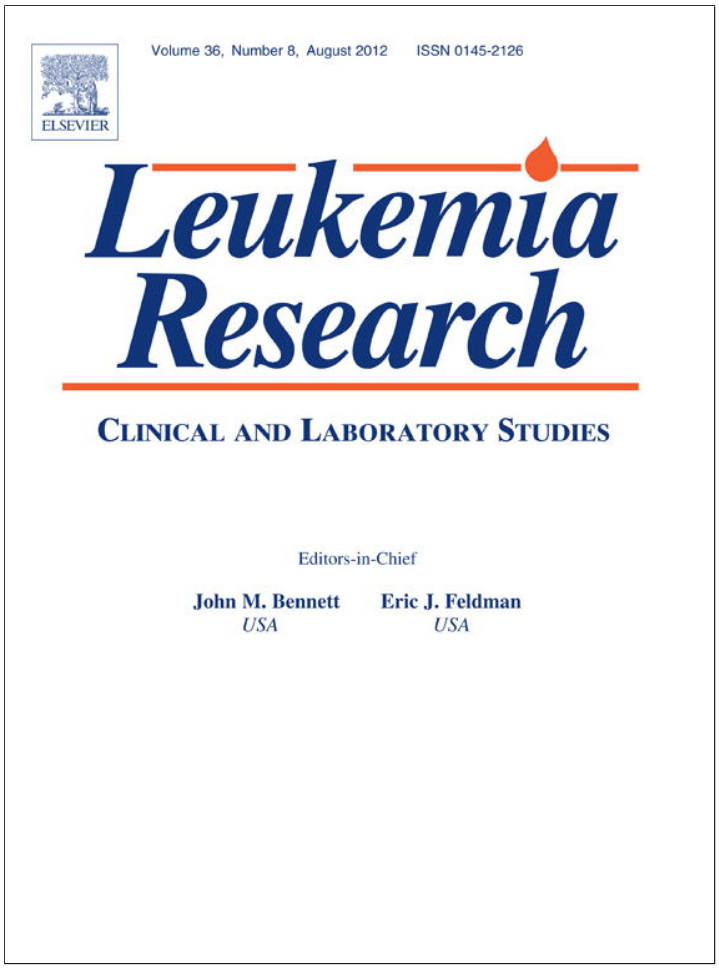

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Invited review

Erythropoietin: The swinging pendulum

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ABSTRACT

Erythropoiesis stimulating agents (ESAs) have been used widely for anemic patients, especially those on dialysis and with cancer. However, reports have suggested shorter survival in erythropoietin (EPO)-treated cancer patients. The purpose of this review is to summarize and evaluate critically the current information about ESA treatment and its possible association with mortality in cancer patients. The pendulum that initially swung in the direction of widespread ESA treatment, and then in the direction of no treatment, is swinging back toward a stable position. This review also provides tools to decide how and when to use ESAs safely, according to accepted guidelines.

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1. Introduction

Erythropoietin (EPO) is produced in the kidney in response to hypoxia; it circulates in the blood and arrives at the target organ – the bone marrow. There, it induces production, proliferation, and maturation of the red cell lineage and prevents apoptosis of these cells. The EPO gene was cloned in 1985, and since 1986 a variety

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of recombinant forms of erythroid stimulating agents (ESAs) have been used in research, and in clinical practice [1,2].

The first patients to benefit from this new medication were those with end-stage renal disease and anemia, because they are unable to produce endogenous EPO [3]. That success (nearly 100%) led to administration of ESAs to patients suffering from other forms of anemia, primarily the anemia associated with malignancies [1,2,4,5]. During the last two decades, recombinant human EPO (rHuEPO) has become almost an inseparable part of the supportive therapy for cancer patients with anemia, and the biologic medication with the highest sales worldwide. A successful treatment is characterized by an increase in the red blood cell count, hemoglobin (Hb) and hematocrit (HCT) levels, a decrease in red blood cell transfusion requirements with many patients becoming transfusion independent, and possibly an improved quality of life (QoL) [1–6].

