Darbepoetin Alfa Administered Every Three Weeks (Q3W) in Anemic Cancer Patients Receiving Chemotherapy (CT)

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Abstract. Background: Darbepoetin alfa, has a longer half-life than epoetin alfa (rHuEPO) due to its increased sialylated carbohydrate content and can be administered less frequently. Its advantage in terms of response is not entirely clear. Patients and Methods: From August 2005 until October 2006, 64 anemic patients (hemoglobin ≤11.5 g/dl) with advanced metastatic cancer receiving chemotherapy (CT), median age 65 years (range 33-77), median Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1 (range 0-1), were treated with subcutaneous (s.c.) darbepoetin alfa 500 μg every 3 weeks (Q3W) and a single intravenous (i.v.) dose of 125 mg of elemental iron at the beginning of the treatment period followed by an oral daily iron supplement (200 mg of elementary iron). The treatment effect was evaluated as a response (Hb increase ≥1 g/dl) or a major response (Hb increase ≥2 g/dl) after 2, 4, 6 and 8 weeks. The patients were questioned about fatigue. Results: After 8 weeks of treatment, a treatment response was observed in 11 out of the 29 evaluable patients (38%) with a major response in 10%. The mean Hb change was 0 g/dl, +0.9 g/dl, +0.75 g/dl and +0.7 g/dl respectively at 2, 4, 6 and 8 weeks. Blood transfusions were required in 9 patients (31%). At baseline, 39 out of the 64 patients (61%) reported grade 1 or 2 fatigue. At 8 weeks the patients with a major response did not show any evidence of fatigue. Conclusion: Darbepoetin alfa Q3W is moderately effective in reducing anemia in heavily pretreated and advanced stage chemotherapy treated patients.

Chemotherapy (CT)-induced anemia in cancer patients is a common symptom (1) and it can be treated with erythropoiesis-stimulating agents, such as epoetin and darbepoetin alfa. Both these drugs are approved for increasing hemoglobin (Hb) levels, reducing the requirement for red blood cell (RBC) transfusions and improving patients’ quality of life (QoL) (2,3). The mean increase in Hb level has been shown to be approximately 1 g/dl after 4 weeks and 2 g/dl after 8 weeks of epoetin-alfa therapy, when administered at dosages of 10,000 to 20,000 IU three times weekly or 40,000 to 60,000 IU once weekly. The mean response rates in different studies have ranged from 53% to 70.5%, response being defined as an Hb increase of ≥2 g/dl after up to 24 weeks of treatment (4). Darbepoetin alfa (Amgen Inc., Thousand Oaks, CA, USA) is a novel erythropoietic protein with an approximately threefold longer half-life than epoetin-alfa. After initial experiences using darbepoetin alfa in a once per week dosing schedule (QW) (3, 5-7), many trials have shown that darbepoetin alfa administered at a fixed dose (300 μg) Q3W showed a ≥1 g/dl rise in hemoglobin concentration during the first 4 weeks of treatment (13). Comparable efficacies have been observed in patients treated with 200 μg Q2W darbepoetin alfa (14). Considering that less frequent dosing provides additional benefits to patients, in an effort to explore the potential for even better response rates with respect to the rapidity and duration of response in anemic cancer patients, a new dosage of darbepoetin alfa regimen utilizing a 3-week schedule (Q3W) was studied. The efficacy and safety of darbepoetin alfa administered as a fixed dose (500 μg) in patients with solid tumors and moderate or severe anemia receiving CT, was evaluated.

Patients and Methods

Patient population. The eligible patients were anemic (Hb≤11.5 g/dl) men and women (≥18 years of age) with a solid tumor malignancy scheduled to receive cyclic CT for at least 8 weeks. Moreover, a life expectancy of 6 months or greater, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-2 and adequate renal, hepatic and hematological
functions, were required. Patients were excluded if they had received allogeneic blood transfusion within 14 days or surgery within 7 days of study entry, had anemia due to factors other than cancer or CT, had received more than two prior CT regimens or if radiation therapy was included in their treatment plan. Patients unable to provide written informed consent or with an uncontrolled hypertension, any unstable medical condition or a history of uncontrolled cardiac arrhythmias, pulmonary embolism, or thrombosis within the previous 6 months were also excluded, as were those with an uncontrolled iron, folate, or vitamin B12 deficiency. Patients previously treated with epoetin-alfa 10,000-20,000 IU 3 times weekly or 40,000 IU once weekly could be enrolled, provided their Hb level had not increased by ≥1 g/dl with such treatment.

Study design. The study was designed as a prospective, open-label pilot single center study. Other than the direct impact of darbepoetin alfa on the Hb levels, the effects of the drug on transfusion requirements, the QoL and safety were also evaluated. All the patients underwent initial screening within 10 days before the first dose of the study treatment, during which baseline information, including demographics and clinical laboratory data (hematology, clinical chemistry, iron profile) were collected and participant eligibility was assessed. Hb, hematocrit and QoL were measured within 3 days before the first dose of the study drug. The patients were stratified by CT type (platinum- or non-platinum-based), cancer type, stage of tumor, ECOG PS and previous or not epoetin alfa treatment. The initial study drug administration occurred on day 1 of week 1 and was required to coincide with day 1 of the CT cycle to minimize early variability in the timing of erythropoietic growth factor administration and response with respect to the CT cycle (15). The study treatment (darbepoetin alfa 500 μg, subcutaneous (s.c.) injection Q3W) was administered for a planned duration of 8 weeks (3 doses of darbepoetin alfa). The patients were considered evaluable if they received at least 2 administrations of darbepoetin alfa with an a observational period of at least 4 weeks. Dose escalation for non-responders (Hb increase <1 g/dl) was not allowed. The study drug was withheld if Hb was >13 g/dl. To avoid restriction of erythropoiesis due to inadequate iron stores or availability, the patients received a single intravenous (i.v.) dose of 125 mg of elemental iron at the beginning of the treatment period and an oral daily iron supplementat (200 mg of elemental iron). The Hb levels were measured weekly and the treatment effect was evaluated as no response (Hb increase <1 g/dl), a minor response (Hb increase ≥1 g/dl and <2 g/dl) or a major response (Hb increase ≥2 g/dl) after 2, 4, 6 and 8 wks. The patients were withdrawn if CT was discontinued before 6 weeks or changed from a platinum- to a non-platinum based regimen or vice versa. QoL was assessed by questioning the patients about fatigue and its change during treatment according to a four-point scale, where 0=no fatigue and 3=severe fatigue.

