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ORIGINAL ARTICLE

Dose reduction of epoetin-alpha in the prevention of chemotherapy-induced anaemia

François Lüthi · Miklos Pless · Serge Leyvraz · Beat Biedermann · Emilie Müller · Richard Hermann · Christian Monnerat

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Abstract
Introduction Anaemia during chemotherapy is often left untreated. Erythropoiesis-stimulating agents are frequently used to treat overt anaemia. Their prophylactic use, however, remains controversial and raises concerns about cost-effectiveness. Therefore, we assessed the efficacy of a dose-reduction schedule in anaemia prophylaxis.
Materials and methods The study included patients with untreated solid tumours about to receive platinum-based chemotherapy and had haemoglobin (Hb) levels ≥11 g/dL. Epoetin-α was administered at a dose level of 3×10,000 U weekly as soon as Hb descended to < 13 g/dL. Dose reductions to 3×4,000 U and 3×2,000 U weekly were planned in 4-week intervals if Hb stabilised in the range of 11–13 g/dL. Upon ascending to ≥13 g/dL, epoetin was discontinued. Iron supplements of 100 mg intravenous doses were given weekly. Of 37 patients who enrolled, 33 could be evaluated.
Results and discussion Their median Hb level was 13.7 (10.9–16.2) g/dL at baseline and descended to 11.0 (7.4–13.8) g/dL by the end of chemotherapy. Anaemia (Hb<10 g/dL) was prevented in 24 patients (73%). The mean dose requirement for epoetin-α was 3×5,866 U per week per patient, representing a dose reduction of 41%. Treatment failed in nine patients (27%), in part due to epoetin-α resistance in four (12%) and blood transfusion in three (9%) patients.
Conclusion Dose reduction was as effective as fixed doses in anaemia prophylaxis but reduced the amount of prescribed epoetin substantially.

Keywords Anaemia · Epoetin · Chemotherapy · Prevention

Introduction

Anaemia is commonly observed in cancer patients. The prevalence is 39% at the time of diagnosis. During chemotherapy, the incidence has been shown to reach 63% [28] and increases with the number of chemotherapy cycles. Incidence of anaemia is also higher in lung (71%) or gynaecological (65%) cancers [22]. Management of anaemia, including the use of erythropoietin proteins, varies widely. The majority of cases (61%) are left untreated. Only 17% of cases are treated with epoetin and 15% with blood transfusions.

Major oncological societies have issued guidelines for the management of anaemia, notably including the American Society of Clinical Oncology [33], the National Comprehensive Cancer Network [1], and the European Organization of Research and Treatment of Cancer [2, 11, 35]. Treatment with erythropoiesis-stimulating agents (ESA's) is recommended for anaemic patients (Hb<10 g/dL) on chemotherapy and/or radiotherapy. For patients with declining Hb levels but less severe anaemia (Hb<12 g/dL), clinical circumstances such as Hb levels prior to cancer treatment shall be considered before initiation of ESA's. Recent guideline updates recommend Hb target levels of 12 g/dL with a view to improve quality

François Lüthi and Miklos Pless contributed equally to the work.

F. Lüthi · S. Leyvraz (✉) · C. Monnerat
Centre Pluridisciplinaire d'Oncologie,
University Hospital–CHUV BH06,
Rue du Bugnon 46,
1011 Lausanne, Switzerland
e-mail: Serge.Leyvraz@chuv.ch

M. Pless · B. Biedermann · E. Müller · R. Hermann
Department of Oncology, University of Basel,
Basel, Switzerland

of life and minimise the risk of blood transfusion. Despite these recommendations, half of all patients affected do not receive treatment, leading to impaired quality of life and potentially decreased survival [12, 27, 28, 43].

Furthermore, the management of anaemia focuses mainly on the treatment of cancer or chemotherapy-induced anaemia and only to a lesser extent on the prevention of chemotherapy-induced anaemia. However, there is some evidence from unblinded studies that immediate versus delayed initiation of erythropoietin-stimulating agents at a Hb threshold can reduce the transfusion rate and improve scores on physical and functional well-being [17, 33, 39].

