Strategies for the Use of Epoetin Alfa in Breast Cancer Patients

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ABSTRACT

Anemia is a common complication in cancer patients undergoing chemotherapy, and its severity depends on both the type of antineoplastic drugs and the clinical status of the patient. Breast cancer patients undergoing standard chemotherapy develop clinically significant anemia in up to 25% of cases. This percentage, moreover, increases up to 63% when more intensive chemotherapy regimens are used.

The therapeutic use of erythropoietin in anemic patients, i.e., in patients with hemoglobin levels below 9-10.5 g/dl, is able to correct the anemic status in nearly 40%-80% of such patients, but it does not completely eliminate the need of blood transfusions: 20%-40% of patients need to be transfused despite the erythropoietin treatment. An alternative strategy for optimizing the erythropoietin treatment is its use in the prevention of anemia, i.e., in patients with normal hemoglobin values but at high risk of becoming anemic. In a phase III study, we evaluated the role of erythropoietin in the prevention of anemia in breast cancer patients undergoing dose-intensive chemotherapy. Clinically significant anemia occurred in 52% (95% CI = 33-69) of control patients and in no patient (95% CI = 0-14) in the erythropoietin arm \( (p = .00001) \). After six cycles of chemotherapy the mean hemoglobin decrease was 3.05 g/dl (± 1.0, 95% CI = 2.6-3.5) in the control arm and 0.8 g/dl (± 1.4 , 95% CI = 0.3-1.4) in the erythropoietin arm. Moreover, 6.4% of control patients needed blood transfusion compared to no patients in the erythropoietin arm.

Erythropoietin is active in both the treatment and the prevention of anemia in cancer patients undergoing chemotherapy. Due to its high economic cost, efforts should be made to identify subsets of patients in whom the preventive use could be cost-effective. Patients undergoing chemotherapy associated with a high risk of anemia could benefit from preventive use of erythropoietin in special circumstances, such as presence of risk of myocardial or cerebral ischemia, uncommon blood group, or religious beliefs hindering blood transfusions. Moreover, anemia prevention could be considered in patients at high risk of requiring blood transfusions, such as patients with low baseline value of hemoglobin or with a hemoglobin decrease of ≥2 g/dl after the first cycle of chemotherapy. The Oncologist 1998;3:314-318

INTRODUCTION

Anemia occurring in cancer patients has a multifactorial etiology with many factors contributing to its development. A direct effect of the neoplasm as well as the effects of cytotoxic drugs are the main causes of anemia in patients undergoing chemotherapy. Chemotherapy-induced anemia is mainly due to both the myelosuppressive effect and the renal impairment induced by antineoplastic drugs. The severity of the direct bone marrow damage, induced by almost all cytotoxic drugs, depends on type, dose, and dose intensity of the drugs and on previous radiotherapy and chemotherapy received by the patient. Renal impairment is primarily induced by cisplatin and leads to a deficient renal production of erythropoietin with a consequent reduction of red blood cell (RBC) production [1]. The probability of developing anemia differs with the type of neoplasm and the type of chemotherapy and is higher in patients receiving cisplatin [2].

The gravity of anemia in a given patient depends not only on the absolute value of hemoglobin but also on clinical conditions which affect the patient’s tolerance of low hemoglobin level [3, 4]. Nevertheless, a hemoglobin level below 10 g/dl is generally considered as a cut-off indicating
the onset of clinically significant anemia [5], which requires careful monitoring.

RBC transfusions are still the most important tool in the management of anemia. Despite quality assurance measures, allogeneic transfusions still harbor risks of immunologic impairments, short-term lung injury, mismatching, and, most importantly, infections [6]. Although the overall risk of infection is low, it should be taken into account, particularly in patients affected with curable or long-life-expectancy cancers, such as early breast cancer patients. In fact, the risk for hepatitis B virus and human immunodeficiency virus infections remains greater than zero [7]. Moreover, the potential introduction of new blood-borne infective diseases remains a hazard of transfusions [8]. A possible strategy for avoiding RBC transfusions is the therapeutic use of erythropoietin. The safety of this drug and its efficacy in various diseases, e.g., end-stage renal disease, AIDS, inflammatory diseases, and rheumatoid arthritis, prompted the evaluation of its role in cancer-related anemia. In cancer patients, this drug is almost always administered at the dose of 150 U/kg or 10,000 units as total dose three times per week [9], and the use of lower doses, i.e., 2,000 units three times per week, has been reported less active [10]. Cancer patients treated with erythropoietin did not develop more toxicities than control patients. In particular, hypertension, which is an important side effect in end-stage renal disease patients treated with erythropoietin, occurred in 5% of cancer patients receiving erythropoietin compared with 3.5% of control patients [11]. However, the potential occurrence of other side effects, such as thrombotic events, should be considered in patients experiencing a quick increase in hemoglobin during erythropoietin treatment, and patients should be monitored to avoid an increase greater than 2 g/dl in hemoglobin during one month of treatment. In addition, erythropoietin treatment should be interrupted when the hemoglobin value is ≥15 g/dl.

