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Anemia in cancer

M. Dicato[1,2]*, L. Plawny[1] & M. Diederich[2]

[1]*Hematology-Oncology;* [2]*Laboratory of the Foundation for Research in Cancer and Blood Disorders, Centre Hospitalier de Luxembourg, Luxembourg*

Inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), among others, play a major role in the pathophysiology of anemia in the cancer patient not only through complex mechanisms of the purely inflammatory situation but also through genetic regulatory aspects of erythropoiesis via GATA-1 and GATA-2, and other factors. In terms of therapy, iron is used more and more; the late side effects of transfusions are not really understood and the recent controversy regarding erythropoietin usage has resulted in regulatory authorities and scientific societies providing several recommendations and guidelines. These various aspects are addressed herein.
Key words: cancer, cytokines, erythropoietin, GATA-1/GATA-2, TNF-a

epidemiology and definition

Anemia is a frequent finding in cancer patients, occurring in >40% of cases [1]. In patients treated with chemotherapy, the incidence of anemia may rise to 90% [2]. Anemia exerts a negative influence on the quality of life of cancer patients as it may contribute to cancer-induced fatigue [3]. Anemia has also been identified as an adverse prognostic factor [4].

Anemia is defined as a hemoglobin level <14 g/dl for men and <12 g/dl for women. It has been subdivided into mild (10 g/dl—normal), moderate (8–10 g/dl), severe (6.5–8 g/dl) and life threatening (<6.5 g/dl or unstable patient) anemia [5].

pathophysiology

The pathophysiological origins of anemia can be grouped into different categories:

- blood loss
- increased destruction of red blood cells
- decreased production of functional red blood cells [6].

These three mechanisms are often intricately linked, and the origin of anemia in cancer patients is often multifactorial. Anemia may be attributed to the underlying co-morbidities such as coagulation disorders, hemolysis, hereditary diseases, renal insufficiency, nutritional insufficiencies or underlying inflammatory disease [7]. Cancer itself can directly cause or exacerbate anemia either by suppressing hematopoiesis through bone marrow infiltration or production of cytokines that lead to iron sequestration, or by reduced red blood cell production. In addition, treatment itself may be a major cause of anemia [6. 7].

Correspondence to: Dr M. Dicato, Hematology-Oncology, Centre Hospitalier de Luxembourg, L-1210 Luxembourg. E-mail: mdicato@gmail.com

cancer-induced anemia

Cancer-induced anemia and anemia of chronic disease result from multiple causes and the fine interplay of pro- and antiapoptotic factors inducing a fine-tuned selective differentiation of the trilineage committed hematopoietic stem cell. A slight disruption of this equilibrium will present as one of the many facets of blood count changes from anemia to thrombocytosis, as commonly seen in cancer patients.

GATA-1 and GATA-2, tumor necrosis factor-α (TNF-α) and other factors are players in this (dis)equilibrium.

TNF-α inhibits hemoglobin production in a proportional fashion to the down-regulation of GATA-1 and also affects erythropoiesis induced by erythropoietin (Epo). TNF-α induces a decrease in the expression of FOG-1, a co-activator of GATA-1, as well as a proteasome-dependent decrease of GATA-1. In addition TNF-α suppresses the acetylated form of GATA-1, the post-translational modification required for DNA binding.

Numerous *in vitro* studies have illustrated the central role of TNF-α in the pathogenesis of anemia [8]. TNF-α might indirectly inhibit the proliferation of erythroid progenitor cells by triggering nuclear factor-κB (NF-κB) and GATA-2 pathways, thus suppressing erythropoietin production [9]. The companion actor GATA-2 is part of these elements affecting control of genetic expression in hematopoiesis. GATA proteins are zinc-finger transcription factors involved in erythropoiesis and megakaryopoiesis [10]. In hematopoietic stem cells, GATA-2 is overexpressed and is believed to ensure maintenance and proliferation, whereas GATA-1 is involved in the survival of erythroid progenitors as well as in the differentiation of erythroid cells. Overexpression of GATA-2 determines megakaryocytic differentiation whereas its down-regulation is required for erythroid differentiation. GATA-1 is key erythroid transcription factor. A cross-regulatory mechanism between GATA-1 and GATA-2 seems to exist [10, 11]. TNF-α might stimulate GATA-2, thus reducing erythroid differentiation in cancer cells [9]. The binding of TNF-α to its ligand, TNF-R1, inhibits GATA-1 and suppresses the

