September 2007 Update on EORTC Guidelines and Anemia Management with Erythropoiesis-Stimulating Agents

MATTI S. AAPRO,* HARTMUT LINKb

aMultidisciplinary Oncology Institute, Genolier, Switzerland; bDepartment of Internal Medicine, Westpfalz Klinikum, Kaiserslautern, Germany

Key Words. Anemia • Erythropoiesis-stimulating agents • 2007 EORTC guidelines

Disclosure: M. A. has received study grants and honoraria for consultancy and/or is on the speakers bureau of Amgen, Johnson and Johnson, Ortho Biotech, Sandoz, and Roche. H.L. has acted as a consultant for Amgen, Johnson and Johnson, and Biogenerix, and has received lecture fees from Amgen and Janssen-Cilag. No other potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

Abstract

Anemia is frequently experienced by cancer patients receiving chemotherapy and can negatively impact the patient’s prognosis. Blood transfusions, iron supplementation (in absolute or functionally iron-deficient anemias), and erythropoiesis-stimulating agents (ESAs) are among the treatment options for anemia. Treatment options for anemia management should be selected based on the best benefit-to-risk ratio for each individual patient. In September 2007, the working party of the European Organization for Research and Treatment of Cancer (EORTC) updated their guidelines on the use of ESAs, which are summarized in this paper. ESAs reduce the number of transfusions required and significantly improve quality of life in patients with chemotherapy-induced anemia. A sustained hemoglobin level of about 12 g/dl should be the target for treatment with ESAs. ESAs should be used according to the EORTC guidelines and within label with carefully considered exceptions. The Oncologist 2008;13(suppl 3):33–36

Introduction

The most common hematological abnormality in cancer patients receiving chemotherapy is anemia [1, 2]. Often, this anemia is either undermanaged or not treated at all, having a detrimental impact on the patient’s quality of life (QoL)[2, 3].

Anemia also is related negatively to cancer patients’ prognosis, and has been shown to be correlated with a higher overall mortality risk up to 65% (Table 1) [4, 5]. The effect of anemia on prognosis may vary by tumor type and choice of treatment. Caro and colleagues reported that shorter survival times were seen in patients experiencing anemia with lymphoma, multiple myeloma, and head and neck, lung, cervicouterine, and prostate cancer [5].

Cancer (EORTC) updated their guidelines on the use of ESAs, which are summarized in this paper. ESAs reduce the number of transfusions required and significantly improve quality of life in patients with chemotherapy-induced anemia. A sustained hemoglobin level of about 12 g/dl should be the target for treatment with ESAs. ESAs should be used according to the EORTC guidelines and within label with carefully considered exceptions. The Oncologist 2008;13(suppl 3):33–36

Strategies for anemia management are first aimed at addressing the underlying cause, that is, iron metabolism disorders, reduced erythroid progenitor cell numbers in the bone marrow, hemolysis, increased levels of inflammatory cytokines, renal failure, cancer, etc. [5–8]. Anemia treatment options may involve blood transfusions, iron supplementation in absolute or functionally iron-deficient anemias, and erythropoiesis-stimulating agents (ESAs).

Although the quality of the supply and the transfusion process have improved greatly, problems still exist with blood transfusions. Such problems include the availability of the blood stock, rigorous checks required to ensure the safety of the recipient, inconvenience to the patient and health care professionals, hospitalization costs, the
possibility of transfusion transmitted diseases, etc. [9, 10]. Furthermore, Vamvakas and Taswell quantified the association between blood transfusion and mortality in a more broadly based U.S. population, and found a dose-response relationship between the number of blood transfusions and a subsequent shorter length of survival (Table 2) [11]. Concern has also been expressed about the quality of stored blood and observations of negative outcomes in transfused patients. Retrospective studies found higher mortality and morbidity rates after transfusion that correlated with the duration of RBC storage [12–15]. This suggested that changes in RBC function during storage may be responsible for adverse outcomes [12]. However, there have been no controlled clinical trials that have evaluated the relationship between clinical outcomes and the age of stored RBCs [12]. In several studies that matched clinical variables, patients who received RBC transfusions had worse outcomes than patients who had not been transfused [12, 16–20].

ESAs
ESAs can overcome some of the problems associated with blood transfusions and improve health-related QoL [21]. Furthermore, a clinical trial with epoetin alfa has demonstrated a direct relationship between increased hemoglobin (Hb) levels and improved QoL [22–24]. The use of epoetin alfa to correct chemotherapy-induced anemia showed the greatest positive QoL changes when a final Hb level of 11–12 g/dl was aimed for [25]. These results were further supported by another earlier study that found that the maximal QoL benefits were obtained at Hb levels of 11–12 g/dl [26]. These data suggest that a final Hb target level around 12 g/dl achieves the greatest incremental gains for QoL.

In 2006, based on an updated systematic literature review, the European Organization for Research and Treatment of Cancer (EORTC) updated its guidelines on the use of ESAs in anemic patients with cancer and confirmed that the target Hb level following treatment with ESAs should be 12–13 g/dl [2, 27].

