



CITINGS

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VELCADE® (bortezomib) 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 VELCADE (bortezomib). This special edition corresponds with the 2008 annual meeting of the American Society of Clinical Oncology (ASCO). In this CITINGS, we have highlighted selected VELCADE data presentations from the ASCO meeting. We also provide references to the latest published journal articles on VELCADE 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

Effect of bortezomib, cyclophosphamide, and filgrastim on complete remission rates and CD34+ stem cell collections in multiple myeloma (MM).

R. Niesvizky, J. Stern, M. Manco, T. Mark, M. W. Schuster, T. B. Shore, J. G. Harpel, R. N. Pearse, F. Zafar, M. Coleman
J Clin Oncol 26: 2008 (May 20 suppl; abstr 8587)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8587

Session Type: General Poster

Poster No: 52E

Time: 8:00 AM - 12:00 PM

Location: S Hall A1

The authors investigate the potential for concurrent cyto-reduction by adding bortezomib to the mobilization regimen and find bortezomib, cyclophosphamide, and filgrastim to be a novel, well tolerated, and effective regimen for stem cell mobilization in myeloma.

Background: Typical stem cell mobilization regimens in MM include G-CSF alone or with high-dose cyclophosphamide. Given the known in vitro/in vivo synergy between bortezomib (Velcade [Vel]) and alkylating agents, we investigated the potential for concurrent cyto-reduction by adding Vel to the mobilization regimen. Methods: Primary objectives of this open-label study were to maximize response pre-transplant and the successful mobilization and harvest of stem cells (goal $>10 \times 10^6/\text{kg}$ in <7 leukaphereses). Eligible patients (pts) had symptomatic, Durie-Salmon stage II/III MM. All pts received six 21-day cycles of Vel/dexamethasone \pm liposomal doxorubicin. Mobilization comprised Vel 1.3 mg/m² on days 1, 4, 8, and 11, cyclophosphamide 3 g/m² on day 8, and filgrastim (rhG-CSF) for 10 days from day 9. Time to post-transplant ANC ($>1.5 \times 10^9/\text{L}$) and platelet ($>20 \times 10^9/\text{L}$) recovery were recorded. Results: Of 24 pts accrued, 14 have been mobilized, and 10 have completed transplant. CD34+ yields greatly exceeded the study goal (table). Median CD34+

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Funded by an educational grant from Millennium Pharmaceuticals, Inc.

collection was $21.3 \times 10^6/\text{kg}$ in a median of 1.5 collection days. Of the 23 evaluable pts 70% had > PR, with 48% CR/nCR. Pts who had not achieved a complete response (CR) prior to mobilization continued to respond positively to treatment during mobilization, including one transition from near-CR to CR and one from stable disease to partial response. Expected grade 3/4 toxicities occurred; no pts discontinued mobilization. Post-transplant, median time to ANC recovery was 11 days and to platelet recovery was 18 days. Correlative studies of biomarkers for stem cell mobilization comparing Vel mobilized to non Vel mobilized stem cells (CD34, gene array analysis, CXCR2-4) will be presented. Conclusion: Vel, cyclophosphamide, and filgrastim is a novel, well tolerated, and effective regimen for stem cell mobilization in MM. It results in high stem cell yields in a short collection time and provides the potential for further cytoreduction. CD34+ stem cell collection and engraftment data by patient.

The effect of pegylated liposomal doxorubicin plus bortezomib in multiple myeloma patients with renal insufficiency.

J. Blade, P. Sonneveld, J. San Miguel, H. Sutherland, R. Hajek, A. Nagler, A. Spencer, T. Robak, J. L. Harousseau, R. Z. Orlowski, The DOXIL-MMY-3001 Study Investigators

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8562)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8562

Session Type: General Poster

Poster No: 47A

Time: 8:00 AM - 12:00 PM

Location: S Hall A1

The authors seek to determine the efficacy and feasibility of pegylated liposomal doxorubicin (PLD) + bortezomib (B) in relapsed/refractory myeloma patients with renal insufficiency (RI). They find that RI does not compromise the efficacy or tolerability of PLD + B in relapsed/refractory myeloma patients and that treatment with PLD + B or B alone appears to improve renal function in relapsed/refractory MM patients with RI.

Background: Renal dysfunction (RD) is common in patients with multiple myeloma (MM) and has been associated with poor outcomes. Orlowski et al, 2007, demonstrated that pegylated liposomal doxorubicin (PLD) + bortezomib (B) for pts with relapsed/refractory MM who have received at least one prior therapy significantly increased median time to progression (TTP) (9.3 vs. 6.5 months, $p = 0.00004$) compared with B alone. We wished to determine the efficacy and feasibility of PLD + B in relapsed/refractory MM patients with renal insufficiency (RI) (creatinine clearance (CrCl) < 60 ml/min). Methods: Eligible pts who were randomized received bolus IV B 1.3 mg/m² on days 1, 4, 8 and 11 of each 3-week cycle ($n = 322$) or the same B regimen plus IV PLD 30 mg/m² on day 4 ($n = 324$) of each cycle. 193 pts with RI from this trial were analyzed retrospectively to determine the impact of RI on the efficacy and safety of PLD + B, as well as the effect on renal function. Pts with severe RI (CrCl < 30 ml/min) were excluded. Results: The mean number of PLD + B cycles administered was comparable between the two subgroups (5.1 in the RI subgroup vs. 5.0 in the non-RI subgroup). For the RI subgroup, median TTP was 10.9 (95% CI: 9.1, n/a) and 6.5 (95% CI: 5.3, 7.2) months in the PLD + B and B arms, respectively ($p = 0.002$). These results are consistent with the benefit of PLD + B demonstrated in the overall study population. There was a steady improvement in renal function over the course of treatment in both the PLD + B and B treatment arms. The incidence of grade 3/4 anemia, diarrhea and pneumonia were more common than in the RI subgroup compared to the non-RI group. Conclusion: RI does not compromise the efficacy or tolerability of PLD + B in relapsed/refractory MM pts. Treatment with PLD + B or B alone appears to improve renal function in relapsed/refractory MM pts with RI.

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. Ferman, 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 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-resolution assessment of chromosomal gains and losses in multiple myeloma tumors from bortezomib clinical trials.

B. Bryant, H. Danaee, D. Lichter, J. D. Shaughnessy, Jr, P. L. Bergsagel, P. Sonneveld, K. Anderson, A. Boral, W. Trepicchio, G. Mulligan

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8570)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8570

Session Type: General Poster

Poster No: 48B

Time: 8:00 AM - 12:00 PM

Location: S Hall A1

To better understand how the genome-wide changes observed in myeloma relate to prognosis and treatment response to a proteasome inhibitor, the authors use single nucleotide polymorphism (SNP) array technology to assess DNA copy number. They conclude that tumor DNA samples from prospective clinical trials can be used to identify myeloma chromosomal aberrations and their association with response to specific therapy.

