Emerging topics in anaemia and cancer

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Erythropoiesis-stimulating agents (ESAs) increase red blood cell (RBC) production by activating the erythropoietin receptor on erythrocytic progenitor cells. ESAs are approved in the United States and Europe for treating anaemia in cancer patients receiving chemotherapy. ESA safety issues include thromboembolic events and there have been concerns about disease progression and/or mortality in cancer patients. This educational supplement paper is based on two recently published papers. We review both clinical trial data on ESAs and disease progression and preclinical data on how ESAs could affect tumour growth. We conclude that ESAs may have little effect on disease progression in chemotherapy patients. We also summarise the mechanisms and clinical consequences of iron deficiency and anaemia in cancer patients. Randomised clinical trials have shown superior efficacy of i.v. iron over oral or no iron in reducing blood transfusions, increasing haemoglobin, and improving quality of life in ESA-treated anaemic advanced cancer patients.

Supportive care of cancer patients allows safer delivery of appropriate treatment and should enhance patient quality of life [1]. This is exemplified by the usage of antiemetics [2] and of white blood cell growth factors [3]. The indication for the use of epoetins [erythropoiesis-stimulating agents (ESAs)] in oncology is to officially decrease the amount of transfusions needed, and for the EORTC guidelines working party and the EMA to reduce anaemia-related symptoms in patients undergoing chemotherapy [4]. These guidelines already mentioned the importance of iron, and the need to correct all causes of anaemia before using ESAs.

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**Key words:** chemotherapy-induced anaemia, disease progression, erythropoiesis-stimulating agents, erythropoietin receptor, hepcidin, iron

Supportive care of cancer patients allows safer delivery of appropriate treatment and should enhance patient quality of life [1]. This is exemplified by the usage of antiemetics [2] and of white blood cell growth factors [3]. The indication for the use of epoetins [erythropoiesis-stimulating agents (ESAs)] in oncology is to officially decrease the amount of transfusions needed, and for the EORTC guidelines working party and the EMA to reduce anaemia-related symptoms in patients undergoing chemotherapy [4]. These guidelines already mentioned the importance of iron, and the need to correct all causes of anaemia before using ESAs.

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**controversies on epoetin safety**

Clinical and preclinical research has examined the benefits and risks associated with ESA use. Although ESAs decrease transfusions, they are associated with an increase in thromboembolic events. The potential for ESAs to affect disease progression and/or mortality in cancer patients has also been discussed. To better understand ESA-related safety issues, several recent large meta-analyses have examined how ESAs affect thromboembolic events and mortality. Disease progression, however, was not always addressed. Difficulties in analysing disease progression include variation in end points (e.g. progression-free survival, locoregional control, tumour response, etc.) and varying quality of disease-assessment measurements. None the less, understanding whether and how ESAs impact disease progression are key issues. We have thus reviewed clinical trial data regarding ESAs and disease progression as well as preclinical research regarding how ESAs could affect disease progression at a cellular/molecular level.

**do ESAs affect disease progression?**

Currently, the ESA product labelling describes eight clinical trials of concern that suggest ESA use increases disease progression and/or mortality in cancer patients. Two studies were carried out in the non-indicated setting of radiotherapy treatment only (code names ENHANCE and DAHANCA-10), two in the non-indicated anaemia-of-cancer setting (patients received neither chemotherapy nor radiotherapy), and four in the indicated chemotherapy setting. Some are discussed here and the others in our review paper.

Although the ENHANCE and DAHANCA-10 trials suggested that ESA use increases disease progression, this finding was not replicated in two randomised, controlled trials in the radiotherapy setting for the treatment of patients with head and neck cancer. The Radiation Therapy Oncology Group (RTOG 99-03) trial, which evaluated 40 000 IU weekly erythropoietin (Epo) to maintain haemoglobin (Hb) between 9.0 and 13.5 g/dl, and the controlled EPO-GBR-7 trial, which evaluated 10 000 IU three times weekly epoetin alfa (Hb <12.5
g/dl) or 4000 IU three times weekly epoetin alfa (Hb ≥12.5 g/dl), did not show ESA use increased disease progression. None the less, based on the ENHANCE and DAHANCA-10 studies, the ESA product labelling does not recommend ESA use in the radiotherapy-only setting.

**the Breast Cancer Erythropoietin Survival Trial (BEST)**
This study was one of the first chemotherapy studies to report an association between increased mortality and ESA use [6]. An article written on behalf of the BEST investigators suggested that study-design issues (including possible imbalances in risk factors between study arms) may have prevented a conclusive interpretation of trial results. In addition, understanding the disease-progression results may have been hampered by lack of prespecified-tumour assessments at the study entry, during the study, and during the follow-up.

