Treatment of Cancer-Related Anemia

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ABSTRACT

Anemia with consequent tissue hypoxia is common problem in cancer patients. Developed via various patophysiological mechanisms, it has deleterious effect on quality of life and survival of patients with cancer. Recognition of symptoms and timely initiation of treatment improve patients' quality of life, as well as efficacy of oncological treatment. Red blood cells transfusions are well known and efficient way of anemia correction. They are »golden standard« in treatment of cancer-related anemia today, and are unavoidable in almost all patients with hemoglobin concentration below 80 g/L. Newest therapy guidelines in developed countries, supported by recent literature, encourage use of recombinant human erythropoietin (rHu-EPO), although detailed meta-analyses and prospective randomized clinical trials have shown that rHu-EPO decreases the need for transfusions in only 9–45% patients with cancer, only if they have mild anemia. rHu-EPO increases incidence of thromboembolic events, and suspicion arises that it supports tumor cells growth and multiplication. Therefore, it is necessary to define subgroups of patients which are best candidates for rHu-EPO therapy, to accomplish lower intensity of transfusion therapy.

Key words: anemia of chronic disease, anemia, cancer, therapy, chemotherapy, radiotherapy

Introduction

Anemia in cancer patients has become significant clinical problem during recent years. Increased efficiency of cancer therapy results in better overall survival as well as in prolonged survival of non-curable patients. Respectively, quality of life of non-curable patients is becoming more and more significant. Fatigue, one of most common symptoms of metastatic cancer, is one of main issues related to quality of life, and probably most neglected in clinical practice. Since anemia is most common cause of fatigue, clinical trials have been conducted that correlated anemia with quality of life and, later, anemia with overall survival. Because of persistent problem of insufficient blood supply, new medications have been developed (recombinant human erythropoietins, rHu-EPO) with purpose to decrease number of blood transfusions.

Definition, etiology and consequences of anemia in cancer patients

Anemia is defined as lowered hemoglobin concentration (in males below 140 g/L, in females below 120 g/L), usually associated with low red blood cells (RBC) count (in males <4.3 ×10⁹/L, in females <3.86 ×10⁹/L). Multiple pathogenic mechanisms are responsible for development of anemia in patients with cancer (Figure 1). It usually presents as anemia of chronic disease, and in the moment of cancer diagnosis is present in about 40–64% of patients. Since myelosuppressive effect of oncological treatment modalities, its incidence during the treatment increases up to 80%¹.

Main molecular mechanisms of listed processes are nonspecific activation of monocytes and consequent secretion of proinflammatory cytokines (neopterin, interferon-gamma, tumor necrosis factor, and interleukin-6) and Fas ligand (FASL) molecules. Apoptotic mechanisms are triggered in erythroblasts by FASL and TNF, and process is amplified by secretion of TNF from tumor cells.

Tissue hypoxia is main consequence of anemia and it leads to changes in cell microenvironment. Cells switch from aerobic to anaerobic metabolism, lactate production is increased and, consequently, acidosis of cell microenvi-
enronment develops. In normal cells apoptotic mechanisms are triggered if hypoxia is prolonged, while malignant phenotype promotion is started in the tumor tissue. Selection of cells resistant to hostile microenvironment begins and on the other hand oncological treatment modalities are less efficient in hypoxic conditions – radiotherapy due to lack of oxygen and reduction of free radicals production, and chemotherapy due pharmacokinetics changes in lowered pH conditions. Apoptotic pathways are modulated by sensors of hypoxia – HIF (hypoxia inducible factors) $\alpha$ and $\beta$. Normally, there is a dynamic balance of synthesis and degradation of HIF-1$\alpha$ in organism. Oxygen and two-valent ions of iron are cofactors for prolyl-hydroxilase activation, the enzyme which carries out HIF-1$\alpha$ degradation, and in their absence the substrate accumulates. HIF-1$\alpha$ accumulation activates transcription mechanisms for erythropoietin synthesis in hematopoietic cells, whilst in other cells expressing HIF receptors it activates anaerobic metabolism and adaptation of tumor cells to hostile microenvironment, transcription mechanisms are activated as well, as follows: for synthesis of vascular endothelial growth factor (VEGF) which reflects in angiogenesis promotion, and for epidermal, insulin-like and transforming growth factors (EGF, IGF-2 and TGF$\beta$) with consequent promotion of tumor cells growth and division. All the worse, this closes the vicious circle of tumor hypoxia, clonal selection and malignant disease progression in anemic cancer patients.

