



EPO in cancer anemia: Benefits and potential risks

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Abstract

Anemia has an incidence both on the quality of life and the evolution of cancer. Anemia may result in cancer from either a bone marrow infiltration of cancer cells or a cytotoxic effect of chemotherapy and/or radiotherapy, or both.

EPO is a glycoprotein which stimulates erythrocyte formation by bone marrow progenitory cells. Recombinant EPO has considerably improved treatment of anemic patients, by increasing hemoglobin serum levels and reducing the need for blood transfusion. The quality of life of cancer patients is thus improved and several studies highlight the beneficial role of EPO on the clinical outcome. A preclinical background and some clinical data suggest however a detrimental role of EPO in cancer by a possible stimulation of tumor growth. There is a need of more clinical trials in order to assess the effects of EPO on tumors and their treatment.

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1. General background

Anemia is a frequent complication in patients with cancer. In cancer, anemia may result either from the evolution of the disease itself or from applied treatments and particularly,

chemotherapy and/or radiotherapy. Anemia is a deficiency in red blood cells or in the hemoglobin level leading to a decrease in the transport capacity of oxygen in blood [1]. Numerous studies have shown that the diagnostic of anemia is based on a level of hemoglobin in the blood of less than 12 g/dL [2–4]. According to the World Health Organisation and the National Cancer Institute, anemia can be considered as minor (10–11.9 g/dL), moderated (8–10 g/dL) or severe (6.5–7.9 g/dL) and below 6.5 g/dL there is a risk of fatal evolution. Cancer-related anemia is usually a normocytic,

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normochromic and hypoproliferative anemia with a low level of reticulocyte count related to the degree of anemia. In a majority of cases anemia is associated with poor utilisation of iron with a reduction in iron in blood and a saturation of transferrin and this, despite a normal level of ferritin [5].

Numerous retrospective studies have reported on the frequency of anemia in cancer [6–10]. Anemia in cancer depends on the type of the tumor and the treatment: chemotherapy may induce anemia, particularly with protocols including platinum derivatives. A prospective study has been recently conducted in Europe (ECAS, European Cancer Anemia Survey [11]) during a survey period of 6 months with the participation of more than 15,000 cancer patients with solid tumors or hematological malignancies. The purpose of this study was to evaluate the prevalence, incidence and treatment of anemia in cancer patients. This study included 750 centers in 24 countries with more than 1000 physicians. At inclusion in the study, 39% of patients had a hemoglobin level below 12 g/dL; patients receiving chemotherapy were more frequent in this group of anemic patients. One third of patients without treatment or in remission were anemic and the occurrence of anemia during the study was 67%. The incidence of anemia was 63% in patients having a hemoglobin level less than 12 g/dL at the start of the study and receiving chemotherapy. This study revealed that a majority of anemic patients had not received specific treatment for anemia.

2. Anemia and quality of life

Anemia affects numerous functions of the organism. Anemia is one of the major sources of alteration in the quality of life of patients with cancer. At the clinical level, the decrease in the hemoglobin level is accompanied by an increase in fatigue and a general weakness leading to a reduction in the capacity to assume daily tasks. This status generates anxiety, irritability and a global loss of motivation [12]. More than 80% of anemic patients complain of fatigue and much less of pain [13].

3. Anemia and cancer progression

It has been suggested that normalisation of blood hemoglobin may improve quality of life and survival in cancer, particularly in the case of a disseminated disease [14,15]. Several studies have shown that survival of anemic patients is reduced and this in various types of cancers (lung, cervix, head and neck, prostate, multiple myelomas, lymphomas); the risk of a fatal outcome increases from 19 to 75% in anemic patients according to the disease localisation [15]. However, it is generally difficult to distinguish whether anemia is or not the direct cause of a poor survival. Studies indicate that anemia can be an independent predictive factor for the response to treatment [16]. Tumor hypoxia is one of the main consequences of anemia. This phenomenon may explain, at least in part, the lesser efficacy of radiotherapy and/or chemother-

apy due to a relative refractory status of cancerous cells to radiotherapy and chemotherapy when they are in hypoxic conditions [17–26]. Hypoxia may also induce neoangiogenesis and thus contribute to tumor growth and progression [23].