Background: Multiple myeloma (MM) tumors have frequent genomic alterations including gains and losses of chromosomes; some of these have been associated with poor clinical prognosis. Bortezomib, a first-in-class proteasome inhibitor, is approved for the treatment of relapsed MM. To better understand how the genome-wide changes observed in myeloma relate to prognosis and treatment response to a proteasome inhibitor, we have used single nucleotide polymorphism (SNP) array technology to assess DNA copy number. Methods: DNA from 112 bone marrow tumor biopsies collected in multi-center phase II and III clinical trials of relapsed MM patients prior to treatment with bortezomib (N=74) or dexamethasone (N=38) were hybridized on SNP arrays to assess genomic aberrations. Copy number profiles were analyzed for common gains and losses, their relationship to Translocation and Cyclin D (TC) subtype, and association with clinical outcome. Results: Commonly seen genomic alterations in myeloma were observed, including deletions of chromosome 13, 1p, 6q, amplifications on 1q and 6p, and hyperdiploidy. Other notable genomic deletions included 8p, 16q, 14q and 12p, as well as small deletions on chromosomes 7 and 11. 1q amplifications are not correlated with other common amplifications, but tend to co-occur with deletions on 13 and amplifications on 20q. Chromosome 13 loss often accompanies loss of 14q. The hyperdiploid gains are very strongly correlated with each other, and to a lesser extent with gains at 6p. 6p gains and 6q losses frequently occur together. Chromosome 13 loss is relatively infrequent in the cyclin D1 TC subtype; hyperdiploidy is rare in the 11q13 and 4p16 TC subtypes. Hyperdiploidy was associated with shorter survival for the dexamethasone cohort, but had no effect on survival in the bortezomib cohort. 8p loss was associated with shorter survival regardless of treatment. Response to bortezomib was observed in patients both with and without chromosome 13 deletions. Individual loci associated with clinical outcome were identified as candidates for further validation. Conclusions: Tumor DNA samples from prospective clinical trials can be used to identify MM chromosomal aberrations and their association with response to specific therapy.

The importance of combined hematologic and CT diagnosis for monitoring response in patients with multiple myeloma treated with Bortezomib based therapy.

M. Horger, K. C. Weisel, H. Brodoefel, B. Denecke, C. D. Claussen, L. Kanz

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8597)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8597

Session Type: General Poster

Poster No: 54A

Time: 8:00 AM - 12:00 PM

Location: S Hall A1

This retrospective analysis indicates that monitoring of lytic bone lesions in patients with myeloma is inaccurate for assessment of progression or relapse of multiple myeloma. The authors find that due to the effects of specific chemotherapy and accompanying bisphosphonates therapy, progression of lytic bone lesions seems to occur much later in the course of the disease showing slower growth kinetics compared with medullary and extra-medullary myeloma manifestations.

Background: To assess the potential role of radiological monitoring (conventional CT) of lytic bone lesions for diagnosis of progressive (PD) or relapsing (R) multiple myeloma (MM) in comparison with laboratory-based diagnosis, soft-tissue based CT-diagnosis and combined hematologic-radiological diagnosis. Materials and Methods: Between 3/03 and 12/07, 201 patients with MM underwent nonenhanced whole-body low-dose multidetector-CT (WBLD-MDCT)

survey parallel to hematological follow up (582 investigations). CT-scans were performed using a standardized low-dose protocol assessing number and size of lytic bone lesions (bone window setting, bW) similar to conventional X-ray diagnosis. In addition, number, size and density of medullary and extra-medullary lesions (soft-tissue window setting, s-tW) were analyzed. Progressive or relapsing myeloma was defined by progression of lytic bone lesions, medullary and extra-medullary tumor infiltration and/or of established basic hematologic parameters. Results: 210/582 investigations showed PD or R. 50/210 (24%) yielded the correct diagnosis by all three methods, 50/210 (24%) were diagnosed correctly by WBLD-MDCT (bW), 133/210 (63%) by laboratory-based testing and 195/210 (93%) by WBLD-MDCT (s-tW) as well as by the combination of the latter two. 8/26 assessments of R were biomarker negative. Only 1 of these examinations proved positive on WBLD-MDCT (bW) while the other 7 were correctly diagnosed by WBLD-MDCT (s-tW) due to progress of medullary infiltration and/or extra-medullary manifestation. Of the biomarker-negative assessments of PD (84/210), only 24 (24/84) showed progress of osteolysis on WBLD-MDCT (bW) while all were correctly assessed by WBLD-MDCT (s-tW). Discussion: This retrospective analysis indicates that monitoring of lytic bone lesions in patients with MM is inaccurate for assessment of progression or relapse of multiple myeloma. Due to the effects of specific chemotherapy and accompanying bisphosphonates therapy, progression of lytic bone lesions seems to occur much later in the course of the disease showing slower growth kinetics compared with medullary and extra-medullary myeloma manifestations.

Monitoring bortezomib therapy in multiple myeloma: Screening of cyclin D1 overexpression as a potential prognostic marker for response to treatment.

T. B. Ngo, J. Felthaus, G. Ihorst, M. Engelhardt, R. Wäsch

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8614)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8614

Session Type: General Poster

Poster No: 56D

Time: 8:00 AM - 12:00 PM

Location: S Hall A1

The authors' finding raise the possibility that CCND1 is a specific marker for predicting a lasting response after bortezomib treatment in myeloma, warranting a prospective study with a larger patient cohort.

Background: Cyclin D1 (CCND1), 2 (CCND2) and 3 (CCND3) are overexpressed in almost all MM and their deregulation has prognostic value. As cyclins are substrates of the proteasome, proteasome inhibition by bortezomib may stabilize the cell cycle and facilitate the induction of apoptosis, as it has been recently shown for breast cancer (Ishii et al, J Nat Canc Inst 2006). Methods: In a clinical approach, our objective was to define the expression levels of D-type cyclins in MM pts treated with bortezomib at our medical center between 1/2003 and 3/2006, aiming to define cyclins D as prognostic markers for monitoring treatment efficacy. We analyzed CCND1, CCND2 and CCND3 by real-time PCR in bone marrow specimens of 20 pts and correlated the expression with clinical features and other prognostic markers such as BM infiltration (BMI), β 2-microglobulin (β 2-MG) levels, 13q14 status and light chain-secretion. Results: The median number of bortezomib cycles in all pts was three and the best response to therapy was CR in one, PR in 11, SD in five and PD in 3/20. All pts who responded to bortezomib showed overexpression (OE) of CCND1. Pts not responding to bortezomib had very low or negative CCND1 cDNA levels. By 3/2007, 50% of all pts in CR, PR or SD had eventually relapsed. Of those pts, three relapsed, despite CCND1 OE prior to therapy. Six pts (66%) with CCND1 OE remained in response. Four pts displaying very high cyclin D1 expression levels were in either PR or SD, even after a follow-up of up to six years. Pts with CCND2 and CCND3 OE responded to bortezomib, but showed a relatively higher relapse rate (50% and 75% respectively). The amplification of the cyclin D genes was not found to correlate with BMI, β 2-MG, light chain secretion or del 13q14. The risk for progression after bortezomib treatment was significantly decreased in pts with cyclin D1 OE (HR 0.102, 95%CI 0.021-0.498, $p=0.0048$). Consequently, the progression free survival was significantly prolonged with cyclin D1 OE compared to those pts with low or negative cyclin D1 cDNA levels ($p=0.0011$). Conclusions: Our findings raise the possibility that CCND1 is a specific marker for predicting a lasting response after bortezomib treatment in MM, warranting a prospective study with a larger patient cohort.

Targeting Cdk4/6 in combination therapy of chemoresistant multiple myeloma.

S. Chen-Kiang, M. Di Liberto, T. Louie, J. Liang, D. S. Jayabalan, S. Ely, M. A. Moore, R. Niesvizky, X. Huang

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8503)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8503

Session Type: Clinical Science Symposia

Time: 8:00 AM - 8:15 AM

Location: E Arie Crown Theater

Targeting Cdk4/6 by PD 0332991 in combination with a selective cytotoxic agent, such as bortezomib, represents a new class of promising cell cycle-based therapy in myeloma, and possibly other cancers.

