



## Study of Plasma Endostatin Level in Patients with Acute Myeloid Leukaemia

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### Abstract:

Endostatin is a broad spectrum angiogenesis inhibitor and may interfere with the proangiogenic action of growth factors.

### Introduction:

Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy characterized by accumulation of immature malignant myeloid cells in the bone marrow and blood due to their clonal proliferation without substantial maturation [1].

Angiogenesis is the formation of new vessels from an existing network of vasculature [2]. Irrespective of cellular origin, induction of angiogenesis requires a shift/switch towards activation/upregulation of inducers of angiogenesis over suppression of angiogenic inhibitors (hereafter AI). Some key angiogenic activators include vascular endothelial growth factor A hereafter VEGF (VEGF-A) [3], Matrix Metalloproteinases (MMPs), Placenta Growth Factor (PlGF), Fibroblast Growth Factor (FGF) and Hepatocyte Growth Factor (HGF) [4]. Endogenous inhibitors of angiogenesis include Thrombospondins (THSBs) endostatin, angiostatin and cytokines such as interleukin- 12 [5].

The crucial role of angiogenesis in the growth, persistence, and metastases of solid tumors has been indicated in many studies [6,7]. There is mounting evidence that angiogenesis is also significant in leukemia [8].

Endostatin, C-terminal fragment of collagen XVIII, is one of the most potent and specific inhibitors of angiogenesis. Endostatin, originally isolated from medium of hemangioendothelioma, is generated from collagen XVIII through cleavage of an Ala- His linkage. On the cellular level, endostatin was shown to inhibit endothelial cell proliferation and migration and to induce apoptosis of endothelial cells [9,10].

The aim of the study is to evaluate the prognostic role of endostatin in AML patients. Subjects and Methods:

This study was conducted in Medical Oncology and Clinical Pathology Departments, Faculty of Medicine, Zagazig University during the period between January 2013 and February 2014.

It comprised 60 patients (28 women and 32 men); they were classified into 2 groups, Group I: Included 30 apparently healthy adult subjects (15 males, 15 females) with a mean age  $35.8 \pm 13.5$  years. They matched well with patients in terms of age and sex. Group II: Included 30 adult patients with newly diagnosed de novo AML (17 males, 13 females) with a mean age  $38 \pm 16.2$  years. Patients and controls were subjected to the following:

(1) Complete history taking and thorough clinical examination particularly for pallor, petechiae, bruising, gum swelling, lymph node swelling and splenomegaly.

(2) Routine laboratory Investigations. 120", together with examination of Leishman stained peripheral blood smears for differential leucocytic count.

- Liver, kidney functions tests and Lactate dehydrogenase using automated analyzer "Dimension RxL Max".

(3) Bone marrow Aspiration for Patients group only: Bone marrow smears were stained by Leishman and peroxidase stains and prepared for Immunophenotyping

by flow cytometry: using Becton Dickenson FacsCalibar device to detect the following markers (MPO, CD13, CD33, HLA-DR, TdT, CD14, CD64, CD34, CD 3, CD20 and CD22) for diagnosis of AML.

(5) Specific laboratory Investigation: Plasma Human Endostatin level estimation by quantitative sandwich enzyme immunoassay technique (Boster Biological Technology Co., USA) Following manufacturer Instructions, sensitivity  $<10$  pg/ml. For patients group only 2 plasma samples were taken at the onset of the disease and after 1 month of induction treatment.

(6) Treatment: Patients were treated by an induction regimen 3 and 7 regimen consisting of continuous infusion cytarabine (100 mg/m<sup>2</sup>) daily for 7 consecutive days combined with 3 days of doxorubicin (30 mg/m<sup>2</sup>) in addition to vesenoid in for patients with acute promyelocytic leukaemia (AML-M3). Patients with 60 years or poor performance status were treated by low dose cytarabine 10 mg/m<sup>2</sup>/12 hours for 14 days. Complete blood count (CBC): by automated cell counter "Advia.

### Results:

The demographic characteristics of group II is shown in Table 1, mean age was  $38 \pm 16.2$  (range 15-64), 56.7% are males (17/30

patients), 80.0% had ECOG performance status (PS  $\leq 1$ ), and fever was a presentation sign in 26 patients (86.7%).

### Discussion:

Acute myeloid leukemia is a heterogeneous group of diseases characterized by uncontrolled proliferation of myeloid progenitor cells that gradually replace normal hematopoiesis in the bone marrow [14].

Whereas cancer angiogenesis is classically thought of in context to solid tumors, there is mounting evidence that angiogenesis is also significant in leukemia [8].

Angiogenesis plays an important role in progression of the premalignant lesions to malignancies, tumor development, entering tumor cells into circulation and transforming the micro-metastases to obvious metastatic lesions [15].

Several studies have demonstrated that there was an increased angiogenesis in the bone marrow of AML patients [16-18]; while, when the patients achieved a CR after induction chemotherapy, histological analysis revealed a decreased microvessel density in the bone marrow [19,20].

Angiogenesis is a highly regulated process under the tight control of activators and inhibitors. Endostatin is an anti-angiogenic agent that blocks endothelial cell proliferation, tumor growth, and metastasis [21].

In the current study, we found higher mean p-endostatin levels in pretreatment period in group II patients than those control participants in group I.

### Conclusion:

Significant higher PE levels in patients with AML during CR period indicate that chemotherapy and angiogenesis inhibitors could modulate the regulation of angiogenesis in AML patients.

Levels of endostatin in patients with AML may be effective in predicting the survival. Wide scale studies are recommended in order to establish the mechanism underlying the association between high PE and poor clinical outcome.

### Conflict-of-Interest Disclosure

The authors declare no competing financial interests.