The usual dose regimen for epoetin-α is either 10,000 U (150 U/kg) administered three times a week or 40,000 U once a week. Longer dosing intervals (every 2 or 3 weeks) using modified ESA's with longer half life are equally efficacious [37]. ESA's administration should be temporarily discontinued if target values are exceeded but should be reinforced in the absence of a Hb response. Findings from several randomised studies and meta-analyses demonstrate that ESA's are capable of both raising Hb levels by ≥2 g/dL in 53% of patients and reducing the risk of blood transfusions from 23–65% to 9–36% [26, 42]. These outcomes are associated with improved health-related quality of life and reduced symptoms after controlling for clinical and demographic aspects [8, 10, 13, 18, 21, 31, 34, 36].

Concerns on the use of ESA's have been raised of an increased risk of venous thromboembolic events (VTEs) and mortality [7]. The higher incidence of VTEs might be due to a high haematocrit and elevated viscosity and therefore controlled by limiting the target Hb levels [38]. A recent meta-analysis on individual patient data estimated a 17% increase in mortality rate in cancer patients [9]. Recent reports also suggest that the erythropoietin receptor on cancer cells may play a role in promoting cell proliferation and survival [3, 24, 25]. These findings emphasise the need to monitor Hb levels closely and also to use the lowest dose of ESA's required to maintain the target level.

ESA's also impose a substantial burden on hospital budgets and the entire healthcare systems. Use of these agents has been estimated to account for over 10% of total expenses for cancer care [19, 29]. Therefore, any strategy that enables better control of epoetin administration would be highly welcomed. Our goal is to develop a strategy that will reduce the dose requirements for ESA's to the lowest level while still offering effective prophylaxis of chemotherapy-induced anaemia.

The objective of the present study was to evaluate the efficacy of a dose-reduction schedule for epoetin-α administered in conjunction with an intravenous iron supplement to prevent anaemia (defined as Hb<10 g/dL) during platinum-based chemotherapy in high-risk patients [22].

Patients and methods

Inclusion criteria Patients (≥18 years old) were recruited at the Centre Pluridisciplinaire d'Oncologie, Lausanne, Switzerland and at the Department of Oncology, University of Basel, Switzerland. All patients gave written informed consent. Histological diagnosis of solid tumours was confirmed in all cases. None of the tumours had been treated previously. All patients were scheduled to receive at least three cycles of platinum-based chemotherapy with minimum doses of 60 mg/m² cisplatin every 3 weeks or carboplatin (AUC=5) every 3 weeks. Further requirements included Hb levels ≥ 11 g/dL, creatinine clearance ≥ 60 ml/min, ECOG performance ≤ 2 and life expectancy ≥ 3 months.

Exclusion criteria Patients were excluded from the study if severe co-morbidities or active pulmonary, gastrointestinal and/or genitourinary bleeding were present. Other criteria leading to exclusion from the study were uncontrolled hypertension (diastolic blood pressure > 100 mmHg); history of seizures; known hypersensitivity to recombinant human erythropoietin or iron (III)-hydroxide sucrose complex; transfusion less than 2 weeks before study entry; acute major illness or infection less than 1 month before study entry; and any previous chemotherapy or radiotherapy.

Treatment with epoetin and dose adjustment Starting on the first day of chemotherapy, 10,000 U epoetin-α were administered subcutaneously three times a week. Patients exhibiting Hb levels ≥ 13 g/dL at baseline were re-examined every 4 weeks and would receive subcutaneous epoetin-α only if Hb fell under 13 g/dL. Doses were adjusted every 4 weeks based on Hb levels. Treatment was temporarily discontinued on reaching the target level of ≥13 g/dL and was resumed 4 weeks later at the previous dose level if the level once again descended to <13 g/dL. In the event that Hb levels stabilised in the range of 11–13 g/dL, the dose was reduced from 10,000 to 4,000 U, or from 4,000 to 2,000 U, over the next 4 weeks. Hb levels descending to <11 g/dL were handled by increasing the dose to the next higher dose level (10,000 to 20,000 U) over the next 4 weeks. Epoetin-α was discontinued in patients classified as non-responders.

Epoetin-α was administered throughout the scheduled duration of chemotherapy until 3 weeks after the last injection. The same timetable was used if chemotherapy was prematurely discontinued due to tumour progression or unacceptable toxicity.

Iron was administered intravenously once weekly in the form of iron (III)-hydroxide sucrose complex at a dose level of 100 mg to all patients irrespective of ferritin levels. No additional iron doses were administered once epoetin-α had been discontinued. Erythrocyte transfusions were per-

formed if Hb levels dropped below 8 g/dL; otherwise this option was left to the discretion of the physician in charge.

