

**0746****TUMOR ANGIOGENESIS AND SENSITIVITY TO THE IL-6 IN MULTIPLE MYELOMA: EXPRESSION OF THE MICROVESSEL DENSITY AND GP-130 INTERLEUKIN-6 TRANSDUCER WITHIN THE BONE MARROW COMPARTMENT**

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The functional interplay between the myeloma cells and the surrounding microenvironment within the bone marrow (BM) includes increased activity of endothelial cells resulting in neovascularisation, and enhanced sensitivity to the IL-6 as a main growth factor in multiple myeloma (MM). This cytokine, as a member of gp130 family, binds on the surface of myeloma cells to the IL-6 receptor  $\alpha$  chain that associates with the gp130 transducer chain (CD130), providing the proliferation signal to the tumor cells. The aim of study was to investigate the correlation between expression of BM angiogenesis estimated as microvessel density (MVD), and expression of the transmembrane signal transducer, gp130, in the bone marrow of MM patients (pts). The study included 60 newly diagnosed MM pts (33 male and 27 female pts, mean age 60 years, range 35-75). According to the clinical stage (CS, Salmon&Durie), distribution of MM pts was as follows: I 8pts, II 22pts, III 30pts. There were 35pts with IgG monoclonal (m) protein, 12pts with IgA, and 12pts with secretion of kappa/lambda chain. None secretory MM was diagnosed in 1pts. All pts were treated with standard chemotherapy regimens. BM vessels were visualized by immunohistochemical staining for CD34 (Bi-3C5, Santa Cruz Biotechnology, USA) on slides of formalin-fixed, paraffin-embedded BM biopsies. MVD was calculated by the number of vessels per 400x high-power microscopy field in the area of the most dense vascularization. All samples were further analyzed for the immunohistochemical expression of the gp130 (AN-H2, Santa Cruz Biotechnology, USA) which showed cytoplasmic and membrane localization. The intensity of these stainings was graded as weak (0-30% myeloma cells), moderate (31-60% myeloma cells), and strong (>60% myeloma cells). Control specimens were obtained from pts without hematological malignancy. According to the CS of myeloma, positive correlation was found between MVD and expression of GP130 in myeloma cells. The expression of MVD was significantly higher in MM pts in III CS than in pts in I CS of myeloma (15 vs. 7.5/  $\times 400$  field,  $p < 0,001$ ). Similarly, significantly higher expression of gp130 was found in pts in III CS of myeloma comparing to the MM pts in I CS (32 vs.15%,  $p < 0,05$ ). These findings of increased angiogenesis in correlation with high IL-6 sensitivity found in II/III CS of myeloma pointed out significantly shorter survival of those pts (26 vs. 43,5 m, log rank,  $p < 0,05$ ). In conclusion, strong activity of angiogenesis in myeloma, combined with high IL-6 sensitivity by immunohistochemical expression of gp130 represents possible predictive factors of poor prognosis.

**0747****CORRELATION BETWEEN THE CYTOGENETIC FINDINGS AND THE PROGNOSTIC FACTORS IN THE GROUP OF PATIENTS FROM THE CMG 2002 CLINICAL STUDY**J. Smejkalova,<sup>1</sup> P. Kuglik,<sup>2</sup> H. Filkova,<sup>2</sup> A. Oltova,<sup>2</sup> Z. Adam,<sup>2</sup> L. Pour,<sup>2</sup> M. Krejci,<sup>2</sup> M. Penka,<sup>2</sup> R. Hajek<sup>2</sup><sup>1</sup>University Hospital, BRNO, Czech Republic; <sup>2</sup>University Hospital, Brno, BRNO, Czech Republic

**Background.** Cytogenetic abnormalities in multiple myeloma (MM) are one of the most important independent prognostic factors. **Aims.** To determine the correlation between the aberration of the chromosome 13 (detected by molecular cytogenetic methods) and the prognostic factors in the pilot group of patients from the CMG 2002 clinical study (only data from one clinical centre covers 1/4 of patients) using three various of cut off levels (9%, 20%, 80%). **Methods.** Interphase fluorescence *in situ* hybridization (I-FISH) and fluorescence *in situ* hybridization and cytoplasm immunoglobulin staining (cIg-FISH) were used to detect the aberration of the chromosome 13. Cytogenetic abnormalities were found in 65 newly diagnosed patients with MM, the median of follow up was 22.8 month. **Results.** The aberration was found in 40% (26/65) patients (cut off levels 9%, 20%) and in 21.5% (14/65) patients (cut off level 80%). We have correlated standard prognostic factors (MIG, LDH,  $\beta 2M$ , Hb, platelet count, albumin), event free survival (EFS), and overall survival (OS) with the occurrence of the aberration of chromosome 13 detected by I-FISH on bone marrow slides and cIg-FISH. Higher MIG and lower albumin concentrations and platelet counts were detected in patients with aberration of chromosome 13 (cut off levels 9%, 20%), similar results were obtained for cut off level 80%. No prognostic sig-

