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REVIEW ARTICLE

Erythropoietin in cancer: the new face of an old friend

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Summary

During the last decade, anemia, a very common situation in patients with malignant diseases, either associated with chemotherapy or not, is being treated with recombinant erythropoietin (rEPO). Recent experimental findings have elucidated the role of EPO as a strongly anti-apoptotic agent in multiple non-erythroid and neoplastic tissues. The discovery of probably functional EPO receptors (EPOR) on malignant cells, hinting that EPO may act as a tumor growth factor, raised embarrassing thoughts regarding the routine administration of erythropoiesis-stimulating agents (ESAs). In addition, the results of a few clinical trials showing a negative impact on overall survival of rEPO-treated cancer patients, although strongly criticized for several methodological pitfalls, led the FDA to force a "black label" warning concerning the use of rEPO and to recommend that physicians should use the lowest possible dose of ESAs in chemotherapy-treated cancer patients. This recommendation comes in accord with the recent guidelines of European Organisation for Research and Treatment of Cancer (EORTC) which are reviewed in this paper, along with the structure of EPO and EPOR, the role of EPO on normal and malignant cells and the clinical applications of EPO.

Key words: anemia, cancer, erythropoietic agents, erythropoietin, erythropoietin receptors

Introduction

According to the European Cancer Anaemia Study 72% of patients with hematological malignancies and 66% of patients with solid tumors have anemia at some point during the course of their disease [1]. The pathophysiology of cancer-related anemia is complex: blood loss, malignancy- or drug-related autoimmune hemolysis, nutritional deficiencies, infiltration of the bone marrow by malignant cells, chemotherapy-induced bone marrow aplasia and above all anemia of chronic disease related to impaired production of EPO, the main erythropoietic agent, or a blunted response to its action.

Anemia is an independent adverse prognostic factor; it increases the relative risk of death by 19% in lung cancer, 75% in head and neck cancer, 47% in prostate cancer and 67% in lymphoma [2].

In oncology it is common practice to correct anemia with the use of rEPO, mainly in patients undergoing chemotherapy, but also in advanced malignancy, as well as part of the adjuvant treatment. Beyond doubt, patients treated with rEPO have higher hemoglobin levels, reduced or absent transfusion requirements and probably a sense of well being, in other words better quality of life [3].

It was plausible that treatment with rEPO, eliminating an adverse prognostic factor, anemia, would result in better tumor control and patients' overall survival. This was never proved: on the contrary, the detection of EPOR in cancer cells, followed by the publication of a few studies reporting an adverse impact of rEPO on overall survival of patients, have raised many theoretical concerns regarding the optimal use of rEPO in cancer patients [4-6].

In this review a brief description of the structure and physiological function of EPO and its receptor on normal erythropoietic tissue and other normal tissues will be presented, as well as their presence and significance on malignant cells, the recent reports on

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the survival of cancer patients treated with ESAs and the Food and Drug Administration (FDA), USA, and EORTC guidelines for the use of ESAs in cancer.

Structure of EPO and EPOR

EPO is a glycoprotein produced by the interstitial cells of the kidney in the adult life and by liver cells during fetal life.

The name "erythropoietin" (greek for "red cells-maker") was introduced in 1957 when it was realized that it was the main agent regulating the daily production of 2×10^{11} red cells in the adult bone marrow [7]. In humans, EPO mRNA encodes a protein with 193 amino acids. After the cleavage of certain peptides, the mature protein consists of 165 amino acids stabilized by two disulfide bonds. 35% of the molecule is carbohydrate (N-linked sugars), necessary for the stability of the EPO molecule in the circulation. Deglycosylated EPO is biologically active but very short-lived. The recombinant ESAs have identical amino acid sequence to the endogenous EPO but the carbohydrate part of the molecule is altered and they have different half-lives [8].

EPO circulates in minute quantities in human plasma and its action is exerted through binding to its receptor (EPOR) which can be found in large numbers on the surface of the red blood cells precursors CFU-E and proerythroblasts [9].

EPOR belongs to the cytokine receptor superfamily, or class I superfamily, along with the receptors for other hematopoietic growth factors, including growth hormone, prolactin, G-CSF, GM-CSF, thrombopoietin, oncostatin M and several interleukins. EPOR is consisted of 108 amino acids and has an extracellular ligand-binding domain, a single transmembrane domain and an intracellular domain without any catalytic activity [10].

