

The Influence of Erythropoietin (EPO) on Cancer Cells and its Role in the Cancer Treatment

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Abstract - The hormone erythropoietin (EPO) is essential for the survival, proliferation and differentiation of the erythrocytic progenitors. The EPO receptor (EPO-R) of erythrocytic cells belongs to the cytokine class I receptor family and signals through various protein kinases and STAT transcription factors. The EPO-R is also expressed in many organs outside the bone marrow, suggesting that EPO is a pleiotropic anti-apoptotic factor. The controversial issue as to whether the EPO-R is functional in tumor tissue is critically reviewed. Importantly, most studies of EPO-R detection in tumor tissue have provided falsely positive results because of the lack of EPO-R specific antibodies. However, endogenous EPO appears to be necessary to maintain the viability of endothelial cells and to promote tumor angiogenesis. This review paper reviews EPO use in cancer patients and its management of anemia. While the findings promise beneficial effects of endogenous EPO and its therapeutic analogues as tissue-protective factors, for example in ischemic and degenerative heart and brain diseases, fear has also arisen that EPO may promote tumor cell survival and stimulate tumor growth. If the cancer patient is being treated with curative intent, the use of ESAs should be avoided. If the treatment plan is more conservative or palliative, ESA should be considered for anemia treatment, but the treatment should be controlled.

Keywords: Erythropoietin (EPO); Proliferation; Tumor Tissue; Tumor Angiogenesis.

I. INTRODUCTION

Erythropoietin (EPO) is a member of the cytokine family of molecules and a humoral regulator of erythropoiesis (red blood cell production). EPO effects on proliferation and survival of erythroid progenitor cells are mediated via the EPO receptor (EPO-R) and downstream intracellular signaling events. It was the first cytokine to be biochemically purified, by massive amounts of urine obtained from anemic patients [3]. The amino acid sequence of the purified EPO molecule led to cloning of the EPO gene. Subsequently, the gene for murine EPO-R was cloned. Having available large quantities of purified recombinant EPO greatly accelerated our understanding of EPO activities. However, studies with recombinant EPO at first only confirmed the then prevailing belief that cytokines would have great cell and tissue specificity of action. It is only recently that expression of the EPO-R has been reported on nonerythroid cells, with stimulation of proliferation and anti-apoptotic effects noted on cells of the nervous system and a number of other tissues [3,4].

EPO, as a tissue-protective factor, showed much more pleiotropic potential than previously thought. EPO-R

mRNA, EPO binding sites and EPO-R signaling have been detected in a variety of non-hemopoietic tissues such as heart, blood vessels, kidneys, liver, gastrointestinal tissues, pancreatic islands, testis, female reproductive tract, placenta and, operating separately from the other parts of the body, the brain [1].

EPO-R mRNA is usually detectable in cultures of human cancer cells, either in primary culture or on establishment as permanent lines [1].

The recombinant growth factors (GFs), erythropoietin (EPO) and granulocyte-macrophage colony stimulating factor (GM-CSF) have important roles in the management of cancer patients. However, the effects of these GFs at a cellular level are not well understood [2,9,17].

Erythropoiesis stimulating agents (ESAs) have been used widely for anemic patients, especially those on dialysis and with cancer. However, reports have suggested shorter survival in erythropoietin (EPO)-treated cancer patients [5,6].

Erythropoietin (EPO), used to treat anemia in cancer patients, has been reported to accelerate tumor progression and increase mortality [8,12,13].

Erythropoietin-induced proliferation of cancer cells was associated with the activation of JAK2, JAK3, STAT3, and STAT5 but not JAK1 or STAT1, AKT phosphorylation, ERK phosphorylation with hTERT gene transcription by JAK2/STAT5/c-MYC, and hTERT protein phosphorylation by PI3K/AKT. Furthermore, the EPO-EPOR pathway stimulated the expression of cyclin D1 and inhibiting the expression of p21cip1 and p27kip1 through the phosphorylation of JAK2 and ERK1/2, led to a more rapid progression through renal cancer cell cycle. Interestingly, EPO or stem cell factor (SCF) alone produced a modest number of cervical cancer cell colonies, whereas the combination EPO/SCF induced a significantly more. Similarly, co-stimulation with EPO/SCF induced a significantly higher number of migrating cervical cancer cells than either cytokine alone. Concurrently, EPO induced a modest, transient activation of ERK1/2, whereas SCF and EPO/SCF prompted a strong, sustained phosphorylation of ERK1/2 [10].