The protocol was approved by the local ethical committee of the two centres participating in the study.

Assessment of study endpoints The main objective of the study was to prevent anaemia defined as Hb<10 g/dL. A secondary endpoint was to assess the mean weekly dose of epoetin-α administered during chemotherapy treatment. Transfusion requirements were also documented. Complete blood counts were obtained weekly throughout treatment. Ferritin levels were measured at baseline and at the end of treatment. Patients were only evaluated if treatment had been carried on for at least 6 weeks. Resistance to epoetin-α was assumed in the presence of persistent Hb levels of <10 g/dL over 4 weeks of treatment at a dose level of 20,000 U. Hb<10 g/dL or transfusion was also defined as treatment failure.

Statistical methods The null hypothesis for the primary endpoint would be rejected if the treatment with epoetin-α prevents anaemia (Hb<10 g/dL) in over 70% of patients compared with 50% in patients undergoing similar (cisplatin-based) treatment without epoetin-α. The sample size required to test this hypothesis was 37 patients (one-sided hypothesis: α=0.05; power: β=0.2) according to Fleming [20]. Thus anaemia had to be effectively prevented in over 22 patients for the null hypothesis to be rejected.

Results

In total, 37 patients were enrolled in the study between April 1999 and September 2002. Pertinent patient characteristics are summarised in Table 1. The cohort included 26 men and 11 women with a median age of 58 years (range 36–69). The majority of these patients had lung cancer (n=28) and was treated with cisplatin (n=33). Patients were treated with a median number of four cycles of chemotherapy (range 1–6).

At baseline, the median Hb level was 13.7 g/dL (range 10.9–16.2) and median ferritin level was 204 μg/L (range 22–988).

Four patients were excluded from efficacy analysis. Two of them never received epoetin-α, one due to treatment refusal after enrolment and another due to chemotherapy-related haemolysis. The other two patients could not be evaluated because of intercurrent adverse events: one patient died of myocardial infarction on day 16 after having received seven injections of epoetin-α (Hb=14.6 g/dL); and the other patient suffered transient cerebral ischemia on day 7 after having received three injections of epoetin-α (Hb=12 g/dL).

At baseline, 21 of 33 patients (64%) had Hb levels ≥ 13 g/dL. Treatment with epoetin-α was initiated after 4 or 8 weeks in all but one of these patients when Hb levels dropped below 13 g/dL. Only one patient never required epoetin-α. For 12 patients with baseline Hb level of 11–13 g/dL, epoetin-α was started concomitantly with the first cycle of chemotherapy.

At the end of therapy, the median Hb level was down to 11.0 g/dL (range 7.4–13.8).

Anaemia with Hb<10 g/dL was prevented in 24 patients (73%). Despite epoetin-α treatment, nine patients developed anaemia (Hb<10 g/dL) but all had Hb≥8 g/dL.

Treatment failed in nine patients (27%). These failures included resistance to epoetin-α in four cases (12 %) despite an increased epoetin-α dose of 20,000 U three times per week, blood transfusion in three cases (9%) and premature end of treatment with Hb level <10 g/dL in two cases (6%).

Table 1 Patient characteristics

	All patients	Evaluable patients
N	37	33
Men/women	26/11	22/11
PS≤½	34/3	30/3
Median age	58 (36–69)	58 (40–68)
NSCLC	22 (59%)	18 (56%)
SCLC	6 (16%)	6 (18%)
Testicular cancer	2 (6%)	2 (7%)
Bladder carcinoma	2 (6%)	2 (7%)
Other carcinoma[a]	4 (11%)	4 (12%)
Regimen with DDP≥75 mg/m^2	33	29
Regimen with CBDCA AUC 5	4	4
Median chemotherapy cycles	4 cycles (1–6)	4 cycles (1–6)
Median Hb at baseline (g/dl)	13.7 (10.9–16.2)	13.7 (10.9–16.2)

DDP cisplatin, *CBDCA* carboplatin

[a] Ovarian carcinoma, unknown primary, urachus carcinoma, neuroendocrine pancreatic carcinoma, mediastinal carcinoma all 1

Epoetin-α was administered for a median of 8 (0–20) weeks.