Background: Deregulation of Cdk4 or Cdk6 is a hallmark in cancer. However, conventional cancer therapy centers on empirical cytotoxic killing. Targeting the cell cycle with broad-spectrum inhibitors has proven ineffective so far due to cross-reactivity with cell survival and the transcriptional machinery. In myeloma, over-expression of Cdk4-cyclin D1 or Cdk6-cyclin D2 predisposes primary bone marrow (BM) myeloma cells to proliferation in vivo. Conversely, silencing Cdk4/6 by its physiologic inhibitor, p18INK4c, is required for cell cycle termination during the generation of normal plasma cells. Targeting Cdk4/6, therefore, represents a rational strategy to control disease progression and drug resistance in myeloma. Methods: An orally bioactive, small molecule PD 0332991 selectively and reversibly inhibits Cdk4/6 (IC50 ~ 60 nM) in primary myeloma cells ex vivo. This leads to exclusive G1 cell cycle arrest

unaccompanied by apoptosis by BrdU labeling and apoptotic assays. Results: By inducing synchronous S phase entry upon release of G1 block or prolonging G1 arrest, inhibition of Cdk4/6 by PD 0332991 profoundly sensitizes primary myeloma cells to killing by proteasome inhibitors bortezomib and NPI-0052, or dexamethasone. Sequential treatments with PD 0332991 and bortezomib rapidly reduces tumor burden in animal models. Importantly, it overcomes chemoresistance in myeloma cells isolated from refractory relapse patients, despite stromal protection. Synergistic killing of myeloma cells lies in induction of cell cycle-specific mitochondria depolarization. Base On this basis and a favorable outcome of Phase I clinical trial, a Phase I/II PD 0332991-bortezomib clinical trial for myeloma is in progress. Conclusion: Targeting Cdk4/6 by PD 0332991 in combination with a selective cytotoxic agent represents a new class of promising cell cycle-based therapy in myeloma, and possibly other cancers.

Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial.

J. L. Harousseau, C. Mathiot, M. Attal, G. Marit, D. Caillot, C. Hullin, T. Facon, I. Webb, H. Avet-Loiseau, P. Moreau
J Clin Oncol 26: 2008 (May 20 suppl; abstr 8505)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8505

Session Type: Clinical Science Symposia

Time: 9:00 AM - 9:15 AM

Location: E Arie Crown Theater

In this phase 3 study, bortezomib/dexamethasone significantly improves post-induction response rates vs. vincristine/doxorubicin/dexamethasone, which translates into significantly better >VGPR rates post-ASCT. Bortezomib/dexamethasone should now be considered the standard induction treatment prior to ASCT.

Background: ASCT is the standard of care for MM patients (pts) aged <65 yrs with high complete plus very good partial remission (CR+VGPR) rate. Improving CR rate has been associated with prolonged PFS and OS. Phase 2 studies have shown bortezomib (VELCADE)/dexamethasone (Vel/Dex) as an effective induction therapy. Methods: In this phase 3 study, Vel/Dex (4 cycles) was compared with vincristine/doxorubicin/dexamethasone (VAD; 4 cycles) as induction prior to ASCT in 482 MM pts aged <65 years. Primary objective was CR+near-CR (nCR) rate. Planned enrolment (480 pts) provided 80% power to detect a 10% difference in CR+nCR rate (10% vs 20%). Consolidation with 2 cycles of Dex, cyclophosphamide, etoposide, platinum (DCEP) was also evaluated. Pts were randomized to 4 arms: A1: VAD (N=121), A2: VAD+DCEP (N=121), B1: Vel/Dex (N=121), and B2: Vel/Dex+DCEP (N=119). Results: In the intent-to-treat analysis (ITT) Vel/Dex had significantly higher CR+nCR/>VGPR vs VAD post-induction (21.3%/46.7% vs 8.3%/18.6%, P=0.0023/<0.0001); Vel/Dex was also superior in pts with >3mg/L or <3mg/L β 2M and in pts with or without del(13). The significant CR+nCR/>VGPR Vel/Dex advantage was maintained post-ASCT, both in pts who received ASCT (40.8%/71.8% vs 28.8%/51%, P=0.0089/<0.0001) and in the ITT population (35%/61.7% vs 23.6%/41.7%, P=0.0056/<0.0001); DCEP did not increase response rates. During induction, grade >3 adverse events (AEs) rates were similar with Vel/Dex and VAD (38.2% vs 40.6%); serious AE rates (25.2% vs 31.0%) and AEs leading to death (0.8% vs 2.9%) were lower with Vel/Dex, while neuropathic symptoms (all grades) were higher with Vel/Dex (35.3% vs 22.6%). Stem cell collection was adequate (>2x10⁶ CD34+/kg) in 97% and 99% of Vel/Dex and VAD pts, respectively. First analyses of the survival data will be presented at the meeting. Conclusion: Vel/Dex significantly improved post-induction response rates vs VAD, which translated into significantly better >VGPR rates post-ASCT. Vel/Dex should now be considered the standard induction treatment prior to ASCT.

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, 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. Knowledge of t(4;14) and delTP53 status is key to identifying myeloma subsets uniquely benefiting from bortezomib.

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, \pm 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.

Efficacy of induction with cybord in newly diagnosed multiple myeloma.

C. B. Reeder, A. K. Stewart, J. G. Hentz, P. L. Bergsagel, N. A. Pirooz, R. Fonseca, C. Chen, S. Trudel, D. Reece, V. Kukreti

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8517)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8517

Session Type: Oral Abstract Presentation

Time: 3:15 PM - 3:30 PM

Location: Room E354b

This study aims to determine the depth of response in newly diagnosed patients with multiple myeloma to oral cyclophosphamide, bortezomib and dexamethasone (CyBorD), as assessed by CR, nCR and VGPR after 4 cycles of therapy. The authors find that the induction regimen CyBorD is highly active in the treatment of newly diagnosed myeloma and produces very good and complete responses exceeding those seen with other induction regimens. The main toxicity is peripheral neuropathy.

Background: The combination of oral cyclophosphamide, bortezomib and dexamethasone (CyBorD) is active in multiple myeloma (MM) producing rapid responses. The goal of this study was to determine the depth of that response in newly-diagnosed patients with multiple myeloma as assessed by CR, nCR and VGPR after 4 cycles of therapy. Methods: Patients with newly diagnosed MM were eligible if they had measurable or evaluable disease, were >18 years of age, had an ECOG PS <3 and were able to give informed consent. Treatment consisted of a single arm of cyclophosphamide 300mg/m² po days 1, 8, 15, 22, bortezomib 1.3 mg/m² IV days 1, 4, 8, 11 and dexamethasone 40mg po days 1-4, 9-12, and 17-20 of a 28 day cycle. A total of 4 cycles was planned with the goal of proceeding on to stem cell transplant. Growth factors were allowed after cycle 1. The primary endpoint was complete response with secondary endpoints of ORR, PFS and toxicity. Results: 33 patients have been enrolled and 23 are evaluable for response and toxicity at the time of writing. Patient characteristics included mean age of 60, 43 % female, and ISS stage II/III in 35/26 %. Prior to transplant the ORR is 100 % with 85 % achieving at least a VGPR. 64 % had a CR or nCR. Responses occurred rapidly with a mean reduction in M-Protein of 66 % and 83 % after 1 and 2 cycles. Grade 3 toxicities included neutropenia in 20%, thrombocytopenia in 9 %, hyperglycemia in 17 % and peripheral neuropathy (PN) in 5 %. Gr 1-3 PN occurred in 69%. There was no grade 5 toxicity. All patients that elected to proceed on to transplant were able to undergo successful stem cell harvests. Conclusions: The induction regimen CyBorD is highly active in the treatment of newly diagnosed MM and produces very good and complete responses exceeding those seen with other induction regimens, mimicking that seen with high-dose therapy and stem cell transplantation. The main toxicity is peripheral neuropathy.

Bortezomib, pegylated-liposomal-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 II (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).

Tuesday June 3rd

Phase I trial of vorinostat plus bortezomib (bort) in relapsed/refractory multiple myeloma (mm) patients (pts).

A. Z. Badros, S. Philip, R. Niesvizk, O. Goloubeva, C. Harris, J. Zweibel, J. J. Wright, A. Burger, M. R. Baer, M. J. Egorin, S. Grant

J Clin Oncol 26: 2008 (May 20 suppl; abstr 8548)

Multiple Myeloma: Lymphoma and Plasma Cell Disorders

Abstract No: 8548

Session Type: Poster Discussion

Poster No: 23

Time: 8:00 AM - 12:00 PM

Location: Room E450a

and

Time: 11:30 AM - 12:30 PM

Location: Room E354b

This study determine the maximum tolerated dosage, pharmacokinetics, and pharmacodynamics of vorinostat plus bortezomib in myeloma pts.