EPO exerts its effects by inducing homodimerization of two molecules of EPOR on the cell surface, and phosphorylation of tyrosine kinase JAK2 [11]. A cascade of phosphorylations begins in the cytoplasmic domain of EPOR, leading to the activation of signaling pathways such as JAK/STAT (Janus kinase/signal transducer and activator of transcription), P13k/Akt and ERK/MAPK (mitogen-activated protein kinase), which regulate cell proliferation and differentiation and exert highly anti-apoptotic action. The stimulation of EPOR simultaneously with the activation of intracellular signaling pathways switches on downregulation mechanisms, so that the signaling proteins return to their basal levels: downregulation is exerted by inhibition of JAK2, activation of the SOCS (suppressor of cytokine signaling) molecules and activation of the SHP2 proteins. The EPOR of erythroid cells is catabolized by lysosomes and proteasomes and after a period of 30-60 min new receptors emerge on the surface of the cell (Figure 1) [12,13].

The anti-apoptotic and cytoprotective role of EPO on red cells and other tissues

There are several factors modulating the EPO production: hypoglycemia, high intracellular calcium, insulin release, cytokines, hormones and steroids. However, the most potent stimulus for its production is the low oxygen tension, i.e. hypoxia. Hypoxia induces EPO gene expression through both transcriptional activation and mRNA stabilization. The upregulation of EPO gene in this case is a direct result of HIF-1 (hypoxia inducible factor-1) activation [14].

The main action of EPO is the promotion of erythropoiesis by stimulating growth, preventing apoptosis and inducing differentiation of red blood cell precursors. Its presence is absolutely necessary for life: it has been shown that murine knockout of either the EPO gene or the EPOR gene results in embryonic death on

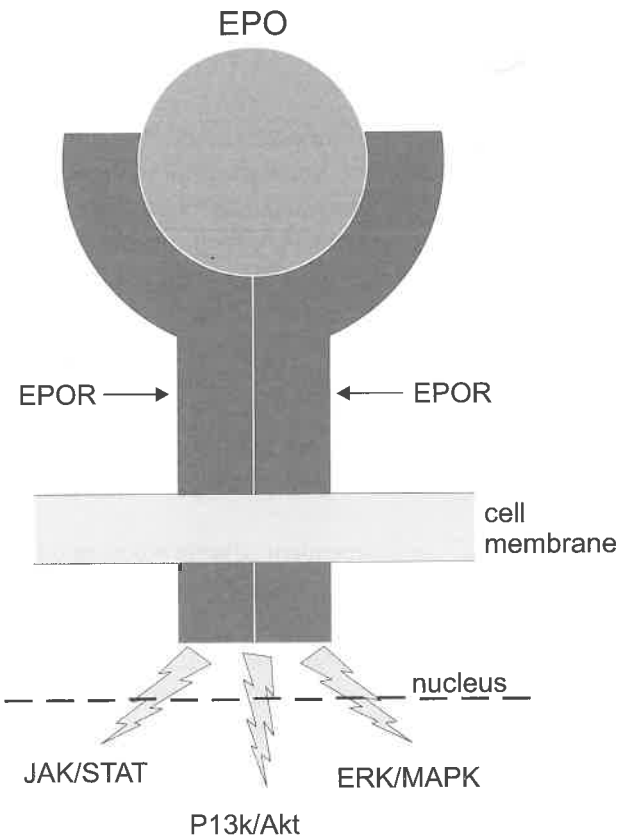


Figure 1. Erythropoietin (EPO), erythropoietin receptor (EPOR) and signal transduction. For abbreviations see text.

day 13.5 because of very severe anemia. Surprisingly, these animals also have significant heart malformations and abnormal brain development [15].