Severity of anemia

The most commonly used classifications of anemia toxicity are by World Health Organization and by National Cancer Institute. Anemia is staged in four groups, according to both (Table 1).$. Anemia has detrimental effect on cancer patients’ quality of life. Main symptoms of anemia are fatigue, dizziness, headache, pallor, dyspnea, tachycardia, palpitations, depression, lowered mental capabilities and loss of libido. Fatigue is most common symptom of metastatic cancer, and is usually caused by anemia. The tumor’s theft of nutrients, infection and disruption of normal body processes also account for fatigue. In clinical practice 80% of oncologists overlook fatigue as main symptom of anemia, and almost two thirds of physicians think that pain is greater problem than fatigue. On the contrary, two thirds of patients think that fatigue is greater problem than chronic malignant pain. Incidence and severity of anemia depend on several factors: type of tumor (anemia is most common in patients with lung, gynecologic, genitourinary tumors and lymphomas), stage of disease, treatment modality (anemia is present in 63% of patients treated by chemotherapy alone, 42% of patients treated...
by chemo-radiotherapy, and in 19.5% of patients treated by radiotherapy alone, patients age, and bone marrow reserve.

Anemia and Survival (Impact on Efficacy of Oncologic Treatment Modalities)

Anemia is an independent prognostic factor of lower survival and lower efficacy of oncologic treatment. Relative risk to death is about 60% higher in anemic cancer patients; 75% in patients with ovarian cancer, 67% in patients with lymphomas, in 47% in patients with prostate cancer, and in 19% in patients with lung cancer.

Anemia has negative effects on both radiotherapy and chemotherapy efficiency. In hypoxic conditions quantity of oxygen in irradiated volume is lowered, and since hypoxic tumor cells are radioresistant, higher radiation dose is necessary for tumor cell eradication. Therefore, radiosensitizers (medications which increase binding of oxygen to hemoglobin) increase radiotherapy efficiency as well as correction of anemia (Figure 2). Optimal hemoglobin level for best effect of radiotherapy is 120–140 g/L.

Hypoxia causes switch of cancer cells to anaerobic metabolism, and acidosis of cellular microenvironment develops. Pharmacokinetic changes lead to lack of efficacy of certain cytotoxic drugs. Dependency of cyclophosphamide, carboplatin and doxorubicin effect on cancer cell killing and tumor oxygenation has been proven in vitro and in vivo. Having in mind that anemia is more common in certain types of tumors, especially ones sensitive to cytotoxic chemotherapy since the treatment is usually more intensive, additional concern should be attributed to this issue. Cumulative myelosuppressive effect is usually fully expressed after fourth cycle of chemotherapy (Figure 3).

Impact of anemia on efficiency of cancer therapy has been tested in few clinical trials. Grogan et al. have shown that 5-yr survival in patients with cervical cancer treated with radiotherapy, 47% patients have been stratified into four groups: patients with low baseline hemoglobin level whose hemoglobin remained low during the treatment (L-L), patients with high baseline hemoglobin whose hemoglobin dropped below 120 g/L during the treatment (H-L), patients with high baseline hemoglobin level whose hemoglobin remained high (H-H), and patients with low baseline hemoglobin whose hemoglobin concentration was corrected by transfusions to value >120 g/L during the treatment (L-H). Patients with corrected hemoglobin level had survival similar to patients with high baseline hemoglobin who remained >120 g/L, while patients with fall in hemoglobin level below 120 g/L during the treatment had similar survival with patients with low hemoglobin whose hemoglobin remained low. Survival difference between the two groups was statistically significant (p<0.0002). Adapted from Grogan M, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix, Cancer 1999;86:1528-1536, by permission of the publisher Wiley InterScience, Copyright © 1999 American Cancer Society.