Vorinostat, a histone deacetylase inhibitor, affects cell growth by modifying the transcription of cellular proteins (histones, transcription factors, ubiquitin E3 ligases and stress response proteins). In vitro, vorinostat showed synergistic cytotoxicity with proteasome inhibitors in MM cells by disruption of aggresome function and induction of ER stress (Pei, 2004). The study aims were to determine the MTD, pharmacokinetics (PK) and pharmacodynamics (PD) of vorinostat plus Bort in MM pts. Twenty-three pts were treated. Median age was 54 yrs (range 39-78). Median time from MM diagnosis to study entry was 5.3 yrs (range 1.5-9). Isotypes were IgG (n=11), IgA (n=4), light chain (n=8). Fourteen pts had complex karyotypes. Median number of prior regimens was 7 (range 3-13), including autologous transplant (n=20), thalidomide (n=23) and lenalidomide (n=17). Nineteen pts had a median of 2 (range: 1-5) Bort-based prior regimens (table below). Median time from last therapy to study was 20 days (range 15-39). Pts received Bort 1.3 mg/m² IV days 1, 4, 8 and 11 and vorinostat

100-400 mg days 4-11. Five 3- pt cohorts were evaluated at each level. Two pts in the 500 mg level had DLTs: prolonged QT and fatigue. Additional 8 pts were treated at MTD. Grade 3-4 toxicities included myelosuppression requiring transfusion (n= 13) and growth factors (n=6), fatigue (n=11), diarrhea (n=5), atrial fibrillation (n=1), shingles (n=1) and pneumonia (n=2). In 21 pts evaluable for response after cycle 2, there were 2 VGPR and 7 PR (ORR of 42%), 10 pts had SD and 2 had PD. The PK of vorinostat after a single oral dose were linear from 100-500 mg with mean AUC of 0.7 + 0.45 to 4.4+ 0.07 mM/h, Cmax 0.3 + 0.14 to 1.2 + 0.06 mM and Tmax 1.3 + 0.4 to 2.3 + 2.5 /h. Ten pts had CD138+ cells isolated from bone marrow on day 1 and on day 11 of cycle 1; PD studies showed reduction of NF-KB, Bcl-2, bcl-xl, p21, XIAP in responders compared to pts with SD/PD. MTD is Bort 1.3 mg/ m2 d 1, 4, 8, 11 and vorinostat 400 mg days 4-11 . The regimen is well tolerated and has promising activity in MM.

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: E450a

and

Time: 11:30 AM - 12:30 PM

Location: 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 II study evaluated Len/Bz/Dex at the phase-I 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

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.

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. In addition to cytotoxicity, they investigate the effects of bortezomib combinations on Noxa and c-myc as markers of activity of bortezomib combinations. The authors find that VDDR shows higher efficacy in preclinical models, providing a rationale for a phase I/II clinical trial in newly diagnosed myeloma, and that based on these preliminary results, specific Noxa induction can be used as a biomarker for pre-clinical evaluation of the efficacy of Velcade-based regimens in 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 pre-clinical evaluation of the efficacy of Velcade-based regimens in myeloma.

VELCADE® Publications – 2nd Quarter, 2008

Proteasome inhibitors: poisons and remedies.

Meiners S, Ludwig A, Stangl V, Stangl K.

Med Res Rev. 2008 Mar;28(2):309-27.



http://www.ncbi.nlm.nih.gov/pubmed/17880010?ordinalpos=93&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This article reviews the current applications of proteasome inhibitors, such as bortezomib, in clinical research according to their cellular effects as poisons or as remedies.

The proteasome inhibitor bortezomib has been approved as a cytostatic drug for the therapy of multiple myeloma, and is currently being tested in clinical trials for a variety of other malignancies. At the same time, a growing number of animal studies suggest that proteasome inhibitors may also prove to be valuable remedies for the treatment of non-tumorous diseases. In this review, we will revisit the current applications of proteasome inhibitors in clinical research according to the cellular effects of proteasome inhibitors as poisons, which induce apoptosis, or as remedies, which modulate cellular function and protect from cell death. We postulate that the correct distinction of a poison from a remedy depends on cell type and on the degree of proteasome inhibition. Dose-dependent and differential inhibition of the proteasome may affect specific sets of substrates, thereby conferring substrate specificity. According to this idea, we suggest that inhibition of the proteasome to a defined degree may offer a promising tool in achieving desired therapeutic effects in various diseases.

A phase I and pharmacologic study of the combination of bortezomib and pegylated liposomal doxorubicin in patients with refractory solid tumors.

Dees EC, O'Neil BH, Lindley CM, Collichio F, Carey LA, Collins J, Riordan WJ, Ivanova A, Esseltine D, Orlowski RZ.

Cancer Chemother Pharmacol. 2008 Mar 8 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18327587?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors conduct a phase I trial of bortezomib and pegylated liposomal doxorubicin in patients with refractory solid tumors and find a regimen of bortezomib that merits further investigation.

PURPOSE: Pre-clinical studies combining the proteasome inhibitor bortezomib with anthracyclines have shown enhanced anti-tumor activity. We conducted a phase I trial of bortezomib and pegylated liposomal doxorubicin (PLD) in patients with refractory solid tumors. **METHODS:** Patients received bortezomib, 0.9-1.5 mg/m², on days 1, 4, 8, and 11 of every 21-day cycle, along with PLD, 30 mg/m², on day 4. The goals were to determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD), and to investigate pharmacokinetic and pharmacodynamic interactions of the combination. **RESULTS:** A total of 37 patients with four median prior therapies were treated. Frequent grade 1-2 toxicities included fatigue, nausea, thrombocytopenia, anemia, neutropenia, constipation, myalgias, and peripheral neuropathy. DLTs included grade 3 nausea and vomiting in 1 of 6 patients receiving bortezomib at 1.2 mg/m², and grade 3 nausea, vomiting, and diarrhea in 1 of 6 patients receiving bortezomib at 1.5 mg/m². Grade 3 toxicities in later cycles included hand-foot syndrome, thrombocytopenia, anemia, neutropenia, nausea, diarrhea, and abdominal pain. Because of frequent dose-delays, dose-reductions, and gastrointestinal toxicity at the 1.4 and 1.5 mg/m² levels, bortezomib at 1.3 mg/m² and PLD at 30 mg/m² are recommended for further testing. Among 19 patients with breast cancer, four had evidence of a clinical benefit. Pharmacokinetic and pharmacodynamic studies did not show any significant interactions between the two drugs. **CONCLUSIONS:** A regimen of bortezomib, 1.3 mg/m² on days 1, 4, 8, and 11 with PLD, 30 mg/m², on day 4 of a 21-day cycle, was safe in this study, and merits further investigation.

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.

 **Bortezomib in relapsed or refractory multiple myeloma: results in a cohort of 39 patients.** [Article in Spanish]

Cánovas Fernández A, Alonso Alonso JJ, Barreiro García JG, Aguirre Errasti C.

Rev Clin Esp. 2008 Apr;208(4):187-92.



http://www.ncbi.nlm.nih.gov/pubmed/18381003?ordinalpos=59&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study verifies the time to treatment failure, overall survival and safety of bortezomib in the treatment of relapsed or refractory myeloma patients.

