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Human recombinant erythropoietic agents do not induce changes in circulating levels of endoglin and vascular endothelial growth factor in anemic cancer patients

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Abstract

The correlation of erythropoietin (EPO) receptor levels with angiogenesis and progression in some cancers has suggested that EPO could acts directly as an angiogenic factor. The purpose of this study was to assess the effect of treatment with human recombinant erythropoietic (rHuEPO) agents in cancer patients with chemotherapy-induced anaemia on endoglin and vascular endothelial growth factor (VEGF) circulating levels as a possible marker of angiogenesis. Endoglin and VEGF were measured in serum samples from 25 cancer patients with chemotherapy-induced anemia before and after 3–4 weeks of treatment with rHuEPO. A group of 28 healthy voluntaries was used as control. VEGF serum levels were significantly higher in cancer patients than in controls. For endoglin, higher levels were observed without reaching statistical significance. No statistically significant differences in endoglin and VEGF serum levels were found between samples obtained before and after treatment with rHuEPO agents. In conclusion, our result do not support that rHuEpo treatment in anaemic cancer patients induce angiogenesis.

Keywords: Endoglin; Vascular endothelial growth factor; Human recombinant erythropoietic agents; Erythropoietin; Anemia

1. Introduction

Chemotherapy-induced anaemia decreases quality of life (QOL) and social functions in cancer patients. Several trials have reported that the treatment with recombinant erythropoietin (rHuEPO) agents in anemic cancer patients significantly improves its overall QOL [1–3]. However, two randomized trials have reported an increase in mortality in patients treated with rHuEPO agents. A first randomized trial was designed to assess the effect of treatment with epoetin alfa on survival and quality of life in women with metastatic breast cancer

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receiving first-line chemotherapy. The study was stopped early in accordance with a recommendation from the Independent Data Monitoring Committee because of higher mortality in the group treated with epoetin alfa [4]. Furthermore, Henke et al. [5] in a study with head and neck cancer patients undergoing radiotherapy that used rHuEPO prophylactically reported a poorer locoregional progression-free survival. It should be mentioned that in both studies patients received rHuEPO with haemoglobin (Hb) levels higher than the recommendation of the American Society of Clinical Oncology for the treatment of cancer patients with anemia. Furthermore, a recent retrospective analysis from the study reported by Henke and colleagues have shown that locoregional progression-free survival was poorer if epoetin beta was administered to patients positive for EPO receptor expression compared with placebo [6]. It has been reported that EPO receptor is present not only in many normal non-erythroid cell types [7–12] but also in human cancer cells [13–15]. The expression of EPO receptors on endothelial cells [8] and the correlation of the EPO receptor levels with angiogenesis and progression in some cancers [16], has suggested that EPO could acts directly as an angiogenic factor. Moreover, EPO, like other growth factors such as G-CSF, GM-CSF, has an angiogenic effect stimulating endothelial proliferation and, in turn, new vessel formation both in vitro and in vivo [17]. Tumour progression is strictly dependent on angiogenesis for both primary tumour growth and metastatic spreading [18]. Vascular endothelial growth factor (VEGF) is an angiogenic factor that initiates angiogenesis and its overexpression has been associated with tumor progression and poor prognosis in several tumor types [18,19]. Endoglin (CD105) is a transmembrane glycoprotein part of the TGF-β receptor complex and expressed mainly on the surface of activated vascular endothelial cells [20–24]. Furthermore, we have recently demonstrated that endoglin-deficient mice show decreased angiogenesis [25]. Endoglin immunoreactivity has been detected in serum, and it has been found to be an independent prognostic factor in some tumors as a marker of neoangiogenesis and metastasis [22,26,27].

It has been postulated that the administration of rHuEPO to cancer patients with anemia may enhance proliferation or survival of cancer cells or stimulate angiogenesis and thus promote tumour growth. The purpose of this study was to assess the potential angiogenic effect of rHuEPO treatment in cancer patients with chemotherapy-induced anemia using circulating levels of endoglin and VEGF as markers of tumor progression. Endoglin can be used as an assessment of neo-angiogenesis and indirectly as a measure of the tumour growth risk. To validate the utility of these angiogenic markers we have compared previously the levels of endoglin and VEGF in a healthy control group.

2. Material and methods

2.1. Patients

This was a prospective study conducted at the University Hospital of Salamanca. Inclusion criteria were defined as follow: cancer patients with chemotherapy-induced anemia defined as haemoglobin levels <10 g/dl in asymptomatic patients or 10–12 g/dl in symptomatic patients. A group of 25 cancer patients treated with darbepoetin alfa or epoetin alfa secondary to chemotherapy-induced anemia were selected for the study. The study was approved by the institutional ethical committee. Patients were informed and a signed consent inform was necessary before entry into the study. A group of 28 healthy voluntaries were used as a control group for angiogenic markers validation. This group of people were also informed about the objectives of the study.

2.2. Treatment

rHuEPO was administered following the guidelines from the American Society of Clinical Oncology for cancer patients with anemia. A total of 25 cancer patients with chemotherapy-induced anemia were selected for the study independently of cancer type and chemotherapy regimen. Chemotherapy-associated anemia was defined as follows: haemoglobin levels <10 g/dl in asymptomatic patients, or 10–12 g/dl in symptomatic patients. Patients received either darbepoetin alfa (150 mcg/weekly) or epoetin alfa (150 U/Kg/body weight three times per week) at physician's discretion.

2.3. VEGF and endoglin determination

Blood samples were taken before rHuEPO administration and after 3–4 weeks of treatment, immediately centrifuged at 4 °C and serum kept frozen until analyzed. Endoglin and VEGF were analyzed using an ELISA commercial Kit (R&D Systems; MN, USA). A group of 28 healthy people were used as control.

2.4. Statistical analysis

Statistical analyses were performed in 25 cancer patients and in 28 healthy volunteers. Results were tabulated into a Microsoft Excel worksheet format and