INCIDENCE OF ANEMIA IN BREAST CANCER PATIENTS

We evaluated the incidence of anemia in breast cancer patients enrolled in three randomized trials carried out from 1991 to 1997. All the trials aimed to evaluate the role of dose-intensive chemotherapy supported by hematopoietic colony-stimulating factors (Table 1). The chemotherapy utilized as a control arm in all the trials is an anthracycline-containing regimen commonly used in Europe both in adjuvant and metastatic settings [12]: CEF (cyclophosphamide 600 mg/m², epirubicin 60 mg/m², 5-fluorouracil 600 mg/m²; all drugs given intravenously on day 1). With this regimen, from 4% to 25% of patients developed anemia, but these percentages sharply rose as the dose intensity increased (Table 1). In the first study, carried out in advanced breast cancer patients, the use of GM-CSF allowed the administration of CEF chemotherapy every 16 days instead of every 20 days, as in the standard arm. Although doses of the drugs were the same in the two treatment arms, the short-interval (accelerated) chemotherapy led to a higher incidence of clinically significant anemia; 28% of patients became anemic, compared with 4% in the standard arm. Also, the units of RBC transfused were higher in the accelerated arm compared with the standard one [13]. In the adjuvant setting, the use of an accelerated CEF, with the support of G-CSF, was confirmed to induce a higher incidence of anemia (MIG-1 study in Table 1). In a pilot study, in particular, we observed a progressive, cumulative anemia during the six cycles of accelerated CEF in early breast cancer patients [14]. In the third study (MIG-3 in Table 1), we compared a standard CEF with a high-dose intensive CEF (HD-CEF), based on both the use of higher doses of cyclophosphamide and epirubicin and on a short-interval (every 14 days) administration with the support of G-CSF [15]. At baseline, mean values of hemoglobin were 12.8 (±1.8) and 13.0 (±1.3) g/dl in standard CEF and HD-CEF, respectively. After eight cycles of chemotherapy, the mean hemoglobin values were 12.0 (±1.3) in the standard arm and

<table>
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<tr>
<th>Study</th>
<th>Subset</th>
<th>Regimens</th>
<th>n patients</th>
<th>Patients developing anemia</th>
<th>RBC transfusions</th>
<th>Actual dose-intensity increase</th>
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</thead>
<tbody>
<tr>
<td>Ardizzoni [13]</td>
<td>Stage IV</td>
<td>CEF (600/60/600) + GM-CSF q 16 days versus CEF (600/60/600) q 20 days</td>
<td>32</td>
<td>28%</td>
<td>43 units</td>
<td>28%</td>
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<td></td>
<td></td>
<td></td>
<td>30</td>
<td>4%</td>
<td>6 units</td>
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<td>MIG-1 (ongoing)</td>
<td>Stage II</td>
<td>CEF (600/60/600) + G-CSF q 14 days versus CEF (600/60/600) q 21 days</td>
<td>513</td>
<td>39%</td>
<td>Not available</td>
<td>48%</td>
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<td></td>
<td></td>
<td>516</td>
<td>17%</td>
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<tr>
<td>MIG-3 [15]</td>
<td>Stage IV</td>
<td>CEF (1,000/80/600) + G-CSF q 14 days versus CEF (600/60/600) q 21 days</td>
<td>75</td>
<td>63%</td>
<td>13% patients</td>
<td>80%</td>
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<td></td>
<td></td>
<td></td>
<td>72</td>
<td>25%</td>
<td>3% patients</td>
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9.7 (±1.5) in HD-CEF. Clinically significant anemia, i.e., hemoglobin ≤ 10 g/dl, occurred in 25% of patients in standard CEF and in 63% of patients in HD-CEF. Moreover, 3% of patients needed to be transfused in standard CEF as compared with 13% of patients in HD-CEF. The higher incidence of anemia and the increased need for RBC transfusions has also been reported in other studies [16, 17]. In locally advanced breast cancer patients, a dose-intensive regimen with epirubicin and cyclophosphamide (EC) was compared with standard CEF. The EC regimen was administered every 14 days with the support of G-CSF, and higher single doses of epirubicin and cyclophosphamide than CEF were used. Although the cumulative doses of E and C were similar in the two arms, the dose-intensive regimen led to a higher incidence of anemia; 49% and 17% of patients developed grade 3-4 anemia in dose-intensive EC and standard CEF arms, respectively.