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Impact of anemia on efficiency of cancer therapy has been tested in few clinical trials. Grogan et al. have shown that 5-yr survival in patients with cervical cancer treated by radiotherapy is 25% worse if average hemoglobin level was below 120 g/L, and that it improves with correction of anemia (Figure 4).

Bookemeyer and associates have proven 21% reduction in 5-yr overall survival (p<0.05) if average hemoglobin level was below 105 g/L in 101 patients with poor prognosis metastatic testicular cancer treated with three cycles of PEI chemotherapy, followed by three cycles of high dose PEI chemotherapy (Figure 5).
Erythropoietin and Correction of Anemia

Erythropoietin is a glycoprotein hormone produced predominantly in the kidney, and only to a minor degree in the liver. It is produced in response to hypoxia, which is caused by a decrease in oxygen supply to the tissues. Its production is regulated by the hypoxia-inducible factor (HIF) and is mediated by the erythropoietin receptor (EpoR). Recombinant human erythropoietin (rHu-EPO) has been used to treat patients with chronic renal failure and in 1993 it was approved for use in cancer patients. There are 3 commercially available products, epoetin alpha, epoetin beta, and darbepoetin.

Transfusion Therapy in Cancer Patients

Scientific and therapeutic application of blood transfusions first started about one hundred years ago, when Landsteiner revealed blood groups at the beginning of the twentieth century. Transfusions are a common medical intervention, particularly in the United States, where 4 million people receive blood transfusions every year. In clinical practice, anemia is treated in only 39% of patients with cancer who receive blood transfusions at least once, and about 16% receive multiple RBC transfusions during the treatment. In clinical practice, anemia is treated in only 39% of patients with cancer, in spite of deleterious effects of anemia on quality of life and survival.

Estimates show that 33% of patients with cancer receive blood transfusions at least once, and about 16% receive multiple RBC transfusions during the treatment. In clinical practice, anemia is treated in only 39% of patients with cancer, in spite of deleterious effects of anemia on quality of life. In Europe, 17% of patients are anemic. In patients with testicular cancer treated with high dose PEI chemotherapy, about 15% of patients presented anemia, whereas 12% of patients were treated with epoetin alpha to avoid one transfusion (95% CI 0.06–0.31) in lower quality studies. Overall, 4.4 transfusions per patient were avoided (95% CI 0.33–0.62) in higher quality studies and 0.14 transfusions per patient in epoetin treated arm compared with control arm was 0.14 (95% CI 0.06–0.31) in lower quality studies. In randomized, placebo-controlled study by Littlewood et al. epoetin alpha 150 to 300 IU/kg was administered to the patients with solid or non-myeloid hematological malignancies and hemoglobin levels below 105 g/L or greater than 105 g/L but 120 g/L or less, after hemoglobin decrease since start of chemotherapy. In epoetin alpha arm transfusions requirements were significantly lower compared with placebo (24.7% vs. 39.5%, p = 0.057) and hemoglobin levels were significantly increased (22 g/L vs. 19 g/L, p < 0.001).

Seidenfeld et al. have done a meta-analysis of the early clinical trials with epoetin alpha by the year 2001. Twenty-two trials were included. Epoetin alpha reduced the percentage of patients transfused by 9% to 45% in patients with basal hemoglobin levels 100 g/L or lower, and by 7% to 47% in patients with basal hemoglobin levels between 100 g/L and 120 g/L. Odds ratio for transfusions in epoetin treated arm compared with control arm was 0.45 (95% CI 0.33–0.62) in higher quality studies and 0.14 (95% CI 0.06–0.31) in lower quality studies. Overall, 44 patients were treated with epoetin alpha to avoid one blood transfusion.

In updated meta-analysis by Bohlius and al. treatment with rHu-EPO reduced the transfusions requirements by 36% (RR 0.64, 95% CI 0.60–0.68), and achieved
hematological response (defined as increase in hemoglobin concentration by 20 g/L) significantly more often (RR 3.43, 95% CI 3.07–3.84)\(^6\).

Meta-analysis of 40 clinical trials including 21378 patients, confirmed the mentioned results\(^8\). The odds ratio for transfusions in studies of epoetin versus control was 0.44 (95% CI, 0.35–0.56) and of darbopoetin versus control 0.41 (95% CI, 0.31–0.55). There were no clinically relevant differences between epoetin and darbopoetin.