expression of genes specific to erythroid differentiation such as globin genes or Epo receptors (EPO-Rs). TNF-α reduces the Epo-mediated hemoglobinization of erythroid progenitors. Interaction of TNF-α with the EPO-R stimulates apoptosis via the NF-κB pathway [9].

GATA-1 is a key erythroid transcription factor and a key target for the inhibiting effect of TNF-α. TNF-α is probably the major, but not the only player in anemia of chronic disease.

Other cytokines, such as interleukin-6 (IL-6), IL-1 and interferon-γ, have also been shown to inhibit erythroid precursors *in vitro* [9], albeit to a lesser extent.

Interestingly, anemia in Crohn's disease and in rheumatoid arthritis improves after primary therapy of the disease with an anti-TNF antibody. It can be shown in an *in vitro* model that inhibition of erythropoiesis could be corrected by the addition of an anti-TNF-α antibody. Hence improvement of anemia is not only due to the improvement of the disease as such but in fact is also due directly to the alleviation of the TNF-α-induced erythropoiesis inhibition.

In addition to the various cytokines discussed above, over the past few years iron therapy has been increasingly addressed.

In inflammation, from whatever cause, IL-6 induces the liver to produce hepcidin. Hepcidin decreases iron absorption from the bowel and blocks iron utilization in the bone marrow. Iron may be abundant in the bone marrow, but is not absorbed and is not in the circulation, and so is not available for erythropoiesis. Hepcidin blocks iron absorption in the gut as well as iron in the bone marrow. Therefore, in inflammatory anemia, iron deficiency should be defined by a low transferrin saturation of <20%, ferritin levels of <100 ng/ml and a low reticulocyte hemoglobin concentration of <32 pg.

In evaluating an anemia patient in whatever clinical condition, other deficiencies such as folic acid, vitamin B12, etc. should be excluded.

chemotherapy-associated anemia

Some chemotherapeutic agents induce anemia by impairing hematopoiesis (Table 1) [12]. In addition, nephrotoxic effects of particular cytotoxic agents such as platinum salts can also lead to the persistence of anemia through reduced Epo production by the kidney [13]. Chemotherapy-associated anemia seems to be frequent in lung cancers and gynaecological malignancy, partly due to the fact that their treatment may require platinum-based regimens [13]. The myelosuppressive effect of cytotoxic agents might accumulate over the course of chemotherapy. This results in a steady increase of the incidence of anemia with every new cycle of chemotherapy. The European Cancer Anaemia Survey showed that anemia increased from 19.5% in the first cycle of chemotherapy to 46.7% after the fifth cycle [14]. Other risk factors for chemotherapy-related anemia include low hemoglobin level, transfusions in the past 6 months, prior radiotherapy to>20% of the skeleton, a previous myelosuppressive chemotherapy and co-morbidities such as chronic inflammatory diseases [5].

treatment

Currently two options are at the disposal of the clinician for the treatment of anemia in cancer patients: transfusion of packed red blood cells and the use of erythropoiesis-stimulating agents (ESAs). The goal of the treatment is to relieve the symptoms of anemia such as fatigue and dyspnea.