Numerous factors may contribute to the instauration of anemia in cancer and notably bone marrow infiltration by tumor cells [5,27,28]. EPO is a glycoprotein of 30,400 Da which stimulates the production of erythrocytes and maintains their viability [5,28]. In the adult, EPO is produced by interstitial peritubular renal cells and by the hepatocytes in the foetus. EPO plasma levels generally range between 4 and 26 mU/mL. The biosynthesis of EPO is influenced by tissue hypoxia, the loss of red blood cells, a diminution in the O₂ pressure and to all factors contributing to reduce the quantity of O₂ delivered to tissues. There is an inverse relationship between the EPO plasma levels and the quantity of hemoglobin, which are reciprocally regulated. Thus, an increase in blood EPO leads to an increase in the amount of red blood cells leading to a diminution in EPO production and vice versa. EPO interacts with erythroid progenitors in bone marrow through the intermediary of specific cell surface receptors; EPO receptors induce molecular intracellular signaling which leads to stimulate cell proliferation and differentiation while maintaining cellular viability [29,30].

Cancer-linked anemia may result in a reduction in EPO production associated to a decrease in the number of erythroid progenitors. Iron sequestration and a diminution in red blood cell survival are other aspects of cancer-related anemia. In addition, tumor secretion of pro-inflammatory cytokines like TNF, γ Interferon and Interleukin I reduce EPO production and alter the response of progenitory cells to the hormone [28]. On the other hand, there are deleterous effects of chemotherapeutic agents like cisplatin which is directly cytotoxic to renal tubules where EPO is produced [27]. Also, radiotherapy may directly impact on erythroid progenitors.

4. EPO and treatment of anemia in cancer

Based on symptomatic considerations and up to the 1980s, the treatment of anemia was performed by blood transfusion, empirically administered when blood levels of hemoglobin were below 10 g/dL. However, the apparition of AIDS has markedly changed this practise and blood transfusions were given only when hemoglobin was inferior to 8 g/dL [31]. Blood transfusion still remains the treatment of reference in cases of rapid and marked fall in hemoglobinaemia together with the well-known risks of transmission of infectious virus and immuno-allergic reactions; these risks are due to difference in plasmatic proteins, red blood cells, lymphocytes and the presence of specific cellular antigens [32,33].

The development and clinical use of human recombinant EPO has univocally improved the management of anemia in chronic renal insufficiency [34]. A recent review was based on randomized controlled studies, with or without blinding, using EPO to treat or prevent anemia in patients with

malignant disease [35]. The analysis covered 57 trials with 9353 patients. The compiled data suggested a significantly improved hematological response for the EPO group with respect to decrease need for red blood cell transfusions and hemoglobin/hematocrit increase [35]. Formulations of EPO, α and β isoforms, are currently in clinical use. These EPO isoforms are classically administered by the subcutaneous route three times per week at doses ranging from 150 to 300 U/kg. However, recent studies suggest that a once-a-week subcutaneous injection of 30,000–40,000 EPO units leads to equivalent results in term of anemia correction [36]. There are no clear pharmacological differences between α and β EPO isoforms [37]. More recently an EPO-related isoform, darbepoetin α , an EPO molecule containing more carbohydrate, has been shown to exhibit a longer elimination half-life thus allowing a once-weekly administration at the dose of 2.25 $\mu\text{g}/\text{kg}$ [38].

5. EPO activity

EPO acts primarily in the correction of anemia [34,35] but it is important to underline that EPO offers other biological properties as, notably, a protective effect on cardiac tissue and on the central nervous system [39].

