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Review

Treatment of Cancer-Related Anemia

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A B S T R A C T

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 $<4{,}3 \times 10^9$/L, in females $<3{,}86 \times 10^9$/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 myelosupressive 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, interpheron-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-

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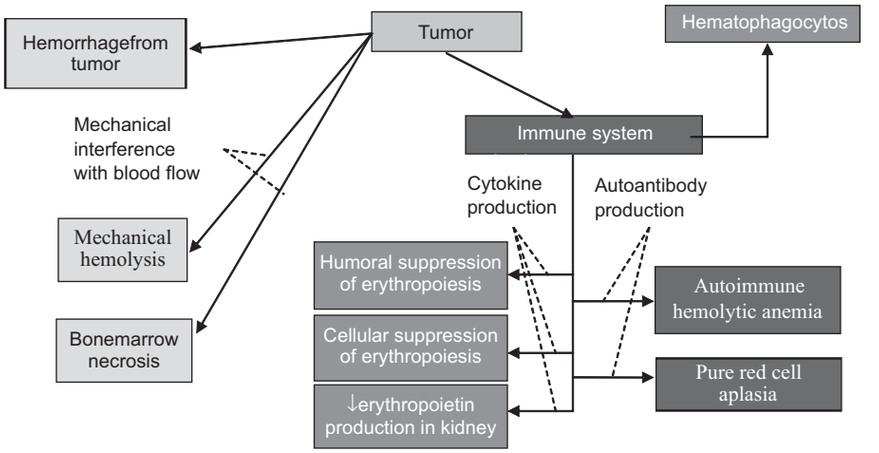

Fig. 1. Causes of anemia in cancer patients. Mechanical (lowered RBC production due to tumor infiltration of bone marrow, and direct lysis of red blood cells during hematogenic dissemination of malignant cells), blood loss (hemorrhage from tumor itself), and activation of immune system (hemophagocytosis; synthesis of antibodies to erythroid cells with consequential autoimmune hemolytic anemia or red blood cells aplasia in bone marrow; and modulation of cytokine expression with consequential humoral and cellular suppression of erythropoiesis and erythropoietin secretion suppression in kidneys).

ronment 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) 1 α and β. Normally, there is a dynamic balance of synthesis and degradation of HIF-1α in organism. Oxygen and two-valent ions of iron are cofactors for prolyl-hydroxilase activation, the enzyme which carries out HIF-1α degradation, and in their absence the substrate accumulates. HIF-1α accumulation activates transcription mechanisms for erythropoietin synthesis in hematopoietic cells, whilst in other cells expressing HIF receptors it activates anaerobic metabolism and apoptotic mechanisms. Besides 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-β) 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)[2].

Anemia and Quality of Life

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[3]. 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

TABLE 1
STAGING OF ANEMIA SEVERITY

Severity of anemia	WHO	NCI
Grade 0	> 110 g/L	WNL
Grade I (mild)	95–109 g/L	100 g/L – WNL
Grade II (moderate)	80–94 g/L	80–110 g/L
Grade III (severe)	65–79 g/L	65–79 g/L
Grade IV (life-threatening)	< 65 g/L	<65 g/L

WNL hemoglobin values are 120–160 g/L for women and 140–180 g/L for men. Adapted from Groopman and Itri, Oxford University Press, 1999.

by chemo-radiotherapy, and in 19,5% of patients treated by radiotherapy alone)[4], patients age, and bone marrow reserve.

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

Anemia is 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[5].

Anemia has negative effect 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, radiosenzitizers (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[6].

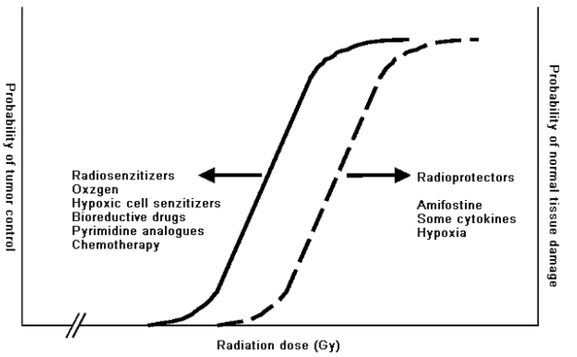

Fig. 2. Dose-effect curve and relation to hypoxia and radiosenzitizers.

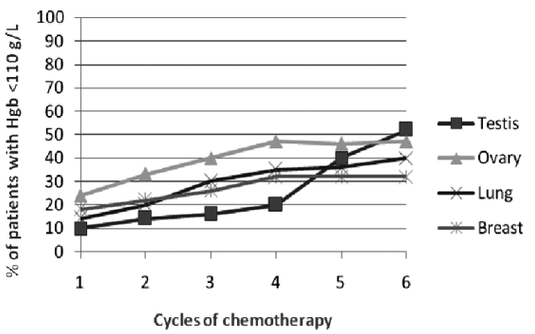

Fig. 3. Cumulative myelosupressive effect of chemotherapy. Reprinted by permission from Macmillon Publishers Ltd: Br J Cancer 82 (2000) 93: Barrett-Lee PJ, Bailey NP, O'Brien MER, Wager E. Large-scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy. Copyright © 2000.