Littlewood et al. showed that epoetin treatment significantly improved patients’ QoL compared with placebo measured by LASA (linear analog scale assessment) and FACT-An (Functional assessment of cancer therapy-anemia subscale)\(^4\). Other randomized and nonrandomized trials confirmed similar results\(^{25–26}\). Regarding darbopoetin alpha and QoL, Vanteenkiste et al. showed no significant improvement in FACT-An score in darbopoetin group but 32% of patients in the treatment group had at least 25% improvement in score compared to only 19% in the placebo group (p=0.019)\(^27\). In another trial Hedenus et al. demonstrated that patients treated with darbopoetin alpha had significantly greater improvement in FACT-An score compared with those given placebo\(^28\). Additional analysis of two community based trials of epoetin beta showed that the largest QoL improvements for each 10g/L increment in hemoglobin level occurred when hemoglobin increased from 110 to 120 g/L\(^29\).

**Erythropoietin in cancer patients – pro et contra: side-effects and overall survival**

The most common side-effects of rHu-EPO treatment are hypertension and thromboembolic events. The meta-analysis of 39 clinical trials including 6769 patients provided conclusive evidence that rHu-EPO treatment increase the risk for thromboembolic events (RR 1.67, 95%CI 1.35–2.06)\(^6\).

Pure red cell aplasia and development of anti-erythropoietic antibodies described in patients with chronic renal failure has not been observed in patients with cancer\(^30\).

Early trials showed better survival in rHu-EPO treated patients. In a nonrandomized study epoetin treated patients undergoing neoadjuvant chemoradiotherapy and resection for squamous cell carcinoma of the head and neck have significantly better local control and survival compared with an untreated historical control group\(^31\). A trend toward survival benefit was demonstrated in randomized trial of patients receiving epoetin alpha and chemotherapy\(^4\). In patients with various pelvic malignancies receiving radiotherapy treatment with epoetin beta improved tumor control and survival\(^32\). Darbopoetin alpha treatment was associated with prolonged progression free survival in patients with small cell lung cancer\(^33\). A meta-analysis by Bohlius and al. reported a trend towards improved survival with epoetin\(^34\) although a recent update showed a shift towards increased mortality HR 1.08 (95%CI 0.99–1.18)\(^5\). Most of the trials included in this meta-analysis were not designed to measure overall and progression-free survival. Epoetin beta meta-analysis has not recorded any survival benefit but there was significantly reduced risk of rapidly progressive disease (HR0.78, p=0.042)\(^35\). MARCH (Management of Anemia under RadioChemotherapy in cervical cancer) study investigated effect of epoetin beta compared with supportive care on overall survival and progression-free survival in anemic patients with cervical cancer receiving radiochemotherapy\(^36\). There was no significant outcome on overall (rR1.0, p=0.99) and progression-free survival (RR 1.16, p=0.57). Similar results were demonstrated in BRAVE (Breast Cancer-Anemia and the Value of Erythropoietin) study\(^27\). It was designed to determine is there a survival benefit with epoetin beta treatment in patients with metastatic breast cancer receiving anthracycline and/or taxane-based chemotherapy.

In conclusion, most of the studies and meta-analyses have not confirmed any positive or negative effect on survival in cancer patients receiving chemotherapy and/or radiotherapy.

Recent results of 4 large randomized trials have raised the question of negative impact of rHu-EPO treatment on survival and tumor progression in cancer patients.

Breast Cancer Erythropoietin trial (BEST) determined higher mortality rate in patients with metastatic breast cancer treated with chemotherapy and epoetin alpha compared with chemotherapy alone\(^38\). This imbalance in mortality occurred in first 4 months mostly due to disease progression (6% vs. 2.8%) or increase incidence of thromboembolic complications (1% vs. 0.2%) in the epoetin group. At 19 months there was a convergence of survival curves\(^39\). This study has several methodological limitations that were confirmed by the authors themselves. Patients in epoetin group have had more risk factors for thromboembolic complications, more advanced disease or poorer performance status at the beginning of the trial. Meta-analysis of 8 randomized epoetin beta trials failed to show increased mortality due to thromboembolic complication (3.17 thromboembolic events yearly in epoetin beta group compared with 3.36 yearly in control group and 1.1% mortality in both groups)\(^40\). Neither the meta-analysis by Apro and el. determined increased mortality due to thromboembolic events in patients treated with epoetin beta although there was increased incidence of thrombosis, deep vein thrombosis and pulmonary embolism (5.9% vs. 4.2%)\(^23\).