Strategies For the Use of Epoetin Alfa in the Management of Anemia in Breast Cancer Patients

Several phase III trials reported the ability of erythropoietin to correct anemia and to reduce the need for RBC transfusions in cancer patients treated with chemotherapy [18-21] (Table 2). Generally, erythropoietin was started at hemoglobin levels below 9-10.5 g/dl. However, such a strategy, i.e., the use of erythropoietin at the onset of clinically significant anemia, did not completely eliminate the need for RBC transfusions. Despite erythropoietin treatment, 20%-40% of anemic patients needed to be transfused. Such a partial failure of the treatment could be due to the inefficacy of the drug in some patients but also to the delay in the beginning of the treatment. In fact, the time to response to erythropoietin in cancer patients ranged from 3 to more than 12 weeks.

An alternative strategy for optimizing the use of erythropoietin could be its use in the prevention of anemia in patients with normal hemoglobin values at high risk of becoming anemic. To verify this hypothesis, we conducted a phase III study to evaluate the capability of epoetin alfa for preventing anemia development in early breast cancer patients undergoing accelerated chemotherapy as adjuvant treatment [22]. Patients with normal baseline values of hemoglobin and without iron deficiency were treated with six cycles of CEF administered every 14 days with the support of G-CSF and randomized to receive epoetin alfa 150 U/kg three times per week or no additional treatment. Thirty-one patients per arm were enrolled. Median baseline values of hemoglobin were 13 g/dl in both arms. Nearly 90% of patients in both arms completed the six planned cycles of chemotherapy. There was no difference in toxicity between the two arms. The main epoetin alfa-related toxicity was local burning during the administration of the drug. During the six cycles of chemotherapy, hemoglobin progressively decreased in the control arm, while it remained quite stable in the epoetin alfa arm. At the end of chemotherapy, mean hemoglobin levels for control versus epoetin alfa arms were: 10 g/dl (±1.1) versus 12.2 (±1.2) (p = .000), with a hemoglobin decrease of 3.05 g/dl (±1.0, 95% CI = 2.6-3.5) in the control arm and 0.8 (±1.4, 95% CI = 0.3-1.4) in the epoetin alfa group. Clinically significant anemia (hemoglobin ≤ 10 g/dl) occurred in 16 patients (52%, 95% CI = 33-69) in the control arm compared with no patients (0, 95% CI = 0-14) in the epoetin alfa arm. Moreover, two control patients (6.4%) required blood transfusions versus no patients in the epoetin alfa arm.

**Comments**

Erythropoietin is able to correct anemia in 40%-80% of anemic cancer patients undergoing chemotherapy. We demonstrated that if epoetin alfa is used before the patient becomes anemic, anemia can be prevented in almost all early breast cancer patients undergoing dose-intensive chemotherapy. The use of epoetin alfa in breast cancer patients...
of the drug in patients with normal hemoglobin value is safe, with only one patient requiring dose reduction due to occurrence of dyspnea and headache.

Because of the low toxicity of the drug, the main obstacle to its use in the clinical setting remains the economic costs. In uremic patients, erythropoietin has been shown to be cost effective only at a weekly maintenance dose of less than 100 U/kg body weight when compared to a regular transfusion requirement of two to three units of blood per month [23]. In cancer patients erythropoietin is generally given at the dose of 150 U/kg three times a week. In Italy, the cost of 10,000 U of erythropoietin is approximately 160,500 Italian lire, which thus implies a monthly cost of 1,926,000 lire (approximately $1,204) for the treatment of a 70-kg patient with the above-reported regimen. Based on this cost, from a strictly economic point of view, the use of erythropoietin in anemia could be useful in patients in whom the success of radiotherapy or O2-dependent chemotherapy may be limited by tumor hypoxia.

Anemia prevention by epoetin alfa in selected subsets of patients may be useful for avoiding RBC transfusions, reducing risks of anemia in patients with concomitant diseases, and increasing the efficacy of antineoplastic treatments.

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### Table 3. Efficacy of epoetin alfa in preventing anemia

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<th>Control arm (n = 31)</th>
<th>Epoetin alfa arm (n = 31)</th>
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<tr>
<td>Patients developing anemia (Hb ≤ 10 g/dL)</td>
<td>16 (52%) (95% CI, 33 - 69)</td>
<td>0 (95% CI, 0 - 14)</td>
</tr>
<tr>
<td>Mean Hb decrease at the end of chemotherapy</td>
<td>3.05 ± 1 g/dl (95% CI, 2.6 - 3.5)</td>
<td>0.8 ± 1.4 g/dl (95% CI, 0.3 - 1.4)</td>
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</tbody>
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**References**

12. Venturini M, Bruzzi P, Del Mastro L et al. Effect of adjuvant chemotherapy with or without anthracyclines on the activity