However, there have been recent concerns of possible risks associated with ESAs. The need to carefully reassess the risks and benefits of ESAs in the light of new data led to the convening of meetings of the Oncology Drug Advisory Committee (ODAC) of the U.S. Food and Drug Administration in 2004 and 2007. The first meeting recommended continued use of ESAs within labeled indications and called for further studies. Following the more recent ODAC meeting, and the involvement in Europe of the Committee for Medicinal Products for Human Use, regulatory authorities are now considering whether the labeling of ESAs should be modified.

The point consistently identified by contributors to this volume is that the optimal use of ESAs requires careful attention to the baseline Hb level at which therapy is started, and the target Hb that their use should be designed to achieve. These considerations are among those recently reassessed by a working party of the EORTC given the task of updating the guidelines on use of ESAs.

2007 EORTC GUIDELINES UPDATED
Certain changes have been made to the guidelines for the use of erythropoietic proteins in cancer patients with anemia, which were last reviewed in 2006 and published in the European Journal of Cancer in 2007 [2]. In brief, the EORTC Working Party’s conclusions and recommendations are now as follows [important changes since 2006 shown in square brackets].

Background
The use of ESAs can significantly improve QoL in anemic cancer patients, with the major goals of therapy being to achieve that improvement and to reduce need for transfusions. ESAs can achieve a sustained increase in Hb level. This is not the case with intermittent transfusions.

Prior to starting treatment with ESAs, additional causes of anemia (i.e., iron deficiency, bleeding, nutritional deficits, or hemolysis) should be considered and corrected.

Patients whose Hb level is <9 g/dl should be assessed for transfusion requirement, in addition to ESAs.

ESAs should be used within accepted guidelines. The EORTC guidelines are presented in the form of a flowchart in Figure 1.

**Treatment with ESAs in Patients Receiving Chemotherapy or Radiochemotherapy**

ESAs should be initiated at an Hb level of 9–11 g/dl in cancer patients receiving chemotherapy or radiochemotherapy, based on anemia-related symptoms.

ESAs may be considered in selected asymptomatic chemotherapy patients with an Hb level of 11–11.9 g/dl if this would prevent a further decline in Hb; such a decision should take into account an individual’s Hb level prior to chemotherapy and the type, intensity, and duration of chemotherapy or other planned treatment. [Words “selected” and “careful assessment of need” added.]

ESAs are not recommended for prophylaxis of anemia in patients with normal Hb values prior to undergoing chemotherapy and/or radiotherapy. (As in 2006, this point is given priority.)

**Treatment with ESAs in Patients with Cancer-Related Anemia Not Undergoing Chemotherapy or Chemoradiotherapy**

ESAs may be given in selected patients with an Hb level of 9–11 g/dl if justified by anemia-related symptoms and careful assessment of need. Note: In certain countries this is not an approved indication. [“May be” used instead of “should”; “selected” and “and careful assessment of need” added.]

**Target of Treatment with ESAs**

The target of treatment with ESAs is to achieve an Hb concentration of about 12 g/dl. [Wording changed from “should be 12–13 g/dl”.]

In patients not responding in 4–8 weeks, there is no recommendation that dose escalation should be the general approach.

In responding patients, treatment should be continued until an Hb level of around 12 g/dl is reached and patients show improved symptoms. [Changed from 13 g/dl in 2006.]

Further treatment of patients reaching the target Hb level should be individualized using an increased dosing interval and/or titrating downwards to the lowest effective maintenance dose.

**Additional Therapy**

There is no evidence that oral iron supplements increase response to erythropoietin proteins. There is evidence of a better response to erythropoietic proteins with i.v. iron. However, i.v. iron use should be reserved for patients with absolute or functional iron deficiency. [Last point added since 2006.]

**Adverse Events**

Combining the data from all available studies indicates that using ESAs to treat anemia in cancer patients leads to a 1.6-fold higher risk for thromboembolic events.

**Dosing**

Epoetin alfa and epoetin beta can be given on a fixed-dose weekly basis.

Darbepoetin can be used on an every-3-week, fixed-dose basis, or once weekly at 2.25 μg/kg. Certain countries also use a 2-week regimen.

**Conclusions**

The major goals of ESA therapy are prevention, reduction, or elimination of transfusions and improvement in QoL.
Following treatment with ESAs, transfusion requirements are reduced and QoL is significantly improved in patients with chemotherapy-induced anemia and in those with anemia of chronic disease [2]. Overall, despite a slightly higher risk for thromboembolic events in patients receiving ESAs, the EORTC treatment guidelines support the efficacy and safety of ESA therapy in correcting anemia in chemotherapy patients to about 12 g/dl. Additionally, the EORTC Guidelines Working Committee continues to review published data and provide direct guidance on the management of anemic cancer patients.

REFERENCES


The September 2007 position of the EORTC Working Party on ESAs is that clinical trials have established that (a) ESAs decrease transfusion needs; (b) Hb levels are sustained on ESAs, which is not the case with intermittent transfusions; (C) ESAs increase QoL; and (d) ESAs should be used within the guidelines.

ACKNOWLEDGMENT

The authors acknowledge the assistance of medical writer Julia O’Regan, Bingham Mayne and Smith, Medical Communication.