INTRODUCTION: Bortezomib has presently become a significant rescue treatment in multiple myeloma (MM) due to its observed effectiveness and safety in multicenter trials. We have aimed to verify both aspects in a setting of non-selected patients. **PATIENTS AND METHODS:** This is an observational, prospective study of the cohort of relapsed or refractory MM patients treated with bortezomib in our Department. The variables analyzed were response, its duration, time to the treatment failure (TTF), overall survival (OS), response related conditions and toxicity. Statistical methods used were Fisher's exact test, log rank-test and Kaplan-Meier survival tables. **RESULTS:** A total of 39 patients, 25 relapsed and 14 refractory to chemotherapy, started the treatment. The mean number of previous treatment was 2.3 and they received an average of 5.8 cycles of bortezomib. Complete response was achieved in 14 patients (36%), partial response in 12 (31%) and minor or no response in 13 ones (33%). Median duration of response was 8 months, median TTF was 10 months and median OS, from the onset of bortezomib was 16.5 months, with a median observation of live patients of 12.5 months. The response was more frequent in males ($p = 0.019$) and in patients with one previous treatment ($p = 0.15$). There were no significant differences regarding to TTF when we considered the cause of treatment (relapse or no response to chemotherapy) nor in the number of previous treatment regimes. The most frequent adverse events were reversible thrombocytopenia (31%), polyneuropathy (28%) and asthenia-anorexia (23%). **CONCLUSIONS:** In our cohort of non-selected, relapsed or refractory MM patients, the observations found in the multicenter randomized trials results regarding response rate and duration, TTF OS and safety of bortezomib therapy were verified.

 **Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression.**

Mateos MV, Hernández JM, Hernández MT, Gutiérrez NC, Palomera L, Fuertes M, Garcia-Sanchez P, Lahuerta JJ, de la Rubia J, Terol MJ, Sureda A, Bargay J, Ribas P, Alegre A, de Arriba F, Oriol A, Carrera D, García-Laraña J, García-Sanz R, Bladé J, Prósper F, Mateo G, Esseltine DL, van de Velde H, San Miguel JF.

Haematologica. 2008 Apr;93(4):560-5 [Epub 2008 Mar 5].



http://www.ncbi.nlm.nih.gov/pubmed/18322252?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors combine melphalan and prednisone with novel agents and find that the regimen of bortezomib plus melphalan and prednisone is highly active and well tolerated in elderly patients with newly diagnosed myeloma.

BACKGROUND: New treatment options offering enhanced activity in elderly, newly diagnosed patients with multiple myeloma are required. One strategy is to combine melphalan and prednisone with novel agents. We previously reported an 89% response rate, including 32% complete responses and 11% near complete responses, in our phase 1/2 study of bortezomib plus melphalan and prednisone (VMP) in 60 newly diagnosed multiple myeloma patients with a median age of 75 years. Here, we report updated time-to-events data and the impact of poor prognosis factors on outcome. **DESIGN AND METHODS:** Updated analyses of time to biochemical progression and overall survival with VMP were conducted, and compared with those of historical controls treated with melphalan and prednisone. A univariate analysis was performed to evaluate the influence of known prognostic factors on the time to progression. **RESULTS:** After a median follow-up of 26 months, the median time to progression with VMP was 27.2 months, compared with 20.0 months with melphalan plus prednisone. The median overall survival with VMP was not reached versus 26 months with melphalan and prednisone; the survival rate at 38 months was 85% versus 38%, respectively. Time to progression was not significantly affected by elevated beta(2)-microglobulin or lactate dehydrogenase levels, advanced age, or cytogenetic abnormalities, but was shorter in patients with albumin < 3 g/dL, Karnofsky performance status < or =70%, bone marrow plasma cell infiltration > or =40%, and, particularly, high plasma cell proliferative activity (> or = 2.5% S-phase cells). **CONCLUSIONS:** VMP is highly active and well tolerated in elderly patients with newly diagnosed multiple myeloma, with 85% of patients alive at 3 years. Moreover, VMP may overcome the poor prognostic impact of various factors, particularly cytogenetic abnormalities.

 **Efficacy of bortezomib combined dexamethasone in 24 patients with multiple myeloma.** [Article in Chinese]

Li J, Zhao Y, Luo SK, Huang BH, Ding Y, Tong XZ, Wang HH, Zheng D, Su C, Peng AH.

Ai Zheng. 2008 Apr;27(4):429-34.



http://www.ncbi.nlm.nih.gov/pubmed/18423132?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that the combination of bortezomib and dexamethasone shows obvious effects on myeloma, especially in the patients with light-chain type. They also conclude that adverse events can be tolerated in most patients, and that the regimen is safe in the patients with renal impairment.

BACKGROUND & OBJECTIVE: Bortezomib, a potent and reversible proteasome inhibitor, induces apoptosis of myeloma cells, resulting in durable responses in patients with multiple myeloma (MM). This study was to explore the medical effects and side effects of

bortezomib combined dexamethasone in treating newly diagnosed and relapsed or refractory MM, and evaluate the safety of this regimen in the patients with renal impairment. **METHODS:** Twenty-four MM patients were treated with bortezomib and dexamethasone in a 21-day cycle. The patients received a median of 3 cycles (range, 1-8 cycles) of the treatment. Response to bortezomib was evaluated according to the criteria of the European Group for Blood and Marrow Transplantation (EBMT) adverse events were graded according to the National Cancer Institute Common Toxicity Criteria. **RESULTS:** During the follow-up with a median of 4 months, 19 (79.2%) patients responded to the treatment. The complete remission (CR) rate was significantly higher in the patients of light-chain type than in those of non-light-chain type (57.1% vs. 5.9%, $P=0.014$). The response rates of the patients with and without renal impairment were similar (100% vs. 70.6%, $P=0.272$), and the renal functions were ameliorated in the patients with renal impairment during chemotherapy. Grade III-IV adverse events, including leucocytopenia (8.3%), thrombocytopenia (33.3%), diarrhea (8.3%) and debility (4.2%), could be relieved by symptomatic treatment or delayed chemotherapy. **CONCLUSIONS:** The combination of bortezomib and dexamethasone shows obvious effects on MM, especially in the patients with light-chain type. The adverse events can be tolerant in most patients, and this regimen is also safe in the patients with renal impairment.

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 bortezomib – 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.

Persistent supravenuous eruption induced by intravenous bortezomib therapy.

Mataix J, Betloch I, Palmero F, Romero A.

Br J Dermatol. 2008 Apr;158(4):863-4 [Epub 2008 Feb 16].



http://www.ncbi.nlm.nih.gov/pubmed/18284402?ordinalpos=45&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

Combined pegylated liposomal doxorubicin and bortezomib is highly effective in patients with recurrent or refractory multiple myeloma who received prior thalidomide/lenalidomide therapy.

Sonneveld P, Hajek R, Nagler A, Spencer A, Bladé J, Robak T, Zhuang SH, Harousseau JL, Orłowski RZ; DOXIL-MMY-3001 Study Investigators.

Cancer. 2008 Apr 1;112(7):1529-37.



http://www.ncbi.nlm.nih.gov/pubmed/18300257?ordinalpos=44&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this study, the authors observe a significantly prolonged time to progression with combined pegylated liposomal doxorubicin (PLD) plus bortezomib compared with bortezomib alone, despite prior immunomodulatory drug (IMiD) exposure. Similarly, the safety profile of the PLD plus bortezomib combination was unaltered by prior IMiD exposure.