Henke et al. investigated epoetin beta treatment compared with placebo in 351 patients with head and neck cancer during radiotherapy\(^41\). Patients were given relatively higher epoetin beta doses (300 IU/kg 3 times weekly) and hemoglobin target levels were 140 g/L for women and 150 g/L for men. Significantly worse survival (relative risk of death 1.39, 95%CI 1.05–1.84, p=0.02) and locoregional progression (RR 1.69, 95%CI 1.67–2.47, p= 0.007) was determined in epoetin group. Patients in treatment group experienced more hypertension, bleeding, thrombosis and pulmonary embolism (11% vs. 5%) and died more often due to cardiovascular incidents.
(5.5% vs. 3%). After 9 weeks of therapy hemoglobin level of 154±17 g/L was achieved, what is above physiological concentration. Theoretically such high hemoglobin concentration could lead to increased blood viscosity and thereby reduced tumor oxygenation. Henke et al. have also made an analysis that has shown that patients who had erythropoietin receptors expressed on tumor cells had poorer progression-free survival after rHu-EPO treatment compared to placebo (adjusted relative risk 2.07; 95% CI, 1.27–3.36; p < 0.01), while in patients who received rHu-EPO treatment and were receptor-negative there was no outcome impairment (adjusted relative risk 0.94; 95% CI, 0.47–1.90; p = 0.86). Concerns have been expressed regarding the specificity of EpoR C20 antibody used because it has been clearly demonstrated that it cross-reacts with heat shock protein–70.

Randomized placebo controlled trial of epoetin alpha in patients with non-small cell lung cancer (NSCLC) was preliminary terminated on unplanned safety analysis due to significant difference in overall survival favoring placebo group (63 vs. 129 days; HR1.84; p = 0.04). Increased mortality was consequence of thromboembolic complications in patients treated with epoetin beta. Primary outcome of the trial was to verify QoL improvement for patients with NSCLC unsuitable for curative treatment and baseline hemoglobin levels less than 121 g/L.

DAHANCA 10 (Danish Head and Neck Cancer 10 trial) was terminated due to increased mortality of the patients treated with darbopoetin alpha compared with placebo (HR 1.25; 95% CI 1.04–1.51). Trial was designed to determine benefit of darbopoetin beta treatment in head and neck cancer patients while not receiving any chemotherapy and/or radiotherapy.

It is important to notice that patients in 2 studies mentioned above were not treated following recommended ASCO guidelines since they received no cancer specific therapy.

Functional EpoR expression has been documented on many nonhematopoietic cell types e.g. vascular endothelial cells, smooth muscle cells, cardiac myocytes, neurons, retinal photoreceptors and many others. Erythropoietin is involved in diverse nonhematopoietic biological functions such as angiogenesis and granulation tissue formation or cellular proliferation.

Expression of EpoR has been reported in many tumor cell lines as well as primary cancers. The question arises regarding autocrine or paracrine erythropoietin effect on tumor proliferation, apoptosis, angiogenesis and possibly even radio or chemo sensitivity.

Some in vitro or animal model studies suggest that erythropoiesis-stimulating agents (ESA) may stimulate tumor cell proliferation but others have failed to show these effects. Tumor regression was demonstrated following local injection of Epo antibodies.

In human cervical cancer cells (HeLa) pretreated with different doses of epoetin and than challenged with cisplatin survival was dose dependent. Same study also demonstrated strong correlation between expression of EpoR and bcl-2. However in another study lower doses of epoetin had no effect on bcl-2 expression or pro-apoptotic effect was determined.

As mentioned before, EpoR has been identified in endothelial cells and there is possibility of correlation between erythropoietin and angiogenesis. A study of tumor cells demonstrated increased production of angiogenic growth factor VEGF following treatment with high doses of epoetin and inhibition of angiogenesis and decreased tumor cell survival after treatment with EpoR antagonist.