1.1. Questions regarding survival

In spite of the successful treatments of anemia, since 2003 the pendulum of ESA treatment in cancer patients began to swing the other way. Reports claimed that cancer patients treated with ESAs had a shorter survival compared with untreated patients. These reports have stirred an ongoing controversy and led to a reduced clinical use of the hormone. Three mechanisms have been proposed to explain the worse prognosis in EPO treated cancer patients:

A. Activation of EPO receptors that exist on the surface of the cancer cells.
B. Thromboembolic events caused by the EPO-induced excessively elevated Hb.
C. EPO-induced angiogenesis that allows the tumor to grow and spread.

Among the approximately 60 publications reporting the negative impact of ESAs there are eight original papers (Table 1); the rest either report the findings in these original papers, or discuss the issue in an attempt to unravel the mechanism of the effect.

In the presence of the many reviews and guidelines that already exist in the literature, the current manuscript offers a critical evaluation of the original clinical studies as well as a concise summary of the guidelines to aid the physician in the management of the patient in clinical practice. It is an attempt to increase understanding of the issues involved, while providing the tools for using ESAs safely.

2. Analysis of the original data

Table 1 shows a list of publications presenting original research data on the controversial issue. Each of these publications has some pitfalls that deserve attention.

2.1. The BEST study [7,8]

Nine hundred thirty-nine women with advanced breast cancer were randomized to receive EPO-α or placebo. rHuEPO-treated patients had a shorter survival than untreated patients (hazard ratio, HR = 1.37, $p = 0.01$). However, a detailed analysis of the data raises serious issues:

a. The two groups were not well balanced, as discussed by the authors themselves.
b. The one-year survival, even in the placebo group, was lower than that expected in general among breast cancer patients: 12 month

Table 1
Eight original trials reporting negative impact of rHuEPO.

Trial	Cancer type	Number of patients	ESA studied	Results
BEST [7,8]	Breast	939	Erythropoietin alpha	OS at 1 year: 70% (E) vs. 76% (NE), HR 1.37, $p = 0.01$
ENHANCE [10]	Head and neck	351	Erythropoietin beta	LR-PFS: RR 1.62, $p = 0.0008$. OS: RR 1.39, $p = 0.02$
AMG 2000-0161 [12]	Lymphoproliferative malignancies	344	Darbepoetin alpha	30-day survival: 94% (E) vs. 98% (NE) 11-month survival: 47% (E) vs. 45% (NE)
EPO-CAN-20 [13]	NSC lung	70 (300 planned)	Erythropoietin alpha	MS: 63 (E) vs. 129 (NE) days, HR 1.84, $p = 0.04$
DAHANCA-10 [14]	Head and neck	522	Darbepoetin alpha	LR control: 56% (E) vs. 69% (NE), RR 1.44, $p = 0.02$ DFS: 48% (E) vs. 63% (NE), RR 1.49, $p = 0.004$ OS: 38% (E) vs. 51% (NE), RR 1.28, $p = 0.08$
AMG-2001-103 [15]	Solid tumors, variety	989	Darbepoetin alpha	OS: 45.7% (E) vs. 48.8% (NE), HR 1.22, $p = 0.022$ Adjusted: HR 1.15, $p = 0.121$
PREPARE [16]	Breast	674	Darbepoetin alpha	DFS at 3 years: 74.3% (E) vs. 80.0% (NE) HR 1.31, $p = 0.061$ OS: 88% (E) vs. 91.8% (NE), HR 1.33, $p = 0.139$
GOG-0191 [17]	Cervical	109 (460 planned)	Erythropoietin alpha	PFS at 3 years: 58% (E) vs. 66% (NE) OS: 60% (E) vs. 74% (NE)

E – with rHuEPO treatment, NE – without rHuEPO treatment, HR – hazard ratio, RR – relative risk, MS – median survival, OS – overall survival, PFS – progression-free survival, LR – loco-regional, DFS – disease-free survival, and NSC – non small-cell.

overall survival of 70% in the EPO group vs. 76% in the placebo group [8].

c. The increased death rate in rHuEPO-treated patients occurred within the first four months of the study. This finding supports the possibility that thromboembolism was the primary cause of death, although the authors suggest that tumor progression was the main cause.
d. Interestingly, despite the difference in overall survival, the progression-free survival was similar in the two arms.
e. The Kaplan–Meier estimate of long term survival showed a convergence of the survival lines at about 19 months after randomization.
f. Many patients reached Hb levels that were higher than generally accepted values, suggesting that thrombosis might have been the main cause of death.
g. The study was performed in centers from 20 countries, including sites where the experience in clinical trials is limited. As such, questions have been raised as to the quality of data management.

