A New Dose-intense Epoetin Alfa Regimen Effective in Anemic Cancer Patients Receiving Chemotherapy: An Open-label, Non Randomized, Pilot Study

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Abstract. Background: Chronic anemia is a well-recognized complication of both cancer and cytotoxic treatments and is associated with symptoms (e.g., fatigue, dyspnea) that may induce or exacerbate functional deterioration. The use of recombinant human erythropoietin (rHuEPO epoetin alfa) clearly increased haemoglobin (Hb) levels, decreased transfusion needs and allowed recovery of quality of life in anemic cancer patients (pts) undergoing chemotherapy (CT). The purpose of this open-label, non randomized, pilot study was to assess the safety and efficacy of an intensive 19-day epoetin alfa treatment in anemic patients with solid tumors receiving chemotherapy. Patients and Methods: Treatment: patients received a single induction s.c. dose of epoetin alfa 40,000 IU day 1 and twice a dose of 10,000 IU s.c. (8:00 a.m.-8:00 p.m.) on days 3, 5, 8, 10, 12, 15, 17 and 19. The total dose of epoetin alfa per patient was 200,000 IU. Iron supplementation: 125 mg i.v. days and 8. Soluble transferrin receptor (sTfR) levels were performed on days 1, 8 and 15. This epoetin induction regimen was not followed by an epoetin maintenance therapy. Patients: Twenty-nine anemic (Hb ≤ 11.5 g/dL) pts with non myeloid malignancies undergoing CT were included in the study. Results: At baseline the mean Hb level was 9.41 g/dl. On day 8, the mean Hb level increased to 10.07 g/dl (p<0.0001), reaching 10.68 g/dl on day 15 (p<0.0001). On days 22 and 29, the mean Hb levels increased to 10.93 and 11.05 g/dl (p=0.002 and 0.033, respectively). No patient received blood transfusions. The global mean increase of Hb level was 1.64 g/dl (basal to d29). It was defined as a major response: an increase of Hb levels > 1.5 g/dl. A rate of 62% (18/29 patients) of major responses was observed on day 21. Moreover, 25/29 patients (86.2%) presented an increase of Hb levels > 1 g/dl after 21 days. On days 8 and 15, the mean sTfR levels had increased significantly (p=0.021 and 0.001, respectively). The increase of mean sTfR level after 15 days correlated significantly with the increase of mean Hb level in the first two weeks of epoetin therapy (p=0.05). Epoetin alfa has been well tolerated so far in the study. Conclusion: The results of the present study suggest that an induction dose of 40,000 IU of epoetin alfa, followed by 8 maintenance doses of 20,000 IU each, may improve the standard response in terms of both time to response and Hb increase. Moreover, the Hb levels seemed to increase after epoetin therapy discontinuation (d22-29). The incidence and extent of anemia in cancer patients is influenced by several factors: the type of malignancy, the myelosuppressive nature of the anticancer therapy and the presence of coexisting morbidities (1,2). Many cancer patients are anemic at baseline, particularly those with hematological malignancies. Moreover, the incidence and severity of anemia increases with successive rounds of chemotherapy and/or radiation therapy (3,4). Three erythropoietic agents: epoetin alfa, beta and darbepoetin alfa, are currently available for the treatment of anemia with different FDA-approved indications based on the clinical evidence submitted in the particular disease states (5-9).
Recombinant human erythropoietin (rHuEPO, epoetin alfa), in several placebo-controlled clinical trials and single-arm, community-based studies, increased Hb levels, decreased transfusion needs and improved QoL in anemic cancer patients undergoing chemotherapy when administered at dosages of either 10,000 IU three times per week or 40,000 IU once per week (10,11). The mean increase in Hb level was approximately 1 g/dl after 4 weeks and 2 g/dl after 8 weeks of epoetin alfa therapy, irrespective of the dosage regimen used (10,11). The doses of 20,000 IU three times per week or 60,000 IU once weekly are only administered to non-responder patients after 4 weeks of induction treatment. The ASH/ASCO guidelines suggest the fractionated dose was evaluated. This report describes the results of a pilot study conducted to examine the efficacy and safety of this dosing regimen in anemic cancer patients receiving chemotherapy.