So, the notion that EPO was exclusively associated with erythropoiesis and that EPOR was present only on immature red blood cells was challenged. Indeed, recent advances in analytical techniques have shown that EPOR mRNA, EPOR protein, binding of EPO to EPOR and subsequent activation of the signaling pathways are present on the surface of many non-hematopoietic tissues, such as the brain, heart, liver, multiple tissues of the gastrointestinal tract, pancreas, kidney, testis and the female genital system (Table 1) [16]. In all these systems EPO acts as a growth and survival-promoter factor. In addition, EPO seems to have a strong angiogenetic action as it preserves endothelial cell integrity and promotes angiogenesis, that is new capillary formation from pre-existing vessels into an avascular area, as for example in physiologic cyclic uterine angiogenesis [17,18]. Probably this action of EPO is responsible for the increased rate of thromboembolic events, the long-known complication in patients treated with rEPO. EPO has strong cytoprotective and anti-apoptotic effect on endothelial cells, nervous tissue and cardiomyocytes against ischemic injury and several preclinical and clinical studies examine its role in patients with recent cerebrovascular accidents and myocardial infarction (Figure 2) [19-27].

As an erythropoietic agent, EPO is a hormone produced in the kidney and exerting its action in a distant target, the bone marrow. In the adult human, local production and use of EPO has been shown in neural tissue, placenta, testis and the female genital tract. In the CNS, EPO is produced by astrocytes and EPOR is expressed by neurons, exhibiting autocrine action as the cells produce EPO for their own use or for adjacent cells (paracrine action) (Figure 2) [28,29].

Table 1. Human normal tissues where erythropoietin (EPO) and erythropoietin receptor (EPOR) have been detected [19]

Tissue	*EPO*	*EPOR*
Neurons	+	+
Astrocytes	+	+
Microglia	+	+
Endothelial cells	+	+
Cardiomyocytes	+	+
Liver Kupfer cells	+	–
Hepatocytes	+	–
Peritubular cells	+	+
Mesangial cells	+	+
Gastric mucosa cells	–	+
Insulin-producing cells	–	+
Prostate epithelial cells	–	+
Erythroid progenitors	+	+
Endothelial progenitors	–	+
Myeloid progenitors	–	+
Megakaryocytes	–	+

Cancer cells, hypoxia, EPO and EPOR

In 1992 Bauer et al. were the first to study the effect of rEPO in cancer tissue [30]. Now, it is well recognized that many solid tumors, including renal, breast and lung cancer, tumors of the female reproductive tract and gastrointestinal tract, head and neck squamous cell carcinoma, tumors of the CNS and even certain leukemias (Table 2) express EPO and EPOR mRNA transcripts and protein [30-43]. As already mentioned, the expression of EPO and EPOR is greatly induced by hypoxia. Indeed, the highest levels of EPO and EPOR genes are found in those parts of the tumor that are most hypoxic. It should be noted that in the samples studied, adjacent regions of normal tissue or tissue with benign lesions did not express EPO and EPOR. Apart from the malignant cells, EPOR expression has been found also in the vascular endothelium of several tumors [44].

A major question is whether the EPO and EPOR genes expressed in cancer cells are functional and if they are whether they differ and in what extent from those in normal cells [45,46]. There is accumulating evidence that there is a functional autocrine or paracrine EPO-EPOR loop in several tumors, as they are capable of producing EPO for their own use [47]. As mentioned earlier, EPO mediates the activation of a number of signaling cascades (ERK/MAPK, P13k/Akt, JAK/STAT, NF-kB) associated with cellular functions that promote cellular survival and proliferation of the progenitor red cells and other normal tissues. This could be true for cancer cells, too [48-52], but the results of a large number of studies are conflicting; there are studies with cell lines and samples of human renal cell carcinomas and breast cancers expressing EPOR mRNA and protein, where it was indicated that the activation of the EPOR by EPO stimulated the proliferation of the cells [33,36,37,39,40]. Moreover, *in vitro* blockade of the EPO signaling pathways either with local soluble EPOR, that is the extracellular part of the molecule, or with neutralizing anti-EPO antibodies or by pharmacological inhibition of the important kinase JAK2, resulted in an increase of apoptotic death of both tumor cells and vascular endothelial cells followed by reduction of the tumors' vascularity and accelerated tumor destruction [33,43]. From these *in vitro* and with experimental models studies it is assumed that EPO may act as a tumor growth factor in certain neoplasms expressing EPOR.