BACKGROUND: Recently, the authors reported improved time to disease progression (TTP) with a combination of pegylated liposomal doxorubicin (PLD) and bortezomib compared with bortezomib alone in a phase 3 randomized trial in patients with recurrent/refractory multiple myeloma (MM). In the current analysis, they determined 1) the efficacy of PLD plus bortezomib versus bortezomib alone in patients with MM who had failed on prior thalidomide/lenalidomide (immunomodulatory drug [IMiD]) treatment and 2) the efficacy and safety profile of PLD plus bortezomib in IMiD-exposed and IMiD-naïve patients. **METHODS:** This prespecified analysis included 646 patients who were randomized to receive either PLD with bortezomib ($n=324$; 194 IMiD-naïve patients and 130 IMiD-exposed patients) or bortezomib alone ($n=322$; 184 IMiD-naïve patients and 138 IMiD-exposed patients). The primary efficacy endpoint was TTP, and secondary endpoints included overall survival, response rate, and safety. **RESULTS:** The median TTP was significantly longer with PLD plus bortezomib compared with bortezomib alone in IMiD-exposed patients (270 days vs 205 days). No statistical difference was noted with respect to TTP between IMiD-naïve (295 days) versus IMiD-exposed (270 days) subgroups who received PLD plus bortezomib. A sustained trend favoring combination therapy was observed in analyses of overall survival. In patients who achieved a response, the response duration was comparable for IMiD-naïve patients and IMiD-exposed patients in the combination treatment group and

lasted a median of 310 days and 319 days, respectively. The incidence of grade 3/4 adverse events was similar with PLD plus bortezomib regardless of prior IMiD exposure. **CONCLUSIONS:** A significantly prolonged TTP was observed with combined PLD plus bortezomib combination therapy compared with bortezomib alone despite prior IMiD exposure. For the combination treatment arm in the IMiD-naive and IMiD-exposed subgroups, TTP was comparable. Similarly, the safety profile of the PLD plus bortezomib combination was unaltered by prior IMiD exposure.

 ***Pulse treatment with the proteasome inhibitor bortezomib inhibits osteoclast resorptive activity in clinically relevant conditions.***

Boissy P, Andersen TL, Lund T, Kupisiewicz K, Plesner T, Delaissé JM.

Leuk Res. 2008 Apr 2 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18394701?ordinalpos=41&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors test bortezomib on cultured osteoclasts in conditions mimicking the pulse treatment used in the clinic, and demonstrate a direct inhibition of osteoclasts by bortezomib in conditions relevant to treatment of myeloma.

Myeloma bone disease is due to bone degradation by osteoclasts, and absence of repair by bone forming osteoblasts. Recent observations suggest that the anti-myeloma drug bortezomib, a proteasome inhibitor, stimulates bone formation and may inhibit bone resorption. Here, we tested bortezomib on cultured osteoclasts in conditions mimicking the pulse treatment used in the clinic, thereby avoiding continuous proteasome inhibition and unselective toxicity. A 3h pulse with 25nM bortezomib followed by a 3-day culture in its absence markedly inhibited osteoclast activity as evaluated through bone resorption, TRAcP release, and RANKL-induced NF-kappaB translocation into nuclei, an event dependent on proteasomes and critical for osteoclast function. The effect on TRAcP was maximal during the first 24h post-pulse, and then tended to subside. Importantly, applying this pulse treatment to cultured myeloma cells drastically reduced their survival. We measured next the levels of two bone resorption markers in patients during the 3 days following five and seven therapeutic bortezomib administrations, respectively. These levels decreased significantly already 1-2 days after injection, and then increased, showing temporary inhibition of osteoclast activity and paralleling the in vitro effect on TRAcP. Our study demonstrates a direct inhibition of osteoclasts by bortezomib in conditions relevant to treatment of myeloma.

 ***p38 mitogen-activated protein kinase inhibitor LY2228820 enhances bortezomib-induced cytotoxicity and inhibits osteoclastogenesis in multiple myeloma; therapeutic implications.***

Ishitsuka K, Hideshima T, Neri P, Vallet S, Shiraishi N, Okawa Y, Shen Z, Raje N, Kiziltepe T, Ocio EM, Chauhan D, Tassone P, Munshi N, Campbell RM, Dios AD, Shih C, Starling JJ, Tamura K, Anderson KC.

Br J Haematol. 2008 Apr 7 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18397345?ordinalpos=39&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This study suggests that LY2228820 represents a promising novel targeted approach to improve myeloma patient outcome both by enhancing the effect of bortezomib and by reducing osteoskeletal events.

The interaction between multiple myeloma (MM) cells and the bone marrow (BM) microenvironment induces proliferation and survival of MM cells, as well as osteoclastogenesis. This study investigated the therapeutic potential of novel p38 mitogen-activated protein kinase (p38MAPK) inhibitor LY2228820 (LY) in MM. Although cytotoxicity against MM cell lines was modest, LY significantly enhanced the toxicity of bortezomib by down-regulating bortezomib-induced heat shock protein 27 phosphorylation. LY inhibited interleukin-6 secretion from long term cultured-BM stromal cells and BM mononuclear cells (BMMNCs) derived from MM patients in remission. LY also inhibited macrophage inflammatory protein-1alpha secretion from patient MM cells and BMMNCs as well as normal CD14 positive osteoclast precursor cells. Moreover, LY significantly inhibited in vitro osteoclastogenesis from CD14 positive cells induced by macrophage-colony stimulating factor and soluble receptor activator of nuclear factor-kappaB ligand. Finally, LY also inhibited in vivo osteoclastogenesis in a severe combined immunodeficiency mouse model of human MM. These results suggest that LY represents a promising novel targeted approach to improve MM patient outcome both by enhancing the effect of bortezomib and by reducing osteoskeletal events.

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

Ciolfi 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/m² 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/m² (30 mg/m² 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.

Fatty acid synthase is a novel therapeutic target in multiple myeloma.

Okawa Y, Hideshima T, Ikeda H, Raje N, Vallet S, Kiziltepe T, Yasui H, Enatsu S, Pozzi S, Breitkreutz I, Cirstea D, Santo L, Richardson P, Anderson KC.

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



http://www.ncbi.nlm.nih.gov/pubmed/18410446?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that Cerulenin shows synergistic cytotoxic effects with various agents, including bortezomib.

This study investigated the biological significance of the inhibition of fatty acid synthase (FAS) in multiple myeloma (MM) using the small molecule inhibitor Cerulenin. Cerulenin triggered growth inhibition in both MM cell lines and MM patient cells, and overcame the survival and growth advantages conferred by interleukin-6, insulin-like growth factor-1, and bone marrow stromal cells. It induced apoptosis in MM cell lines with only modest activation of caspase -8, -9, -3 and PARP; moreover, the pan-caspase inhibitor Z-VAD-FMK did not inhibit Cerulenin-induced apoptosis and cell death. In addition, treatment of MM cells with Cerulenin primarily up-regulated apoptosis-inducing factor/endonuclease G, mediators of caspase-independent apoptosis. Importantly, Cerulenin induced endoplasmic reticulum stress response via up-regulation of the Grp78/IRE1alpha/JNK pathway. Although the C-Jun-NH(2)-terminal kinase (JNK) inhibitor SP600215 blocked Cerulenin-induced cytotoxicity, it did not inhibit apoptosis and caspase cleavage. Furthermore, Cerulenin showed synergistic cytotoxic effects with various agents including Bortezomib, Melphalan and Doxorubicin. Our results therefore indicate that inhibition of FAS by Cerulenin primarily triggered caspase-independent apoptosis and JNK-dependent cytotoxicity in MM cells. This report demonstrated that inhibition of FAS has anti-tumour activity against MM cells, suggesting that it represents a novel therapeutic target in MM.

Anti-myeloma effect of homoharringtonine with concomitant targeting of the myeloma-promoting molecules, Mcl-1, XIAP, and beta-catenin.

Kuroda J, Kamitsuji Y, Kimura S, Ashihara E, Kawata E, Nakagawa Y, Takeuchi M, Murotani Y, Yokota A, Tanaka R, Andreeff M, Taniwaki M, Maekawa T.

Int J Hematol. 2008 Apr 17 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18415656?ordinalpos=35&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that, in combination, homoharringtonine enhances the effects of several agents, including bortezomib.

