD/Rd followed by SCT.

Total therapy (TT) for myeloma (MM)--10% cure rate with TT1 suggested by >10yr continuous complete remission (CCR): Bortezomib in TT3 overcomes poor-risk associated with T(4;14) and DelTP53 in TT2.

B. Barlogie, E. J. Anaissie, F. van Rhee, J. D. Shaughnessy, Jr, J. Haessler, M. Pineda-Roman, K. Hollmig, J. Epstein, J. J. Crowley

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8516)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8516 **Session Type: Oral Abstract Presentation**

Time: 3:00 PM - 3:15 PM **Location: Room E354b**

The authors establish a historical framework of long-term outcomes with the total therapy (TT) approach, including thalidomide, introduced in 1989 and conclude that a CCR plateau apparent at 10yr in TT1 is consistent with a ~10% cure rate, and that significant improvements beyond TT1 with TT2 and especially TT3 bode well for marked increases in 10-yr OS and cure rates.

Background: The introduction of transplants in the 1980's and novel agents in the 1990's has markedly improved MM survival. TT trials applied all active treatment ingredients up-front with the objective to maximize long-term disease control. As novel agent combinations are increasingly being applied at the exclusion of transplants, it appears useful to establish a historical framework of long-term outcomes with our TT approach introduced in 1989. Methods: An update is provided of overall survival (OS), event-free survival (EFS), CR rates and CR durations for TT1 (n=231; phase II, interferon maintenance), TT2 (n=668; phase III, ± thalidomide, post-transplant consolidation) and TT3 (n=303; phase II, added bortezomib and thalidomide throughout). Results: Stringently defined CR increased significantly from 40% in TT1 to 50% in TT2 to 60% in TT3. Median CR duration increased from 2.5yr in TT1 (16 in CCR beyond 10yr) to 5.0yr in TT2; the 3-yr estimate in TT3 is 90%. Median EFS and OS were 2.6yr and 5.7yr for TT1 and 5.0yr and 9.0yr for TT2; the 3-yr estimates in TT3 are 80% and 85%. A gene array-based high-risk score adversely affected OS, EFS and CR duration in both TT2 and TT3. However, the independent adverse implications, for all 3 endpoints, of t (4;14) and TP53 deletion observed in TT2 did not pertain to TT3, supporting a major role of bortezomib, added in TT3, for the management of these hitherto high-risk MM subsets. Conclusions: A CCR plateau apparent at 10yr in TT1 is consistent with a ~10% cure rate. Significant improvements beyond TT1 with TT2 and especially TT3 bode well for marked increases in 10-yr OS and cure rates. Knowledge of t(4;14) and delTP53 status is key to identifying MM subsets uniquely benefiting from bortezomib.

Bortezomib, pegylated-lyposomal-doxorubicin and dexamethasone (PAD) as induction therapy prior to reduced intensity autologous stem cell transplant (ASCT) followed by lenalidomide and prednisone (LP) as consolidation and lenalidomide alone as maintenance.

A. P. Palumbo, P. Falco, P. Corradini, C. Crippa, F. Patriarca, F. Rossini, M. Offidani, A. M. Liberati, M. T. Petrucci, M. Boccadoro

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8518)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8518 **Session Type: Oral Abstract Presentation**

Time: 3:30 PM - 3:45 PM **Location: Room E354b**

The authors evaluate bortezomib as induction pre-ASCT, followed by consolidation/ maintenance with lenalidomide in elderly myeloma patients. They find that PAD as induction pre ASCT followed by lenalidomide-prednisone as consolidation induced a high response rate, with a 56% CR rate recorded at the end of a reduced intensity ASCT regimen for elderly patients.

Background: New agents have been introduced as induction treatment prior to ASCT and as consolidation or maintenance thereafter to improve complete response (CR) rates. In this study, we evaluate Bortezomib as induction preASCT, followed by consolidation/maintenance with Lenalidomide in elderly myeloma pts. Methods: Newly diagnosed MM pts aged 65-75 years were eligible. The induction included four 21-day PAD cycles (bortezomib1.3mg/m2 days 1,4,8,11, pegylated-liposomal-doxorubicin 30mg/m2 day 4 and dexamethasone 40mg days 1-4,8-11,15-18 for cycle 1 and days 1-4 for cycles 2-4).

Cyclophosphamide (3g/m2) plus G-CSF was used to harvest stem-cells. Pts were then conditioned with tandem Melphalan 100mg/m2 and stem-cell support (MEL100). After ASCT pts received four 28-day LP cycles (Lenalidomide 25mg/day on days 1-21 plus Prednisone 50mg every other day) followed by Lenalidomide alone (10mg/day on days 1-21 every 28 days) as maintenance. Primary endpoints were safety (any Grade-3 non-hematologic toxicity<30%) and efficacy (near complete > response rate, nCR, >35%). According to Simon procedure, 100 pts were planned to be enrolled. Results: Ninety-four pts have been enrolled. After the 4 PAD cycles 95% of pts achieved at least partial response (PR), 60% at least very good partial response (VGPR), 23% at least nCR, and 13% CR. After tandem MEL100, 95% of pts showed PR, 80% at least VGPR, 60% at least nCR, and 33% CR. After LP consolidation regimen all patients achieved PR, 89% at least VGPR rate, 78% at least nCR, and 56% CR. During PAD, 25% of pts experienced grade3-4 hematologic toxicity, 17% grade3-4 peripheral neuropathy and 11% grade3-4 infections. During LP consolidation one DVT and one discontinuation due to prolonged anemia and thrombocytopenia were recorded. Conclusion: PAD as induction pre ASCT followed by LP as consolidation induced a high response rate with a 56% CR rate recorded at the end of a reduced intensity ASCT regimen for elderly patients. Updated results and molecular remission data will be presented at the meeting.

Safety and efficacy of lenalidomide (Len), bortezomib (Bz), and dexamethasone (Dex) in patients (pts) with newly diagnosed multiple myeloma (MM): A phase I/II study.

P. G. Richardson, S. Lonial, A. Jakubowiak, S. Jagannath, N. Raje, D. Avigan, I. M. Ghobrial, R. Knight, D. Esseltine, K. C. Anderson

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8520)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8520 **Session Type: Oral Abstract Presentation**

Time: 4:15 PM - 4:30 PM **Location: Room E354b**

This phase I/II study finds that lenalidomide/bortezomib/dexamethasone is very active and well tolerated in newly diagnosed myeloma patients.

Background: Single-agent Bz and Len/Dex are approved for pts with relapsed MM following >1 prior therapy. Len/Bz±Dex is active in relapsed/refractory MM, and Len/Dex and Bz/Dex are active in frontline MM. Primary objectives of this phase I/II study were to define the MTD and assess response rate to Len/Bz/Dex in previously untreated MM pts. Methods: Pts received Len 15-25mg on d 1-14, Bz 1.0-1.3mg/m2 on d 1, 4, 8, 11, and Dex 40/20mg (cycles 1-4/5-8) on day of and after Bz for up to eight 21-d cycles, initially at 4 planned dose levels (table). Dose escalation proceeded depending on dose-limiting toxicities (DLTs). Based on safety data, dose level 4M was added with a reduced Dex starting dose (20/10mg). Toxicities were graded by NCI CTCAE v3.0. Pts with G>2 peripheral neuropathy (PN) were excluded. Responses were assessed by modified EBMT and Uniform Criteria. Pts with >PR could proceed to ASCT after >4 cycles. Results: 66 pts have been enrolled to date. Data are available on 53 pts (median age 58 yrs, 51% men, 68% IgG MM, 49% ISS Stage II/III): 33 in Phase I, including 17 at the maximum planned dose (dose level 4M), and 20 in Phase ll (at max planned dose). Pts have received a median of 6 cycles; 16 (32%) have completed all 8 cycles, 14 have discontinued. Two DLTs of G3 hyperglycemia due to high-dose Dex were seen in dose level 4. Dose reductions in cycle 2 and beyond have occurred for Len in 12 pts, Bz in 11 pts, and Dex in 18 pts, mostly in dose levels 1-4. Toxicities have been manageable, with no unexpected toxicities, no G4 PN, 2 DVTs, and no treatment-related mortality. Response rate (>PR) to date is 98% in 42 evaluable pts, including 52% CR/nCR/VGPR (table). After median follow-up of 4 months, median TTP, PFS, and OS have not been reached. Median stem cell collection in 7 pts was 11.5 x 106 CD34+ cells/kg. Conclusions: Len/Bz/Dex is very active and well tolerated in newly diagnosed MM pts. Phase II enrollment is almost complete. Updated response data will be presented. Responses by phase/dose level (subject to confirmation)

A randomized Southwest Oncology Group study comparing dexamethasone (D) to lenalidomide + dexamethasone (LD) as treatment of newly-diagnosed multiple myeloma (NDMM): Impact of cytogenetic abnormalities on efficacy of LD, and updated overall study results.

J. A. Zonder, J. J. Crowley, V. Bolejack, M. A. Hussein, D. F. Moore, B. F. Whittenberger, M. H. Abidi, B. G. Durie, B. Barlogie

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8521)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8521 **Session Type: Oral Abstract Presentation**

Time: 4:30 PM - 4:45 PM **Location: Room E354b**

The authors find that myeloma patients with abnormal karyotype treated with lenalidomide/dexamethasone had higher progression free survival and overall survival compared to those on dexamethasone alone.

Background: We recently reported superior 1-yr prog. free survival (PFS) for pts with NDMM treated with LD vs D alone. High-risk cytogenetic abnormalities (HRCA) confer poor prognosis with standard therapies, including high dose melphalan. It is unknown if pts on LD with HRCA will also have inferior results. We prospectively examined the impact of abnormal karyotype (AK) and HRCA (defined as deletion of chromosomes 13 and/or 17 by FISH) on 1-yr PFS and overall survival (OS), as well as updated overall study results. Methods: 198 pts with NDMM were randomized to L 25 mg/day (28 of 35 days x 3 cycles, then 21 of 28 days as maintenance) + D (40 mg d1-4, 9-12, 17-20 induction; d1-4, 15-18 maintenance) or D (same induction and maintenance schedules) + placebo. Cross-over to LD was allowed for progressive disease on D. Aspirin 325 mg/d was mandated. Pts had a baseline bone marrow aspirate for karyotypic analysis and FISH for deletions of chromosomes 13 and 17. The response rate (RR) by IMWG criteria, PFS, and OS of pts in each study arm were updated.