In contrast with the BEST study, several subsequent studies have failed to demonstrate shorter survival in breast cancer patients treated with rHuEPO [9].

2.2. ENHANCE trial [10]

This trial included 351 patients with head and neck cancer. The mortality was increased in rHuEPO-β-treated patients compared to the placebo group (HR = 1.39). Careful examination of the study reveals the following:

a. The target Hb was very high (>14 g/dl for women and >15 g/dl for men). Moreover, many patients achieved levels of 17–19 g/dl. Eighty-two percent of the patients reached Hb levels above the target value, also higher than that of the guidelines (see below).
b. This study included patients receiving only radiotherapy, while the guidelines restrict ESA administration to oncologic patients receiving only chemotherapy.
c. There was an imbalance between the two groups regarding baseline characteristics, including age, smoking history, disease stage, and primary versus recurrent disease.
d. In the rHuEPO-treated group, there was a greater percentage of patients with tumors of the hypopharynx, known to be more aggressive than tumors of other head and neck regions.
e. Upon examination of the 121 patients who actually received the complete therapeutic protocol, there was no difference in survival between the two groups.

Of note, the lead author of the BEST trial [7,8] Leyland–Jones in an editorial about the ENHANCE trial, writes that these adverse findings "generate more questions than answers [11]."

2.3. The AMG 2000-0161 study [12]

This trial including 344 patients examined the effect of Darbepoetin (Aranesp) on anemia in patients with lymphoproliferative malignancies (lymphoma and multiple myeloma). It was not designed to evaluate survival. While there were more deaths in the Aranesp group, the difference was minimal. The authors do not state whether the difference in survival was statistically significant during the time that the patients were taking the study drug or after 30 days from the last dose. However, they do state explicitly that the progression-free survival after a median follow-up period of 11 months was similar in both groups (47% in the Darbepoetin group and 45% in the placebo group).

2.4. EPO-CAN-20 trial [13]

This study was designed to compare the survival rate between rHuEPO-α-treated and placebo-treated lung cancer patients. Although the study was planned to include 300 subjects, the safety committee stopped the study after only 70 patients had been recruited. This was not because of findings in the study itself, but because of other reports about the risk of rHuEPO in such patients – in particular the risk of thromboembolic complications. When the codes were opened for the 70 participating patients, it was found that the survival rate for the control group was longer (HR = 1.84, $p = 0.04$). Hence, in this study as in those described above, there are some reservations that need attention.

a. Only 70 of the 300 planned patients were recruited (see above).
b. There was an imbalance between the groups, including time from diagnosis, surgery and performance status.
c. Only a few of the patients (23%) had been treated with systemic chemotherapy before entering the study, and none had chemotherapy during the study. This is not in accordance with the guidelines.
d. Target Hb was 12–14 g/dl, above the level specified in the guidelines.
e. According to the authors, external factors, namely reports of the results of the BEST and ENHANCE trials contributed to the decision to terminate the trial prematurely. This makes it very difficult to determine whether rHuEPO had any impact on survival in this trial.

2.5. Danish Head and Neck Cancer 10 study (DAHANCA-10) [14]

There were 522 head and neck cancer patients enrolled in this study. They were treated with radiotherapy, and half of them were treated with Darbepoetin (Aranesp). This study was terminated earlier than originally planned, because it was determined that the placebo group achieved a 10% greater loco-regional response to radiotherapy than did the Aranesp group. This study suffered from several problems, as detailed.

a. Patients were treated with radiotherapy and not chemotherapy, in contrast with guidelines (see ENHANCE trial, comment 2b above).
b. The target Hb was very high (14–15 g/dl).
c. The study was terminated early.
d. Although the overall survival was worse in the Aranesp group, the difference did not reach statistical significance ($p = 0.08$).

