Darbepoetin α as treatment for anemia in patients receiving chemotherapy: a single-center experience

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We evaluated Darbepoetin α (Aranesp; Amgen), a novel erythropoietic protein, in patients who developed anemia while receiving chemotherapy. Seventy-five patients (median age 62 years, range 40–81 years) undergoing different cancer chemotherapy regimens were treated with darbepoetin α. Therapy was started if hemoglobin (Hb) levels fell below 10 g/dl or if symptomatic anemia developed. Treatment effect was evaluated after 4 weeks, 8 weeks and at the end of therapy (up to 12 weeks). If no increase in Hb was seen after 4 weeks, the dose of darbepoetin α was increased to 300 μg. Patients were questioned about fatigue and any change during treatment, with evaluation according to a four-point scale, where 0 = no fatigue and 3 = severe fatigue. We observed a treatment response in 54 of 75 patients (72%). Dose escalation was necessary in 30 of 75 patients (40%) and blood transfusions were required in 13 of 75 patients (17.3%). Response was observed in 32 of 43 patients (74.4%) who had a baseline Hb < 10 g/dl and in 22 of 32 (68.8%) patients who had a baseline Hb ≥ 10 g/dl. At baseline, 60 of 75 patients (93.3%) reported fatigue of grade 2 or 3, but at the end of the 12-week follow-up period, only 26 of 68 patients (38.3%) reported fatigue at these levels. We conclude that darbepoetin α is a highly effective and well-tolerated drug in the treatment of chemotherapy-associated anemia. Patients benefited both in terms of Hb levels and control of chemotherapy-related symptoms. ***Anti-Cancer Drugs*** **16:617–620 © 2005 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2005, **16:**617–620

Keywords: chemotherapy-induced anemia, darbepoetin α, fatigue, quality of life

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Received 10 January 2005 **Revised form accepted** 12 April 2005

Introduction

Anemia is a very common condition in patients with cancer [1]. Low hemoglobin (Hb) levels are associated with diminished quality of life and potentially decreased overall survival [2]. While the latter point has not yet been proven in patients receiving chemotherapy, it is well known that low Hb levels are associated with a decreased response to radiation therapy [3]. However, it is only recently that the impact of anemia on the patient's quality of life has been recognized [4]. Until a few years ago, blood transfusion was the only available treatment for anemia, usually administered when Hb ≤ 8 g/dl, making fatigue a generally accepted condition in cancer patients [5]. In addition to this, there is a possible immunosuppressive effect of blood product transfusion, resulting in detrimental effects on cancer treatment [6].

The arrival of recombinant erythropoietins in the 1990s dramatically changed the situation. These drugs were originally developed to treat anemia in patients with chronic renal failure, but now made it possible to treat the symptoms of cancer-related anemia, and its associated effects on energy level, activity level and quality of life. Furthermore, studies were able to show that improvements in fatigue levels were associated with significant reductions in anxiety and depression [7]. Today, three erythropoietic agents are available: epoetin α, epoetin β and darbepoetin α, the agent used in the current study.

Darbepoetin α shows some distinctive differences compared with the other two substances. In particular, it shows enhanced biological activity and a 3-fold longer serum half-life than that of the recombinant human erythropoietins (rHuEPOs), because of its increased sialic acid-containing carbohydrate content, which results in a higher molecular weight and a greater negative charge. Furthermore, despite having lower receptor binding, darbepoetin α is significantly more potent *in vivo* than rHuEPO [8].

Multiple factors lead to the development of anemia in cancer patients [9]. Cancer-related anemia often develops because of the infiltration of malignant cells into the

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bone marrow, by impaired Hb production related to chemotherapy or radiation therapy, iron deficiency, or low endogenous erythropoietin levels. In cancer patients the relative erythropoietin deficiency is potentiated by decreased responsiveness to erythropoietin, mediated by the effects of inflammatory cytokines on the marrow and on ferrokinetics, thereby leading to a high incidence of anemia.

Although the positive impact of erythropoietic therapy on the quality of life of the patient is well recognized, the high cost of these treatments means that pharmacoeconomic aspects are widely discussed [10]. A particularly crucial point is the question of whether therapy should start early during the development of anemia or only after Hb levels fall below a certain threshold.

In this prospective phase II trial, we evaluated the effect of darbepoetin α on Hb levels in patients who developed anemia during anti-cancer chemotherapy. We also evaluated the influence of baseline Hb levels on response to erythropoietic therapy.

Methods

All data were collected from the Department for Internal Medicine I, Division of Oncology at the Medical University of Vienna, Vienna, Austria.

Patients

Seventy-five patients were enrolled into the study, all of whom were evaluable for response to treatment, quality of life and adverse events. Patients were receiving anti-cancer chemotherapy for various, mainly advanced, tumors. Patients on immunotherapy or endocrine therapy were excluded from the study.

Patients were included if their Hb levels fell below 10 g/dl, or if they developed symptomatic anemia, defined as tiredness, decline in energy level, activity level or anemia-associated dyspnea.

Treatment and assessments

Patients received darbepoetin α 150 μg every 7 days by s.c. injection. Response was evaluated after four injections. If there was no response (defined as an increase in Hb levels of at least 1 g/dl), the dose of darbepoetin α was escalated to 300 μg every 7 days. Further blood tests were performed at week 8 and 12 or, in case of discontinuation of chemotherapy, at the end of therapy. No iron supplementation was performed. Symptoms of anemia were assessed at the time of treatment initiation, after 4 weeks and at the end of follow-up. Patients were questioned about current symptoms and changes from baseline. Patients' fatigue levels were assessed at baseline, week 4 and end of follow-up, according to a four-point scale with 3 as the most severe level of fatigue or anemia-associated fatigue and dyspnea and 0 as no episode of fatigue. Adverse events were recorded throughout the treatment period and were graded according to WHO toxicity criteria.