The impact of AK and HRCA by FISH on PFS and OS was assessed by log-rank analysis. Results: Informative baseline karyotypes and FISH results were available for 103 and 80 pts, respectively. AK were seen in 10/52 samples from pts on D, and 11/51 on LD. Twelve of 45 samples from pts on D and 8/35 on LD had HRCA. For pts on LD without AK, 1-yr PFS and OS were 86% and 97% respectively, vs 55% (p=0.13) and 82% (p=0.02) in pts with AK. Pts on D alone with AK had 1-yr PFS and OS of 33% and 77% (p=NS). 1-yr PFS and OS for pts on LD were both 100% with HRCA vs 73% and 92% without HRCA (p=NS). Conclusions: In this sub-group analysis, pts with NDMM on LD with AK had lower PFS and OS compared to those without AK. HRCA as defined in this study did not seem to account for this difference, but sample size limited the statistical power of the analysis. Pts with AK treated with LD had higher PFS and OS compared to those on D alone. Further characterization of observed karyotypic and FISH abnormalities, as well as extended follow-up for PFS, OS, and RR (including >VGPR rates) for S0232 will be presented at ASCO.

Final analysis of MM-014: Single-agent lenalidomide in patients with relapsed and refractory multiple myeloma.

M. A. Hussein, P. G. Richardson, S. Jagannath, S. Singhal, W. Bensinger, R. Knight, J. B. Zeldis, Z. Yu, M. Olesnyckyj, K. C. Anderson

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8524)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8524 **Session Type: Oral Abstract Presentation**

Time: 5:15 PM - 5:30 PM **Location: Room E354b**

The authors seek to determine the efficacy and safety of lenalidomide monotherapy in patients with relapsed/refractory myeloma and find encouraging overall response, duration of response, time-to-progression, progression free survival and overall survival at a dose of 30 mg once daily, 3 weeks on, 1 week off.

Background: Lenalidomide (Len) in combination with high-dose dexamethasone (Dex) is approved for previously treated patients (pts) with multiple myeloma (MM). This study determined the efficacy and safety of Len monotherapy in pts with relapsed/refractory MM. Methods: Len monotherapy (30 mg qd) was given to pts with relapsed/refractory MM in a single-arm, open-label multi-center study. Len was administered daily on days 1-21 every 28 days. Concomitant Dex was not permitted. No anticoagulation prophylaxis was recommended. Treatment was continued as tolerated until disease progression. Response was assessed every month using modified EBMT criteria and toxicity using NCI-CTCv3. Results: All 222 enrolled pts had received >2 prior anti-MM therapies, including bortezomib (43%), thalidomide (80%), and SCT (45%); 46% had >4 prior therapies with a mean time from diagnosis of 4 years. At database lock, 64 pts (29%) had received treatment for >9 months. For the intention-to-treat population (n=222), the overall response (OR: CR+PR) was 26%. An additional 66% of the pts experienced stable disease (SD). OR for the efficacy-evaluable population (n=184) was 32% and 68% experienced SD. By study completion, 151 pts (69%) had progressed with a median time-to-progression (TTP) of 5.4 months. Median progression-free survival (PFS) was 4.7 months, and median overall survival (OS) was 1.9 years with 41% of pts alive after 3 years. Median duration of response was 13 months (median FU: 14 months). The most common grade 3/4 lab toxicities were neutropenia (60%), thrombocytopenia (39%) and anemia (20%). Only 4% of pts developed febrile neutropenia and DVT; no grade 3/4 peripheral neuropathy was seen. Conclusions: The encouraging OR, duration of response, TTP, PFS, and OS seen in this study demonstrate that Len monotherapy at a dose of 30 mg once daily (3 wks on, 1 wk off) is effective, durable, and well tolerated steroid-sparing therapy for heavily pretreated pts with relapsed/refractory MM.

Long-term responses observed with lenalidomide therapy for patients with relapsed or refractory multiple myeloma.

S. Jagannath, P. G. Richardson, S. Zeldenrust, M. Alsina, K. Wride, J. B. Zeldis, R. Knight, M. Olesnyckyj, K. C. Anderson

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8525)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8525 **Session Type: Oral Abstract Presentation**

Time: 5:30 PM - 5:45 PM **Location: Room E354b**

Early results from this phase II study previously determined that lenalidomide was active and well-tolerated in pts with relapsed/refractory myeloma. Here, the authors present long-term follow-up results of patients who remained on this therapy. The authors conclude that a subset of patients responding to lenalidomide with or without dexamethaxsone could remain on treatment for at least 4.1 years, and therefore lenalidomide can be considered as an effective, durable, and well tolerated therapy for heavily pretreated patients with relapsed/refractory myeloma.

Background: Lenalidomide is a potent immunomodulatory drug and long-term administration in responding patients may have clinical benefit to patients. Early results from this phase II study previously determined that Len was active and well-tolerated in pts with relapsed/refractory MM (Richardson Blood 2006). Here, we present long-term follow-up results of pts that remained on therapy. Methods: Len (30 mg qd or 15 mg bid on days 1-21 every 28 days) was given to pts with relapsed/refractory MM in a multi-center, open-label, randomized phase II study. Concomitant Dex was permitted in pts with disease progression or stable disease. Treatment was continued as tolerated until disease progression. Response was assessed monthly using modified EBMT criteria and toxicity using NCI-CTCv2. No follow-up was done for pts who came off study drug. Overall survival was not included in follow-up. Results: From May 2002 to July 2003 102 were enrolled on the study, and 15 were still on therapy (11 on 30 mg qd and 4 on 15 mg bid) as of December 2006. 60% had received

>3 prior anti-MM therapies, including radiation therapy (40%) and stem cell transplantation (27%). With a median follow-up of 4.1 yrs, pts receiving 30 mg qd spent 4.2 years on study drug; pts on 15 mg bid had 4.1 years. All pts had Len dose reductions or interruption, but all stayed on study drug. Average daily dose was 25 mg for pts on 30 mg qd and 12 mg for pts on 15 mg bid. Len monotherapy was given to 6 pts, while 9 received concomitant Dex. Median time to dose reduction was 19.6 months for pts on 30 mg qd and 2.5 months for pts on 15 mg bid. A partial or complete response was achieved in 11 pts. Of 6 pts on Len monotherapy, 4 responded (1 progressed after 3.7 yrs) and 2 had stable disease (SD). Of 9 pts who received concomitant Dex, 7 responded and 2 had SD. The most common grade 3/4 toxicity was neutropenia (67%). No grade 3/4 thrombocytopenia, anemia, peripheral neuropathy, or DVT was reported. Conclusions: A subset of pts responding to Len with or without dex, could remain on treatment for at least 4.1 years. Len can be considered as an effective, durable, and well tolerated therapy for heavily pretreated pts with relapsed/refractory MM.

Tuesday June 3rd

The efficacy and safety of lenalidomide plus dexamethasone in relapsed or refractory multiple myeloma patients with impaired renal function.

D. M. Weber, A. Spencer, M. Wang, C. Chen, M. Attal, R. Niesvizky, M. Prince, Z. Yu, R. Knight, M. A. Dimopoulos, for the MM-009 and MM-010 Investigators

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8542)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8542 **Session Type: Poster Discussion**

Poster No: 17

Time: 8:00 AM - 12:00 PM **Location: Room E450a**

and

Time: 11:30 AM - 12:30 PM **Location: Room E354b**

The authors find that patients with moderate or several renal impairment respond equally well to treatment with lenalidomide/dexamethasone (len/dex) for relapsed or refractory myeloma. With careful monitoring of adverse events and appropriate dose adjustments, this study showed that a favorable outcome could be achieved with len/dex despite renal impairment.

Background: Renal impairment (RI) is common among patients (pts) presenting with myeloma (MM) and requires aggressive early intervention. Two recently published phase III trials showed significant benefit after treatment with lenalidomide plus dexamethasone (Len/Dex) over Dex alone for pts with refractory or relapsing MM. Methods: In pooled data, 682 pts with serum creatinine (Cr) <2.5 mg/dL received treatment at a starting dose of 25 mg/day Len on days 1-21 and 40 mg/day Dex on days 1-4, 9-12, and 17-20days 1-4, every 28-day cycle. We now evaluate efficacy and safety of Len/Dex and Dex alone in the subgroup of pts who had normal (CLcr >80 mL/min), mild (50< CLcr <80 mL/min), moderate (30< CLcr <50 mL/min), or severe (CLcr <30 mL/min) RI despite Cr <2.5mg/dL. Results: Len/Dex significantly improved time-to-progression and response rate compared with Dex for pts with normal to moderately impaired RI (Table; P<0.001); in severe RI TTP was significantly longer with Dex alone, but shorter than for pts without RI or with mild RI. At the starting doses for Len and Dex, the limited number of pts with CrCl < 30 mL/min had a higher percentage of myelosuppression compared with those with CrCl > 30 mL/min (Table). In pts treated with Len/Dex, 78% (42/54) of those with moderate to severe RI had improvement in renal function within 4 months of treatment. Conclusions: Pts with moderate or severe RI respond equally well to treatment with Len/Dex for relapsed or refractory MM. With careful monitoring of adverse events and appropriate dose adjustments, this study showed that a favorable outcome could be achieved with Len/Dex despite renal impairment. Prospective trials will define the activity and tolerability of Len/Dex in patients with RI.

Impact of lenalidomide therapy on stem cell mobilization in myeloma.

H. Paripati, A. K. Stewart, R. Fonseca, A. C. Dueck, J. L. Slack, C. B. Reeder, J. Leis, P. L. Bergsagel, A. S. Torloni

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8543)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8543 **Session Type: Poster Discussion**

Poster No: 18

Time: 8:00 AM - 12:00 PM **Location: Room E450a**

and

Time: 11:30 AM - 12:30 PM **Location: Room E354b**

Due to the clinical observation of difficulty mobilizing stem cells in patients treated with lenalidomide/dexamethasone (len/dex), the authors perform a retrospective chart review and find a relative inefficiency of stem cell mobilization after len/dex based induction therapy. They conclude that other strategies for mobilization of stem cells following lenalidomide induction should be considered.