Cloning of the EPO gene and expression and purification of recombinant EPO set the stage for EPO to become the first cytokine to demonstrate clinical efficacy. EPO has been used in clinical settings of disease- and treatment-induced erythropoietic insufficiency. It was first tested successfully in dialysis patients suffering from severe anemia whose only previous treatment at the time was blood transfusions with inherent possibilities of

infectious episodes and build-up of toxic levels of iron [3]. EPO was approved in 1989 by the United States Food and Drug Administration for treatment of the anemia of chronic kidney disease to increase or maintain red blood cell levels [3]. It has been used in a plethora of cases to enhance erythropoiesis including during treatment of patients with cancer. However, side effects of EPO treatment, some life-threatening, have necessitated revised EPO treatment guidelines. These side effects, in part, may relate to nonerythropoietic responses to EPO, especially in treatment of patients with cancer [3].

Following the purification of EPO in 1977 in urines from patients with aplastic anemia, the first recombinant human EPO (rhEPO) became available in treating anemia with chronic kidney disease (CKD) and chemotherapy-induced anemia associated with non-myeloid malignancies [4,6,7,8]. Use of rhEPO in clinical practice has dramatically improved management of anemia and reduced chances of adverse effects such as viral infections and iron overload by transfusion therapy [4].

This review paper represents discussion of EPO use in cancer patients and management of anemia. Several professional and regulatory organizations and authorities have issued various guidances.

II. INFLUENCE OF EPO ON CANCER CELLS

Undoubtedly, the introduction of EPO in the medical market contributed greatly to the management of anemia in end stage renal disease (ESRD) patients, improving their quality of life. Meanwhile, it remains elusive whether normalization of anemia by EPO could also improve renal outcomes in CKD [4].

In one randomized controlled trial, an early initiation of EPO therapy in non-diabetic, predialysis patients with mild-to-moderate anemia significantly slowed the progression of renal disease. However, subsequent three large randomized studies failed to follow these observations [4,5,6].

One of the plausible explanations for the observed differences may be the distinct rate of anemia correction. In the former study, a slow correction of mild-to-moderate anemia to subnormal levels over a long period of months may have been advantageous [4].

Furthermore, increased mortality but not increased tumor progression was reported in patients with non-small cell lung cancer (NSCLC), multiple myeloma and lymphoma, and in patients with anemia of cancer and active disease not undergoing chemotherapy or radiotherapy [1].

In the earlier clinical study, rhEPO appeared to be beneficial in patients with acute stroke. The trial resulted in a trend for reduction in the infarct size in the EPO treatment group, which was associated with a markedly improved neurological recovery and clinical outcomes. However, EPO failed to show any beneficial effect in acute ischemic stroke, especially in those receiving systemic thrombolysis [4].

In the cardiovascular system, EPO treatment reduced myocardial infarct size, protected against ischemia-reperfusion injury and promoted ventricular remodeling in

experimental animals subjected to coronary artery ligation. In addition, EPO induced angiogenesis by mobilizing bone-marrow derived endothelial progenitor cells (EPC) [4].

A surprising finding in the research of neuronal protection by EPO was that the carbamylated EPO, which fails to bind to the canonical EPO-R and transduce the signaling cascade mediated by JAK2-STAT5, also exhibited neuroprotective effects. Carbamylated EPO also retained the cardioprotective effect of EPO. Similarly, asialoerythropoietin, which is stripped of sialic acid and is therefore of short half-life, failed to increase erythropoiesis but conferred neuron protection in vivo. In a subsequent study, it turned out that the pleiotropic effect of EPO was mediated by the non-canonical heteromultimers composed of EPO-R and the common β subunit (β cR), the subunit common to the granulocyte-macrophage colony stimulating factor (GM-CSF) and the IL-3 and IL-5 receptors, in the mouse spinal cord injury [4].

Moreover, EPO is also expressed in several nonhematopoietic tissues, where it plays a role in the protection from apoptosis and inflammation due to hypoxia, toxicity or injury. These protective effects are mainly known and studied in cardioprotection and neuroprotection but are also reported in retina degeneration, auditory injury and pancreatic-related diseases [8].

Table I represents beneficial or not beneficial effect of erythropoietin and its important roles in the management of cancer patients.

