POSTER SESSION II

Myeloma and other monoclonal gammopathies IV

0751

THE RISK OF THROMBOCYTOPENIA AND NEUROPATHY AFTER BORTEZOMIB THERAPY DEPENDS ON THE BASELINE PLATELET COUNTS AND PREVIOUS NEUROPATHY RESULTS OF CZECH MYELOMA GROUP

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Thrombocytopenia and neuropathy are the most frequent and serious complications of bortezomib therapy. However, previous data suggested that the risk of these adverse events depends on the baseline involvement associated mostly with previous therapy. Bortezomib as monotherapy was given to 82 consecutive patients with refractory/relapsed multiple myeloma in 5 centers in Czech republic. Thrombocytopenia and neuropathy were, of course, the most frequent complications, observed in 65,9% and 52,4% of patients, respectively. In 63 patients baseline platelet counts were within normal range, in 38 of them thrombocytopenia developed during the course of therapy. Nineteen patients had mild thrombocytopenia before the start of bortezomib treatment. The risk of thrombocytopenia was 60,3% (grade 3/4 thrombocytopenia 30,2%) in patients with normal baseline values and 84,2% (gr. 3/4 63,2%) in patients with previous abnormality. Similar relationship was observed in the case of neuropathy. The risk of neuropathy was 45,2% in patients without any signs of neurological involvement before the start of therapy compared with 75% risk in the patients with grade 1 of any type of neuropathy in the history. Grade 3/4 neuropathy occurred in 1,6% of patients in the first group and in 25% in the second one. *Conclusions.* Thrombocytopenia and, especially, neuropathy could lead to dose adjustment and/or premature termination of bortezomib therapy in myeloma patients. The association between the risk of these complications and the baseline involvement supports the statement that it would be advantageous to start treatment with bortezomib earlier in the course of disease.

0752

BORTEZOMIB (VELCADE) IN COMBINATION WITH LIPOSOMAL DOXORUBICIN (DOXIL) AND THALIDOMIDE IS AN ACTIVE SALVAGE REGIMEN IN PATIENTS WITH RELAPSE OR REFACTORY MULTIPLE MYELOMA: FINAL RESULTS OF A PHASE II STUDY

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Background. Tumor microenvironment (ME) plays an important role in MM. It is associated with disease progression, metastasis, and resistance to therapy. Therefore, targeting the ME and the tumor cell simultaneously may be an effective way to overcome resistance in pts with rel/ref MM. *Aims*. Orlowski *et al*. reported improved anti-tumor responses when bortezomib (V) was combined with doxil (D) in pts with hematologic malignancies. We investigated clinically, this approach i.e., targeting the MM cell as well as its ME, using a combination of V, D and low-dose thalidomide (T) as salvage therapy for pts with rel/ref MM. Here we report the final results of this phase II study. *Methods.* All pts with rel/ref disease were eligible for this study. V was given at 1.3mg/m^2 (D1,4,15,18) and D at 20mg/m^2 (D1,15) every 4 weeks with daily T (200 mg) for 4-6 cycles. SWOG criterion was used to assess response. Low-dose coumadin (1-2 mg po qd) was used for prevention of venous thromboembolism (VTE). *Results.* Twenty three pts (9M, 14F; median age -58 , range 43-80 yrs; 21MM, 2 WM) have been enrolled to date. All pts had Stage III disease, median b2M was 3.8 and median number of prior therapies were 3 (range 1-7). Prior therapies included stem cell transplant(SCT) in (41%), T (41%), adriamycin(A) (65%) steroids (82%) and velcade (12%). 74% had refractory disease. Seventeen pts have completed at least 1 cyc and are available for toxicity and response evaluation. One pt died of sepsis prior to completing 1 cyc and 1 pt with PR was taken off study for non-compliance after 1 cyc. ORR was with 65%(CR+PR) with 23% CR all of whom were IFE negative. Toxicity: 2 pts developed Gr. II plantar-palmar erythrodysthesia (PPE) and 1 had Gr. III cellulitis. No VTE was noted. No significant non-hematologic Gr. III/IV toxicity were seen. Despite prior exposure to anthracycle, we did not noted any cardiotoxicity with D. *Conclusions.* Pt with rel/ref MM usually have aggressive disease with paucity of effective regimens. VDT is a highly active salvage regimen that demosntrates high response rates including CR and acceptable toxicity in patients with relapsed/refractory multiple myeloma.Responses were noted despite prior failure of steroids, T ,A and even V. VTE does not appear to be a problem with this low dose coumadin prophylaxis. Final results of this phase II study will be presented at the annual EHA meeting.