Numerous clinical trials based on the use of EPO for treating cancer-related anemia or in prevention and correction of cytotoxic treatment-related anemia have been reported [33,40]. EPO increases hemoglobin levels and reduces transfusional needs in 50–60% of anemic cancer patients [41–43]. This activity was particularly noted in patients whose anemia is subsequent to administration of platinum-based chemotherapy [44].

The beneficial effect of iron supplementation during EPO treatment has been recently demonstrated for correcting chemotherapy-induced anemia [45]. This clinical trial also tested the difference of impact of iron when administered *iv* as compared to *per os*. The hemoglobin increase was superior in patients receiving iron by the *iv* route. Oral absorption of iron is erratic but iron by the *iv* route adds supplementary weight in the treatment of anemia. Above all, a clear biological definition of patients who can potentially draw benefit from iron supplementation during EPO treatments still needs to be provided. Several quality of life questionnaires, based on daily activity and fatigue, have been used to analyse the impact of EPO on patient quality of life [42]. Several studies have shown that EPO treatment significantly improves quality of life and particularly in anemia subsequent to chemotherapy and/or radiotherapy [46–49]. Interestingly there is a positive association between the quality of life improvement and the increase in the hemoglobin level and more particularly in the 8–12 g/dL range and for patients in whose the hemoglobin augmentation is more than 2 g/dL [46,50,51]. In contrast, there is no improvement in the quality of life for patients responding to anti-cancer treatment but without an increase in the hemoglobin level.

A recent interesting overview review by Ross et al. [52] analysed the clinical benefits and risks with EPO treatment in cancer patients. The frequency of thromboembolic complications was 5.2% among EPO patients and 3.1% among control patients. When all trials comparing epoetins with controls were meta-analysed, the change in risk was not significant (OR = 1.41; 95% CI = 0.81–2.47). This conclusion contrasts with the meta-analysis of Bohlius et al. [35] which was performed on the basis of 6769 patients in 35 trials. The authors noted thrombo-embolic events in 229 of the 3728 patients treated with epoetin or darbepoetin (median = 4.5%; range = 0–30%) and in 118 of 3041 untreated control patients (median = 1.4%; range = 0–22.6%). This led to a significant risk with a RR at 1.67, 95% CI = 1.35–2.06.

6. EPO and cancer progression

Recent data reviewed by Farrell and Lee [53] have shown that EPO receptor is present not only in many normal non-erythroid cell types but also in nonerythroid tumor cells and tumor cell lines. Tumor specimens have also been examined for their content in EPO receptor. Arcasoy et al. [54] reported on the immunohistochemical analysis for EPO and EPO receptor expression in breast cancer. They found high levels of EPO receptor expression in cancer cells in 90% of tumors. Interestingly, EPO and EPO receptor colocalisation in tumor cells was present in many cases. The authors also demonstrated that EPO receptors were functional in breast cancer cells by using an experimental cellular model including anti-EPO antibody, soluble EPO receptor and an inhibitor of Jak2, a cytoplasmic tyrosine kinase essential for EPO-mediated mitogenesis. The possibility of a functional autocrine loop of EPO–EPO receptor was recently suggested in melanoma [55]. In another recent study, Dagnon et al. [56] reported that co-expression of EPO and its receptor at the mRNA and protein levels was a common finding in non-small cell lung carcinoma regardless of the subtype. Statistically significant differences were found for EPO receptors expression between benign ovarian tissue and increased levels in ovarian low malignant potential tumor and carcinoma [57]. Lai et al. found increased levels of EPO and EPO receptor in lymph node metastases as compared to primary tumors from head and neck cancer patients suggesting a role of EPO/EPO receptor in the progression and metastatic progression of this cancer type [58]. It must be underlined that a number of studies measuring EPO and EPO receptor used antibodies which are not specific enough to produce robust results. In light of these results a potential interaction between therapeutic recombinant EPO and EPO/EPO receptor signaling pathways must be considered with a notion of risk for tumor progression under the presence of EPO.