However, there are other reports indicating that

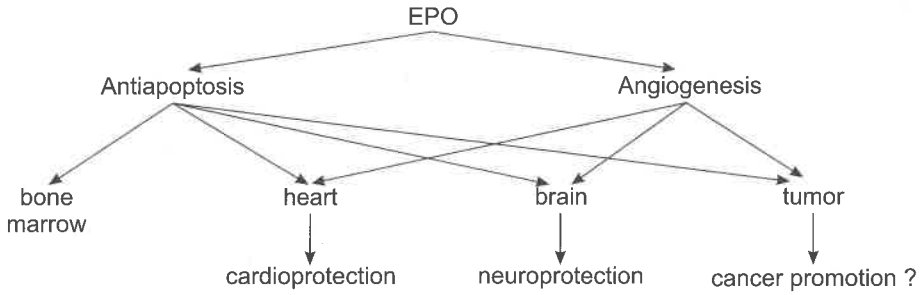


Figure 2. Actions of erythropoietin (EPO) in normal and tumor cells.

Table 2. Some human malignant tissues where erythropoietin (EPO) and erythropoietin receptor (EPOR) have been detected. SCC: squamous cell carcinoma, ADC: adenocarcinoma [46,64]

Tissue	*EPO*	*EPOR*
Breast cancer	+	+
Cervical cancer SCC	+	+
Cervical cancer ADC	–	+
Endometrial cancer	+	+
Ovarian cancer	+	+
Gastric adenocarcinoma	–	+
Colon adenocarcinoma	–	+
Head and neck tumors	+	+
Renal cell carcinoma	–	+
Wilms tumor	+	+
Hepatoma	+	+
Lung cancer	+	+
Melanoma	+	+
Astrocytoma	+	+
Neuroblastoma	+	+
Prostate adenocarcinoma	+	+
Sarcoma	+	+
Papillary thyroid carcinoma	±	+
Acute myelogenous leukemia	–	+

the administration of rEPO to malignant nonerythroid cell lines expressing EPOR does not influence their rate of growth or proliferation, as it has been shown that in cancer cell lines there is expression of EPOR splice variants, which might modulate the cellular effects of EPO [33,47,53-58]. In one particular study, Westphal et al. investigated the influence of exogenously administered EPO on 25 different benign and malignant human cell lines. EPOR mRNA and protein were identified by reverse transcriptase-polymerase chain reaction (RT-PCR), Western blot and immunochemistry in most tumor cell lines and the cellular responses were evaluated with tritiated thymidine uptake, Northern blot and tyrosine-kinase activity assay. Treatment with various concentrations of EPO did not influence the proliferation rate of EPOR-positive tumor cells. In the same study, malignant cells expressing the G-CSF receptor were treated with recombinant G-CSF; no increase of the cells' proliferation was noted [35].

The presence of paracrine and autocrine EPO/EPOR signaling in cancer cells may also explain the high prevalence of anemia among patients with malignancies, as well as the remark that cancer patients do not respond to rEPO as predicted: the tumors, avid for EPO, have the ability to modify the EPO/EPOR signaling system so as to promote their own progression, consuming big quantities of both endogenous and exogenous EPO and thus depriving erythroid cells of their own physiologic growth factor [45,59].

Another apparently important prognostic factor is the degree of tumor hypoxia. It has been shown that tumor hypoxia is an adverse prognostic factor associated with aggressive disease, treatment resistance and poor survival as cancer cells show reduced sensitivity to radiotherapy and chemotherapy [14,60]. Most solid tumors are hypoxic because cancer cells demand a lot of oxygen, which cannot be supplied by the incomplete regional vasculature. Hypoxia induces the transcription of several genes - the EPO gene included- encoding proteins that promote the survival and growth of cancer cells [61]. *In vitro* and *in vivo* experiments have shown that the systemic administration of rEPO decreases the hypoxic fraction of solid tumors and improves tumor oxygenation [62]. Although anemia is contributing to tumor hypoxia, this effect is independent of the hemoglobin levels [63]. Better oxygenation of the tumor microenvironment inactivates the HIF-1a/VEGF pathway that promotes angiogenesis and the ability of tumor for metastasis. As previously mentioned, the expression of EPOR in the vascular endothelium of tumors suggests that rEPO may potentially have some effect on the tumor microenvironment, such as the stimulation of tumor angiogenesis or neovascularization [64].