Since a variety of cell intrinsic and extrinsic molecular abnormalities cooperatively promote tumor formation in multiple myeloma (MM), therapeutic approaches that concomitantly target more than one molecule are increasingly attractive. We herein demonstrate the anti-myeloma effect of a cephalotaxus alkaloid, homoharringtonine (HHT), an inhibitor of protein synthesis, through the induction of apoptosis. HHT significantly reduced Mcl-1, a crucial protein involved in myeloma cell survival, in all three myeloma cell lines examined, whereas certain BH3-only proteins, such as Bim, Bik, and Puma, remained unchanged following HHT treatment, and their expression levels depended on the cell type. HHT also reduced the levels of c-FLIP(L/S), activated caspase-8, and induced active truncated-Bid. Thus, HHT-induced apoptosis appears to be mediated via both intrinsic and extrinsic apoptosis pathways, and the resultant imbalance between BH3-only proteins and Mcl-1 may be pivotal for apoptosis by HHT. In addition, HHT treatment resulted in reduced levels of beta-catenin and XIAP proteins, which also contribute to disease progression and resistance to chemotherapy in MM. In combination, HHT enhanced the effects of melphalan, bortezomib, and ABT-737. These results suggest that HHT could constitute an attractive option for MM treatment though its ability to simultaneously target multiple tumor-promoting molecules.

Completion of pre-maintenance phases in total therapies 2 and 3 improves clinical outcomes in multiple myeloma: an important variable to be considered in clinical trial designs.

Barlogie B, Haessler J, Pineda-Roman M, Anaissie E, van Rhee F, Kiwan E, Steward D, Gurley J, Jenkins B, Crowley J.

Cancer. 2008 Apr 23 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18433012?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In this study the authors find that, after adjusting for completion of therapy, event-free survival is superior in the total therapy program that included bortezomib, thereby supporting its beneficial role.

BACKGROUND.: Total Therapy (TT) programs are complex and their execution over the course of several years is fraught with patient attrition due to failure and toxicity of therapy and patient/physician acceptance. METHODS.: The impact of completion versus

noncompletion of intended treatment steps was examined in protocols TT2 (n = 668) and TT3 (n = 303) on overall survival (OS) and event-free survival (EFS). RESULTS.: By using appropriate landmarks of 36 months with TT2 and 18 months with TT3, representing the maxima to completion of pre-maintenance phases, postconsolidation OS was superior for 211 patients completing versus 311 patients not completing pre-maintenance steps on TT2 (P = .001), which also pertained to the 161 patients completing versus 47 not completing intended treatment steps on TT3 (P = .01). On multivariate analysis that included all patients, completion of therapy independently favored longer OS and EFS in the context of both standard prognostic factors and gene expression profiling-defined risk; in addition, TT3 prolonged EFS over results obtained with TT2. CONCLUSIONS.: 1) Completion of intended therapy was a significant independent variable conferring superior OS and EFS in TT programs; and 2) after adjusting for completion of therapy, EFS was still superior with TT3 versus TT2, supporting the beneficial role of bortezomib included in TT3. Collectively, these data point to the importance of designing clinical trials that balance the treatment requirements for disease control with host acceptance and tolerance.

 ***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/m² (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/m². 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/m² 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).

 ***Updated follow-up of patients treated with bortezomib for relapsed multiple myeloma.***

Santini D, Vincenzi B, Tonini G.

Nat Clin Pract Oncol. 2008 Apr 29 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18446143?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

No abstract available.

 ***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, Delilieri GL, Sacchi S.

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



http://www.ncbi.nlm.nih.gov/pubmed/18452078?ordinalpos=27&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.

Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up.

Popat R, Oakervee HE, Hallam S, Curry N, Odeh L, Foot N, Esseltine DL, Drake M, Morris C, Cavenagh JD.

Br J Haematol. 2008 May;141(4):512-6 [Epub 2008 Mar 26].



http://www.ncbi.nlm.nih.gov/pubmed/18371113?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that bortezomib, doxorubicin and dexamethasone is highly active as front-line induction in myeloma, and that bortezomib dose reduction may help manage toxicities while retaining efficacy.

Bortezomib, doxorubicin and dexamethasone (PAD) was evaluated as induction before stem cell transplantation in newly diagnosed multiple myeloma (MM) patients, using bortezomib 1.3 mg/m² (PAD1, N = 21) or 1.0 mg/m² (PAD2, N = 20). Complete/very good partial response rates with PAD1/PAD2 were 62%/42% postinduction and 81%/53% post-transplant. Progression-free survival (29 vs. 24 months), time to re-treatment (36 vs. 29 months) and overall survival (1 year: 100% vs. 95%; 2 years: 95% vs. 73%) were statistically similar but favoured PAD1 versus PAD2. Toxicity was lower in PAD2; bortezomib dose reduction may help manage toxicities while retaining efficacy. PAD is highly active as front-line induction in MM.

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 bortezomib.

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.

Redox homeostasis modulates the sensitivity of myeloma cells to bortezomib.

Nerini-Molteni S, Ferrarini M, Cozza S, Caligaris-Cappio F, Sitia R.

Br J Haematol. 2008 May;141(4):494-503 [Epub 2008 Mar 12].



http://www.ncbi.nlm.nih.gov/pubmed/18341633?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find tight links between sensitivity to proteasome inhibition and redox homeostasis in myeloma cells, a relationship with potential implications for myeloma patient treatment.

The use of proteasome inhibitors have been a major advance in the treatment of multiple myeloma (MM), but their mechanisms of action remain largely unclear. A better understanding of the cellular events downstream of proteasome inhibition is essential to improve the response and identify new combination therapies for MM and other malignancies. This study analysed the relationships between redox homeostasis and bortezomib treatment in MM cells. Our data showed that decreasing intracellular glutathione through buthionine sulfoximine treatment strongly enhances bortezomib toxicity, whilst antioxidants protect MM cells from bortezomib-mediated cell death. Bortezomib treatment decreases intracellular glutathione both in MM cell lines and in malignant plasma cells obtained from MM patients. Glutamate-cysteine ligase (GCLM) and haem-oxygenase-1 (HMOX1), two genes involved in the Nrf-2-mediated antioxidant response, as well as two eIF2 α -downstream transcription factors, activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP), are upregulated, indicating that redox-related adaptive responses are initiated in bortezomib-treated MM cells. These findings demonstrate tight links between sensitivity to proteasome inhibition and redox homeostasis in MM cells and have potential implications for treatment.

 ***Treatment of patients with multiple myeloma complicated by renal failure with bortezomib-based regimens.***

Roussou M, Kastritis E, Migkou M, Psimenou E, Grapsa I, Matsouka C, Barmparousi D, Terpos E, Dimopoulos MA.

Leuk Lymphoma. 2008 May;49(5):890-5.



http://www.ncbi.nlm.nih.gov/pubmed/18464107?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find that bortezomib based regimens can be administered to myeloma patients with renal impairment; their toxicity and efficacy are similar to those observed in patients without renal impairment. Moreover, bortezomib-based regimens induce improvement of serum creatinine in most patients and reversal of renal failure in approximately one-third.

Renal failure is a common feature of multiple myeloma and a major management problem. However there is limited data regarding the reversibility of renal failure, the kinetics of serum creatinine and the safety of novel agents such as bortezomib when administered to newly diagnosed or relapsed/refractory patients with renal failure. **PATIENTS AND METHODS:** We evaluated 20 consecutive patients with newly diagnosed or relapsed/refractory multiple myeloma and renal failure, defined as a serum creatinine ≥ 2 mg/dl. All patients received bortezomib with dexamethasone or in combination with other agents (thalidomide, doxorubicin or melphalan). **RESULTS:** Reversal of renal failure was documented in 40% of all patients and the median time to reversal was 17 days. Moreover 10 patients (50%) had 50% decrease in serum creatinine and the median time to decrease was 35 days. Some decrease of creatinine was documented in 85% of patients. The objective response rate was 65%. Toxicities were similar to those seen in myeloma patients without renal failure. **CONCLUSIONS:** Bortezomib based regimens can be administered to myeloma patients with renal impairment and their toxicity and efficacy are similar to those observed in patients without renal impairment. Moreover, bortezomib-based regimens induce improvement of serum creatinine in most patients and reversal of renal failure in approximately one-third.