Global use of erythropoietin (EPO) continues to increase as a proven agent for the treatment of anemia. Yet, EPO is no longer believed to have exclusive biological activity in the hematopoietic system and is now considered applicable for a variety of disorders such as diabetes, Alzheimer's disease, and cardiovascular disease. Treatment with EPO is considered to be robust and can prevent metabolic compromise, neuronal and vascular degeneration, and inflammatory cell activation. On the converse side, observations that EPO administration is not without risk have fueled controversy [6].

While the findings promise beneficial effects of endogenous EPO and its therapeutic analogues as tissue-protective factors, for example in ischemic and degenerative heart and brain diseases, fear has also arisen that EPO may promote tumor cell survival and stimulate tumor growth [14].

Although there is no clinical proof that the administration of erythropoiesis stimulating agents (ESAs) promotes tumor growth and mortality, present recommendations are that ESAs should be administered at the lowest dose sufficient to avoid the need for red blood cell transfusions, ESAs should not be used in patients with active malignant disease not receiving chemotherapy or radiotherapy, ESAs should be discontinued following the completion of a chemotherapy course, (iv) the target Hb should be 12 g/dL and not higher and (v) the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target Hb <12 g/dL. EPO mRNA is also detectable in several cancer cell lines, and stimulation of EPO production under hypoxic

conditions has been suggested as a paracrine mechanism favouring the survival of cancer cells [10,11].

TABLE I. Beneficial or not beneficial effect of erythropoietin

EPO failed to show any beneficial effect	Beneficial of erythropoietin (EPO) and therapeutic avenues
in acute ischemic stroke, especially in those receiving systemic thrombolysis	beneficial in patients with acute stroke
in patients with anemia of cancer and active disease not undergoing chemotherapy or radiotherapy	management of anemia
in non-diabetic, predialysis patients with mild-to-moderate anemia significantly slowed the progression of renal disease	management of anemia in end stage renal disease
increased mortality but not increased tumor progression was reported in patients with non-small cell lung cancer (NSCLC)	reduction in the infarct size
increased mortality in patients with multiple myeloma	improved neurological recovery
increased mortality in patients with lymphoma	improves clinical outcomes
	In the cardiovascular system, EPO treatment reduced myocardial infarct size, protected against ischemia-reperfusion injury and promoted ventricular remodeling in experimental animals subjected to coronary artery ligation
	EPO induced angiogenesis by mobilizing bone-marrow derived endothelial progenitor cells
	neuronal protection
	biological activity in the hematopoietic system
	applicable for a variety of disorders such as diabetes, Alzheimer's disease, and cardiovascular disease
	prevent metabolic compromise, neuronal and vascular degeneration, and inflammatory cell activation
	highlighted for its action on the hematopoietic system
	protective effects are mainly known and studied in cardioprotection and neuroprotection

Clarification of these underlying mechanisms will open a new way to develop an agent which activates the pleiotropic EPO signaling without stimulating erythropoiesis, and protect ischemic organs from injury. However, organ protection by ESA seems to be counterbalanced by some potential harms. Efforts are under way to understand the molecular mechanisms of these disadvantages and potential antidotes are now being explored [4]. With the development of biomedical engineering not only great attention to accurate and reliable medical equipment is in focus of attention [22-24] but also the development of new treatment techniques. Some of the new techniques are based on machine learning techniques and made for diagnosis of certain disease, as well as

development of new drugs [25-29] and it is yet to be seen whether they have impact on the topic discussed here.

III. CONCLUSION

A plethora of scientific evidence demonstrates a growth-promoting, anti-apoptotic action of EPO and other ESAs on non-hematopoietic cells, both normal and malignant, and this is supported by numerous clinical observations showing adverse effects of EPO administration on the clinical management of tumor growth and progression. As anticipated just a few years ago, physicians who care for anemic cancer patients have been facing a dilemma, whether to treat the anemic patient with an ESA, thereby potentially increasing the risk of worsening the malignancy, or to withhold ESA treatment, with resultant patient fatigue, reduced physical activity, increased hypoxic stress, and reliance on transfusion therapy. Primary tumors are not yet EPO-R typed (like breast cancers are assessed for ER/PR expression) though this idea should be considered [17,18]. Perhaps, the following "rule" used by several clinicians should be considered [19,20]. If the cancer patient is being treated with curative intent, avoid the use of ESAs. If the treatment plan is more conservative or palliative, consider ESAs for anemia treatment, but proceed with great caution [10,21].

Despite these limitations, optimized use of rhEPO will continue to be a major strategy to manage anemia in patients with CKD and malignancies of non-myeloid origin [15,16].

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