Table 1. Incidence of anemia with different chemotherapy agents

Agent/regimen	Grade 1/2	Grade 3/4	Cancer
Cisplatin	–	11%	Head and neck
Docetaxel	73–85%	2–10%	Non-small cell lung cancer
5-FU	–	11%	Head and neck
Paclitaxel	93%	7%	Breast
Topotecan	–	32%	Small cell lung cancer
Vinorelbine	67–71%	5–14%	Breast
Cisplatin + cyclophosphamide	43%	9%	Ovarian
Cisplatin + etoposide	59%	16–55%	Small cell lung cancer
VIP	–	52%	Small cell lung cancer
5-FU + carboplatin	42%	14%	Head and neck
CHOP	49%	17%	Non-Hodgkin lymphoma
Paclitaxel + daunorubicin	78–84%	8–11%	Breast
Paclitaxel + carboplatin	10–59%	5–34%	Non-small cell lung cancer

Adapted from Groopman [13].

CHOP, cytoxan, hydroxyrubicin, oncovine and prednisone; 5-FU, 5-fluorouracil; VIP, Vp16, ifosfamide and csiplatin.

transfusion

Transfusion of packed red blood cells offers a rapid increase in hemoglobin and hematocrit levels and is hence the ideal option in patients requiring rapid correction of anemia. Transfusion of 1 unit of packed red blood cells has been estimated to result in an increase in the hemoglobin level of 1 g/dl in a normal-sized adult [15, 16]. The results of a number of studies evaluating the impact of transfusion on mortality in critically ill patients are conflicting. One study of 56 esophageal cancer patients receiving chemoradiation therapy showed that blood transfusions increased overall survival [hazard ratio (HR) 0.26, 95% confidence interval (CI) 0.09–075, $P = 0.01$] [17].

Though transfusions bring obvious advantages, they are, however, not devoid of risk, including transfusion-related reactions, congestive heart failure, bacterial contamination, viral infections and iron overload [5.18]. The introduction of numerous safety interventions for infectious organisms has dramatically decreased the incidence of transfusion-related infections. Leukoreduction has been shown to reduce the incidence of febrile non-hemolytic transfusion reactions [19]. A recent study conducted in 60 US medical centers between 1995 and 2003 found an increased risk of venous and arterial thromboembolism and mortality associated with packed red blood cell transfusion [20]. Iron overload is a frequent complication in patients with myelodysplastic syndrome (MDS) requiring transfusion over a long period of time. This condition is rarely seen however in patients with solid tumors in which the transfusion period lasts less than a year [21].

ESA therapy

Three types of ESA are currently available. Epoietin alfa (EPREX®), epoetin beta (Neorecormon®) and darbepoetin alfa (Aranesp®). A pegylated form of Epo (methoxy PEG Epoetin beta, Mircera®, CERA®) has been approved in some European countries, and some biosimilars are readily available (Epoetin zeta, Retacrit®).

Treatment with Epo has been shown to reduce transfusion rates in cancer patients. The Littlewood study conducted in 2001 on breast cancer patients showed that patients receiving epoietin beta had a decreased transfusion rate compared with patients receiving placebo (24.7% versus 39.5%, $P = 0.057$). Patients on Epo also achieved a higher rise in hemoglobin levels than controls. (2.2 g/dl versus 0.5 g/dl, $P = 0.01$) [22]. Similar results were obtained with darbepoetin alfa where a double-blind placebo-controlled randomized phase III trial in lung cancer conducted by Vansteenkiste showed that patients receiving darbepoietin required fewer transfusions than patients receiving placebo (27% versus 52%, 95% CI 14% to 36%, $P < 0.001$) [23]. A 2006 Cochrane review confirmed the ability of ESA treatment to reduce the tranfusion rate [relative risk (RR) 0.64, 95% CI 0.6–0.68). The same review indicated that there was a trend towards an increase in quality of life in patients receiving ESA treatment [24].

Over the last few years, however, many concerns regarding the safety of ESA treatment in terms of mortality, venous thromboembolism (VTE) and tumor progression have been raised.