2.6. AMG-2001-103 study [15]

This trial of 989 patients with a variety of solid tumors was conducted with half of them receiving Darbepoetin and half receiving placebo. Here, as well as in the studies described above, the mortality was higher in the Darbepoetin group (26% vs. 20%, with HR = 1.29). The issues raised regarding this trial were as follows.

a. The study included patients who had not yet received therapy for their malignancy, in contrast with the guidelines.
b. The target Hb was high (>12 g/dl in women and >13 g/dl in men).
c. The primary endpoint of the trial was not survival but rather transfusion requirement, which surprisingly was found to be statistically similar in both groups.
d. When adjusted for baseline imbalances or for known prognostic factors, statistical significance of the apparent increased mortality was lost ($p = 0.121$).

2.7. PREPARE trial [16]

This trial was a complex one, comparing various chemotherapeutic regimens in 733 breast cancer patients prior to surgery. There was a double randomization including a comparison between Aranesp (Darbepoetin) and placebo. After median follow-up of 43.5 months, there were more deaths in the Aranesp group. Disease free survival (DFS) for the non-Darbepoetin and the Darbepoetin groups was 80% vs. 74.3%, respectively (HR 1.31; $p = 0.061$), and overall survival (OS) was 91.8% vs. 88% respectively (HR 1.33; $p = 0.139$). However, there is criticism of this study as follows:

a. While there was a trend toward poorer survival in the Aranesp group, it was not statistically significant. Hence the conclusion that patients should not be treated with ESA in the neoadjuvant setting is not necessarily warranted. The only subgroups that had a significantly worse DFS were those with a tumor size greater than 40 mm (HR 2.06, $p = 0.007$), or tumor grade III (HR 1.84, $p = 0.01$). There was no difference in OS for those or any other subgroup.
b. The target Hb was 12.5–13, and Darbepoetin was discontinued only for Hb > 14.

2.8. GOG-0191 trial [17]

In this trial of patients with cervical cancer, approximately half of the 114 patients were given ESAs and half were given placebo. After three years, progression-free survival (PFS) was 58% and 65% in the rHuEPO and placebo groups respectively, and the OS was 61% and 75%, respectively. However, the following points deserve attention.

a. The number of patients in the study was small (114 – only 25% of the originally planned recruitment), and the study was terminated early due to the possibility of thromboembolic complications.
b. Tumors in the placebo group tended to be smaller at baseline than those of the ESA group (e.g. 52% of the control group and 33% of the ESA group had tumors $\leq$5 cm, while 23% of the ESA and 19% of the control group had tumors >8 cm).

It should be noted that in contrast to the GOG-0191 study, other studies with the same cervical cancer patient population did not result in disease progression or shorter survival in ESA-treated patients [9,18].

In summary, there are eight important papers relating to the poor survival of patients treated with ESAs, but one cannot ignore the pitfalls in each one of these studies. Particularly, the discrepancies between the groups, excessively elevated Hb, administering rHuEPO not in accordance with the accepted guidelines (e.g. patients not being treated with chemotherapy), and early termination of the trials. Aapro and Spivak [9] support these analyses and conclusions. They summarize 59 controlled phase III studies in oncology, of which 8 trials (see above) raised concerns regarding the use of ESAs in cancer patients.

In contrast to these eight trials there have been a number of controlled trials where no difference in survival was noted between the ESA-treated and placebo groups [18–26].

Several meta-analyses have also been performed. Seidenfeld et al. [27], Wilson et al. [28] and Paladini et al. [29] found no significant difference between those who were or were not treated with ESAs. The Cochrane group performed a meta-analysis three times. The first [30] found a survival benefit for the ESA group, and the second [31] found no difference. The third [32] found higher rates of mortality during the active study period and overall mortality in the ESA group (HR = 1.17, and HR = 1.06, respectively). However, if only cancer patients receiving chemotherapy were analyzed, no difference was found between the ESA-treated and the untreated patients. Of note, this last meta-analysis was a patient level study that pooled the patient data for analysis. The most recent meta-analysis of 60 studies comprising more than 15,000 patients failed to demonstrate any significant effect of ESAs on survival or disease progression [33].

It is worthwhile mentioning the many reports, including from our group [34,35] and from others [36–38] suggesting a survival advantage among patients suffering from various malignant diseases who were treated with ESAs. However, it should be noted that these studies were not designed as controlled prospective trials.