Background: Lenalidomide (len) with dexamethasone (dex) is increasingly used as induction therapy in newly diagnosed myeloma patients prior to transplant. We performed a retrospective chart review after the clinical observation of difficulty mobilizing stem cells in patients treated with len/dex was made. Methods: Patients with multiple myeloma (MM) undergoing stem cell collection between January 2005 and October 2007 were analyzed for type and duration of induction therapy, collection efficacy and engraftment in patients who went to transplant. 61 patients were identified, of whom 20 received induction therapy with len/dex, and 41 received other induction therapies. The selected criteria for failure of first and total stem cell collection were defined as: 1. Collection not attempted as peripheral blood CD34+ cell count consistently < 10 cells/microliter; 2. Total CD34+ cells collected < 2 x 106 CD34+ cells/kg body weight. Results: In the len/dex group, stem cell collection was unsuccessful in 9 of 20 (45%) patients on first attempt, compared with 3 of 41(7.3%) patients (p=0.001) treated with alternate regimens. The mean peripheral blood CD34+ counts (14.0 versus 28.9 cells/microliter; p=0.0002) and mean total stem cells collected (5.1 x 106 cells/kg vs 7.4 x 106 cells/kg; p=0.0025) were also significantly lower in the len/dex group versus other induction therapies. Conclusions: These findings have implications for the management of patients with MM proceeding to autologous stem cell transplant. Given the relative inefficiency of stem cell mobilization after len/dex based induction therapy, other strategies for mobilization of stem cells following lenalidomide induction should be considered.

Lenalidomide and stem cell collection in patients with multiple myeloma.

R. J. Cook, D. Vogl, P. A. Mangan, K. Cunningham, S. Luger, D. L. Porter, D. E. Tsai, M. Raguza-Lopez, K. Wiley, K. Masters, E. A. Stadtmauer

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8547)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8547 **Session Type: Poster Discussion**

Poster No: 22

Time: 8:00 AM - 12:00 PM **Location: Room E450a**

and

Time: 11:30 AM - 12:30 PM **Location: Room E354b**

In this study the authors find that initial therapy with lenalidomide does not prevent harvest of adequate numbers of CD34 cells for ASCT, but mobilization with G-CSF alone may be inferior to combination therapy such as G-CSF and CYT.

Background: Lenalidomide is an active agent for intial treatment of multiple myeloma. Autologous stem cell transplant (ASCT) as part of first line therapy has been shown to prolong survival. Marrow suppression from lenalidomide may reduce the ability to adequately collect stem cells for ASCT. Recent reports have suggested that (1) the number of CD34+ cells collected is reduced, (2) the number of collections to obtain a target number of cells increased, and (3) the number of failed collections is increased in pts whose initial therapy contained lenalidomide when mobilized with G-CSF alone. We report here our experience with stem cell collection when comparable pts were mobilized primarily with G-CSF and cyclophosphamide (CYT). Methods: Pts were eligible for analysis if they had a diagnosis of myeloma, an initial treatment regimen was documented, and underwent stem cell mobilization and harvest at Penn between 2004 and 2007. Of 158 pts, 21 had a lenalidomide-containing induction regimen. For initial mobilization of these pts, 17 received CYT (16 at 3g/m2, 1 at 4.5 g/m2) and G-CSF 10 ug/kg, 2 received GCSF alone (10 ug/kg) and required salvage G-CSF and AMD3100, and 2 received G-CSF (10 ug/kg) and AMD3100. Results: Adequate numbers of CD34+cells x 10 6/kg (CD34 cells) to proceed with ASCT were collected on all pts in the lenalidomide group (median 6.3, range 2.4-19.7). 2/21 pts required repeat mobilization (both pts who received G-CSF alone) and were mobilized successfully on the second attempt with AMD3100. Median # of collections and CD34 cells and range were: G-CSF/CYT mobilization 3 (1-8) and 6.3 (3.0-19.7); G-CSF alone both failed to collect; G-CSF/AMD mobilization 4.5 (2-6) and 8.4 (5.6-12.3). The median # of cycles of lenalidomide induction therapy was 4 (1-16) and did not influence the # of collections or total CD34 cell counts. We also analyzed 137 pts who received non- lenalidomide containing induction therapy. 2 pts did not collect adequately. Among the remaining 135 pts, 3 pts required repeat mobilization. Median # of collections was 2.0 (1-11) with 7.3 (2.4-72.5) CD34 cellls collected. Conclusions: Initial therapy with lenalidomide does not prevent harvest of adequate numbers of CD34 cells for ASCT, but mobilization with G-CSF alone may be inferior to combination therapy such as G-CSF and CYT.

Phase II study of lenalidomide (Len), bortezomib (Bz), and dexamethasone (Dex) in patients (pts) with relapsed or relapsed and refractory multiple myeloma (MM).

K. C. Anderson, S. Jagannath, A. Jakubowiak, S. Lonial, N. Raje, R. Schlossman, N. Munshi, R. Knight, D. Esseltine, P. G. Richardson

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8545)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8545 **Session Type: Poster Discussion**

Poster No: 20

Time: 8:00 AM - 12:00 PM **Location: Room E450a**

and

Time: 11:30 AM - 12:30 PM **Location: Room E354b**

The authors find lenalidomide/bortezomib/dexamethasone to be active and well tolerated in relapsed/refractory myeloma pts, including those who received prior lenalidomide, bortezomib, thalidomide, and stem cell transplant.

Background: Single-agent Bz and Len/Dex are approved for pts with relapsed MM following >1 prior therapy. In a phase I study, Len/Bz (MTD: 15mg/1.0mg/m2) ± Dex 20-40mg achieved a 58% response rate in relapsed/refractory MM pts. This phase ll study evaluated Len/Bz/Dex at the phase-l MTD in up to 65 pts with relapsed/refractory MM, following 1-3 prior lines of therapy. Methods: Pts received Len 15 mg, d 1-14, Bz 1.0 mg/m2, d 1, 4, 8, 11, and Dex 40/20 mg (cycles 1-4/5-8) on days of/after Bz, for up to eight 21d cycles. Based on safety data, Dex dosing was reduced to 20/10 mg. After cycle 8, pts with stable or responding disease received Len (d 1-14)/Bz (d 1, 8) at doses tolerated at end of cycle 8, and Dex 10 mg, d 1, 2, 8, 9. Pts received concomitant antiviral and anti-thrombotic prophylaxis. Response was assessed every 3 weeks according to modified EBMT and Uniform Criteria. Toxicities were assessed using NCI CTCAE v3.0. Pts with G> 2 peripheral neuropathy (PN) were excluded. Primary end point was TTP; secondary end points included response rate, DOR, PFS, and OS. Results: 43 pts enrolled to date, with data available on 41 pts (median age 67 years, 66% men, 63% IgG MM, 59% Durie-Salmon stage III at diagnosis); 24 with relapsed and 17 with relapsed/refractory MM. Median number of prior therapies was 2, including Len (2%), Bz (68%), Dex (90%), thalidomide (78%), and stem cell transplant (32%). Pts received a median of 7 cycles; 18 (44%) completed 8 cycles, 12 continue on maintenance, and 16 discontinued. In 33 evaluable pts, response rate (>MR) to date is 73% (95%CI 55.6-85.1%), including 55% >PR and 36% VGPR/nCR/CR. Median DOR is 39 weeks (95% CI 13.5-63 weeks) with median TTP, PFS, and OS not yet reached. Toxicities have been manageable, consisting mainly of G1/2 myelosuppression. Attributable non-hematologic toxicities include DVT (2 pts), G3 PN (1 pt), and G3 atrial fibrillation (2 pts). Dose reductions have been required for Len (9 pts), Bz (5 pts), and Dex (14 pts). Conclusions: Len/Bz/Dex is active and well tolerated in relapsed/refractory MM pts, including those who received prior Len, Bz, thalidomide, and stem cell transplant. Durable responses have been seen. Accrual is ongoing and updated response data will be presented.

Publication Only

Efficacy and safety of low dose versus full dose anticoagulation for prevention of thalidomide-related venous thromboembolism.

S. Y. Farhan, J. Vega, A. Hanbali, P. Kuriakose, N. Janakiraman

J Clin Oncol 26: 2008 (May 20 suppl; abstr 19518)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 19518

This study address thalidomide's association with an increased risk for venous thromboembolic events (VTE) and finds that full dose anticoagulation might be more effective than low dose anticoagulation in decreasing VTE in patients receiving thalidomide in combination with dexamethasone or chemotherapy, with an acceptable bleeding risk.

Background: Thalidomide has been found to be effective in the treatment of Multiple Myeloma. However, its use is associated with an increased risk for venous thromboembolic events (VTE) ranging from 10 to 28% when used in combination with dexamethasone or chemotherapy. VTE prophylaxis should be considered at the initiation of thalidomide treatment. Current practice varies from low dose to full dose warfarin, use of low-molecular weight heparin, or aspirin. Data to guide the clinicians on the most effective VTE prophylaxis strategy are very limited. Methods: To further investigate this topic, we reviewed the records of 74 patients treated with thalidomide in combination with dexamethasone (n=55), chemotherapy (n=13), or both (n=6) in our institution between 1999 and 2007. Thirty patients received low dose anticoagulation, defined as warfarin 1-2 mg (n=11), or enoxaparin 1mg/kg once a day (n=9). Eighteen patients received full dose anticoagulation, defined as warfarin intended to raise the INR to 2-3 (n=17), or enoxaprin 1 mg/kg twice a day (n=1). Twenty- six patients did not receive anticoagulation. Thalidomide-related VTE was defined as deep venous thrombosis or pulmonary embolism occurring while on thalidomide treatment or within 2 weeks of it being stopped. Results: Seven (9.5%) of the 74 patients developed thalidomide-related VTE. Five patients (19%) who were not prescribed prophylactic anticoagulation developed VTE, compared to 2 patients (6.7%) in the low dose anticoagulation group (p=0.23), and none in the high dose anticoagulation group (p=0.068). Two patients (11.1%) in the full dose anticoagulation group experienced bleeding complications (epistaxis, gastrointestinal bleed), compared to none in the low dose anticoagulation and no anticoagulation groups (p=0.16). Conclusions:

Full dose anticoagulation might be more effective than low dose anticoagulation in decreasing VTE in patients receiving thalidomide in combination with dexamethasone or chemotherapy, with an acceptable bleeding risk. The absence of statistical significance in this trial could be due to the small number of patients studied. In view of the prevalent lack of consensus, we propose this question be addressed within the context of a formal randomized trial.

