Erythropoietic-stimulating agents: where do we stand?

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introduction

At present three erythropoietic-stimulating agents (ESAs) are available, these being epoietin alpha, epoietin beta and darbepoietin. In oncology the marketing licence given in the early 1990s was and still is for reduction of red blood cell (RBC) transfusion in chemotherapy-induced anaemia (CIA) in non-haematological neoplasia. Regulatory bodies as well as various scientific societies have issued guidelines and updated these regularly in accordance with additional data from numerous studies published since first marketing. Over the past few years, worrisome data have shown adverse effects in trials comparing ESAs with controls (transfusion or placebo). In fact reviewing the published literature closely does not allow at the time of writing (March 2008) the exclusion of a survival decrease due to an effect of ESAs on the cancer itself. Haemoglobin (Hb) target dosing has been an issue and is addressed in the dosing of ESAs in patients on therapy.

In addition to survival and tumour progression, published articles also address at length thromboembolic diseases (TEDs), these being more frequent in ESA-treated patients compared with the controls in various studies.

The three agents epoietin alpha, epoietin beta and darbepoietin can be considered as the same pharmacological class as regards indications of CIA, Hb limits and dose adjustments, as well as regards warnings in respect of adverse effects.

The purpose of this paper is not to be a substitute for recommendations or official recently published guidelines (ASCO, ASH, ESMO, EORTC, NCCN, etc.) but to present an overview of the data which have motivated ongoing regulatory authorities’ assessments and reviewing of guidelines.

An updated Cochrane review is underway, and the regulatory authorities such as the Food and Drug Administration (FDA) after the recent ‘Oncology drug advisory committee to the FDA’ (ODAC) of March 15, 2008, and the EMEA will most probably refine the present safety recommendations. Various aspects and adverse effects are to be considered here. (i) The realization that TED is a major issue in routine treatment. (ii) The fact that several studies have shown progression of disease and/or decreased survival in the ESA-treated group of patients compared with controls. Erythropoietin receptor (EpoR) data on malignant cells from a ‘Head and Neck Cancer’ trial with radiotherapy treatment and a target Hb beyond 14 g/dl have been and still are largely commented on in the medical literature [1]. (iii) Furthermore, quality of life (QoL) has been considered as an additional benefit of ESA therapy, and the latest analyses cast doubts on the validity of this presumed benefit [2].

thromboembolic disease

TED risk was not considered in the early guidelines and recommendations.

The available information from reviews and trials points to an increased risk of TED in ESA-treated patients [3]. Cancer patients as such already have an increased risk of TED due to their neoplasia, and the circumstances they are in such as hospitalization, surgery, prolonged immobilization, indwelling catheters, and personal and family history of previous TED. Patients with plasma cell disorders treated with thalidomide and lenalidomide, in conjunction with corticosteroids and/or chemotherapy, especially doxorubicin (standard as well as pegylated liposomal), are at significant risk [4]. A Cochrane meta-analysis reported a statistically increased risk for TED including venous thromboembolic events as well as cerebral strokes, transient ischaemic attacks and myocardial infarcts, with a relative risk (RR) of 1.67 [95% confidence interval (CI) 1.35–2.06] [5]. Active screening for TED has not been done in various studies, except for a lung cancer trial [6] that included a survey of TED in the darbepoietin versus the control group, and in this study the difference was not statistically significant, however, with a wide confidence interval (RR 1.44, 95% CI 0.47–4.43). A very recent meta-analysis [7] came to the conclusion that there was a mortality hazards ratio (HR) of 1.10 (95% CI 1.01–1.20). If these data were to be confirmed, a ready explanation for the mortality secondary to TED would be available. However, some of the more recent studies have not been included; the meta-analysis included off-label use studies and, correcting for possible errors in the table from which the meta-analysis has been calculated, a final result with a lower mortality of 1.04 is found [Amgen, in ref. 16].

There are to date no controlled randomized data available regarding prophylactic anticoagulant or aspirin use in this setting.

The risk of TED is dependent on the target Hb, i.e. the stopping level. Thus the RR is 0.7 for a target of 13 g/dl, 1.71 for 13–14 g/dl, and up to 1.92 when the Hb rises up to 15 g/dl [3]. Possible mechanisms of TED have been considered, such as increasing viscosity of the blood with an increasing Hb level and the possible presence of EpoRs on endothelial cells. A recent study hints at a possible hypothesis of an angiogenic
effect of high Epo levels in normal as well as tumour vessels in a murine model, and at present this seems conjectural [9].