The BEST study and the PREPARE study, two double-blind placebo-controlled phase III treatments investigating the effect of ESA therapy in breast cancer patients receiving chemotherapy, both indicated a higher mortality rate in patients receiving ESA treatment [25, 26]. In head and neck cancer, the ENHANCE study and the DAHANCA-10 study showed a reduction of time to locoregional progression in patients receiving Epo [27, 28]. A reduction of overall survival in ESA patients was seen in the ENHANCE study [27]. In the palliative setting, the AMGEN 103 anemia of cancer study, ESA treatment was associated with a significantly shorter overall survival and darbepoetin treatment was not able to achieve the end point of transfusion reduction [29]. Three recent meta-analyses performed by Bennett, Bohlius and Tonnelli confirmed that patients receiving ESA treatment had a significantly increased RR of mortality of 1.17, 1.15 and 1.1, respectively [30–32]. Interestingly, in the Bennett meta-analysis, patients treated for cancer-related anemia fared less well than patients treated for chemotherapy-induced anemia (HR 1.29, 95% CI 1–1.67 versus HR 1.09, 95% CI 0.99–1.19) [30]. The three above-mentioned meta-analyses contain patients included in studies where Epo was used off-label with a target hemoglobin >12 g/dl. More recently, a meta-analysis conducted by Glaspy showed that when considering only the patients included in studies where the target hemoglobin was <12 g/dl, the overall mortality did not seem to vary between patients receiving ESA therapy or patients receiving placebo [33].

Recent concerns regarding the risk of thromboembolism in patients treated with ESA have been corroborated by the meta-analyses conducted by Tonnelli and Bennett (RR 1.95, 95% CI 1.27–2.24, and RR 1.57, 95% CI 1.31–1.87) [30, 32]. In breast cancer patients, the BRAVE study conducted by Aapro randomized breast cancer patients receiving chemotherapy to either epoetin beta or best supportive care. Patients under ESA experienced more thromboembolic events than controls (13% versus 6%). There was however no difference in grade III–IV VTE- or in thromboembolic event (TEE)-related deaths [34]. An analysis of six trials of darbepoetin alfa by Glaspy and colleagues found an increased thromboembolic risk for patients with a hemoglobin level >12 g/dl or with an increase in hemoglobin of >1 g/dl in 14 days [35]. An ODAC review found that the thromboembolic risk throughout studies varied with the target hemoglobin level. When targeting 13 g/dl, the relative risk for VTE is 0.7. It rises to 1.7 for a target hemoglobin between 13 and 14 g/dl. In studies targeting levels >15 g/dl, it rises to 1.92 [36]. The different meta-analyses which have been assessing mortality and VTE may be biased by the fact that they include studies where ESAs have been used off-label with a target hemoglobin >12 g/dl [30–32]. In the meta-analysis conducted by Bennett in 2008, the BEST study where the target hemoglobin was >12 g/dl accounted for >20% [30] The 2006 meta-analysis and Cochrane review by Bohlius showed an RR of VTE in ESA patients of 1.67 (95% CI 1.13–1.93). When addressing only patients where the target hemoglobin lay under 12 g/dl, the RR was somewhat smaller [24].

Concerns about tumor progression under ESA treatment have been raised in the last years; however, pre-clinical evidence for the existence of EPO-Rs on tumor cells remains inconclusive [37, 38]. In fact, immunohistochemical studies might be biaised by the fact that anti-EPO-R antibodies, in particular C20 (Santa Cruz, California), are not specific and might in fact detect heat shock protein-70 (HSP-70), which is expressed in cases of anoxia and is considered as a marker of a poor prognosis [39–41] Moreover, in 2006, Elliott demonstrated that an EPO-R knockout mouse model showed the same uptake of anti-EPO-R antibodies as controls [39]. Some *in vitro* studies showed that cancer cell lines treated with Epo at high concentration displayed increased phosphorylation of ERK1/2 or STAT-5 AKT/ERK, which are signaling kinases found downstream of the EPO-R. Phosphorylation of these signals was, however, not correlated to proliferation [42, 43]. Furthermore, the Epo concentrations used in these experiments surpassed those currently encountered in patients treated with ESA. In clinical studies, one author showed a substantially lower progression-free survival in head and neck cancer patients and identified a subgroup with a poor prognosis expressing the EPO-R [27]. As the anti-Epo antibody used to detect the EPO-R was non-specific, it is likely that the authors have identified a subpopulation expressing HSP-70 [38].