An exploratory feasibility study examining the addition of arsenic trioxide (ATO) and ascorbic acid (AA) to bortezomib, thalidomide, and dexamethasone (VTD) in the treatment of relapsed and refractory multiple myeloma.

J. N. Valent, R. M. Snyder, A. S. Azmi, R. Mohammad, T. Weyer, K. O'Riley, S. Lalo, M. Rivero-Perry, J. A. Zonder

J Clin Oncol 26: 2008 (May 20 suppl; abstr 19541)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 19541

The authors generate preliminary data on the combination of arsenic trioxide (ATO), ascorbic acid (AA), and bortezomib/thalidomide/dexamethasone (VTD) for the treatment of relapsed refractory multiple myeloma (RRMM). They find that adding ATO/AA to VTD was well tolerated and conclude that although their data suggest that treatment with VTD plus ATO/AA may increase NF-κB inhibition more than VTD alone in some patients, further studies would be needed to elucidate whether the addition of ATO/AA adds to the clinical efficacy of VTD.

Background: VTD is a highly active combination in pts with relapsed/refractory multiple myeloma (RRMM). ATO alone has modest activity but AA may enhance the cytotoxic effects of ATO. V, T, and ATO inhibit NF-κB, but it is unknown if combining these agents results in increased NF-κB inhibition. This study was undertaken to generate preliminary data on the combination of ATO, AA, and VTD for the treatment of RRMM. Methods: Five male pts (ages 49-77 yrs old) were enrolled in this IRB approved study between Sept 2005 and Aug 2006. The mean number of prior treatments was 3 (range 1-7; autologous transplant in 3 pts). Pts received D 40 mg po/IV and V 0.7 mg/m2 IV on days 1, 4, 8, and 11 of a 21-day cycle and T 50 mg daily po. Starting with cycle 2, ATO (given at an initial dose of 0.10 mg/kg IV) and AA (1000 mg IV) were added on days 1, 4, 8, and 11. Blood samples were drawn prior to and 1 hour after the administration of V on day 1 of cycle 1, and 1 hour after administration of therapy (V + ATO/AA) on day 1 of cycles 2 and 3 in two pts to assess the added effect of ATO/AA on NF-κB inhibition using EMSA. Results: Four of 5 pts completed >3 cycles of treatment. Two pts responded to treatment: 1 partial response (71% decrease in M-Protein and decreased bone pain) and another patient with nonsecretory MM had a decrease in size of plasmacytoma. The regimen was well tolerated, with only one pt discontinuing therapy due to side effects: grade 1 peripheral neuropathy with pain after 6 cycles of therapy. In one non-responder, adding ATO/AA did not increase NF-κB inhibition beyond that achieved with VTD alone; in contrast, in one responder, there was a 15-fold decrease in post-therapy NF-κB activation in cycle 3 compared to baseline. Conclusion: Adding ATO/AA to VTD to treat RRMM was well tolerated. There were no unexpected grade 3 or 4 toxicities. Although these data suggest that treatment with VTD plus ATO/AA may increase NF-κB inhibition more than VTD alone in some pts, further studies would be needed to elucidate whether the addition of ATO/AA adds to the clinical efficacy of VTD, as well as the maximally tolerated doses of each drug.

Linolinamide-dexamethasone combination in symptomatic multiple myeloma: An Indian experience.

S. Datta, J. Saha, S. Mukhopadhyay, A. Sen, A. Mukhopadhyay

J Clin Oncol 26: 2008 (May 20 suppl; abstr 19531)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 19531

The authors aim to evaluate the activity of thalidomide-dexamethasone combination in patients of symptomatic myeloma as first line therapy and to assess the toxicity of lenalidomide in Asian-Indian population. They find that lenalidomide with dexamethasone induced a high frequency of response and low incidence of serious irreversible toxicity, results encouraging the combinations use as first line therapy within this population.

Background: Linolinamide is a well-established anti-angiogenic agent used extensively in relapsed & refractory multiple myeloma. The aim of our study was to evaluate the activity of Thalidomide-dexamethasone combination in patients of symptomatic Myeloma as first line therapy and to see the toxicity of Linolinamide in Asian-Indian population. Materials and Method: During period from July 2006 to December 2007 we selected consecutive 24 patients of symptomatic multiple Myeloma in the haemato-oncology department of Netaji Subhash Chandr Bose Cancer Research Institute. The age range of the patients was from 25 years to 72 years (with median age of 43 years) and there was a male preponderance in the study. All patients were treated with Linolinamide (Reddys Laboratory) 10mg / daily orally at bedtime and they received dexamethasone 40 mg for 4 days beginning on days 1, 9 and 17. From second cycle onwards dexamethasone was given only for 4 days. Response evaluation was done after 3rd & 6months. Response was assessed on the basis of reduction in para-protein levels in the serum and reduction in Myeloma Cells in the Bone Marrow. Results: Complete response were seen in 15 patients (62.5%) and 21 patients (87.5%) after 3rd & 6th cycle of chemotherapy. The median time for achieving the best response was 8.2 weeks. Three patients (12.5%) showed documented disease progression. Most commonly observed toxicities include peripheral neuropathy 33.33%, Constipation 29.17%, sedation 12.5% and rashes 4.17%. No grade 3/4 toxicity was observed in any of the patients during the study. Conclusion: The combination of Linolinamide with Dexamethasone induced a high frequency of response and low incidence of serious irreversible toxicity. The result is encouraging to use this combination as first line therapy.

A phase II study of low dose thalidomide and dexamethasone in previously untreated multiple myeloma.

B. Thomas, K. Pavithran, P. Narayan, M. Unni, K. Kumar, A. Majeed, T. S. Ganesan

J Clin Oncol 26: 2008 (May 20 suppl; abstr 19520)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 19520

The authors evaluate the efficacy and safety of low dose thalidomide and dexamethasone in previously untreated patients with myeloma, with results showing that thalidomide and dexamethasone at lower doses is a safe an effective regimen. They conclude that the mechanism of the increased response to thalidomide needs further evaluation within the Indian patient population.

Background: To evaluate the efficacy and safety of low dose Thalidomide and Dexamethasone in previously untreated patients with Multiple Myeloma. Methods: 34 patients (M/F: 21/13), of median age 57.8 years (range 37-74) with previously untreated symptomatic Myeloma were recruited between October 2005 and June 2007 and were treated with Thalidomide 100mg daily and Dexamethasone (40mg daily x 4days) once monthly for 6 months. All patients were investigated with serum protein electrophoresis, skeletal survey and bone marrow aspiration & biopsy. In addition, b2-microglobulin (18/34) and immunoglobulin electrophoresis (24/34) were done in a subset. Patients had IgG (12), IgA (8), IgM (1) & light chain (3) Myeloma. Response was determined as per the EBMT criteria (CR defined as Plasma cells <_5% in bone marrow) after 6 months of therapy. Results: 33 patients are evaluable for toxicity as 1 was lost for follow up after she developed a second malignancy (CA Breast). 28 patients are evaluable for response, as they have completed 6 months of therapy. Toxicity observed were as follows: 2 deaths on treatment, severe skin rashes (2/33), DVT (1/33), peripheral neuropathy (4/33) (all grade1), pedal edema (6/33), constipation (4/33) and sedation in (2/33). In addition, one patient had pneumonia, which required hospitalization. The response after 6 months of therapy was CR in (16/28), PR (6/28), S.D (3/28) & P.D (3/28). Those in CR received either Thalidomide (50mg) alone or Thalidomide (50mg) & Dexamethasone (10mgX4days) or no treatment. Of the 28 patients who were evaluable and completed 6 months of therapy, 6 died subsequently because of myeloma. Conclusion: The above results show that Thalidomide and Dexamethasone at a lower dose is a safe and effective regimen in previously untreated Multiple Myeloma. The complete response (57% 16/28) rate in Indian patients is significantly higher than that reported in the literature (<10%). The mechanism of the increased response to Thalidomide needs further evaluation in Indian patients.

Pre-clinical evaluation of bortezomib, doxorubicin, dexamethasone, and lenalidomide in multiple myeloma (MM).

M. Hari, Z. Hector-Word, D. Lebovic, M. Soengas, A. Jakubowiak

J Clin Oncol 26: 2008 (May 20 suppl; abstr 19513)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 19513

The authors evaluate whether combining 4- drugs—bortezomib, doxorubicin, dexamethasone, and lenalidomide (VDDR) can further improve elimination of myeloma cells and find that VDDR shows higher efficacy in preclinical models, providing a rationale for a phase I/II clinical trial in newly diagnosed myeloma.