**the Preoperative Epirubicin Paclitaxel Aranesp (PREPARE) study**
This study evaluated the effect of preoperative dose-dense, dose-intensified chemotherapy with anthracyclines and taxanes in breast cancer patients (N = 733). A second randomisation assigned patients to receive or not receive darbepoetin alfa 4.5 μg/kg every 2 weeks to maintain Hb concentrations between 12.5 and 13 g/dl. Secondary end points included the effect of darbepoetin alfa on disease-free survival and overall survival. After a median follow-up of ~3 years, an unplanned interim analysis of 733 patients indicated that survival and progression-free survival rates were lower in ESA-treated patients (this difference was not statistically significant). Final results from the PREPARE trial were recently published in two manuscripts [7, 8]. When comparing ESA-treated patients with control patients, the 3-year estimated HR (95% CI) was 1.31 (0.99–1.74; P = 0.061) for disease-free survival and 1.33 (0.91–1.95; P = 0.139) for overall survival. Though these results suggest a trend of decreased disease-free survival with darbepoetin alfa use, the findings were not statistically significant. Darbepoetin alfa use did not affect the pathological complete response.

A recent study-level meta-analysis reported an odds ratio for disease progression for each of the eight studies of concern. These results also suggested that only the ENHANCE and DAHANCA-10 studies demonstrated a statistically significant impact of ESA use on disease progression.

**additional chemotherapy studies**
Results from an Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) phase 3 trial were recently published. This trial compared dose-dense chemotherapy with conventionally scheduled chemotherapy in high-risk primary breast cancer patients (stage II–IIIA with ≥4 positive axillary lymph nodes). Patients in the dose-dense arm (N = 641 evaluated) were additionally randomly assigned to receive or not receive epoetin alfa. The ad hoc analyses reported that epoetin alfa did not affect overall survival or event-free survival (defined as locoregional or distant relapse, contra-lateral breast cancer, second primary cancer occurrence, or death), but that detailed information will be communicated in a later publication (of note, the most recent available data from the AGO trial were used in the meta-analysis of controlled ESA trials by Glaspy et al. that examined the impact of ESAs on mortality/disease progression).

In recently reported preliminary final results, the ARA Plus study (N = 1234) prospectively evaluated event-free survival and overall survival in a randomised, controlled study of adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer patients. After a median follow-up of 40 months, there were no significant differences in 3-year event-free survival (89.2% versus 87.6%, P = 0.97) or overall survival (95.4% versus 95.1%, P = 0.85) between patients receiving darbepoetin and standard of care, respectively.

Results from the large GHSG HD15EPO trial were also recently published. Patients (N = 1328 evaluated for safety) with advanced Hodgkin’s lymphoma receiving chemotherapy were randomly assigned to receive epoetin alfa or placebo. Results indicated that after a median observation period of 3 years, epoetin alfa had no impact on freedom from treatment failure (HR = 0.87; 95% CI: 0.63–1.20) or overall survival (HR = 0.74; 95% CI: 0.45–1.22).

An LNH03-6B Groupe d’ Etude des Lymphomes de l’Adulte (GELA) study is currently being conducted in patients with large B cell lymphoma receiving chemotherapy (R-CHOP). Patients were secondarily randomised to darbepoetin alfa (N = 238) (initially to maintain Hb at 13–15 g/dl; later amended to 13–14 g/dl) or to receive best supportive care (ESA and transfusions administered according to usual practices) (N = 362). A second interim analysis was recently reported and indicated that 3-year progression-free survival was 66% in the darbepoetin alfa arm and 58% in the control arm (HR = 0.77; 95% CI: 0.59–0.99). In an exploratory analysis comparing patients treated with or without ESAs (40% of controls received ESAs as supportive care), the HR for progression-free survival was 0.73 (95% CI: 0.57–0.94).

Based on the balance of evidence to date, six meta-analyses discussed in our review do not support an effect of ESAs on disease progression. However, safety data from some individual, controlled trials suggest that ESAs might affect disease progression and/or mortality in certain cancer patient populations (head-and-neck cancer patients receiving radiotherapy only may be at particular risk). The need for additional research to understand whether and how ESAs affect tumour cell growth has stimulated much preclinical work in this field.