Efficacy evaluation. The analysis of the primary efficacy end-point was based on data from the first 61 patients who completed 4 weeks of study treatment. Hb response by week 4 and 8. After 4 weeks of treatment, the Hb was 10.6±1.5 g/dl (mean±SD), with a mean increase from baseline of 0.9 g/dl (95% CI, 0.52-1.28) in the 61 evaluable patients. After 8 weeks of treatment, the Hb was 10.4±1.2 g/dl (mean±SD), with a mean increase from baseline of 0.7 g/dl (95% CI, 0.27-1.13) in the 29 evaluable patients (Figures 1 and 2). The percentage of patients who achieved an Hb increase ≥1 g/dl by week 4 of treatment was 36.0% (22/61 patients). When summarized by CT type, 12% and 24% of...
patients, respectively in the platinum vs. non-platinum groups achieved an Hb increase ≥1 g/dl by week 4 (p<0.05, t-test). There were no significant differences when response to darbepoetin alfa therapy was stratified according to oral or subcutaneous vs. intravenous CT schedule and to pre-treatment vs. no-pre-treatment with rHuEPO. The Hb increase at 4 weeks was ≥2 g/dl in 10 patients, 1-<2 g/dl in 12 patients, and ≤1 g/dl in 20 patients. Hb increase at 8 weeks was ≥2 g/dL in 3 patients and 1-<2 g/dL in 8 patients (Figure 3). After 8 weeks of treatment, a treatment response was observed in 11/29 (38%) patients with a major response in 10% of cases.

**Time to Hb response.** The Kaplan-Meier estimates of the median time to an Hb rise of ≥1 g/dl and ≥2 g/dl were 35.0 days and 38.0 days respectively which indicated that the major response in patients receiving darbepoetin alfa was not time related.

**Change in Hb and transfusion requirement.** The biweekly changes in Hb from baseline are shown in Figure 1. The mean Hb increases after 2, 4, 6 and 8 (end of study) weeks of treatment were 0, 0.9, 0.75 and 0.7 g/dl, respectively. Blood transfusions during the study were required in 9/61 evaluable patients (15%) with the transfusion rate ranging from 7.9% (week 2) to 3.3% (week 8). The mean number of packed red blood cell (PRBC) units received per transfused patient was 2 units (range, 1-3) and the total absolute number of PRBC units transfused in the study treatment was 18.

**QoL evaluation.** Mean improvements from baseline to week 4 and to the end of the study were observed for the fatigue assessment and a positive correlation between the changes in QoL scores and Hb level was observed. At baseline, 39 out of the 64 patients (61%) reported fatigue grade 1 or 2. After 4 weeks, 27 out of the 61 patients (44%) reported fatigue at the same levels. At 8 weeks the patients with a major response did not show any evidence of fatigue (Spearman’s coefficient r., p<0.01) while for the minor responders fatigue grade 1 was reported in 3/8 patients.
Safety evaluation. The incidences and patterns of AEs were similar and generally those expected for patients with cancer receiving CT. All the AEs were judged to be unrelated to the study treatment, not clinically significant thrombotic vascular events were reported, blood pressure throughout the study remained within normal limits (100-160 mmHg systolic blood pressure / 70-90 mmHg diastolic blood pressure) in all the patients.

Discussion

Darbepoetin alfa at 500 μg s.c. every 3 weeks for the amelioration of CT-induced anemia effectively increased and maintained the Hb levels in most patients within the daily oncology routine. The once every 3 weeks regimen provides further convenience by offering the possibility of synchronising its administration with most CT regimens. However, in our cohort of patients, darbepoetin alfa appeared to produce suboptimal results compared to historical data with Epoetin alfa at 4 and 8 weeks (4). In the same way darbepoetin alfa did not provide a faster Hb response in respect to other erythropoietic proteins. This lack of efficacy in respect to international data on darbepoetin alfa could be related to four principal characteristics of the present population: 26% patients result with multiple bone metastases and suspected for bone marrow infiltration; 30% patients result heavily pretreated; few patients were evaluable weeks (29/61) for final consideration at 8 weeks and the median baseline Hb was <10 mg/dl and all international trials emphasize the benefits of initiating erythropoietic therapy when patient hemoglobin concentrations are 10 g/dl rather than <10 g/dl.

In conclusion darbepoetin alfa Q3W may simplify the life of patients and the treatment of chemotherapy-induced anemia. The drug appears to be well tolerated, but moderately effective in heavily pretreated and advanced stage patients and randomized trials and non-inferiority studies are needed to better define the role of darbepoetin-alfa in this context.
References


Figure 3. Hb response rate.