Background: Treatment with bortezomib combinations have shown to improve efficacy in MM. In clinical studies, among the most active are 3-drug combinations of bortezomib, liposomal doxorubicin and dexamethasone (VDD), with 93% patients achieving at least 50% disease reduction (PR), and lenalidomide, bortezomib, Dexamethasone (RVD) with 89% PR rate. However, > 90% reduction of the disease (VGPR) associated with longer survival was seen in only 63% and 35% patients, respectively. In this study, we evaluated whether combining 4- drugs (VDDR) can further improve elimination of myeloma cells. In addition to cytotoxicity, we investigated the effects of bortezomib combinations on Noxa and c-myc as markers of activity of bortezomib combinations. Methods: MM cell lines MM1.S, NCI H929 and RPMI 8226 were treated with combinations of bortezomib (Vel), doxorubicin (Dox), dexamethasone (Dex) and lenalidomide (Rev) and cytotoxicity was measured by MTT assays. Noxa and c-myc induction, and caspase-3,-8 and -9 activation were evaluated by immunoblotting after treatment with drugs in MM cells and normal PBMCs. Results: VDDR showed 2-4 fold higher cytotoxicity than Vel/Dox, Vel/Dex and Vel/Rev, and comparable toxicity to VDD in NCI H929 cells. In cells sensitive to Rev (MM1.S), VDDR showed higher cytotoxicity than VDD. Vel selectively increased Noxa levels in MM cell lines but not in normal PBMCs. In studies to date, the combination of VDD resulted in higher levels and faster kinetics of Noxa induction than Vel alone and leads to more potent caspase activation observed within 16hrs of treatment. Neither Dox nor Dex had any effect on Noxa levels. Noxa induction correlated with higher c-myc levels upon Vel treatment in RPMI 8226 cells. Knocking down c-myc with shRNA resulted in partial loss of Noxa suggesting that c-myc is required for Noxa induction. Conclusions: VDDR shows higher efficacy in preclinical models providing a rationale for a phase I/II clinical trial in newly diagnosed MM to be activated in the MMRC. Based on the preliminary results, tumor specific Noxa induction can be used as a biomarker for preclinical evaluation of the efficacy of Velcade-based regimens in myeloma.

Side effects and efficacy of thalidomide and low dose dexamethasone combination in newly diagnosed symptomatic multiple myeloma patients in India--A pilot study.

P. Jain, V. R. Pai, K. Prabhash, S. Gupta, P. M. Parikh

J Clin Oncol 26: 2008 (May 20 suppl; abstr 19530)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 19530

The authors undertake a phase II study of low dose dexamethasone and thalidomide as initial treatment of myeloma in the Indian population, with the primary end point of establishing the adverse effect profile of this combination. They find the initial treatment to be well tolerated with minimal grade 3 and 4 toxicities, and conclude it to be effective and feasible in the Indian patient population.

Background: The standard schedule of thalidomide and dexamethasone combination in untreated myeloma includes three pulses (each of four days with 40 mg per day) of dexamethasone and thalidomide 200 mg/day every 28 days. Poor tolerance to this schedule, low feasibility of stem cell transplant, uncertain access to myeloma care resources and higher rate of infections and hyperglycemia are the limitations in our clinical setting. We undertook a phase II, one stage study of low dose dexamethasone and thalidomide as initial treatment of myeloma with the primary end point of establishing the adverse effect profile of this combination. The secondary end point was evaluation of efficacy. Methods: Twenty consecutive patients of untreated myeloma were treated with thalidomide 200 mg/day with dexamethasone 40 mg per day D1 to D4 every 21 days. Patients were evaluated after 3rd and 6th cycles. Zolendronic acid was given monthly. Antithrombotic prophylaxis and erythropoietin were not routinely used. Patients were monitored for thrombosis, neuropathy and other known adverse effects. Results: There was no occurrence of thrombosis, skin rash, bradycardia or deaths. There were no grade 3 or 4 toxicities except one patient who had grade 3 constipation after 6 cycles. All patients (100%) had grade 2 constipation at the end of three cycles and 13/20 (65 %) after 6 cycles. At the end of 3rd and 6th cycles, 50 % of patients had grade 2 sensory neuropathy and 95 % developed grade 2 fatigue. Sixteen of the 20 patients (80%) had a response to therapy after 3 cycles and 19 of the 20 patients (95%) after 6 cycles. At the completion of 6 cycles, four patients (20 %, 95% CI 2 -37 %) had CR, six had VGPR (30 %, 95% CI 1 -50 %) and PR was seen in nine patients (45%, 95 % CI 23 to 66%). Conclusions: For the initial treatment of myeloma low dose dexamethasone with thalidomide seems well tolerated with minimal grade 3 and 4 toxicities. It is effective and feasible in our patient population. It merits further study with and formal comparison with high dose dexamethasone regimen.

Thalidomide/Revlimid Publications – 2nd Quarter, 2008

Treatment for elderly patients with multiple myeloma.

Mehta J.

Lancet. 2008 Mar 22;371(9617):983; author reply 984-5.

http://www.ncbi.nlm.nih.gov/pubmed/18358917?ordinalpos=63&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Comment on: *Lancet. 2007 Oct 6;370(9594):1209-18.*

Treatment for elderly patients with multiple myeloma.

Tsubokura M, Kami M.

Lancet. 2008 Mar 22;371(9617):983; author reply 984-5.

http://www.ncbi.nlm.nih.gov/pubmed/18358919?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Comment on: *Lancet. 2007 Oct 6;370(9594):1209-18.*

Extramedullary progression of multiple myeloma under thalidomide therapy despite concomitant response of medullary disease.

Candoni A, Simeone E, Fanin R.

Am J Hematol. 2008 Mar 26 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18459108?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma.

Hicks LK, Haynes AE, Reece DE, Walker IR, Herst JA, Meyer RM, Imrie K; on behalf of the Hematology Disease Site Group of the Cancer Care Ontario Program in Evidence-based Care.

Cancer Treat Rev. 2008 Mar 30 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18381234?ordinalpos=60&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that thalidomide appears to improve the overall survival of patients with newly diagnosed myeloma both when it is added to standard, non-transplantation therapy, and when it is given as maintenance therapy following ASCT.

A systematic review and meta-analysis was performed to determine the efficacy and toxicity of thalidomide in previously untreated patients with myeloma. Medline, Embase, Cochrane Controlled Trials Register, and abstracts from the American Society of Hematology and the American Society of Clinical Oncology were searched for randomized controlled trials (RCTs) of either induction or maintenance thalidomide in adults with previously untreated myeloma. Nine RCTs of induction thalidomide, three RCTs of maintenance thalidomide, and one RCT of induction and maintenance thalidomide were identified, involving a total of 4144 subjects. When thalidomide was added to standard, non-transplantation myeloma therapy, overall survival (OS) improved (HR 0.67; 95% CI 0.56-0.81). When thalidomide was given as maintenance following autologous transplantation (ASCT), there was a trend to improved OS (HR 0.61, 95% CI 0.37-1.01); when the only trial which combined induction and maintenance thalidomide was excluded from this analysis, a significant survival advantage emerged (HR 0.49, 95% CI 0.32-0.74). The relative risk of venous thromboembolism (VTE) with induction thalidomide was 2.56 (95% CI 1.88-3.49). A meta-analysis of trials/sub-groups administering low molecular weight heparin (LMWH) as VTE prophylaxis, suggested a persistently increased relative risk of VTE with induction thalidomide (RR 1.54, 95% CI 1.07-2.22). The relative risk of VTE was substantially lower, but still elevated, when thalidomide was given as maintenance therapy following ASCT (RR 1.95, 95% CI 1.15-3.30). In summary, thalidomide appears to improve the overall survival of patients with newly diagnosed myeloma both when it is added to standard, non-transplantation therapy, and when it is given as maintenance therapy following ASCT. However, thalidomide is associated with toxicity, particularly a significantly increased risk of VTE.

Renal safety of zoledronic acid with thalidomide in patients with myeloma: a pharmacokinetic and safety sub-study.

Spencer A, Roberts A, Kennedy N, Ravera C, Cremers S, Bilic S, Neeman T, Copeman M, Schran H, Lynch K.

BMC Clin Pharmacol. 2008 Mar 31;8:2.

http://www.ncbi.nlm.nih.gov/pubmed/18377658?ordinalpos=56&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors conduct a safety study of zoledronic acid and thalidomide in myeloma patients participating in a trial of maintenance therapy and find that the combination of zoledronic acid and thalidomide appears to confer no additional renal safety risks over zoledronic acid alone.

BACKGROUND: Cases of impaired renal function have been reported in patients who had been treated with both zoledronic acid and thalidomide for myeloma. Hence, we conducted a safety study of zoledronic acid and thalidomide in myeloma patients participating in

a trial of maintenance therapy. METHODS: Twenty-four patients who were enrolled in a large randomized trial of thalidomide vs no thalidomide maintenance therapy for myeloma, in which all patients also received zoledronic acid, were recruited to a pharmacokinetic and renal safety sub-study, and followed for up to 16 months. RESULTS: No significant differences by Wilcoxon rank-sum statistic were found in zoledronic acid pharmacokinetics or renal safety for up to 16 months in patients randomized to thalidomide or not. CONCLUSION: In myeloma patients receiving maintenance therapy, the combination of zoledronic acid and thalidomide appears to confer no additional renal safety risks over zoledronic acid alone.

Single-institute phase 2 study of thalidomide treatment for refractory or relapsed multiple myeloma: Prognostic factors and unique toxicity profile.

Hattori Y, Okamoto SI, Shimada N, Kakimoto T, Morita K, Tanigawara Y, Ikeda Y.

Cancer Sci. 2008 Mar 31 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18384432?ordinalpos=57&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors conduct a Japanese single-institute phase II study with 56 patients and obtain new information on the optimal dose and prognostic factors as well as the correlation of toxicities with treatment schedule.

We previously reported a pilot study of thalidomide monotherapy for Japanese patients with refractory or relapsed multiple myeloma. In the present work, we have extended this clinical trial to a single-institute phase 2 study with a larger number of patients and longer follow-up time. New information on the optimal dose and prognostic factors as well as the correlation of toxicities with treatment schedule was obtained. Fifteen of 56 (27%) patients achieved a partial response, including three cases with near-complete remission. Most patients suffered toxicities at a dose of 400 mg per day, but there was no clear dose-response relationship. Thus, a lower dose such as 200 mg per day or less is considered optimal. Multivariate analyses identified only lack of response to therapy as an adverse prognostic factor for progression-free survival. Chromosomal abnormality, C-reactive protein >10 mg/L, and more than six previous courses of chemotherapy were significantly associated with shorter overall survival. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 23 and 11% of patients, respectively. Grade 4 interstitial pneumonia and grade 5 pulmonary hypertension were observed; however, no patient suffered deep vein thrombosis, which has frequently been observed in other studies. Duration of therapy was closely related to the development of peripheral neuropathy. The efficacy and prognostic factors of this treatment were confirmed in long-term observation. However, special attention should be paid to toxicities such as hematological and pulmonary complications as well as peripheral neuropathy in long-term users.