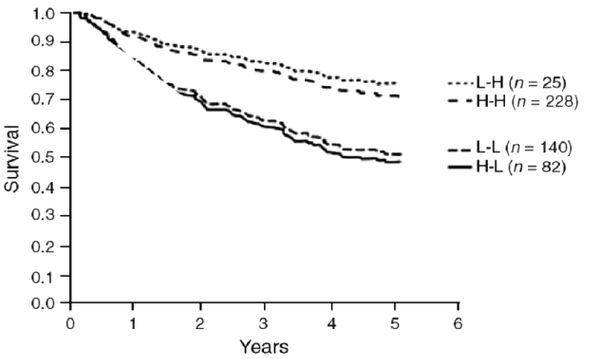

Fig. 4. Dependency of survival to hemoglobin concentration in patients with cervical cancer treated with radiotherapy. 475 patients have been stratified into four groups: patients with low baseline hemoglobin level whose hemoglobin remained low during the treatment (L–L), patients with high baseline 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.

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*[7]. 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 myelosupressive 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 by radiotherapy is 25% worse if average hemoglobin level was below 120 g/L, and that it improves with correction of anemia (Figure 4)[8].

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)[9].

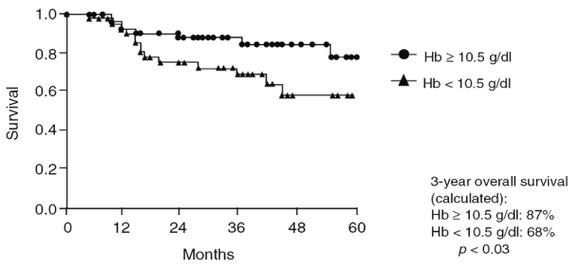

Fig. 5. Dependency of survival to hemoglobin concentration in patients with testicular cancer treated with high dose PEI chemotherapy. Reprinted by permission from Macmillon Publishers Ltd: Br J Cancer 87 (2000) 1066:Boekemeyer C, et al. Treatment-induced anaemia and its potential clinical impact in patients receiving sequential high dose chemotherapy for metastatic testicular cancer, Copyright © 2002.

Transfusion Therapy in Cancer Patients

Scientific and therapeutical application of blood transfusions first started about one hundred years ago, when Landsteiner revealed blood groups at the beginning of twentieth century. Thanks to modern techniques of preparation and storage, they can be stored before application even ten years after blood collection. RBC transfusions are common medical intervention; in United States, about 4 million people receive blood transfusion every year, mainly surgical patients (60–70%). Cancer patients generally receive blood transfusions when hemoglobin level drops to about 70–80 g/L, with higher cut off value in patients with cardiac and pulmonary comorbidity, since symptoms and signs of anemia are usually more intensive. Estimates show that 33% of patients with cancer receive blood transfusion at least once, and about 16% receive multiple RBC transfusions during the treatment[10]. In clinical practice, anemia is treated in only 39% of anemic cancer patients, in spite of deleterious effect of anemia on quality of life. In Europe, 17% of patients are treated by rHu-EPO, about 15% by RBC transfusions, and about 9% by iron supplements[11]. Prompt effect in anemia correction in practically every patient who receives it, as well as relatively low cost of treatment (about 208 US$ per patient during 4 cycles of chemotherapy), are main advantages of transfusion therapy in cancer patients[12].

Three main controversies remain in transfusion therapy of cancer patients. Harmful immunomodulatory effect has never been proven in patients with cancer, while risk of transmission of infectious diseases has been minimized by modern techniques of detection and preparation of blood derivates. Certain risk of transfusional reactions still remains, but with adequate caution they can almost always be avoided.

Insufficient blood supply is the crucial problem in transfusion therapy of cancer patients, especially in developed countries. Cancer patients are too numerous to be adequately treated by transfusion therapy with current blood supply. In clinical practice, this is usually reflected through delaying transfusions until hemoglobin level drops significantly.

Blood transfusions should be given on individual basis rather than predefined hemoglobin concentrations, to treat acute anemia if crystalloid fluids have no effect on correction of intravascular anemia, and to treat chronic anemia if iron supplements or rHu-EPO have no effect. In patients with cancer RBC transfusions should also be given when there is not enough time to wait for (possible) effect of rHu-EPO, i.e. when rapid malignant disease progression is expected.