nificance was found between aberration of chromosome 13 and the worst prognostic feature (EFS shorter than one year) in all cut off levels for aberration of chromosome 13. **Summary/Conclusion.** We have analysed the data from homogenous group of patients undergoing autologous transplantation in the CMG trial of Czech Myeloma Group. We have correlated standard prognostic factors (MIG, LDH,  $\beta 2M$ , Hb, platelet count, albumin), EFS, and OS with the occurrence of the aberration of chromosome 13 using three variants of cut off levels (9%, 20%, 80%). Higher MIG and lower albumin concentrations and platelet counts (for cut off level 80%) were detected in patients with aberration of chromosome 13 (cut off levels 9%, 20%). This analysis will be extended for all centres of CMG 2002.

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**0748****LOW-DOSE THALIDOMIDE AS MAINTENANCE THERAPY FOLLOWING SINGLE OR TANDEM AUTOTRANSPLANT IN ADVANCED MULTIPLE MYELOMA IMPROVES OVERALL RESPONSE WITH MILD TOXICITY**

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**Background.** Thalidomide has been introduced few years ago in the treatment of MM. At present is part of many clinical trials, especially as front line therapy in combination with desamethasone or chemotherapy. Although the activity of Thalidomide as monotherapy is widely accepted in relapsed or refractory MM, its role as maintenance therapy following autotransplant is still under investigation. The drug is effective but the toxicity, i.e the DVT, remains one of the main reasons of concern for many investigators, so that the schedule, dose and anti-thrombotic prophylaxis are still matter of debate. **Methods.** In 1999 we started a trial with conventional chemotherapy (3 cycles of VAD), followed by high-dose cyclophosphamide (7 g/m<sup>2</sup> i.v.) and peripheral stem cells (PBSC) harvest, followed by single or tandem autotransplant with melphalan (200 mg/m<sup>2</sup> i.v.), in patients affected by advanced MM (stage II-III Salmon-Durie). Thalidomide 100 mg a day was then given as maintenance to all patients regardless the type of response, and discontinued at the time of relapse or progression, or for toxicity. No anti-thrombotic prophylaxis has been administered. **Patient characteristics.** Between January 1999 and June 2005, 75 consecutive MM patients were enrolled. Seventy patients, median age 55 (range 46-66 years), M/F 43/27, are valuable. All these patients completed chemotherapy without major problems, and no toxic deaths occurred: 10/70 patients were in complete remission (CR) at the time of PBSC transplant, 34/70 reached CR after transplant (60/70 cases underwent tandem transplant), so that after chemotherapy 44/70 (62%) were in CR, defined as bone marrow plasmacytosis below 5% and absence of serum and urine paraprotein. Thalidomide was started when possible within 6 months following transplant: 21/70 patients could not be treated because of different reasons: progression of disease (6 cases), psychological problems (3), performance status <70% (2), neurological problems (2), refusal (1). Three cases were followed in other Institutions. Only 4 patients discontinued the drug in few weeks because of mild neurological toxicity (WHO < 2). The remaining 49 patients (70%) continued the drug until relapse or progression, for a median time of 24 months after transplant. **Results.** The CR rate after PBSC transplant was 69% in the group treated with thalidomide and 52% in the remaining patients. With a median follow-up of 38 months we compared the number of relapses/progressions, the time to relapse/progression, the disease free survival (DFS) and the overall survival (OS) in the two groups of patients. **Toxicity.** Most patients reported peripheral neuropathy, somnolence and constipation: when severe, a temporary adjustment of drug dose was able to control these symptoms. Despite the absence of anti-thrombotic prophylaxis, no DVT were observed. **Conclusions.** Low-dose Thalidomide following single or tandem autotransplant appears to be a safe and feasible maintenance treatment improving overall response rate without severe side effects. No anti-thrombotic prophylaxis is needed.

**Table 1. In results, after in the two groups of patients.**

	rel/progr (%)	time rel/prog	4 ys OS%	4 ys DFS % (p<0.08)
with thal	23/49 (46%)	31 mo	76	45
w/o thal	16/21 (76%)	24 mo	35	35