 ***Small-molecule inhibition of proteasome and silencing by vascular endothelial cell growth factor-specific siRNA induce additive antitumor activity in multiple myeloma.***

Koldehoff M, Beelen DW, Elmaagacli AH.

J Leukoc Biol. 2008 May 5 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18458152?ordinalpos=14&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

This data suggest that small-molecule inhibition of proteasome and silencing by vascular endothelial growth factor-specific small interfering RNA may be associated with an additive antitumor activity, including in combination with bortezomib, and might be a suitable target for new, myeloma therapeutic strategies.

Angiogenesis plays an important role in the pathogenesis and progression in multiple myeloma (MM), and MM cells secrete vascular endothelial growth factor (VEGF), which further promotes proliferation of the tumor cells. Therefore, we evaluated the anti-myeloma effect of VEGF small interfering RNA (siRNA) silencing in MM cells and whether it can be augmented by the additional application of bortezomib directed against the 26S proteasome. After transfection with VEGF siRNA, we observed a reduction of VEGF expression in all studied cell lines: OPM-2, RPMI-8226, INA-6, Jurkat, Raji, and Karpas-299, as well as in cells of MM and lymphoma patients. VEGF siRNA significantly induced apoptosis and inhibited proliferation in OPM-2 cells ($P < 0.0001$), RPMI-8226 ($P < 0.0001$), and INA-6 ($P < 0.01$) versus controls. Cotreatment with VEGF siRNA and bortezomib in MM cells resulted in an exaggerated inhibition of proliferation and induction of apoptosis compared with VEGF siRNA or bortezomib alone ($P < 0.001$). In addition, the combination of VEGF siRNA and bortezomib significantly ($P < 0.01$) reversed multidrug resistance gene 1-dependent resistance of MM cells. Our data suggest that small-molecule inhibition of proteasome and silencing by VEGF-specific siRNA may be associated with an additive antitumor activity and might be a suitable target for new, therapeutic strategies using RNA interference in MM.

 ***Safety and efficacy of bortezomib and melphalan combination in patients with relapsed or refractory multiple myeloma: updated results of a phase 1/2 study after longer follow-up.***

Berenson JR, Yang HH, Vescio RA, Nassir Y, Mapes R, Lee SP, Wilson J, Yellin O, Morrison B, Hilger J, Swift R.

Ann Hematol. 2008 May 8 [Epub ahead of print].



http://www.ncbi.nlm.nih.gov/pubmed/18463870?ordinalpos=10&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors find bortezomib plus melphalan to be a steroid- and immunomodulatory drug-free regimen that may provide a treatment alternative for elderly patients and patients with significant comorbidity.

Bortezomib synergizes with melphalan in preclinical and early clinical studies. Updated data from our phase 1/2 study assessing the safety and efficacy of bortezomib plus melphalan in relapsed/refractory multiple myeloma (MM) are presented. Bortezomib (0.7, 1.0, or 1.3 mg/m²) on days 1, 4, 8, and 11 and oral melphalan (0.025-0.25 mg/kg) on days 1-4 of a 28-day cycle were administered. Hematologic toxicities defined the maximum tolerated dose as bortezomib 1.0 mg/m² and melphalan 0.10 mg/kg. Because dose-limiting toxicities were attributed to the more myelosuppressive melphalan, cohorts 9 and 10 with higher bortezomib (1.3 mg/m²) and lower melphalan (0.025 and 0.10 mg/kg) doses were added. Responses occurred in 32/46 (70%) evaluable patients: two complete (4%), five near-complete (11%), 16 partial (35%), and nine minimal (20%). Complete and near-complete responses were observed only with higher bortezomib doses. Response rates were similar in patients with prior melphalan or bortezomib. Median progression-free survival was 9 months (range, 1-24), and overall survival was 32 months (range, 1-54). The most common grade 3/4 hematologic adverse events (AEs) were neutropenia

(31%/0%), thrombocytopenia (25%/2%), and anemia (13%/0%). Grade 4 tumor lysis syndrome was reported in one patient. Fewer grade 3/4 hematologic AEs were reported in cohorts 9 and 10 than in cohorts receiving lower bortezomib and higher melphalan doses. In conclusion, bortezomib plus melphalan is a steroid- and immunomodulatory drug-free regimen that may provide a treatment alternative for elderly patients and patients with significant comorbidity.

Expanding role of bortezomib in multiple myeloma: nursing implications.

Colson K, Doss DS, Swift R, Tariman J.

Cancer Nurs. 2008 May-Jun;31(3):239-49.



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The authors present the latest efficacy and safety data for bortezomib in relapsed multiple myeloma and characterize common side effects associated with bortezomib and the implications for nursing. They also highlight practical strategies for preventing and managing side effects, thereby enhancing the clinical benefit of bortezomib-based therapies to patients.

Multiple myeloma is the second most common hematologic malignancy and remains incurable, despite advances in chemotherapy and stem cell transplantation. Bortezomib, a novel proteasome inhibitor, is approved for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. In the assessment of proteasome inhibition for extending remissions phase III trial of bortezomib versus high-dose dexamethasone, bortezomib led to significantly longer survival and time to progression and higher response rate in patients with relapsed multiple myeloma. The principal adverse events were gastrointestinal effects, fatigue, transient thrombocytopenia, and reversible peripheral neuropathy. The side effect profile of bortezomib is extensively characterized, predictable, and generally manageable; retreatment or extended bortezomib therapy seems well tolerated. Nurses play a unique role in bortezomib treatment: they are often closest to the patients and are most able to educate patients about side effects and, if necessary, take appropriate action, independently or collaboratively with healthcare team members. In this review, we present the latest efficacy and safety data for bortezomib in relapsed multiple myeloma and characterize common side effects associated with bortezomib and the implications for nursing. We also highlight practical strategies for preventing and managing side effects, thereby enhancing the clinical benefit of bortezomib-based therapies to patients.

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.

Alkylating agents induce activation of NFkappaB in multiple myeloma cells.

Baumann P, Mandl-Weber S, Oduncu F, Schmidmaier R.

Leuk Res. 2008 Jul;32(7):1144-7 [Epub 2008 Feb 20].



http://www.ncbi.nlm.nih.gov/pubmed/18083229?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The authors show that the co-incubation of bortezomib with melphalan or doxorubicin reduces activation of NFkappaB, suggesting that the drug-sensitizing effect of bortezomib on myeloma cells is due to inhibition of melphalan- and doxorubicin-induced activation of NFkappaB activity. This study, therefore, supports the idea of combining a NFkappaB inhibitor with alkylating drugs in the therapy of multiple myeloma.

Multiple myeloma is still not curable and drug combination strategies are currently being evaluated in order to achieve high remission rates with tolerable toxicity. Bortezomib has been shown to exert inhibitory effects on NFkappaB activity. NFkappaB in turn is known to be activated by cytokines, growth factors and by cellular adhesion to bone marrow stromal cells and represents an important mediator of primary and secondary drug resistance in multiple myeloma that confers to proliferation and survival. In this study we confirm that bortezomib sensitized MM cells to the DNA-damaging drugs melphalan and doxorubicin. Further, we demonstrate that the sole incubation of MM cells with melphalan or doxorubicin leads to a vast activation of NFkappaB activity. Additionally, we show that the co-incubation of bortezomib with melphalan or doxorubicin reduces activation of NFkappaB. These data suggest that the drug-sensitizing effect of bortezomib on MM cells is due to inhibition of melphalan- and doxorubicin-induced activation of NFkappaB activity. This study, therefore, supports the idea of combining a NFkappaB inhibitor with alkylating drugs in the therapy of multiple myeloma.

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

van Marion AM, Auwerda JJ, Lisman T, Sonneveld P, de Maat MP, Lokhorst HM, Leebeek FW.

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 dexamethasone, 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 months 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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