Regarding the effect of rEPO on the efficacy of chemotherapy and radiation, the results are also contrasting. In preclinical models, correction of anemia and hypoxia with rEPO is shown to restore radiosensitivity and cytotoxicity of chemotherapeutics with resulting delay of tumor growth. In some cases treatment of cell lines with rEPO before incubating them with

cisplatin showed reduced sensitivity, while in other instances pretreatment of cells with rEPO resulted in an increase in apoptosis in response to daunorubicin and vinblastine, due to inactivation of the NF-kB pathway [65-72]. So it is quite probable that not all cancers behave in the same manner [71].

In summary, the role of detected EPOR on malignant cells remains unclear. Exogenously administered EPO may potentially stimulate tumor growth by binding to EPOR expressed in tumor cells and may also induce tumor angiogenesis by binding to EPOR expressed on tumor vessels. On the other hand, rEPO may correct tumor hypoxia and therefore cells may become more sensitive to the effects of chemotherapy and radiotherapy.

Anemia, recombinant EPO and cancer: unexpected findings, conflicting data

In 2003 two pharmaceutical company-sponsored, multicenter, randomized, double-blind, placebo controlled phase III trials, designed to show increased survival of rEPO-treated patients who were undergoing chemotherapy and radiotherapy, reported an increased rate of death from accelerated cancer progression. The first trial led by Henke et al. studied the effect of rEPO, namely epoietin beta, on 351 anemic head and neck cancer patients randomly assigned to receive radiotherapy along with either placebo or epoietin beta at a rather high dose of 300 IU/kg 3 times per week targeting normalization of Hb at >14 g/dL for women and >15 g/dL for men. The group who received epoietin had shorter progression-free survival and overall survival than the control group [73]. The second study (BEST/Breast Cancer Erythropoietin Survival Trial) had overall survival as the primary endpoint. It enrolled 939 patients with metastatic breast cancer. Patients with Hb less than 13 g/dL were treated with either placebo or rEPO for one year. This trial closed earlier because patients treated with rEPO died earlier because of cancer progression [74]. There was also increased rate of thromboembolic events, the long-known complication of rEPO observed mainly in non-anemic chronic renal failure patients [75], but these events were not associated with increased mortality. In both studies increased rate of thromboembolic events of the rEPO-treated patients was noted.

Although both trials were heavily criticized [29], they sparked embarrassment, concern and a storm of trials, papers and editorials about the matter. Among them the Cochrane Database of Systematic Reviews for the period 01/1985 to 04/2005 was published, aiming to assess the effects of ESAs for prevention of anemia or treatment of anemic cancer patients. Overall 57 trials with 9,353 patients were evaluated. The conclusions were that treatment with ESAs reduced the relative risk for blood transfusions and the number of units transfused in cancer patients, but there was a substantial increase of the relative risk for thromboembolic complications. However, regarding the effect of ESAs on tumor response and patients' survival, there were not definite conclusions [76].

At the same time - beginning 2007 - 4 new trials confirmed the statistically significant adverse impact of rEPO on cancer patients' survival: a phase III trial involving 70 patients with metastatic non small-cell lung cancer treated weekly with epoietin alpha for 12 weeks and a target Hb 12-14 g/dL, a phase III trial with 989 patients with advanced malignancies not receiving anticancer therapy but treated to reach Hb levels more than 13 g/dL, another trial with 522 patients with locally advanced head and neck cancer planned to receive definitive radiotherapy aiming to Hb 14-15.5 g/dL and one study with 344 patients with lymphoid malignancies targeting Hb up to 14-15 g/dL (Table 3) [5,77-80]. In all these trials the arm treated with ESAs showed a significantly shorter overall survival compared with the arm treated with placebo or red blood cells transfusions (hazard ratio for death 1.30 and 1.37). It should be stressed, though, that all trials were aiming for a high Hb target (13-15 g/dL).

In interpreting data both from experimental studies and from clinical trials it should be kept in mind that their results are not undisputable for several reasons. As far as the laboratory part is concerned, the methods used for the detection of EPOR on the cell surface or intracellularly are not well validated and have several limitations.