Similar controversy exists in the literature (NHCT, CREATE and CHOIR trials) concerning the optimal dose of EPO for patients with chronic and end-stage kidney disease, based on the incidence of thrombovascular events and mortality [39–43]. There is no consensus from the studies whether EPO treatment with the goal of achieving a normal Hb causes greater morbidity or mortality than treatment with a goal of achieving a lower Hb. Most recently, the TREAT trial demonstrated an increased stroke risk in those reaching a higher Hb level [44]. These studies have led the FDA to recommend a lower Hb target in these EPO-treated patients. Moreover, they do support the concept that the "danger" in EPO treatment is likely due to thromboembolic events when the Hb is higher than necessary.

QoL is a controversial issue: while many demonstrate rHuEPO's positive effect on QoL, others fail to show such effect. For example, Witzig et al. showed that rHuEPO treatment had no effect on QoL in patients receiving myelosuppressive chemotherapy [26]. On the other hand, Nilsson-Ehle et al. demonstrated that the treatment was associated with improved QoL in low-risk MDS patients [45]. The difference may be related to the disease, the method used to measure QoL, or most likely to the treatment; i.e. patients receiving chemotherapy may have a poor QoL that even rHuEPO treatment and higher Hb cannot significantly improve.

An important issue to be considered is the fact that some tumors express the receptor to EPO, such that treatment with EPO may enhance the growth of the tumor. In this respect, the relationship between EPO-receptor expression and tumor proliferation is actually unclear [46–49]. Longmore has emphasized that the presence of EPO receptors on a (tumor) cell does not necessarily mean that it is functional [50]. In fact, there is a long way from the presence of the receptor to its action or to its being functional. Most recently it has been found that although EPO-receptor mRNA was expressed in many tissues, and tumor cell lines, EPO-receptor protein was not detected on the cell surfaces [51–53].

3. Guidelines from the FDA and other societies

These reports have led the Food and Drug Administration (FDA) and especially the Oncology Drugs Advisory Committee (ODAC) to discuss and evaluate this subject several times and to issue an FDA alert requiring the drug companies to issue a black box warning, and to establish the need for physician and patient education at the expense of these companies [54]. In any event it is important to emphasize that the FDA, despite calls for removing the medications from the shelf, refused to do so and instead called for treating according to certain guidelines.

Finally, specific guidelines have been issued by various professional societies and organizations, including the National Comprehensive Cancer Network (NCCN), and the European Organization for Research and Treatment of Cancer (EORTC), as well as the combined initiative of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH). These guidelines were published first in 2003, then in 2007, and most

recently in November 2010 [55]. They provide clear direction as to who should receive the treatment and how. Of note, while the FDA limits ESA treatment only to those receiving chemotherapy for palliative intent, the authors point out that no trial has examined EPO therapy by subgroups defined by chemotherapy intent. The following is a concise summary of the guidelines:

Transfusions: Treat only for the purpose of avoiding blood transfusions.
Chemotherapy: Only chemotherapy-treated cancer patients (with the exception low-risk myelodysplastic syndromes and in some patients with lymphoproliferative disorders).
Cure: If the treatment goal is cure, do not treat with ESAs.
Actively follow the patients: Make sure that the Hb will not rise above 12 g/dl and that it will not rise too quickly (more than 1 g/dl in any two-week period).
Range of 10–12: Start treating when the Hb is below 10 g/dl, and ensure that the target Hb of 12 g/dl is not exceeded.
Six to eight weeks: If a response is not achieved by 6–8 weeks, the therapy should be stopped.

4. Summary

The ESAs have proven themselves to increase Hb and improve the quality of life for many cancer patients. Along with this there have been questions raised about the safety of this treatment. We feel that given the deficiencies of the eight studies analyzed above as well as the "positive" studies, including those that emphasize QoL improvement, there is an important place for ESA treatment, but that it must be done carefully while following the guidelines of the FDA and ASCO/ASH. The pendulum initially swung in the direction of widespread ESA treatment, and in the wake of the eight "negative" studies swung too far in the other direction. The pendulum is swinging back, and will eventually find a stable position with new studies that further clarify this subject.

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There is no connection between sources of funds and this manuscript.

Conflict of interest statement

MM is chief scientist of XTL Co., focusing on applications of erythropoietin, and all other authors have no conflict of interest to declare.

Disclosure

The authors declare openly that they study EPO effects, and have published several manuscripts on EPO as an immunoregulator and anti-neoplastic agent.

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