The experimental data at our disposal do not permit however to univocally conclude on a stimulatory effect of EPO on tumor cell proliferation. A recent Japanese study sug-

gests that an EPO-like peptide may favor tumor growth and neoangiogenesis [59]. In contrast, recent experimental results show that the expression of EPO receptor in breast carcinoma models is not associated with stimulatory effects of recombinant epoetins on growth and migration [60]. It has also been reported that α EPO administration could induce tumor regression and improve survival in a murine model of myeloma [61]. This observation can be put in line with the recent findings by Carvalho et al. showing that, at least in a specific subset of tumors, EPO receptor agonists can prevent activation of the apoptosis-regulating NF κ B pathway thus enhancing the capacity of EPO receptor-positive tumor cells to undergo apoptosis [62]. It has been suggested at the clinical level that a low level of hemoglobin before treatment is a factor of poor prognosis and treatment with α EPO may reverse this tendency [63]. A controlled study, on a group of 375 cancer patients receiving a chemotherapy without cisplatin [4], confirms the benefit of EPO treatment in terms of quality of life improvement but also points to an increase in survival brought on by EPO (survival at 12 months: 60% in the EPO group versus 49% in the control group). Other studies support the notion of beneficial effects of EPO on the local control of the disease, event-free survival and overall survival [64,65].

Two recent clinical studies raise however questions about the positive contribution of EPO in the management of cancer and suggest deleterious effects of EPO. A clinical trial in breast cancer evaluated the effect on survival and quality of life of maintaining hemoglobin in the range of 12–14 g/dL with α EPO versus placebo in women with advanced disease receiving first-line chemotherapy [66]. A more rapid progression of the disease has been observed in the α EPO arm as compared to the control without EPO. However, it should be noted that in this study the risk factors were not well balanced between the two groups with worse performance status in the EPO group. Another recent study also indicates that treatment with β EPO may have a detrimental effect on the management of anticancer treatments [67]. It was a group of 351 head and neck cancer patients receiving irradiation with or without β EPO treatment. Eighty-two percent of patients receiving EPO achieved hemoglobin concentrations higher than 14 g/dL (women) or 15 g/dL (men) compared with 15% given placebo. The results indicate that patients in the EPO group had shorter progression-free and overall survivals as compared to the placebo group. The deleterious effect of EPO concerned the subgroup of hypopharynx cancers (20% of the whole group) only and the proportion of heavy smokers was higher in the EPO group. However, neither of these trials administered EPO in accordance with current product labels. Both used EPO in cancer patients who were not anemic and, of note, continued treatment until patients reached hemoglobin values close to 15 g/dL which are higher than those currently recommended. Henke and coworkers recently examined if the effect of β EPO on survival was correlated with the

tumoral expression of EPO receptor [68]. They found that progression-free survival was significantly poorer if β EPO was given to patients positive for EPO receptor expression compared with placebo. Treatment by EPO did not influence outcome in receptor-negative patients. This latter study draw the attention on a potential risk for tumor progression under EPO treatment but more controlled trials are needed to more firmly conclude on this potentially important aspect of the deleterious effects brought on by EPO treatment in cancer.

7. EPO and guidelines for treating cancer-related anemia

The American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH) [69], the European Organisation for Research and Treatment of Cancer (EORTC) [48] and the Standards-Options-Recommendations (SOR) of the French Federation of the Cancer Centers [70] have proposed guidelines for treating patients with anemia. The main points are as follows:

- In solid tumors: for a hemoglobin level between 8 and 10 g/dL and in case of necessity to quickly correct anemia (less than 3 weeks) one can give blood transfusions. In the case of an instaurated treatment or of programmed therapy, the administration of EPO is recommended.
- In hematological malignancies: for a hemoglobin level between 8 and 10 g/dL and when no specific cancer treatment is planned, a treatment with EPO is possible for hematological tumors only and this is due to direct impact of the disease on the hematopoietic capital.
- For a hemoglobin level between 10 and 12 g/dL, it is possible to give an EPO supplementation or to wait until the hemoglobin level reaches a value below 10 g/dL.
- There is no indication for treatment with EPO when hemoglobin levels are higher than 12 g/dL.

