

## **Session IV: Micro-environment and Immune Regulation in WM**

### **Abstract 120**

#### **Presenter: E. Terpos**

**Angiogenesis in Waldenström's Macroglobulinemia.** Evangelos Terpos<sup>1</sup>, Anna Tasidou<sup>2</sup>, Efstathios Kastiris<sup>1</sup>, Evangelos Eleftherakis-Papaiakovou<sup>1</sup>, Maria Gavriatopoulou<sup>1</sup>, Magda Migkou<sup>1</sup>, Meletios-Athanassios Dimopoulos<sup>1</sup> <sup>1</sup>Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece & <sup>2</sup>Department of Hematopathology, Evangelismos Hospital, Athens, GREECE.

Angiogenesis represents an essential step of disease progression in several hematological malignancies. A Mayo Clinic study reported that microvessel density is increased (intermediate- or high- grade angiogenesis) in 30% of patients with Waldenström's macroglobulinemia (WM), showed only weak correlation with marrow infiltration and had no impact on patients' survival [Rajkumar et al, *Semin Oncol* 2003;30:262-4]. Our group has evaluated the serum levels of angiogenic cytokines in 56 WM patients during different disease phases (24 untreated, 20 relapsed/refractory and 12 patients at remission) and in 11 patients with IgM-MGUS. Patients with either WM or IgM-MGUS had increased levels of angiogenin, VEGF, VEGF-A, and bFGF compared with controls. The ratio of Angiopoietin-1/Angiopoietin-2 was reduced in WM but not in IgM-MGUS. Angiogenin levels correlated with disease status: continuous elevation from healthy subjects to IgM-MGUS and untreated patients with WM; then reduced in WM patients at remission and increased again in relapsed/refractory WM. Angiogenin correlated with albumin levels, while VEGF-A correlated with  $\kappa_2$ -microglobulin. Angiopoietin-1/Angiopoietin-2 ratio showed a strong negative correlation with  $\kappa_2$ -microglobulin, and positive correlations with albumin, hemoglobin and lymphadenopathy [Anagnostopoulos et al, *BJH* 2007;137:560-8]. We have also reported that serum levels of macrophage inflammatory protein-1 alpha (MIP-1 $\alpha$ ) are elevated in WM [Terpos et al, *BJH* 2006;133:301-4]. MIP-1 $\alpha$  is a potent chemoattractant for macrophages, which contribute to increased angiogenesis in several malignancies, including multiple myeloma [Ribatti et al, *Leukemia* 2007;21:2085-9]. To further elucidate the role of angiogenesis in WM, we investigated the association between MVD, MIP-1 $\alpha$  and the macrophage numbers in trephine biopsies of 37 patients with newly-diagnosed WM. Bone marrow biopsies were studied using double immunostaining with CD34 (endothelial cells) and CD68 (macrophages). We have also used double immunostaining for CD20/MIP-1 $\alpha$  and for CD138/MIP-1 $\alpha$ . Thirteen patients (35%) showed intermediate-grade and 4 (10%) high-grade angiogenesis. There was a strong correlation between the grade of angiogenesis and the number of macrophages into the hot-spots ( $r=0.825$ ,  $p<0.0001$ ). We have also observed that WM cells produce MIP-1 $\alpha$ . Furthermore, patients with high numbers of CD68(+) macrophages had increased expression of MIP-1 $\alpha$  by their WM cells. The results of our on going study will illustrate the role of macrophages in the angiogenesis procedure and reveal possible implications for the biology of WM.