0753

FLOW CYTOMETRIC IMMUNOPHENOTYPIC ANALYSIS OF 25 CASES OF PLASMA CELL LEUKEMIA

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The aim of the study was to determine expression of adhesion molecules CD11a (LFA-γ), CD18 (LFA-1γ), CD11b, CD29, CD49d, CD44 (H-CAM), CD54 (ICAM-1), CD56 (N-CAM) and CD117 (c-kit) on peripheral blood (PB) and bone marrow (BM) lymphoid cells in 25 plasma cell leukemia patients (PCL), at diagnosis and in the control group of 10 healthy subjects. Immunophenotyping was performed on freshly collected blood and bone marrow samples by means of flow cytometry. Plasma cells were identified as showing high-density expression of CD38 and CD138 (syndecan-1). *Results*. of analysis were presented both as relative and absolute (omitted in abstract) values of numbers of cells with antigen expression and as relative fluorescence indices (RFIs) of studied antigens. Statistical analysis was performed using Wilcoxon's test. All below presented differences are statistically significant. The study revealed in PCL patients a significantly higher relative and absolute number of CD54+ cells (in brackets: means±SD of PCL pts vs control) both in BM (63±29% vs 13±5%) and PB (49±25% vs 8±3%) as well as that of CD38+ cells both in BM (84±12% vs 54±11%) and PB (74±11% vs 52±7%). In turn, PCL patients showed a decreased relative number of BM: CD11a+cells (40±28% vs 73±10%), CD18+cells (47±25% vs 88±7%), CD11a+CD18+cells (42±27% vs 72±10%), CD44+cells (71±26% vs 93±4%), CD11b+cells (17±12% vs 35±10%) and PB: CD11a+cells (58±28% vs 96±3%), CD18+cells (58±29% vs 99±0,2%), CD11a+CD18+cells (58±29% vs 96±3%), CD44+cells (86±15% vs 98±0,9%). In BM of PCL patients compared with the control there were found decreased RFIs of CD18 (15,0±1,3 vs 16,6±0,7) and CD29 (8,6±1,4 vs 10,4±0,8) and increased RFIs of CD54 (16,9±2,5 vs 13,0±0,5) and CD11a (18,4±1,5 vs 14,7±0,9). In PB of PCL patients RFIs of CD29 (10,4±1,2) was lower than this in control (11,6±0,9) while RFIs of CD38 (16,9±3,0 vs 14,8±1,3), CD54 (16,1±2,8 vs 12,3 ±0,3), CD11a (20,4±1,8 vs 18,3±0,8) were higher. BM leukemic cells with strong CD38 expression and CD138 expression showed antigen coexpression in following number of cases: CD54 in 16/19 (82% tested), CD29 in 12/12 (100%), CD49d in 9/9 (100%), CD44 in 9/11 (82%), CD11a in 3/20 (15%), CD11b in 3/12 (25%), CD18 in 2/17 (11%), CD56 in 13/23 (56%), CD117 in 5/13 (38%) and CD19 in 0/13 (0%) tested cases. PB leukemic cells showed coexpression of CD54 in 17/19 (89%), CD29 in 12/13 (92%), CD49d in 11/11 (100%) CD44 in 9/10 (90%), CD11a in 9/20 (45%), CD11b in 8/12 (66%), CD18 in 11/17 (64%), CD56 in 13/22 (59%), CD117 in 5/13 (36%), CD19 in 0/16 (0%) of tested cases. *Conclusions*. Immunophenotype of leukemic plasma cells characterizes mainly increased expression of CD38, CD54 and CD138 also expression of CD29, CD49d, CD44 and disturbed expression of CD18, CD11a and CD11b. In one half cases tumor cells show expression of CD56 and CD117.

0754

INORGANIC POLYPHOSPHATE IS PRESENT AND INDUCES APOPTOSIS SPECIFICALLY IN HUMAN PLASMA CELLS

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Backgrounds. Inorganic polyphosphate (polyP), a ubiquitous phosphate polymer with ATP-like bonds, participates in a variety of functions including blood coagulation and cell proliferation. Recently, we have reported that human platelets have massive quantities of polyP accumulated in dense acidic granules known as acidocalcisomes, in a similar way to that occurring in unicellular microorganisms (*Ruiz et al. J Biol Chem 2004: 279:44250*). *Aims*. We have investigated here the presence of polyP in human plasma cells (PC), responsible for the production and maintenance of antibodies in response to antigens. We also study the effects of extracellular polyP in the biology of the human PC. *Methods*.We measured levels of polyP in the U266 and IM9 myeloma cell lines by a