Arterial thrombosis and thalidomide.

Goz M, Eren MN, Cakir O.

J Thromb Thrombolysis. 2008 Apr;25(2):224-6.

http://www.ncbi.nlm.nih.gov/pubmed/17514361?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report arterial thrombosis in two cases of multiple myeloma treated with thalidomide.

Arterial emboli are largely a reflection of cardiac disease. Thalidomide is an antiangiogenic drug used in cancer therapy. Venous thrombosis incidence increased during treatment with thalidomide. We reported arterial thrombosis in two cases with multiple myeloma implemented in thalidomide treatment. Standard emergency intervention was applied. In the postoperative period, enoxiparine was given to all the patients. Warfarin treatment was started in the level of INR 2-2,5. ASA with a dose of 100 mg/day was added to the treatment. In conclusion, this side effect of the use of thalidomide should be taken into consideration while doing examinations with respect to the etiology in arterial thromboembolism and because of this vascular complication that threatens life; we suggest stopping the thalidomide treatment.

Concurrent radiation therapy and lenalidomide in myeloma patient.

Marchand V, Decaudin D, Servois V, Kirova YM.

Radiother Oncol. 2008 Apr;87(1):152-3 [Epub 2008 Feb 20].

http://www.ncbi.nlm.nih.gov/pubmed/18077032?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Novel anti-myeloma agents and angiogenesis.

Anargyrou K, Dimopoulos MA, Sezer O, Terpos E.

Leuk Lymphoma. 2008 Apr;49(4):677-89.

http://www.ncbi.nlm.nih.gov/pubmed/18398734?ordinalpos=53&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This review summarizes all available preclinical and clinical data for the effect of novel agents that are used in myeloma therapy—including thalidomide and lenalidomide—on angiogenesis, which is at least partially responsible for their remarkable anti-myeloma efficacy.

During the last decade several novel agents have been used in the management of patients with multiple myeloma. Immunomodulatory drugs and proteasome inhibitors exert their efficacy both directly by inducing apoptosis of myeloma cells and indirectly through the

interruption of the interactions between myeloma and stromal cells in the bone marrow (BM) microenvironment. These interactions are crucial for myeloma cell growth and survival. The adherence of myeloma cells to BM stromal cells leads to the overproduction of several cytokines with angiogenic properties that enhance the survival and growth of myeloma cells through paracrine and autocrine loops. The correlation of these molecules with clinical features and survival of myeloma patients supports the importance of angiogenesis in the pathogenesis of the disease and reveals these cytokines as suitable targets for the development of novel anti-myeloma therapies. This review summarises all available preclinical and clinical data for the effect of novel agents that are used in myeloma therapy, such as thalidomide, lenalidomide, bortezomib and VEGF inhibitors, on angiogenesis, which is at least partially responsible for their remarkable anti-myeloma efficacy.

Thalidomide in consecutive multiple myeloma patients: single-center analysis on practical aspects, efficacy, side effects and prognostic factors with lower thalidomide doses.

Haas PS, Denz U, Ihorst G, Engelhardt M.

Eur J Haematol. 2008 Apr;80(4):303-9 [Epub 2007 Dec 21].

http://www.ncbi.nlm.nih.gov/pubmed/18182082?ordinalpos=49&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In a single center analysis, the authors assess whether lower thalidomide doses are feasible and result in favorable treatment response in multiple myeloma patients and find that the strategy doses seems a feasible and attractive approach.

PURPOSE: In this single-center analysis, we assessed whether lower thalidomide doses are feasible and result in favourable treatment response in multiple myeloma (MM) patients. RESULTS: Between May 2001 and October 2006, 38 consecutive MM patients received thalidomide. Their median age was 62.4 yr, all had stage II/III MM and 31.6% had deletion 13q14 (del13q14). Prior to thalidomide, patients had received a median of two treatment lines. The median thalidomide dose was 100 mg/d (range 50-800) and the median treatment duration was 34 wk. The median cumulative thalidomide dose was 24 g. Sixteen patients received thalidomide as a single agent and 22 in combination (+dexamethasone n = 18; others n = 4). The median time-to-treatment failure (TTF) after thalidomide initiation was 30.4 wk. Analysis of prognostic factors showed a significantly prolonged TTF without del13q14 (38.1 vs. 8.9 wk with del13q14; P = 0.006). Our analysis of TTF between thalidomide given alone vs. in combinations showed a better TTF for the combination (23.6 vs. 30.6 wk), albeit not reaching significance (P = 0.20). Other parameters, such as age, stage, and prior SCT showed no difference in TTF. Peripheral polyneuropathy (PNP) frequencies were increased with longer (>28 wk) and increased cumulative thalidomide doses (>40 g), which emphasizes (a) the need to carefully escalate thalidomide from 50 to 200 mg/d, thereby reducing side effects and increasing patient compliance, and (b) that PNP occurs more frequently with longer and higher thalidomide doses. CONCLUSION: The strategy to lower thalidomide doses seems a feasible and attractive approach in MM patients, this being currently tested in prospective randomized trials.

Ultra low dose thalidomide in elderly patients with myeloma.

Bowcock SJ, Minchom A, Yates LR, Ryali MM.

Br J Haematol. 2008 Apr;141(1):120-2 [Epub 2008 Feb 12].

http://www.ncbi.nlm.nih.gov/pubmed/18279458?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Urinary cytology in multiple myeloma.

Patil S, Schwarer A, McLean C.

Cytopathology. 2008 Apr;19(2):130-1 [Epub 2007 May 3].

http://www.ncbi.nlm.nih.gov/pubmed/17488260?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Thromboembolic events with lenalidomide-based therapy for multiple myeloma.

Menon SP, Rajkumar SV, Lacy M, Falco P, Palumbo A.

Cancer. 2008 Apr 1;112(7):1522-8.

http://www.ncbi.nlm.nih.gov/pubmed/18278812?ordinalpos=45&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors evaluate the incidence and risk factors of thromboembolism associated with lenalidomide therapy in newly diagnosed myeloma and find the incidence of deep vein thrombosis is lower than previously reported in the literature.

BACKGROUND: The purpose was to evaluate the incidence and risk factors of thromboembolism associated with lenalidomide therapy in newly diagnosed myeloma. METHODS: A pooled analysis was performed of patients with previously untreated multiple myeloma enrolled in clinical trials of lenalidomide-based therapy at the Mayo Clinic, Rochester, Minnesota, and the Italian Myeloma Network, Italy. The incidence of thrombosis, the effect of risk factors such as steroid dose and erythropoietin supplementation, and the effect of prophylaxis were examined. RESULTS: In all, 125 patients enrolled in 3 clinical trials were identified. Patients were stratified based on the concomitant corticosteroid dose. Fifty-two patients were in the high-dose group (dexamethasone 40 mg, 12 days a month); 73 patients were in the low-dose group (prednisone at any dose; or dexamethasone 40 mg, 4 days a month). A total of 110 patients were initiated on thromboprophylaxis; of these, 104 patients (95%) received aspirin. Ten patients (8%) developed deep vein thrombosis, including 4

who were not receiving any thromboprophylaxis at the time of the event. The rate of thromboembolic events was not different between patients who received concomitant erythropoietin therapy and those who did not, 4.8% and 8.6%, respectively (P= .54). A higher number of venous thrombotic episodes occurred in the high-dose corticosteroid group compared with the low-dose corticosteroid therapy group (12% vs 6%), but the difference was not statistically significant (P= .3). CONCLUSIONS: The incidence of deep vein thrombosis is lower than previously reported in the literature. There was a trend to a higher incidence of thrombosis in patients receiving high-dose corticosteroid therapy.

The addition of liposomal doxorubicin to bortezomib, thalidomide and dexamethasone significantly improves clinical outcome of advanced multiple myeloma.

Ciolli S, Leoni F, Casini C, Breschi C, Santini V, Bosi A.

Br J Haematol. 2008 Apr 10 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18410447?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study finds an improved quality of response when liposomal doxorubicin is added to a bortezomib/thalidomide/dexamethasone treatment regimen.

Relapsed/refractory myeloma has a poor outcome because of multi-drug resistance, patient low-performance status and toxicity of conventional chemotherapy. To improve results, standard chemotherapeutics and drugs targeting the microenvironment are applied at the same time. Bortezomib, by inhibiting proteasome function, may enhance chemosensitivity to other drugs and overcome drug-resistance. Notably, doxorubicin and bortezomib may reciprocally increase their efficacy. Thus, to improve outcome whilst minimizing therapy-related toxicity, liposomal doxorubicin was added to a bortezomib-based combination. From January 2004, relapsed/refractory myeloma patients referred to our Institution received bortezomib 1.0 mg/m(2) i.v. twice weekly for 2 weeks in a 28-d cycle for up to six cycles, oral dexamethasone 24 mg with the standard scheduling and thalidomide 100 mg continuously (VTD). From January 2005, liposomal doxorubicin, 50 mg/m(2) (30 mg/m(2) for patients older than 75 years), was added on day 4 of each cycle [VTD plus Myocet (MyVTD)]. In total, 70 patients were treated: 28 received VTD and 42 MyVTD. Baseline demographic and clinical characteristics were similar between the two groups. Toxicity was manageable although more pronounced with MyVTD. The overall response rate (81% vs. 50%, P = 0.009), time to progression (19 vs. 11 months, P = 0.01) and progression-free survival (15 vs. 8 months, P = 0.001) were significantly higher with MyVTD regimen, suggesting an improved quality of response.

Pulmonary embolism in a patient with multiple myeloma receiving thalidomide-dexamethasone therapy.

Jeng WJ, Kuo MC, Shih LY, Chu PH.

Int J Hematol. 2008 Apr 15 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18414984?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors report on a patient with a rare complication of pulmonary embolism from thalidomide-treated multiple myeloma.

Massive pulmonary embolism is an uncommon complication of multiple myeloma treated with thalidomide-dexamethasone regimen. In 2006, multiple myeloma was diagnosed in a 72-year-old man, who received thalidomide-dexamethasone therapy. In January 2007, echocardiography and computerized tomography identified massive pulmonary embolism in the pulmonary arteries and a deep vein thrombus of the right leg. The patient also had an elevated concentration of B-type natriuretic peptide. After heparinization and warfarin therapy, the patient's condition improved. This is the first report of a patient with a rare complication of pulmonary embolism from thalidomide-treated multiple myeloma.