When evaluating preclinical studies, we have to consider that doses of epoetin used are several times higher than physiological doses or those achieved in patients treated with rHu-EPO.

In conclusion, rHu-EPO therapy plays a significant role in lowering the need for blood transfusions, as well as in improving of quality of life of patients with cancer. It seems that rHu-EPO therapy has no negative but neither has positive effect on overall survival and malignant

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**TABLE 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of cancer</th>
<th>Number of patients</th>
<th>Erythropoietin</th>
<th>Target Hgb level g/L</th>
<th>Adverse outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henke et al.</td>
<td>Locally advanced head and neck cancer</td>
<td>351</td>
<td>Epoetin beta 300 IU/kg 3x/wk</td>
<td>≥120 in women ≥130 in men</td>
<td>Hazard ratio for local-regional progression 1.69 (P 0.007); hazard ratio for death 1.39 (P 0.02)</td>
</tr>
<tr>
<td>Leyland-Jones et al.</td>
<td>Metastatic breast cancer</td>
<td>939</td>
<td>Epoetin alfa 40000 U/wk</td>
<td>≥130</td>
<td>Survival at 12 mo. vs. placebo 70% vs. 76% (P 0.01)</td>
</tr>
<tr>
<td>Wright et al.</td>
<td>Metastatic NSCLC</td>
<td>70</td>
<td>Epoetin alfa 40000 U/wk</td>
<td>120–140</td>
<td>OS vs. placebo 63 vs. 129 days; hazard ratio for death 1.84 (P 0.04)</td>
</tr>
<tr>
<td>Goldberg</td>
<td>Locally advanced head and neck cancer</td>
<td>522</td>
<td>Darbepoetin alfa 150 μg/wk</td>
<td>140–155</td>
<td>10% increase in local-regional failure (P=0.01); trend toward shorter survival (P=0.08)</td>
</tr>
</tbody>
</table>

disease progression while approved guidelines are followed. Results of four mentioned clinical trials with negative impact on survival allow certain suspicion regarding safety of rHu-EPO therapy, especially having in mind contradictory results of preclinical trials exploring EpoR role in tumor cells (Table 2).

Conclusion
Correction of anemia should be one of priorities when treating patients with cancer, because of consequential tumor hypoxia and progression of malignant disease. Anemia reduces both quality of life and overall survival of cancer patients as well as efficacy of both main oncological treatment modalities – radiotherapy and chemotherapy. Anemia is separate prognostic factor for survival in patients with cancer.

REFERENCES
LIJEČENJE ANEMIJE U ONKOLOŠKIH BOLESNIKA

S A Ž E T A K

Anemija s posljedičnom tkivnom hipoksijom čest je problem u onkolozkim bolesnika. Nastaje različitim patofizijološkim mehanizmima i ima loš učinak na kvalitetu života i preživljenje bolesnika s malignim bolestima. Prepoznawanjem simptoma i pruvovremenim započinjanjem liječenja poboljšavamo kvalitetu života bolesnika, kao i učinkovitost onkolozkog liječenja. Transfuzije eritrocita dobro su poznat i učinkovit način korekcije anemije. Danas predstavljaju "zlatni standard" liječenja anemije uzrokovane malignom bolešću i neizbježne su u gotovo svih bolesnika s koncentracijom hemoglobinina ispod 80 g/L. Najnovije terapijske smjernice u razvijenim zemljama, sukladno novijim znanstvenim spoznajama, ohrabruju uporabu rekombinantnog humanog eritropoetina (rHu-EPO), iako su detaljnije meta-analize i prospektivna randomizirana istraživanja pokazala kako rHu-EPO smanjuje potrebu za transfuzijama u samo 9–45% onkoloških bolesnika, i to samo ukoliko imaju blagu anemiju. rHu-EPO povećava učestalost tromboembolijskih incidenta, a postavljena je i sumnja o promotivnom učinku na rast i razmnožavanje tumorskih stanica. Potrebno je jasno definirati skupine bolesnika koji su najpogodniji kandidati za liječenje s rHu-EPO, a s ciljem smanjenja intenziteta transfuzijskog liječenja.