Dose levels could be effectively reduced from 10,000 to 4,000 U or less in ten patients (30%). Doses were increased to 20,000 U in seven patients (21%). The median dose level of epoetin-α used was 5,866 U three times per week.

No adverse events related to the intravenous iron supplements were reported. The median ferritin level was 941 μg/L (range 346–1275) at the end of treatment.

Discussion

Our data demonstrate that a 30% reduction of the epoetin-α dose can be achieved in patients with anaemia induced by platinum-based chemotherapy. Anaemia was effectively prevented in 24 of 33 patients (73%) using the dose-reduction schedule described above. The mean dose requirement of 5,866 U three times per week per patient was 41% below the recommended standard dose. These findings support current recommendations for a dose decrease to reduce the risk of thrombovascular events associated with ESA's treatment [33].

To our knowledge, this is the first study to explore the lowest epoetin-α dose level that effectively prevents anaemia (defined as Hb level < 10 g/dL) induced by platinum-based chemotherapy. A previous randomised study included 130 small-cell lung center patients with Hb levels > 10.5 g/dL who were treated three times a week with epoetin-α 150 U/kg (10,000 U) or 300 U/kg (20,000 U) or received no treatment [40]. A total of 66% of patients in the control group exhibited anaemia (Hb<10 g/dL) compared with 48% and 39%, respectively, in the two treatment groups. Transfusions were performed in 59%, 45% and 20% of patients, respectively. Administration of ESA's was temporarily discontinued when Hb levels reached >15 g/dL and was resumed with the dose reduced by half upon Hb relapsing to ≤13 g/dL. Thus, the mean weekly doses in the two treatment groups were 335 and 612 U/kg (equivalent to 7,500 and 13,600 U three times weekly), representing a dose reduction of 25% and 32%, respectively.

In another randomised trial of epoetin-α, a mean dose level of 10,000 U three times weekly prevented anaemia (Hb<10 g/dL) in 83% of patients, and the transfusion rate was 15% [5]. The same efficacy was demonstrated with a dose administration of 40,000 U once weekly, which effectively controlled anaemia in 82% of patients, with 12% requiring transfusion [15]. Our low transfusion rate (9%) is possibly the result of a fairly restrictive transfusion policy. Transfusions were only prescribed when Hb levels fell to < 8 g/dL and were otherwise left to the discretion of the physician in charge. A similar transfusion rate (8.6%) was obtained in a randomised study that also evaluated anaemia prevention with similar transfusion guidelines as ours [14]. In that study, weekly doses of 40,000 U epoetin-α were decreased by 25%. Doses were withheld when Hb levels reached >14 g/dL in 29% of patients or were increased (to 60,000 U) in 9% of patients.

The efficacy findings in our trial are similar to those reported in the cited studies despite notably different target Hb levels and a different general strategy. This demonstrates that the reduction strategy we adopted was not detrimental to achieving target Hb levels.

One factor that may have contributed to our results was the concomitant weekly intravenous administration of iron. The benefit of parenteral iron had been demonstrated in a number of controlled randomised trials [4, 6, 23, 41]. In 157 anaemic cancer patients undergoing chemotherapy, iron supplements to epoetin-α, administered either orally at 650 mg/day or intravenously at 100 mg weekly, increased Hb levels by 1.5 or 2.5 g/dL, respectively, compared with 0.9 g/dL in the placebo group [4].

In our study, two serious vascular events were reported after the initial doses of epoetin-α and were considered unrelated to the study medication by the treating physicians on the basis that the patients' Hb levels remained within normal range. Indirect toxicity of epoetin-α, however, cannot be excluded. These two patients were treated for advanced non-small cell lung cancer and a high rate of cardiovascular events has been documented to occur frequently in this patient population [30]. Although our Hb target of 13 g/dL is higher than current recommendations, the median Hb level (11 g/dL) reached at the end of the treatment period is considered safe.

Our findings and those of the cited studies show that the intensity and thereby the economic burden of ESA's treatment could be substantially decreased if appropriate dose-reduction strategies together with intravenous iron supplements were to be widely adopted. Finally, a dose-reduction strategy with stringent rules (target Hb≤12 g/dL) is also important given the controversially discussed the impact of epoetins on survival [7, 16, 32].

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Conflict of interest statement None of the authors has any financial or potential conflict of interest to disclose.

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