Patients and Methods

Patient selection. Twenty-nine patients were enrolled. Requirements for inclusion were: a non-haematological malignancy, haemoglobin level 11.5 g/dl or less, to be receiving concomitant chemotherapy, 3 months or greater of life expectancy and to be able to understand and provide written informed consent. Exclusion criteria were uncontrolled hypertension, active infection, primary bone marrow malignancy and a known history of anemia caused by factors other than cancer or chemotherapy (i.e. iron or folate deficiencies, haemolysis, gastrointestinal bleeding, myelodysplastic syndromes). We also excluded patients who had previously received epoetin alfa, were planning to have a bone marrow transplant or were receiving peripheral-blood progenitor cell therapy.

Baseline information were patients’ demographics, weight and blood pressure, tumor histology, current chemotherapy and radiation therapy regimens, and history of cisplatin chemotherapy regimens and transfusion use. During the screening phase of the study, demographic data were obtained, and medical history (including disease-related information) and physical examination (including vital signs, weight) and Eastern Cooperative Oncology Group (ECOG) performance status, were performed for each patient. Routine hematology and chemistry series were done, including: complete blood count with differential, serum chemistry panel (including creatinine, electrolytes, albumin, aspartate aminotransferase, total bilirubin), serum iron, serum ferritin and total iron binding capacity. Soluble transferrin receptor (sTfR) levels were performed on days 1, 8 and 15.

Baseline demographic and clinical characteristics are reported in Table I.
Treatment plan. This was an open-label, non randomized pilot study in which anemic patients with solid tumors submitted to multicycle chemotherapy received a new dose-intense epoetin alfa induction regimen (EPREX®, Ortho Biotech/Janssen-Cilag Inc.). Patients received one single induction s.c. dose of epoetin alfa 40,000 IU on day 1 and twice a dose of 10,000 IU s.c. (8:00 a.m.- 8:00 p.m.) on days 3, 5, 8, 10, 12, 15, 17 and 19. The total dose of epoetin alfa administered per patient was 200,000 IU. Iron supplementation: 125 mg i.v. on days 1 and 8. This epoetin induction regimen was not followed by an epoetin maintenance therapy. Hemoglobin levels were detected on days 1, 8, 15, 22 and 29 and soluble transferrin receptor (sTfR) levels were performed on days 1, 8 and 15 (Figure 1).

Efficacy endpoints. The efficacy endpoints were the evaluation of: the percentage of patients who achieved a major response defined as Hb increase ≥ 1.5 g/dl from baseline or a minor response defined as Hb increase ≥ 1 g/dl from baseline; the proportion of patients transfused after the first 3 weeks of treatment; the change in hemoglobin median level from baseline to last value (day 29); the determination of the time to treatment failure (response duration); the safety of the new dose-intensity epoetin alfa induction regimen; the predictive value of sTfR levels.

Results

Responders. The percentage of patients who achieved a major response was 62% after a 3-week treatment and 69% after 4 weeks (Figure 2). Moreover, the proportion of patients who achieved a minor response was 86% after 3 weeks of treatment and 93% after 4 weeks (Figure 2).

Transfusion requirements None during the 29 days of the protocol.

Change in Hb levels. Mean Hb levels increased from 9.41 g/dL (±1.10, SD) to 10.93 g/dL (±1.68, SD) after 3 weeks (day 22), and to 11.05 g/dl (±1.72, SD) at day 29 (Figure 3). In particular, at baseline the mean Hb level was 9.41 g/dl. On day 8, the mean Hb level increased to 10.07 g/dl (p<0.0001) and on day 15 reached 10.68 g/dl (p<0.0001). On days 22 and 29, the mean Hb levels increased to 10.93 and 11.05 g/dl (p=0.002 and 0.033, respectively). The mean Hb gain in 4 weeks was 1.64 g/dl (Figure 4).

Time to treatment failure (response duration). The median time to treatment failure was 9 weeks (95%C.I.: 5.78; 12.22) (Figure 5).

Safety. All 29 patients were eligible for safety evaluation. The induction dosage regimen of epoetin alfa was well-tolerated. Adverse events were unrelated to therapy and commonly occurring in patients undergoing chemotherapy. Twelve patients experienced serious adverse events, none of which were considered by the investigator to be related to epoetin alfa. Two patients reported an adverse event (respectively, blood hypertension and arthralgia/myalgia) that was considered by the investigator to be possibly related to epoetin alfa administration.

