Prognostic significance of cellular vascular endothelial growth factor expression in chronic phase myeloid leukemia

Srdan Verstovsek, Hagop Kantarjian, Taghi Manshouri, Jorge Cortes, Francis J. Giles, Anna Rogers, and Maher Albitar

The impact of elevated vascular endothelial growth factor (VEGF) expression on the course of chronic myeloid leukemia (CML) is unknown. By radioimmunoassay, we measured pretreatment cellular VEGF protein in bone marrow samples from 184 (148 chronic and 36 accelerated/blastic phases) CML patients and found the levels to be 1.6-fold higher than in 31 normal control bone marrow samples (P = .0001). No significant differences were found in VEGF levels by different phases of CML (P = .1). VEGF levels correlated with older age (P = .01) and higher platelet count (P = .0003), but also with smaller spleen size (P = .004), lower white blood cell count (P = .0006), and lower percentage of peripheral blasts (P = .04). With the use of Cox proportional hazard model and VEGF levels as a continuous variable, high VEGF levels correlated with shorter survival of patients in chronic CML (P = .008). Multivariate analysis showed that VEGF was not independent of the synthesis stage (P = .09). These data suggest that VEGF plays a role in the biology of CML and that VEGF inhibitors should be investigated in CML. (Blood. 2002;99:2265-2267)

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Brief report

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Predictors of shorter survival of patients with chronic phase CML

- VEGF level
- Risk group assignment
- Age
- Spleen size
- White blood cell count
- Platelet count
- Hemoglobin level
- Percentage of peripheral basophils

CML indicates chronic myeloid leukemia; VEGF, vascular endothelial growth factor.

Results and discussion

Western blot analysis showed detectable VEGF protein in samples with significantly increased VEGF protein (Figure 1). RIA, a more sensitive assay, showed VEGF protein in all bone marrow samples. VEGF levels in 184 CML samples were normalized to the median VEGF level in 31 normal control bone marrow samples, which was assigned a value of 1. The median VEGF value in CML samples was 1.6-fold (range, 0.8–11.3-fold) higher than in normal control samples. Normal control donor and 16 CML patient samples. Western blot includes 1 sample from a normal control (N) donor and 16 CML patient samples.

A number of studies have confirmed the presence of high VEGF levels in samples from patients with leukemias.\(^1\)\(^2\)\(^7\)\(^9\) The prognostic significance of VEGF expression has been analyzed in chronic lymphocytic leukemia and in acute myeloid leukemia (AML).\(^5\)\(^7\)\(^10\)

In AML, high levels of cellular VEGF were independent predictors of shorter survival and lower complete remission rates.\(^3\) In this study, we showed cellular VEGF protein levels to be highly expressed in all phases of CML and to have significant influence on survival in patients with chronic phase CML. The mechanism behind this observation is not clear. Previous studies have suggested the presence of both autocrine and paracrine VEGF/VEGF-R systems in leukemia.\(^3\)\(^8\)\(^11\)

The CML progenitor cell has been recently suggested to arise from a hemangioblastic progenitor cell, the progeny of which are malignant blood cells and genotypically clonal endothelial cells.\(^12\)

If this is correct, then malignant endothelial cells might play a role in the increased marrow vascularity in CML, and VEGF might be pathophysiologically linked to CML development. Thus, the examination of endothelial cell mitogens as well as surface markers in the bone marrow of CML patients may contribute to our understanding of its pathophysiology and offer targets for new type of treatments. Results of our previous work in AML\(^3\) and current findings in CML suggest that targeting VEGF might be a potential therapeutic strategy in myeloid leukemias.

Table 1. Study patients

<table>
<thead>
<tr>
<th>Disease phase</th>
<th>No.</th>
</tr>
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<tbody>
<tr>
<td>Chronic (early/late)</td>
<td>148 (118/30)</td>
</tr>
<tr>
<td>Accelerated</td>
<td>25</td>
</tr>
<tr>
<td>Blastic</td>
<td>11</td>
</tr>
</tbody>
</table>

Characteristics of patients with chronic phase CML, %

- Age at least 60 years: 17
- Spleen at least 10 cm below costal margin: 11
- White blood cell count at least 30 × 10⁹/L: 10
- Platelet count at least 700 × 10⁹/L: 11
- Peripheral blasts at least 3%: 5
- Marrow blasts at least 5%: 5
- Marrow basophils at least 7%: 17
- Marrow basophils at least 3%: 26

Predictors of shorter survival of patients with chronic phase CML

- (univariate analysis), \(P\)
  - VEGF level: .008
  - Risk group assignment: .01
  - Age: .1
  - Spleen size: .2
  - White blood cell count: .9
  - Platelet count: .002
  - Hemoglobin level: .9
  - Percentage of peripheral basophils: .1

Role of vascular endothelial growth factor (VEGF) and placenta-derived growth factor (PIGF) in regulating human haemopoietic cell growth. Br J Haematol. 1998;103:969-979.

References

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