This latter point is strengthened by a study in cancer patients showing that improvement in tissue oxygenation is observed with a hemoglobin level higher than 12 g/dL [71].

8. Financial considerations

The financial impact of EPO treatment also must be taken into consideration. A recent EPO controlled trial considered the cost of treatment [72]. It concerned patients with myelodysplasia receiving either EPO plus G-CSF or a blood transfusion. The use of a quality of life questionnaire did not put into evidence a difference between the two arms for the improvement of the quality of life; in contrast, the arm receiving growth factors generated costs three-fold higher compared to the arm receiving a blood transfusion. However, it must be underlined that the combination with G-CSF made treatment more expensive than

with EPO alone. It must be also borne in mind that the deleterious effect of repeated blood transfusions may induce some specific management (iron overexposure) with costs which are not taken into account in an immediate analysis. In addition, treatment with EPO must be accompanied by a biological follow-up which adds an additional significant cost.

9. Conclusions

The occurrence of anemia is frequently observed in cancer patients and may markedly alter the quality of life. The presence of anemia may also have detrimental effects on disease progression. The administration of EPO has a corrective impact on hemoglobin levels and reduces transfusional needs in anemic cancer patients. Patient quality of life is improved by EPO in parallel to the gain in hemoglobin. There are numerous reports showing the presence of functional EPO receptors in human tumors. Adequate trials are needed to further evaluate the effects of EPO treatment on the evolution of certain types of cancers.

Reviewers

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Biography

Morgan Milano started his career at the Institut Gustave Roussy de Villejuif in the 60's. He was assistant in the Medical Oncology Department of Prof Georges Mathé who made the first bone marrow graft in the world, in a leukemic patient. He was also responsible of the treatment of infectious diseases in cancer patients. In 1972, he joined the Centre Antoine Lacassagne de Nice where he was Deputy Director until 1985 and a member of the Medical Oncology Department. He was a university Professor in Oncology at the medical faculty of Nice Sophia-Antipolis. He was, for 13 years, elected member of the National Council of Universities. He created ESMO (European Society for Medical Oncology) with Prof Georges Mathé in 1975 and he was the first Secretary General of the Society. He is also a member of the following international medical societies: ASCO (American Association of Clinical Oncology), AACR (American Association for Cancer Research), EACR (European Association for Cancer Research), SIOG, EORTC (European Organization for Research and Training in Cancer), he was chairman of the Screening Group of the EORTC, and the following national organisations: FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) and FFOM (Fédération Française d'Oncologie Médicale) and ECAS. He also regularly contributes to the work of the National Cancer League and he

is President of the departmental committee in the Alpes-Maritimes. He was Editor in Chief of a European review of cancerology : *Cancer Futures*.

The most achievements in his professional life: First, he understood in Villejuif what is a team. No progress is possible in oncology without pluridisciplinarity with all specialists, physicians, nurses, and scientists. He is much involved in student's medical education with all the new programs of medical studies and in continuous medical education. He was promoted as a professor of medical oncology and he had the pleasure to form and to promote several of his pupils who are today in different French cities. He fought for years with other colleagues for the recognition of oncology in France and oncology is now a medical specialty. In the National Council of Universities, he was one of the six members who are responsible of the nomination and the promotion of Professors of cancerology and of the contents of oncologic education.

As a physician, he gave his contribution to the progresses in the treatment strategies of many cancer localisations, such as Hodgkin disease, non-Hodgkin's lymphomas, chronic and acute leukaemias with bone marrow graft, and several solid tumours: bladder, kidney, testis cancer, breast, sarcoma, melanoma and particularly head and neck cancer. As a medical oncologist, he participated to numerous studies of new chemotherapeutic drugs and in the development of immunotherapy with adoptive immunotherapy, non-specific active immunotherapy and the new cytokines and now the monoclonal antibodies. He has about 500 references in the medical literature. He is now Emeritus Professor of oncology.