Other side effects of Epo such as pure red cell aplasia or hypertension have not yet been described in cancer patients. A worrying publication in November 2009 showed a substantial increase in strokes in diabetes patients [44]. This could be a further argument cautioning against ESA therapy in general.

treatment of anemia

The treatment of chemotherapy-induced anemia depends on the grade and on the symptoms of anemia. Transfusion remains

Table 2. Dose increments or decrements proposed by NCCN and ESMO for subcutaneous epoetin alfa, epoetin beta and darbepoetin alpha

Agent	Initial schedule	Increase for no response	Titration for response
Epoetin alfa	150 U/kg 3×/week	300 U/kg 3×/week	Adjust for the lowest dose sufficient to maintain Hb level
	40 000 U/week	60 000 U/week	
	80 000 U/2 weeks	No increase proposed	
	120 000 U/3 weeks	No increase proposed	
Epoetin beta	30 000 U/week	60 000 U/week	If increase >1 g/dl in 2 weeks reduce by 25–50%
Darbepoetin alfa	2.25 mg/kg/week	Up to 4.5 mg/kg/week	Withhold dose if Hb >13 g/dl
	100 mg/week	150–200 mg/week	
	200 mg/2 weeks	300 mg/2 weeks	
	300 mg/3 weeks	500 mg/3 weeks	
	500 mg/3week	No increase proposed	

Adapted from NCCN 2010 [5] and ESMO 2009 [45].
ESMO, European Society for Medical Oncology; Hb, hemoglobin; NCCN, National Comprehensive Cancer Network; U, units

an option for patients who need immediate correction of anemia. In patients who do not require immediate correction, treatment options include transfusion and ESA therapy. The National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) caution against ESA therapy in patients receiving chemotherapy with curative intent [5, 45].

In asymptomatic patients with risk factors for the development of symptomatic anemia, ESA therapy might be considered [5, 45]. It must, however, be noted that ESA treatment, when used within the guidelines, does not change the course of the underlying malignancy. So, clinicians should weigh the possible risks and benefits of ESA treatment and discuss them with the patient [5, 45].

The most common dosing schedules for epoetin alfa are 150 units/kg three times weekly and 40 000 units once weekly subcutaneously [22]. Other dosages may be considered including extended dosing of 80 000 units every 2 weeks and 120 000 units every 3 weeks [46, 47]. Darbepoetin alfa is initially administered at 2.25 μg/kg every week [48]. Studies using higher doses at longer intervals (500 μg every 3 weeks) showed more efficacy than the standard doses [49]
Dosing schedules in the case of insufficient response are shown in Table 2.

A functional iron deficiency is often seen in patients receiving Epo. Iron supplementation should be given in patients to maintain erythropoiesis [5, 45]. Iron is available in oral or intravenous forms. Studies in anemic patients receiving ESA with oral iron supplementation, intravenous iron dextran or no iron at all showed that patients receiving an intravenous bolus experienced a higher rise in hemoglobin levels than patients receiving oral iron or no iron supplementation at all [50–52]. Moreover, no statistically significant difference could be found between patients receiving oral iron or no iron supplementation [50].

alternatives to EPO and transfusions

Currently, relatively few alternatives to Epo or transfusions exist: polymerized pegylated human hemoglobin (Polyheme®) has been used with success in cardiogenic shock when blood was not available. It is, however, not readily available in European countries or in the USA [53]. GATA-2 inhibitors could be used in the future to raise endogenous Epo production and stimulate erythroid differentiation [54]. Development of these drugs is not proceeding at present.

conclusion

Over the past few years, many aspects of the pathophysiology of anemia in cancer are better understood. However, more needs to be clarified, including the place of iron therapy and transfusion-related side effects.

The various recent recommendations and guidelines have at least partially indicated how best to use ESAs and probably more will be learned about how best to treat patients and to retain the cost–benefit balance of all the therapies.

disclosures

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