**ESAs and disease progression mechanisms: evidence from preclinical studies**
To explain the conflicting clinical data, several mechanisms for disease progression have been postulated. The most widely studied is whether an Epo-specific receptor exists on tumour cells, endothelial cells, or other non-erythrocyte progenitor cells.
the erythropoietin receptor and tumour cells

Like endogenous Epo, ESAs bind to and activate the Epo receptor (EpoR) on erythrocytic progenitors (colony-forming units—erythroid) in bone marrow. This stimulates erythrocytic progenitor cells to proliferate and differentiate into red blood cells (RBCs). It has been postulated that if tumour cells express EpoR, ESAs could activate these receptors to induce tumour cell proliferation. Thus, examining whether tumour cells express ESA-responsive EpoR has been of interest.

Several studies have suggested that tumour tissues and tumour cell lines express EpoR mRNAs and also contain EpoR protein as demonstrated by western blot analysis or immunohistochemistry. However, technical issues have limited the validity of these findings, and often qualitative, rather than quantitative, studies were carried out. For example, studies examining EpoR-mRNA levels often used bulk tumour tissue, which can contain stromal cells and other cell types that infiltrate from blood. Moreover, several studies using western blot and/or immunohistochemistry may have yielded false-positive results due to the use of commercially available polyclonal or monoclonal anti-EpoR antibodies later shown to lack specificity for EpoR. In addition, many studies did not address whether EpoR was localised to the cell surface and/or whether it could be activated by an ESA. Recent results have suggested that Epo can activate Jak2-mediated signalling and antagonise anti-HER2 (trastuzumab) therapy in breast cancer cells, and a non-significant decrease was observed in progression-free survival for patients treated with Epo and trastuzumab in a small, retrospective subgroup analysis. Another recent study also indicated partial reduction in the efficacy of cytotoxic therapy when combined with Epo in a mouse model of metastatic breast cancer. However, interpretation of these studies is difficult due to the non-specific antibodies used to establish EpoR expression. Additional studies indicate that the EpoR gene is not amplified in tumour cells and that Epo exposure does not induce tumour cell-line proliferation or affect mortality in many animal tumour models. Recently, a monoclonal antibody specific for EpoR was developed enabling detailed analysis of EpoR protein expression and function. Studies using this antibody have indicated that many tumour cell lines express low-to-undetectable levels of EpoR and that any EpoR present is not functional (expression of the cell lines to Epo does not activate signalling molecules such as STAT5 that function downstream of EpoR). In a study carried out in primary human tumour samples from multiple epithelial tumour types, no cell-surface or functional EpoR was detected. These findings do not support the hypothesis that ESAs could increase the risk of disease progression by activating EpoR on tumour cells.

The following text is drawn from another recent paper which provides all references [9].

introduction

Iron deficiency (ID) and anaemia are frequent complications in cancer patients, in particular during treatment with chemotherapeutic agents. ID, even in the absence of anaemia, may be associated with impaired physical function, weakness, and fatigue, which can be ameliorated by iron therapy.

causes and diagnosis of ID and anaemia

impaired iron utilisation in chronic disease

Anaemia of chronic disease (ACD) and chemotherapy-induced anaemia (CIA) are the major causes of anaemia in cancer patients and can be aggravated by chronic blood loss and nutritional deficiencies (e.g. due to cancer-induced anorexia or resection of gastrointestinal malignancies). In patients with ACD, the availability of iron is affected by hepcidin, the key regulator of iron homeostasis. In patients with inflammation, iron release is reduced to 44% compared with normal subjects. Thus, even iron-replete patients can experience a shortage of available iron, especially when exposure to ESAs rapidly increases RBC production.

diagnostic markers of ID in patients with chronic disease

Serum ferritin, the most commonly assessed marker, generally reflects the status of iron stores, while transferrin saturation (TSAT), the percentage of hypochromic red cells, and the Hb content of reticulocytes better reflect the availability of iron. Since serum ferritin, an acute-phase protein, can be elevated due to inflammation and liver cell damage, normal or elevated ferritin levels do not necessarily indicate sufficient iron stores, particularly in cancer patients. Thus, routine blood analysis should also include C-reactive protein and alanine-amino transferase to check for inflammation and liver function. Soluble transferrin receptor levels, recently suggested for the allocation of cancer patients to treatment with ESA alone, iron alone, or a combination thereof, rather reflect the erythropoietically activity than the iron status and cannot be used as iron status parameter when erythropoiesis is stimulated, e.g. with ESAs. Therefore, in routine clinical practice, serum ferritin levels <100 ng/ml probably indicate insufficient iron stores for successful ESA therapy in patients with cancer, and the combination of low TSAT (<20%) and normal or even elevated serum ferritin may indicate FID.