Erythropoietin and Correction of Anemia

Erythropoietin is glycoprotein hormone produced predominantly in kidney, and only to a minor degree in liver[13]. Its production is regulated by hypoxia through transcriptional factor HIF-1 and effect is mediated by receptor (EpoR) on erythroid progenitor cells in bone marrow stimulating their proliferation[14]. Recombinant human erythropoietin (rHu-EPO) has initially been used to treat patients with chronic renal failure[15] and in 1993 FDA approved its use in cancer patients. There are 3 commercially available products, epoetin alpha, epoetin beta and darbopoetin.

Erythropoietin, blood transfusion requirements and quality of life

It is unequivocal that rHu-EPO treatment can reduce the need for blood transfusions in cancer patients and, consequently, improve patients' quality of life (QoL).

In randomized, placebo-controlled study by Littlewood et al. epoetin alpha 150 to 300 IU/kg was administered to the patients with solid or nonmyeloid 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[16]. 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. 5 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[17]. 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 4.4 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)[18].

Meta-analysis of 40 clinical trials including 21378 patients, confirmed the mentioned results[19]. The odds ratio for transfusions in studies of epoetin versus control was 0.44 (95% CI, 0.35–0.55) 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[20–26]. Regarding darbopoetin alpha and QoL, Vancteenkiste 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)[6]. 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[37]. 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 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[42]. 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)[43]. 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[44–46].

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)[47]. 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)[48]. 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[49], smooth muscle cells[50], cardiac myocytes[51], neurons[52], retinal photoreceptors[53] and many others. Erythropoietin is involved in diverse nonhematopoietic biological functions such as angiogenesis and granulation tissue formation[54] or cellular proliferation[55].

Expression of EpoR has been reported in many tumor cell lines as well as primary cancers[56]. The question arises regarding autocrine or paracrine erythropoietin effect on tumor proliferation, apoptosis, angiogenesis and possibly even radio or chemo sensibility.

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[57]. Tumor regression was demonstrated following local injection of Epo antibodies[58].

In human cervical cancer cells (HeLa) pretreated with different doses of epoetin and than challenged with cisplatin survival was dose dependent[59]. 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[60]. Decreased sensitivity to cisplatin of cancer cell lines exposed to epoetin was reported in two studies[61,62] while in others there was no such effect[63] or pro-apoptotic effect was determined[64].

As mentioned before, EpoR has been identified in endothelial cells[33] 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[65] and inhibition of angiogenesis and decreased tumor cell survival after treatment with EpoR antagonist[66].

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[40].

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

TABLE 2
ADVERSE OUTCOMES ASSOCIATED WITH ERYTHROPOIETIN TREATMENT IN CANCER PATIENTS

Study	Type of cancer	Number of patients	Erythropoietin	Target Hgb level g/L	Adverse outcome
Henke et al.	Locally advanced head and neck cancer	351	Epoetin beta 300 IU/kg 3x /wk	≥120 in women ≥130 in men	Hazard ratio for local-regional progression 1,69 (P 0,007); hazard ratio for death 1,39 (p 0,02)
Leyland-Jones et al.	Metastatic breast cancer	939	Epoetin alfa 40000 U/wk	≥130	Survival at 12 mo. vs. placebo 70% vs. 76% (p 0,01)
Wright et al.	Metastatic NSCLC	70	Epoetin alfa 40000 U/wk	120–140	OS vs. placebo 63 vs. 129 days; hazard ratio for death 1,84 (p 0,04)
Goldberg	Locally advanced head and neck cancer	522	Darbepoietin alfa 150 μg/wk	140–155	10% increase in local-regional failure (p=0,01); trend toward shorter survival (p=0,08)

NSCLC – non-small-cell lung cancer, OS – overall survival. Modyfied from Khuri FR, 2007.

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.

Two main questions are to be answered by ongoing clinical trials: *when* to start treating anemia, and *which target hemoglobin value* to strive? According to currently available data, hemoglobin concentration optimal for maximum efficiency of oncological treatment is 120–130 g/L, and treatment of anemia should be started as soon as hemoglobin level drops below 110 g/L, since best improvement in quality of life can be achieved.

Two main available modalities for treatment of anemia are supportive therapy (blood transfusions) and recombinant human erythropoietins. Prophylactic application of rHu-EPO is still under clinical evaluation, as well as identification of patients optimal for erythropoietic therapy. Question if erythropoietic agents are suitable for patients with all types of cancer remains unanswered. Predictive factors for erythropoietic therapy are probably going to be defined in near future.

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LIJEČENJE ANEMIJE U ONKOLOŠKIH BOLESNIKA

S A Ž E T A K

Anemija s posljedičnom tkivnom hipoksijom čest je problem u onkoloških bolesnika. Nastaje različitim patofiziološkim mehanizmima i ima loš učinak na kvalitetu života i preživljenje bolesnika s malignim bolestima. Prepoznavanjem simptoma i pravovremenim započinjanjem liječenja poboljšavamo kvalitetu života bolesnika, kao i učinkovitost onkološkog 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 hemoglobina 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 incidenata, 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.