Regarding vascular risk, one might also mention, outside the oncology field, the CHOIR study performed in patients with chronic renal insufficiency aiming for a target Hb level of 13.5 g/dl where cardiovascular adverse events were increased in the treated group versus the control arm [10], and the SPINE study in patients who underwent elective spinal surgery where the ESA arm had an increased incidence of deep vein thrombosis compared with the control group [11].

ESAs are to be considered for CIA when the level of Hb is tending towards 10 g/dl or has fallen below this level, with the aim of diminishing transfusions, which can also be considered an option. Starting ESAs at levels above 10 g/dl does not result in a statistically significantly decrease in transfusion requirements; however, there is a statistically significant difference in TED in favour of delayed treatment in some studies [12], but not in others [13,14].

CIA
The initiation threshold for ESAs has been specified in various guidelines, the most recent being from ASCO/ASH [15], as a Hb >10 g/dl, but <12 g/dl. In the case of a declining Hb <12 g/dl but never close to 10 g/dl previously, the decision to use ESAs should be guided by clinical circumstances. One should take into account the individual patient’s situation regarding other possible causes of anaemia, e.g. age, coronary heart disease, co-morbidities and ability to carry out daily activities, and at the same time weigh up the possible advantages of ESA treatment against an increased risk of TED. The TED risk was not really considered in previous recommendations.

quality of life
Fatigue, energy, strength and daily activity are certainly related to a low Hb level, and correction may improve these side effects. Whether other aspects of QoL not related to Hb level are improved by ESAs is not established and has not been an issue in recent guidelines.

QoL assessments are improved in some [1] and not in other studies [13,14]. A meta-analysis 2 evaluated the benefit of ESAs in mild anaemia (Hb ≥10 g/dl) compared with moderate anaemia (Hb <10 g/dl). The weighted summary RR for transfusion with earlier ESAs was 0.55 (95% CI 0.42–0.73; P = 0.0001), concluding that ESAs in those with Hb ≥10g/dl is associated with a significant reduction of transfusions compared with a lower level. Overall, however, many uncertainties remain regarding the validity and possible conclusions about QoL. AHRQ CER and the 2006 Cochrane review advised caution regarding interpretation of QoL results because of methodological issues [3].

progression of cancer and/or decrease in overall survival
A large body of medical literature has been published over the past few years on the presence of EpoRs on cancer cells and their possible implication in tumour progression.

Three studies of small cell lung cancer (SCLC), N93-004, 2001-0145 and a subset 980297 of SCLC patients in a general lung cancer study, have shown an improvement of outcome with ESAs given for CIA. On the other hand, eight studies have shown deleterious results. Four chemotherapy studies, BEST (breast cancer), 2000-0161 (lymphoid malignancies), PREPARE (neo-adjuvant breast cancer) and GOG 0191 (cervical cancer), have all shown decreased overall survival (OS) in the ESA arm compared with the controls. Two studies of radiotherapy as the only treatment, ENHANCE and DAHANCA, have shown a decrease in OS for the first study and a decrease of local control for the second. Two other studies without anticancer treatment, EpoCAN-20 (NSCLC) and 2001-0103 (non-myeloid malignancies), both showed decreased OS [16]. In these eight studies, Epo was given with a target level beyond current recommendations, and in four studies to patients not on chemotherapy.

The ENHANCE study, a radiotherapy study on head and neck cancer patients treated with epoietin beta with a target Hb >14 g/dl, has been widely publicized as the treated arm had a significantly poorer progression-free survival and overall mortality compared with the control arm [17]. The same authors reported data [1] on a subgroup of patients of the above study regarding the presence or absence of EpoRs in cancer cells. Those samples considered positive for EpoR were shown to be from patients who fared less well than those with non-EpoR-staining tumours who had about the same outcome as the placebo group. The possibility of an Epo-related effect in patients with EpoR expression in their tumour is obviously raised. The publication of this study has started a controversy on the validity of the EpoR measurement modality. The standard reagent used was the EpoR antibody C-20 (Santa Cruz Biotechnology Inc.). The specificity of the antibody has been questioned. An EpoR knock-out model showed the same staining as the wild-type control, raising the question of whether the antibody detects some other protein(s) such as heat shock protein 70 (hsp70) [18,19]. As hsp70 is increased in more aggressive tumours, the positive staining in these patients could be a surrogate marker of poor prognosis and hence explain the outcome in this subgroup of patients. At present a final conclusion with the available data is difficult; studies with more specific antibodies are needed for a final interpretation of EpoR as well as hsp70 positivity in order to confirm or rule out a possible tumour progression effect due to ESAs. Another radiotherapy-only study in head and neck cancer, performed by a Danish group, has been published in abstract form and preliminary data have been presented at the 2007 ESMO Congress. This study also showed a deleterious effect in the Epo-treated group compared with the controls [20].