treatment of ID and anaemia

Current anaemia treatment guidelines in oncology acknowledge that i.v. iron enhances efficacy of ESAs in patients with absolute or functional ID. Since iron-replete anemic patients may benefit from i.v. iron supplementation only after the initiation of ESA therapy, iron status assessment is recommended at baseline, before each cycle of chemotherapy, and throughout any kind of anti-anaemia therapy to ensure...
timely commencement of iron supplementation. Oral iron supplementation is presently recommended only in cases of absolute ID.

supplementation of ESA therapy with i.v. iron
Seven randomised, controlled clinical trials investigating the efficacy of i.v. iron supplementation in ESA-treated anaemic cancer patients have been published between 2004 and 2011. Six studies focused on CIA and one on patients not receiving chemotherapy. All studies except one with an unusual (off-label) dosing schedule showed substantial benefit of i.v. iron supplementation. Despite the trials covered different patient populations, i.v. iron formulations, and concomitant chemotherapies, generalisability of the results has been questioned. In particular, the wide range of differences in Hb response rates between treatment and control groups (13%–43%) and a study that seemed to show no benefit of parenteral iron may have raised concerns about the heterogeneity across the trials. However, grouping the results from trials that included patients with FID and trials that focused on iron-replete patients at enrolment showed comparable substantially improved response rates within each of the two populations.

dosing of i.v. iron
In the first published trial on i.v. iron supplementation of ESA therapy that included iron-deficient patients, total iron doses up to 3000 mg were given. In five of the subsequent trials, planned total iron doses were ~1000 mg. The maximum single doses and minimum infusion times of available parenteral iron preparations depend on their tolerability profiles, mainly determined by the biochemical properties and the manufacturing process. Stable iron complexes can be administered at high doses of 20 mg iron/kg body weight within 15 min (ferric carboxymaltose) to 6 h (iron dextran). Compounds that release iron at a faster rate should be given at a lower pace and dose per infusion. There is still debate whether repeated weekly administration or a single 1000 mg dose (when possible) gives the best result, but many experts opt for a single large dose.

potential role for i.v. iron as first-line therapy of CIA?
Guidelines recommend treatment of underlying causes of anaemia such as ID before the initiation of an ESA. However, studies examining i.v. iron as sole anaemia treatment in cancer patients are only just starting to emerge. Two small (N = 44 and N = 75 patients), controlled, randomised clinical trials have been published to show that i.v. iron supplementation substantially reduced the number of required blood transfusions. In the absence of further randomised, controlled clinical trials, the trial by Steinmetz et al. may be instructive. This prospective, multicentre, parallel group study showed that Hb response rates (Hb increase >1 g/dl from baseline) were comparable between patients receiving i.v. iron alone and those receiving ESA alone.

tolerability of i.v. iron in clinical routine
One common prejudice against i.v. iron refers to potential hypersensitivity reactions. However, three analyses evaluating adverse event reports from 1997 to 2009 have shown that allergic and anaphylactoid reactions, even if rare, are mainly related to iron dextran preparations. Even with low molecular weight iron dextran (numbers from Europe only), the rate of anaphylactic reactions is substantially higher compared with iron sucrose or sodium ferric gluconate (15.6, 0.9, and 0.4 per million 100 mg iron dose equivalents, respectively). Another frequently raised question asks whether i.v. iron increases the infection risk. To date, no increased rate of infections was observed in patients receiving i.v. iron for the treatment of cancer-related anaemia. However, although not specifically investigated in human studies, animal studies suggest that administration of i.v. iron should be avoided in patients with active sepsis.

limitations to the use of i.v. iron in clinical practice
One potential limitation to the use of i.v. iron in cancer patients might be the interaction of iron with certain chemotherapies, in particular anthracycline- and platinum-based therapies. Currently available clinical studies with i.v. iron in cancer patients reported no signs of drug-related iron toxicity and only non-clinical data are available on this topic. Until the availability of such human data, one should consider separating the administration of cardiotoxic cancer treatments and give i.v. iron at the first visit after the administration of a potentially cardiotoxic chemotherapy.

Unfortunately, most trials on i.v. iron supplementation of cancer patients were not designed to collect long-term data. One prospective randomised, controlled study that is reported in abstract form only monitored patients with lymphoid malignancies who received darbepoetin alfa and i.v. iron following autologous stem cell transplantation. In this preliminary study, 3-year progression-free survival was independent of i.v. iron treatment.

Table 1. Excerpt from the ESMO Guidelines 2010 [10]

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<th>ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.</th>
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ESMO has published guidelines on the safe use of the cited agents which, along with indications of regulatory authorities, should help clinicians in their decisions (Table 1).
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references