Thalidomide for treatment of multiple myeloma: 10 years later.

Palumbo A, Facon T, Sonneveld P, Bladè J, Offidani M, Gay F, Moreau P, Waage A, Spencer A, Ludwig H, Boccadoro M, Harousseau JL.

Blood. 2008 Apr 15;111(8):3968-77 [Epub 2008 Feb 1].

http://www.ncbi.nlm.nih.gov/pubmed/18245666?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss various thalidomide treatment regimens that have led to improved outcomes for both young and elderly newly diagnosed myeloma patients.

Thalidomide, bortezomib, and lenalidomide have recently changed the treatment paradigm of myeloma. In young, newly diagnosed patients, the combination of thalidomide and dexamethasone has been widely used as induction treatment before autologous stem cell transplantation (ASCT). In 2 randomized studies, consolidation or maintenance with low-dose thalidomide has extended both progression-free and overall survival in patients who underwent ASCT at diagnosis. In elderly, newly diagnosed patients, 3 independent randomized studies have reported that the oral combination of melphalan and prednisone plus thalidomide (MPT) is better than the standard melphalan and prednisone (MP). These studies have shown better progression-free survival, and 2 have shown improved overall survival for patients assigned to MPT. In refractory-relapsed disease, combinations including thalidomide with dexamethasone, melphalan, doxorubicin, or cyclophosphamide have been extensively investigated. The risks of side effects are greater when thalidomide is used in combination with other drugs. Thromboembolism and peripheral neuropathy are the major concern. The introduction of anticoagulant prophylaxis has reduced the rate of thromboembolism to less than 10%. Immediate thalidomide dose reduction or discontinuation when paresthesia is complicated by pain or motor deficit has decreased the severity of neuropathy. Future studies will define the most effective or the best sequence of combinations which could improve life expectancy.

Thalidomide and lenalidomide: Mechanism-based potential drug combinations.

Vallet S, Palumbo A, Raje N, Boccadoro M, Anderson KC.

Leuk Lymphoma. 2008 Apr 23;:1-8 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18452080?ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors review the mechanism of action of thalidomide and lenalidomide, providing a rationale for combination studies in order to improve patient outcome and reduce side effects.

Thalidomide and its analogue lenalidomide are potent anti-inflammatory, anti-angiogenic and immunomodulatory drugs, successfully used for the treatment of hematological cancers, in particular multiple myeloma (MM). Both drugs reveal a dual mechanism of action: they target tumour cells by direct cytotoxicity and, indirectly, by interfering with several components of the bone marrow microenvironment. Lenalidomide and thalidomide are versatile drugs with a broad range of activities that potentiate the anti-MM effects of conventional and novel agents. Here, we review the mechanism of action of these drugs, providing a rationale for combination studies in order to improve patient outcome and reduce side effects.

VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma.

Pineda-Roman M, Zangari M, van Rhee F, Anaissie E, Szymonifka J, Hoering A, Petty N, Crowley J, Shaughnessy J, Epstein J, Barlogie B.

Leukemia. 2008 Apr 24 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18432260?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study combines bortezomib (V) with thalidomide (T) and dexamethasone (D) in a phase I/II trial to determine dose-limiting toxicities and clinical activity of the VTD regimen in 85 patients with advanced and refractory myeloma.

Bortezomib (V) was combined with thalidomide (T) and dexamethasone (D) in a phase I/II trial to determine dose-limiting toxicities (DLT's) and clinical activity of the VTD regimen in 85 patients with advanced and refractory myeloma. The starting dose of V was 1.0 mg/m(2) (days 1, 4, 8, 11, every 21 day) with T added from cycle 2 at 50 mg/day, with 50 mg increments per 10 patient cohorts, to a maximum dose of 200 mg. In the absence of DLT's, the same reiteration of T dose increases was applied with a higher dose of V=1.3 mg/m(2). D was added with cycle 4 in the absence of partial response (PR). Ninety-two percent had prior autotransplants, 74% had prior T and 76% abnormal cytogenetics. MTD was reached at V=1.3 mg/m(2) and T=150 mg. Minor response (MR) was recorded in 79%, and 63% achieved PR including 22% who qualified for near-complete remission. At 4 years, 6% remain event-free and 23% alive. Both OS and EFS were significantly longer in the absence of prior T exposure and when at least MR status was attained. The MMSET/FGFR3 molecular subtype was prognostically favorable, a finding since reported for a VTD-incorporating tandem transplant trial (Total Therapy 3) for untreated patients with myeloma (BJH 2008).

The oral PKC-beta inhibitor enzastaurin (LY317615) suppresses signalling through the AKT pathway, inhibits proliferation and induces apoptosis in multiple myeloma cell lines.

Neri A, Marmiroli S, Tassone P, Lombardi L, Nobili L, Verdelli D, Civallero M, Cosenza M, Bertacchini J, Federico M, De Pol A, Deliliers GL, Sacchi S.

Leuk Lymphoma. 2008 Apr 30;:1-10 [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/18452078?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that enzastaurin has additive or synergistic cytotoxic effects with thalidomide and conclude that phase II studies in myeloma patients of enzastaurin alone or in combination with other drugs are warranted.

Deregulation of the protein kinase C (PKC) signalling pathway has been implicated in tumor progression. Here we investigated the PKC inhibitor enzastaurin for its activity against multiple myeloma (MM) cells. Enzastaurin suppresses cell proliferation in a large panel of human myeloma cell lines (HMCLs), with IC(50) values ranging from 1.3 to 12.5 microM and induces apoptosis, which is prevented by the ZVAD-fmk broad caspase inhibitor. These results are consistent with decreased phosphorylation of AKT and GSK3-beta, a downstream target of the AKT pathway and a pharmacodynamic marker for enzastaurin. Furthermore, enzastaurin cytotoxicity is retained when HMCLs were cocultured with multipotent mesenchymal stromal cells. Enzastaurin has additive or synergistic cytotoxic effects with bortezomib or thalidomide. Considering the strong anti-myeloma activity of enzastaurin in vitro and in animal models and its safe toxicity profile, phase II studies in MM patients of enzastaurin alone or in combination with other drugs are warranted.

Does the addition of thalidomide to MP or low-intensity SCT improve survival in elderly multiple myeloma patients?

Corradini P, Montefusco V.

Nat Clin Pract Oncol. 2008 May;5(5):254-5 [Epub 2008 Mar 18].

http://www.ncbi.nlm.nih.gov/pubmed/18349855?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Eight-year median survival in multiple myeloma after total therapy 2: roles of thalidomide and consolidation chemotherapy in the context of total therapy 1.

Zangari M, van Rhee F, Anaissie E, Pineda-Roman M, Haessler J, Crowley J, Barlogie B.

Br J Haematol. 2008 May;141(4):433-44 [Epub 2008 Mar 26].

http://www.ncbi.nlm.nih.gov/pubmed/18371114?ordinalpos=11&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This phase 3 trial total therapy 2 (TT2) evaluates the benefit of up-front administration of thalidomide and finds that TT2 is superior to TT1 in terms of complete response duration, event-free and overall survival.

In comparison to total therapy 1 (TT1), the phase 3 trial total therapy 2 (TT2) evaluated the benefit of up-front administration of thalidomide (THAL); TT2 also introduced post-transplant consolidation chemotherapy. With median follow-up times of 5 and 12 years, respectively, outcome comparisons were made of 668 patient's enrolled on TT2 and 231 patients treated on TT1. Complete response (CR) rates were similar at 40% for TT1 and TT2 without THAL versus 60% on the THAL arm of TT2. CR durations were similar with either TT2 arm and both were superior to results of TT1. Event-free and overall survivals were extended from 2.6 to 5.7 years, respectively, with TT1 to 4.8 and 8.0 years with TT2. TT2's major advance vis-à-vis TT1 pertained to the subgroup without cytogenetic abnormalities (CA), supporting the role of post-transplant consolidation therapy, whereas the improved survival of the CA subgroup on the experimental versus control arm of TT2 attests to the role of THAL in this setting. Adjusting for prognostic variables in multivariate and pair-mate analyses, TT2 was superior to TT1 in terms of CR duration, event-free and overall survival. These results provide a basis for the prospective evaluation of the consolidation strategy in a randomized clinical trial design.

The insulin-like growth factor-I receptor inhibitor NVP-AEW541 provokes cell cycle arrest and apoptosis in multiple myeloma cells.

Maiso P, Ocio EM, Garayoa M, Montero JC, Hofmann F, García-Echeverría C, Zimmermann J, Pandiella A, San Miguel JF.

Br J Haematol. 2008 May;141(4):470-82 [Epub 2008 Mar 12].

http://www.ncbi.nlm.nih.gov/pubmed/18341634?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that NVP-AEW541 potentiates the action of myeloma drugs, including lenalidomide.

Multiple myeloma (MM) is a B-cell malignancy characterized by accumulation of monoclonal plasma cells in the bone marrow (BM). Despite recent advances in the treatment, MM represents an incurable disease for which development of new therapies is required. We report the antimyeloma effect of NVP-AEW541, a small molecule that belongs to the pyrrolo[2,3-d]pyrimidine class, identified as a selective inhibitor of the insulin-like growth factor-I receptor (IGF-IR) in vitro kinase activity. NVP-AEW541 had a potent cytotoxic effect on fresh cells and in a murine MM model. NVP-AEW541 partially abrogated the proliferative advantage conferred by the coculture with BM stromal cells and the presence of growth factors produced by the BM microenvironment. In addition, NVP-AEW541 potentiated the action of drugs, such as bortezomib, lenalidomide, dexamethasone or melphalan. Moreover the triple combination of NVP-AEW541, dexamethasone and bortezomib resulted in a significant increase in growth inhibition. Mechanistic studies indicated that NVP-AEW541 provoked a marked cell cycle blockade accompanied by pRb downregulation. Interestingly, NVP-AEW541 increased the levels of p27 associated with a reduction in the CDK2 activity. Finally, NVP-AEW541 induced cell death through caspase-dependent and -independent mechanisms. All these data, suggest the potential effect of IGF-IR kinase inhibitors as therapeutic agents for MM patients.