EPO and EPOR are studied by immunochemistry that detects specific proteins on the cell surface, *in situ* hybridization which detects EPOR mRNA, Western blot analysis and the RT-PCR, a very sensitive, qualitative method, which detects EPOR transcripts but cannot recognize if the detected EPOR is functional, too. In most studies EPOR is detected by the antibody C-20 that lacks specificity for the EPOR. C-20 antibody (Santa Cruz Biotechnology, Santa Cruz, CA) detects, in addition to EPOR, a peptide of different molecular weight—heat shock protein 70 (HSP70), that exerts an antiapoptotic effect by interacting with the apoptotic protease activation factor-1 and whose expression is upregulated in rapidly proliferating cells and is therefore likely to be expressed by tumor cells [77,81-84].

Regarding the way the ESAs were used, in many preclinical studies evaluating the potential effects of rEPO on cancer cells, the doses administered and the plasma levels obtained were much higher than those

Table 3. Trials in which erythropoiesis-stimulating agents (ESAs) were associated with adverse outcome in patients with malignant diseases (adapted from [5])

Trial [reference]	*Disease*	*No. of patients*	*Treatment*	*Dose of ESA*	*Target Hb (g/dL)*	*Outcome*
Henke et al. [73]	Head and neck cancer	351	Radiotherapy only	EPO-β 300 IU/kg/3 per week	12 in women 13 in men	Hazard ratio for locoregional progression 1.69 (p=0.007); hazard for death 1.39 (p=0.02)
Leyland-Jones et al. [74]	Metastatic breast cancer	939	First-line chemotherapy	EPO-α 40.000 U/wk	13	Survival at 12 mos vs. placebo: 70 vs. 76% (p=0.01)
Wright et al. [79]	Metastatic non small-cell lung cancer	70	None	EPO-α 40.000 U/wk	12-14	Overall survival vs. placebo: 63 vs. 129 days; hazard ratio for death 1.84 (p=0.04)
Goldberg [78]	Locally advanced head and neck cancer	522	Radiotherapy only	Darbepoietin-α 150 μg/wk	14-15.5	10% increase in locoregional failure (p=0.01); trend toward shorter survival (p=0.08)
Anemia of Cancer Study [5,80]*	Non- myeloid cancers	989	None	Darbepoietin-α 6.75 μg/kg/wk	13	Shorter overall survival; hazard ratio for death 1.30 (p=0.008)
Lymphoid Cancers Anemia Study [5, 80]*	Lymphoproliferative malignancies	344	Several	Darbepoietin-α 2.25 μg/kg/wk	< 15 in men < 14 in women	Shorter overall survival; hazard ratio for death 1.37 (p=0.04)

*www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-00-index.htm

used and obtained in humans following administration of exogenous EPO. Besides, in the above-mentioned clinical trials the target Hb level, although within normal limits, was rather high, taking into consideration the clinical background of the patients.

Another important issue in clinical trials and in common clinical practice is the concomitant administration of iron either intravenously or per os in rEPO-treated patients. In humans, a physiologic defense mechanism to malignancy, infection and inflammation is to deprive cells of iron by reducing iron absorption and transferrin saturation. In patients with chronic non-malignant disorders treatment with iron often reactivates chronic infections and collagen diseases. This may be happening in malignancy too, a hypothesis strengthened by the view that iron chelators may have an antitumor effect [85]. In this case iron may be cancer-promoting.

EORTC guidelines and FDA warnings

In the USA FDA approved treatment with rEPO in patients with renal failure in 1989 and in cancer patients with chemotherapy-related anemia in 1993.

In Europe there are 3 erythropoietic agents approved at the moment - erythropoietin alpha (Eprex, Janssen), erythropoietin beta (Neo-Recormon, Roche) and darbepoietin (Aranesp, Amgen) which has a slightly altered molecule with longer half-life. Newer ESAs are being prepared in order to fit distinct clinical situations [86,87].

The use of ESAs is widespread in routine oncology practice, with estimated sales of a two-digit billion dollars bill annually as they are administered not only for chemotherapy-induced anemia, but also as adjuvant drugs and for correcting anemia in patients with advanced disease. Since they were considered absolutely safe, this practice remained unchanged for many years.

