Blood Abstracts: 54th ASH Annual Meeting Abstracts; Vol. 120, Issue 21, 16 Nov 2012

Abstract 943 Treatment with Bendamustine-Bortezomib-Dexamethasone (BBD) in Relapsed/Refractory Multiple Myeloma Shows Significant Activity and Is Well Tolerated

Heinz Ludwig[1], Hedwig Kasparu[2*], Richard Greil, MD[3], Clemens Leitgeb[1*], Ercan Müldür[1*], Elisabeth Rauch[1*], Niklas Zojer[1*], Eva Maria Autzinger[1*], Werner Linkesch[4*], Thomas Kuhr[5], Ludek Pour, MD, PhD[6*] and Zdenek Adam[7*]

[1]1st Department of Internal Medicine, Center for Oncology and Hematology, Wilhelminenhospital, Vienna, Austria
[2]Dpt. of Internal Medicine, Hospital Elisabethinen, Linz, Austria
[3]Department of Internal Medicine III, University Hospital Salzburg, Salzburg, Austria
[4]Department of Hematology, Medical University of Graz, Graz, Austria
[5]Department of Internal Medicine IV, Klinikum Wels-Grieskirchen, Wels, Austria
[6]Department of Internal Medicine,Hematology and Oncology, University Hospital Brno, Brno, Czech Republic
[7]Dept. of Internal Medicine - Hematooncology, University Hospital Brno, Brno, Czech Republic

Introduction: Bendamustine has emerged as attractive treatment option for low grade lymphomas and seems to exert synergistic activity with bortezomib. Here we evaluate the efficacy and tolerance of bendamustine in combination with bortezomib-dexamethasone in patients with relapsed/refractory multiple myeloma and focus on individual factors associated with outcome.

Patients and Methods: 74 patients with relapsed/refractory MM have been enrolled. Median age: 65 years (range 40-86), male/female: 34/40, ISS stage I/II/III: 24, 30, and 20, respectively. ECOG status 0/I/II: 39, 32, and 3 patients, respectively. Previous treatment lines: 1-2: 48, 3-4: 21, >4: 5 patients, respectively. Full data documentation for response evaluation (≥ 2 cycles) is available for 66 patients. Treatment regimen: bendamustine 70 mg/m^2 day 1+4, bortezomib 1.3 mg/m^2 days 1, 4, 8 and 11, dexamethasone 20 mg on days 1, 4, 8 and 11, repeated every 4 weeks. Planned number of treatment cycles was 8, with discontinuation after 4 cycles in case of no response. Kaplan Mayer curves were compared using the log-rank test and Cox regression was used for univariate and multivariate analysis of possible prognostic factors (FISH, age, LDH, Hb, Ca, pretreatment with lenalidomide, bortezomib and both lenalidomide+bortezomib).

Results: After a median follow up of 8.9 months, myeloma response (ORR: CR+VGPR+PR) was noted in 43 (65.2%) of the 66 evaluable patients. 14 (21.2%) patients achieved CR/nCR, 11 (16.7%) VGPR, 18 (27.3%) PR, 10 (15.2%) MR, and 13 (19.7%) remained stable; PD was not observed within the first 4 cycles. Median time to response was 108 days (3.65 months). Responses (CR-PR) were seen in 14 of 24 (58.3%) of patients with FISH determined high risk [ampl.1q21, del17p, t (4; 14)] and in 23 of 33 (69.7%) with standard risk (del13 or no aberration) cytogenetics (p=0.84). ORR (CR-PR) was 69.7% (30 of 43) and 56.5% (13 of 23) in patients with 1-2 or 3-6 prior treatment lines, respectively (p=0.77).

Median PFS was 9.7 months in the entire cohort and 12.9 and 7.8 months in patients with 1-2 or 3-6 prior treatment lines. Median overall survival in the entire cohort was 21 months. Univariate analysis showed a significant impact of pre-treatment with lenalidomide + bortezomib on response rate ($p<0.03$), TTP ($p<0.0001$) and OS

($p<0.022$), while in multivariate analysis, pre-exposure with Revlimid was correlated with a lower response rate (p=0.04) and shorter TTP ($p<0.007$). Other parameters correlating in multivariate analysis independently with TTP were age above 70 years

($p<0.006$) and increased LDH ($p<0.04$).

Tolerance. The regimen was well tolerated with low incidence of infections and gastrointestinal toxicities. Hematological toxicity remained stable from baseline to cycle 4, with G4 anemia, leucopenia and thrombopenia being recorded in < 5%. Patient self reported neuropathic symptoms at baseline were recorded as G1-2 in 54.7% and as G3-4 in 18.7%, respectively. This pattern changed from cycle 1 to 8 with twice as many (42.9%) patients reporting G3-4 PNP at cycle 8. A similar pattern was noted for physician assessed neurotoxicity using the CTC grading system. Frequency of G1-2 PNP increased from 18.9% at baseline to 63.2% at termination of therapy (cycle 8). Grade 3-4 PNP was reported only occasionally.

Conclusions: The BBD regimen yielded an ORR rate of 65.2% and median PFS of 9.7 months in the generally heavily pretreated patients. Poor risk cytogenetics were not associated with inferior outcome, but pre-treatment with lenalidomide was established as independent prognostic marker for lower response rate and shorter TTP. Although patients reported a doubling of the incidence of self-assessed G3-4 neurotoxicity from baseline to cycle 8, no unexpected or increased other toxicities were observed. These results highlight the BBD regimen as an active, relatively well tolerated protocol for patients with relapsed refractory multiple myeloma.

Disclosures: Ludwig: *Celgene:* Honoraria; *Janssen Cilag:* Honoraria; *Mundipharma:* Honoraria.

**signifies non-member of ASH*