From a clinical point of view it has to be underlined that in both the radiotherapy-only studies above, as well as the four chemotherapy studies mentioned, Epo was administered to non-anaemic patients, not on chemotherapy, with the purpose of further increasing the Hb level beyond normal with the intention of improving tumour oxygenation and anticancer treatment efficacy. This indication failed and is off-label.

Progression of tumour growth has been and is presently widely discussed and remains controversial. However, most
data do not support direct stimulation of and increase in tumour proliferation. Some data have been summarized in the literature, recently [21] assuming that:

(i) EpoR is not an oncogene product. The EpoR gene is not amplified or overexpressed in solid tumours. When overexpressed such as in Chuvash’s disease, polycythaemia results and cancer incidence is not increased in these patients and affected families.

(ii) EpoR mRNA is not present in higher concentrations in tumour cells or in tumour cell lines compared with the normal corresponding tissue.

(iii) The evidence of EpoR in cells is mostly intracellular, and the function depends on the tagging of the extracellular ligand (Epo) to the transmembrane receptor.

The indications and precautions that can be derived from available data are in the process of being reviewed again through the Cochrane Library, and hopefully some of the pressing questions raised above will be answered.

**comment**

At present the different studies show that between 20 and 45% of patients on ESAs respond and avoid transfusions. This also means that the majority will not respond and will be given therapy. They might have an adverse effect without a benefit. To date there is no good predictor of response available. The best predictive factor is early response [22]. An initial increase according to body weight has not been shown to be useful [23]. In addition non-responding patients usually have a poorer prognosis.

An interesting aspect of all these studies are the comparisons of targeted and achieved Hb levels, the latter being generally lower than the initial target. This was also the case in the two studies mentioned above on anaemia in cancer patients without chemotherapy or radiotherapy. In view of this fact, the FDA points out that there are no randomized double blind trials ‘…ruling out clinically important effects on survival or tumor outcomes.’ when ESAs are given for target Hb values <12 g/dl for solid tumours other than SCLC [16], hence the recommendation to use the lowest possible dose to avoid transfusion.

Regarding failure of response to ESA treatment one may ask if other players are involved. In non-CIA with inflammatory conditions, cytokines are important, and are most likely to be so also in CIA. Anti-tumour necrosis factor (TNF) antibody treatment has been shown to correct anaemia of chronic disease in rheumatoid arthritis and in Crohn’s disease. We could show that an anti-TNF antibody abrogates the TNF-induced inhibition of erythropoiesis in a cellular *in vitro* model [24], thus showing that the above-mentioned effect is not indirectly due to improvement of the diseases. A recent study has shown the implication of Gas6 (growth arrest-specific gene6) in Epo resistance in a murine model. Interestingly, the Gas6 protein synergizes with Epo in restoring the haematocrit level to normal, but not above [25]. Also GATA2 and NF-κB inhibit the Epo promoter. GATA2 inhibitors prevent this suppression and have become available recently [26]. The possible implications for non-responsive patients are open.

ESAs are supportive care drugs and it is obviously not acceptable to increase unduly the side effects and risks to patients when there is no counterpart improvement in their malignant disease. ESAs are given to avoid transfusions. Although it is true that the risks of transfusions have decreased over the past 15 years since the initial approval of ESAs for CIA, it is remarkable that in all the trials done to compare ESAs and Hb levels achieved, no systematic information is available regarding adverse effects of transfusion.

More data are needed through additional studies regarding prognostic and predictive markers of side effects and of response to ESAs in order to avoid treating patients who might be harmed or who will not benefit from these drugs or from transfusion avoidance.

As a take-home message, with the presently available data, after having followed the studies of ESAs over years, this author’s personal view is that these drugs are useful in medical practice provided they are given within the label indications and using sound clinical judgement in regard to the individual patient’s profile.

**disclosures**

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**references**