However, in March 2007, after the reports of the possible adverse impact of rEPO on cancer patients, the FDA Oncologic Drugs Advisory Committee issued a "black box" warning, or a "black label" warning, -that is the strongest warning the FDA can impose on prescription drugs, so named for the black border that usually surrounds the text of the warning-, about the potential for tumor promotion and thromboembolic events for non-approved uses of erythropoietic agents in cancer. It is expected that the approved indication, for treatment of chemotherapy-induced anemia targeted to Hb levels in the range of 10-12 g/dL, will be reconsidered [88].

In Europe, EORTC has produced evidence-based guidelines on the use of erythropoietic proteins in anemic patients with malignancy. The most recent update, published in January 2007, states that "in cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 9-11 g/dL, based on anemia-related symptoms rather than a fixed Hb concentration" and recommends that "the target Hb concentration following treatment with erythropoietic proteins should be 12-13 g/dL". Regarding the hot matter of the effect of EPO on the survival of cancer patients, the EORTC group declares "there is still insufficient data to determine the effect on survival following treatment with erythropoietic proteins in conjunction with chemotherapy or radiotherapy" [89].

Questions, thoughts and a few conclusions

Many questions arose after the disclosure of the potential effect of EPO on tumor growth.

- Concerning the presence of cancer anemia, how are EPO levels and anemia associated in cancer? The ominous sign of anemia is associated with the presence of anemia *per se* or with high endogenous EPO levels?
- About the EPOR, what is the best method to detect them? What is their real significance? Do they function in cancer cells in the same manner as in normal erythropoietic and other tissue cells? Do hematological malignancies differ from solid tumors in that matter? Is the presence of EPO receptors associated with shorter survival in rEPO-treated patients? Does the presence of EPOR on tumor cells carry a prognostic significance?
- Accepting the hypothesis that EPO may act as tumor growth factor, do non-cancer patients who are long-term treated with rEPO for other reasons- for example chronic renal failure-develop more frequent solid malignancies than other comparable groups?
- Do the new erythropoietic agents have the same probable cancer-promoting effect with rEPO?

Not all questions have been asked, and of course, no definite answers have been given in the numerous excellent reviews and editorials [5,6,19,90-97] published on the matter. The final conclusion is that in-depth research and well-designed studies are mandatory.

In the meantime clinicians wonder how they should cope with the complex task of cancer treatment. There is a long and rewarding experience with ESAs [98-111], so it would be unfair to deprive patients of agents that, along with other hematopoietic agents, the new antiemetic drugs and monoclonal antibodies, literally changed routine oncology practice, until their role in cancer has been fully elucidated.

Since the most obvious adverse impact of ESAs in tumor progression and patients' survival has been noted in studies where Hb was targeted high enough, there comes the conclusion that they should be withheld from patients whose Hb level exceeds 12 g/dL until the level falls below 11 g/dL. Also, instead of defining a Hb level at which treatment with ESAs should be initiated, it would be more prudent to evaluate each patient's symptoms and needs [90]. Probably, ESAs should not be used in asymptomatic patients with mild degree of anemia. Definitely EPO should be used in cancer patients with Hb levels less than 8 or 9 g/dL so as to avoid red blood cells transfusions.

Regular reevaluation of the patients' clinical and laboratory status is necessary. Besides, at the moment and until adequate trials are completed and more data reviewed, there is no reason to restrict these agents in specific tumor types [5].

The paradigm of EPO

During the hard and often desperate fight against cancer, we use every available weapon, sometimes with unpredictable results. However, the thoughtless administration of dozens of drugs, as it often happens in routine practice, can be harmful, because, as an old Greek saying goes: "KATHE (every) PHARMAKO (drug) PHARMAKI (poison)", that is "every drug may potentially act as a poison".

This is the case with rEPO: this drug surely benefits thousands or even millions of patients, but there may be others who are actually harmed by it. So it is absolutely necessary to make a distinction which patients should be treated with which drug and to establish criteria, instead of blindly administering this and every drug to all patients [112].

Hippocrates, whose oath we all take upon graduation from the medical school, is also the father of another, wise in its simplicity Greek saying "ΩΦΕΛΕΕΙΝ Η ΜΗ ΒΛΑΠΤΕΙΝ" that is "(a physician) should try to benefit (the patient) or (at least) not to harm him/her".

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