Predictive value of sTfR levels. On days 8 and 15, the mean sTfR levels increased significantly (p=0.021 and 0.001, respectively). The increase of mean sTfR level after 15 days correlated significantly with the increase of mean Hb level in the first 2 weeks of epoetin therapy (p=0.05).
Discussion

The new epoetin alfa regimen, utilizing a 3-week induction fractionated dose, was found to significantly increase Hb levels in patients receiving chemotherapy and was well-tolerated. The evaluated induction treatment was faster than standard dosages in patients needing transfusion. In particular, the mean Hb increase was 1.5 g/dl after 3 weeks and 1.64 g/dl after 4 weeks of induction treatment, with 86% of patients gaining at least 1 g/dl. These results are consistent with an increase in Hb of approximately 1 g/dl at week 4 achieved in previous studies of anemic cancer patients undergoing chemotherapy who received initial epoetin alfa doses of 150–300 U/kg s.c. tiw or 10,000–20,000 U s.c. tiw (17, 18).

Comparison of responders with other loading regimens (Table II) shows that epoetin alfa response is dose-dependent: the higher the dose, the greater and faster the response. The few epoetin induction feasibility studies published in the literature, as the present paper, showed a dose-response curve with faster responses when a high dose of epoetin was administered over short times (13-15).

Cortesi et al. (13) performed a pilot study on a subset of solid tumor patients with a baseline Hb 8.2 g/dl. The induction treatment with epoetin alfa 40,000 twice a week for 2 weeks followed by no treatment allowed a Hb gain of 1.7 g/dl in 2 weeks and 2.9 g/dl in 6 weeks; the percent of responders was 82% at 6 weeks compared to 21% of a historical control group. Comparison to standard treatment revealed that there was also an advantage in chemotherapy compliance in the group quickly overcoming anemia.

Furthermore, the present feasibility study demonstrated that a fractionated dose is more effective than one weekly administration (18-20). One-weekly epoetin alfa dosing has been widely adopted by oncologists in the U.S. and incorporated into treatment guidelines (17,18). In Patton et al’s study (14), one weekly dosage of 60,000 IU epoetin alfa...
Table II. Comparison among loading dose regimens.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Pts</th>
<th>Mean Hb gain at week 4 (g/dl)</th>
<th>Responders Rate at week 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epo alfa 40K induction dose plus 60K/week (three times week) X 4 weeks</td>
<td>Present paper</td>
<td>29</td>
<td>1.6</td>
<td>62%</td>
</tr>
<tr>
<td>Epo alfa 80K/week X 2 weeks</td>
<td>Cortesi³</td>
<td>19</td>
<td>2.9</td>
<td>82%</td>
</tr>
<tr>
<td>Epo alfa 60K/week X 4 weeks</td>
<td>Patton⁴</td>
<td>20</td>
<td>1.1</td>
<td>nd</td>
</tr>
<tr>
<td>Epo alfa 60K/week X 4 weeks</td>
<td>Chap⁶</td>
<td>20</td>
<td>1.1</td>
<td>nd</td>
</tr>
<tr>
<td>Nesp 4.5 mcg/ Kg/week (= 60K) X 4 weeks</td>
<td>Glasy⁷</td>
<td>32</td>
<td>0.53</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>0.7</td>
<td>22%</td>
</tr>
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For 8 weeks allowed a mean Hb increase of 1.1 g/dl in 4 weeks and 2.8 g/dl in 8 weeks in anemic cancer patients receiving chemotherapy. Chap et al. (15) performed an open-label, non randomized pilot study to evaluate the response rate of epoetin alfa at a dose of 60,000 IU weekly in anemic patients with non myeloid malignancies undergoing chemotherapy. The hemoglobin gain was 1.1 g/dl in 4 weeks and 2.6 g/dl in 8 weeks with respect to a mean baseline Hb concentration. Data from this pilot study suggest that a high induction dose (40,000 U) followed by high fractionated doses (10,000 x 2) three times a week may allow patients to more quickly achieve a significant increase in Hb level or a >12 g/dl target Hb level compared with epoetin alfa once per week. New studies evaluating a number of extended dosing schedules for epoetin alfa are underway. Some authors have investigated, with contrasting results, the role of serum soluble transferring receptor (sTfR - a marker of functional iron deficiency), as well as of the early sTfR increment (a quantitative measure of erythropoietic activity) in predicting epoetin response (21,22). In the present study, we demonstrated that the increase of mean sTfR level after 15 days correlated significantly with the increase of mean Hb level in the first 2 weeks of epoetin therapy (p=0.05).

In conclusion, these results establish the feasibility of a new epoetin alfa regimen utilizing a 3-week induction fractionated dose in anemic cancer patients undergoing chemotherapy. A variety of epoetin alfa doses, schedules and dosage regimens currently are being investigated in larger clinical studies. Further studies are required to define the most appropriate induction dosage of epoetin alfa.

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References


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