Lenalidomide: A new therapy for multiple myeloma.

Palumbo A, Miguel JS, Sonneveld P, Moreau P, Drach J, Morgan G, Einsele H.

Cancer Treat Rev. 2008 May;34(3):283-91 [Epub 2008 Jan 29].

http://www.ncbi.nlm.nih.gov/pubmed/18230411?ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors discuss the current and future roles of lenalidomide in myeloma treatment, alone and in combination.

The last decade has seen rapid evolution in the management of multiple myeloma. Cytogenetic, molecular, and proteomic techniques have led to a better understanding of the pathophysiology and prognostic markers of this heterogeneous malignancy. New immunomodulatory drugs, such as lenalidomide, which interrupt myeloma growth and survival pathways have entered into clinical usage. Combined with dexamethasone, oral lenalidomide has proved to be highly effective in patients whose disease has become resistant to conventional therapy. Currently, several clinical trials are ongoing in order to define the optimal use of this new agent and its combinations across the spectrum of patients with myeloma. Whether the ultimate outcome of future research will be a single-treatment solution for all patients, or whether treatments will become better-tailored to the individual (based on prognostic markers and pre-existing co-morbidities) has yet to be determined.

Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma.

Rajkumar SV, Rosiñol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, Olesnyckyj M, Yu Z, Knight R, Zeldis JB, Bladé J.

J Clin Oncol. 2008 May 1;26(13):2171-7 [Epub 2008 Mar 24].

http://www.ncbi.nlm.nih.gov/pubmed/18362366?ordinalpos=17&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors compare thalidomide plus dexamethasone (thal/dex) versus placebo plus dexamethasone as primary therapy for newly diagnosed myeloma and find that thal/dex results in significantly higher response rates and significantly prolongs time to progression compared with dexamethasone alone in patients with newly diagnosed myeloma.

PURPOSE: The long-term impact of thalidomide plus dexamethasone (thal/dex) as primary therapy for newly diagnosed multiple myeloma (MM) is unknown. The goal of this study was to compare thalidomide plus dexamethasone versus placebo plus dexamethasone (placebo/dex)as primary therapy for newly diagnosed MM. PATIENTS AND METHODS: In this double-blind, placebo-controlled trial, patients with untreated symptomatic MM were randomized to thal/dex (arm A) or to placebo plus dexamethasone (dex) (arm B). Patients in arm A received oral thalidomide 50 mg daily, escalated to 100 mg on day 15, and to 200 mg from day 1 of cycle 2 (28-day cycles). Oral dex 40 mg was administered on days 1 through 4, 9 through 12, and 17 through 20 during cycles 1 through 4 and on days 1 through 4 only from cycle 5 onwards. Patients in arm B received placebo and dex, administered as in arm A. The primary end point of the study was time to progression. This study is registered at http://ClinicalTrials.gov (NCT00057564). RESULTS: A total of 470 patients were enrolled (235 randomly assigned to thal/dex and 235 to placebo/dex). The overall response rate was significantly higher with thal/dex compared with placebo/dex (63% v 46%), P < .001. Time to progression (TTP) was significantly longer with thal/dex compared with placebo/dex (median, 22.6 v 6.5 months, P < .001). Grade 4 adverse events were more frequent with thal/dex than with placebo/dex (30.3% v 22.8%). CONCLUSION: Thal/dex results in significantly higher response rates and significantly prolongs TTP compared with dexamethasone alone in patients with newly diagnosed MM.

Thalidomide: mechanisms of action.

Paravar T, Lee DJ.

Int Rev Immunol. 2008 May-Jun;27(3):111-35.

http://www.ncbi.nlm.nih.gov/pubmed/18437602?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors review both the positive and negative studies of thalidomide in order to improve understanding of the possible mechanisms of this drug in treating a variety of diseases.

The classification of thalidomide as an orphan drug with anti-inflammatory actions has led to its off-label use in conditions refractory to other medications. Although the observed clinical effects of thalidomide suggest it to have immunomodulatory capabilities, the mechanism of action is unclear. Here we review both the positive and negative studies of thalidomide at the bench in order to improve our understanding of the possible mechanisms of this drug in treating a variety of diseases at the bedside. Studies on the effects of thalidomide on the innate and adaptive immune system as well as tumorigenesis and angiogenesis are discussed.

Lenalidomide in the treatment of multiple myeloma: a review.

Armoiry X, Aulagner G, Facon T.

J Clin Pharm Ther. 2008 Jun;33(3):219-26.

http://www.ncbi.nlm.nih.gov/pubmed/18452408?ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this review, the authors summarize the pharmacokinetic, pharmacodynamic and clinical trial data on lenalidomide.

Lenalidomide is an immunomodulatory drug derived from thalidomide. It was developed to maximize the anti-inflammatory and anti-neoplasic properties of thalidomide and to reduce its toxicity. The molecular mechanism of action of lenalidomide is unclear, but its therapeutic activity is mainly due to its well defined anti-inflammatory, immunomodulatory, anti-proliferative and anti-angiogenic properties. In relapsed or refractory multiple myeloma (MM), lenalidomide, combined with standard dose dexamethasone, is superior to dexamethasone alone in terms of time to progression, response rate and overall survival. The most commonly reported adverse events include haematological toxicity with manageable neutropenia and thrombopenia. Lenalidomide does not trigger the limiting toxicities of thalidomide: somnolence, neuropathy and constipation. Lenalidomide, in combination with dexamethasone, is indicated for the treatment of MM patients who have received at least one prior therapy and is administered orally at the dose of 25 mg q.d. for 21 days of 28-day cycles. The drug is being investigated for the treatment of newly diagnosed MM. In this review, we summarize the pharmacokinetic, pharmacodynamic and clinical trial data on lenalidomide.

Rapid complete remission in multiple myeloma with bortezomib/thalidomide/ dexamethasone combination therapy following development of tumor lysis syndrome.

Chim CS.

Cancer Chemother Pharmacol. 2008 Jun;62(1):181-2. Epub 2007 Aug 31.

http://www.ncbi.nlm.nih.gov/pubmed/17846773?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Low efficacy of thalidomide in improving response after induction in multiple myeloma patients who are candidates for high-dose therapy.

Corso A, Mangiacavalli S, Barbarano L, Montalbetti L, Mazzone A, Fava S, Varettoni M, Zappasodi P, Morra E, Lazzarino M.

Leuk Res. 2008 Jul;32(7):1085-90 [Epub 2007 Dec 21].

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The authors find that the addition of a thalidomide-dexamethasone regimen does not seem useful for intensification before transplant.

Giving the impact of complete response (CR) on outcome of multiple myeloma patients addressed to high-dose melphalan, we explored the role of a pre-transplant intensification with 3months thalidome plus dexamethasone therapy (Thal-Dex), after pulse-VAD induction. Seventy-four multiple myeloma patients (MM pts) uniformly treated, were retrospectively studied. The response rate after pulse-VAD were: CR 6%, VGPR 40%, PR 23%, MR 23%, and progression 8%. The response rate after Thal-Dex were similar: CR 11%, VGPR 39%, PR 17%, MR 9%, and progression 24%. Giving no advantage in terms of response rate with an additive toxicity, Thal-Dex does not seem useful for intensification before transplant.

Prospective evaluation of coagulopathy in multiple myeloma patients before, during and after various chemotherapeutic regimens.

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Leuk Res. 2008 Jul;32(7):1078-84 [Epub 2008 Feb 1].

http://www.ncbi.nlm.nih.gov/pubmed/18241919?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this prospective study, coagulation factor levels are evaluated longitudinally before, during induction and after intensification. 138 myeloma patients are randomized to induction treatment consisting of adriamycin and dexamethasone, in combination with either vincristin, thalidomide, or bortezomib followed by high-dose melphalan and autologous stem cell transplant. The authors observe several changes in coagulation factor levels during induction treatment, which may result in a prothrombotic state. They conclude that larger studies are required to establish whether these changes contribute to the increased risk of venous thromboembolism in myeloma patients.

BACKGROUND: Venous thromboembolism (VTE) occurs frequently in multiple myeloma patients, especially during induction treatment with thalidomide in combination with anthracyclines and/or dexamethasone. Several coagulation abnormalities have been described in untreated myeloma patients, but these have not been prospectively evaluated during and after treatment. PATIENTS AND METHODS: We performed a prospective study in 138 multiple myeloma patients in whom coagulation factor levels were evaluated longitudinally before, during induction and after intensification. Patients were randomized to induction treatment consisting of adriamycin and dexamethason, in combination with either vincristin (VAD), thalidomide (TAD), or bortezomib (PAD) followed by high-dose melphalan (HDM) and autologous stem cell transplant (ASCT). RESULTS: Factor VIII:C (FVIII:C) and von Willebrand factor (VWF) were significantly elevated before treatment (median FVIII:C 2.26U/ml, VWF:Ag 1.95U/ml). Irrespective of the type of induction regimen, these variables increased strongly during induction therapy (FVIII:C 2.55U/ml and VWF:Ag 2.96U/ml). Fibrinogen also showed a significant increase after induction therapy (3.5g/l pre-treatment and 4.0g/l after treatment, respectively, P<0.001). This was significantly higher in TAD than VAD treated patients. Three to six month after ASCT levels of VWF and FVIII:C had decreased to values lower than observed before treatment (1.71 and 1.67U/ml respectively). There was no correlation between the increased levels at start and the response of multiple myeloma to treatment. High levels of VWF, fibrinogen and FVIII:C before start of treatment were significantly associated with mortality. Fourteen patients (10%) developed a venous thrombotic event (VTE). The coagulation factor abnormalities before and during treatment were not associated with the development of VTE. CONCLUSION: During induction treatment several changes in coagulation factor levels are observed, which may result in a prothrombotic state. Larger studies are required to establish whether the changes in these coagulation factors during induction treatment contribute to the increased risk of venous thromboembolism in multiple myeloma patients.

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