Serum levels of vascular endothelial growth factor in chronic leukemias. A comparative study with emphasis on myeloproliferative disorders

We tested the differences in vascular endothelial growth factor (VEGF) serum levels adjusted for the platelet count (VEGF/10^6 platelets) in a series of patients with chronic leukemias and myeloproliferative disorders. The highest serum levels were observed in patients with chronic myeloid leukemia (CML) and myelofibrosis with myeloid metaplasia (MMM). These findings suggests that VEGF serum levels may surrogate the increased bone marrow (BM) angiogenesis characterizing either CML or MMM.

Angiogenesis has a major role in tumor growth, dissemination and metastasis of solid tumors.[1] The reported increased bone marrow (BM) vascularity in acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML) and myelodysplastic syndromes (MDS), the prognostic importance of vascular endothelial growth factor (VEGF) in AML and the detection of angiogenic factor receptors in leukemia cell lines suggest that angiogenesis has a central role in the pathophysiology of leukemias.[2] Aguayo *et al.*[3] evaluated the role of VEGF protein in the leukemogenic process of chronic leukemias taking into account the pattern of increase of different angiogenic factors. The highest plasma levels of VEGF were found in chronic myeloid leukemia (CML) and the lowest in chronic lymphocytic leukemia (CLL). Information dealing with other myeloproliferative disorders such as essential thrombocythemia (ET) or myelofibrosis with myeloid metaplasia (MMM) are lacking.[3]

On this background we studied a series of patients suffering from either CLL (n=67) or different myeloproliferative disorders [CML (n=30), ET (n=47), MMM(n=19)] whose frozen serum samples were analyzed for the presence of VEGF using an ELISA assay (R & D Systems, Minneapolis, MN, USA). A group of 15 age- and sex-matched healthy controls was utilized for statistical comparison. All measurements were carried out on peripheral venous blood samples collected in sterile tubes at the time of diagnosis, centrifuged at 2,000 g and stored at –70°C. High levels of VEGF have been reported in platelets, and it is possible that during the clotting process and the separation of the serum, VEGF is released from the platelets and white blood cells (WBC) leading to high levels in the serum.[4,5] To take into account the influence of platelet-transported VEGF, we adjusted serum levels for the platelet count (VEGF/10^6 platelets).

The profile of VEGF serum expression differed significantly among groups ($p<0.0001$; Kruskal-Wallis test; Figure 1). All patient groups had a significantly higher level of VEGF than healthy controls did: patients with CML ($p=0.0001$) and MMM ($p=0.0007$) showing the highest levels of VEGF while patients with CLL ($p=0.02$) and ET ($p=0.008$) had the lowest ones (Figure 1).

Data concerning patients with CLL were further analyzed looking for possible changes of serum VEGF levels in different clinical stages. Median serum levels of VEGF (VEGF /10^6 platelets) were as follows: stage A, 0.88; stage B, 1.07; stage C, 1.16 ($p=0.327$; Kruskal-Wallis test). Thus, in this cohort of patients increased levels of VEGF did not reflect status of disease.

In conclusion, our results, although based on a relatively small number of patients, provide an interesting profile of VEGF expression in the serum of patients suffering from different myeloproliferative disorders and CLL. The results of Aguayo *et al.* have been validated in an independent series and, interestingly, MMM resulted as being a disease with high angiogenic activity. This is in keeping with results recently published by Mesa *et al.*[6] who analyzed 114 MMM patients. Visual inspection of microvessel density showed a grade 3 or 4 increase of BM angiogenesis in 70% of MMM, in 33% of polycythemia vera (PV) and in 12% of ET patients. The possible clinico-therapeutic implications of these observations are worthy of investigation in well-designed studies.[7]

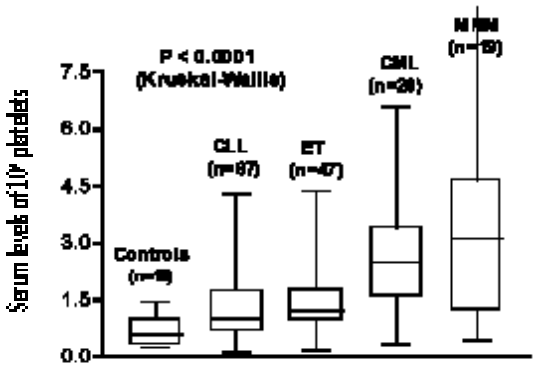

Figure 1. (a) Box plot comparing median serum levels of VEGF/10^6 platelets in healthy controls and patients with CLL, CML, ET and MMM.

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