Results

Patient characteristics

Seventy-five patients, median age 62 years (range 40–81 years), who developed anemia during chemotherapy were included in this study. Seventeen of these patients (27.7%) were receiving adjuvant chemotherapy, mostly for primary breast cancer; 58 patients (77.3%) were receiving a variety of chemotherapy regimens for advanced cancers, mainly metastatic breast cancer and renal cell carcinoma. Eleven patients (14.7%) were on regimens containing anthracycline antibiotics, nine (12%) on taxanes and three (4%) on a combination of the two. Platinum derivatives were administered to five patients (6.7%). Darbepoetin α treatment was started in 17 patients on adjuvant therapy and the following numbers on palliative treatment: 31 on first line, 14 on second line, nine on third line, two on fourth line and two on fifth line. Granulocyte colony stimulating factor (G-CSF) support was necessary in 19 of 75 patients (14 responders and five non-responders). Only one patient (1.3%) had previously received erythropoietic therapy, and this patient showed a response both to darbepoetin α and to the earlier treatment.

Efficacy

All 75 patients were evaluable for treatment response. Treatment with darbepoetin α produced a response in 72% (54 of 75) of patients, of whom 16.9% (nine of 54) patients required dose escalation to 300 μg. Of the total 75 patients, the dose was escalated in 40% (30 of 75) of patients, with 28% (21 of 75) of patients failing to respond even at the higher dose. A total of 32 blood transfusions were necessary in 17.3% (13 of 75) of patients during the study. However, only two of these transfusions were required in a single patient in the responder group, while the remainder were received by non-responders. Median Hb levels increased from 9.8 g/dl at baseline to 10.7 g/dl at week 4, 11.0 g/dl at week 8 and 11.4 g/dl at the end of follow-up (Table 1). The corresponding numbers for responders and non-responders are also shown in Table 1. The responder who required a transfusion of two erythrocyte concentrates during the first 4 weeks of treatment showed a further increase in Hb levels of 1 g/dl after dose escalation and so was deemed to be a responder.

Patients were also analyzed according to baseline Hb < 10 g/dl or Hb ≥ 10 g/dl. In patients with a baseline Hb < 10 g/dl ($n = 43$), response rate was 74.4% (32 patients), with dose escalation necessary in 14 (37.2%) patients and blood transfusion required in eight (18.6%)

Table 1 Median Hb concentrations following treatment with darbepoetin α

Group	*n*	Median Hb [g/dl (range)]			
		Baseline	Week 4	Week 8	Follow-up
Overall	75	9.8 (8.1–10.9)	10.7 (8.1–14.1)	11.0 (7.2–13.8)	11.4 (10–13)
Responders	54	9.8 (8.4–10.9)	11.2 (8.6–14.1)	11.5 (10.2–13.8)	11.4 (10.2–13)
Non-responders	21	9.9 (8.1–10.9)	9.7 (8.1–10.9)	9.8 (7.2–11.2)	NA

NA = not applicable, as non-responders not evaluated after week 8.

Table 2 Median Hb concentrations following treatment with darbepoetin α in patients according to baseline Hb level

Baseline Hb (g/dl)	*n*	Median Hb [g/dl (range)]			
		Baseline	Week 4	Week 8	Follow-up
<10	43	9.4 (8.1–9.9)	10.6 (8.1–14.1)	10.7 (7.1–13.8)	11.3 (10–13)
≥ 10	32	10.4 (10–10.9)	11.4 (9.2–13)	11.2 (8.1–13.5)	11.5 (10.5–12.7)

patients. Of the total 32 blood transfusions administered during the study, 20 (62.5%) were given to patients in this group. Hb levels in these patients increased from a median of 9.4 g/dl at baseline to 10.6 g/dl at week 4, 10.7 g/dl at week 8 and reached 11.3 g/dl at the end of follow-up (Table 2).

In the patients with a baseline Hb ≥ 10 g/dl ($n = 32$), response rate was 68.8% (22 patients), with dose escalation necessary in 14 (43.8%) patients and blood transfusion required in five (15.6%) patients. Of the overall 32 blood transfusions administered during the study, 12 (37.5%) were given to patients in this group. Hb levels increased from a median of 10.4 g/dl at baseline to 11.4 g/dl at week 4, 11.2 g/dl at week 8 and 11.5 g/dl at the end of follow-up (Table 2).

Fatigue

In all patient groups except the non-responders, a reduction in the number of patients reporting grade 2 or 3 fatigue was observed with darbepoetin α treatment. Overall, at the initiation of therapy, 70 of 75 (93.3%) patients reported grade 2 or 3 fatigue, decreasing to 26 of 68 (38.3%) patients at the end of follow-up (Table 3). Corresponding numbers for the subgroups are also shown in Table 3.

Tolerability

In the patients evaluated in this study, many of whom were receiving multiple regimens of chemo, immuno and endocrine therapies, darbepoetin α was well tolerated, and no local injection site reactions were noted. In addition, only one case of deep vein thrombosis was observed—an event which could be regarded as a systemic side-effect of treatment. No other systemic adverse effects were reported.

Table 3 Percentage of patients with grade 2 or 3 fatigue before or after darbepoetin α treatment

Group	*n*	Grade 2 or 3 fatigue (% patients)	
		Baseline	Follow-up
Overall	75	93.3	38.3
Responders	54	92.5	12.8
Non-responders	21	100	95.2
Hb <10 g/dl	43	95.4	42.1
Hb ≥ 10 g/dl	32	90.6	33.3
Adjuvant	17	88.2	40.0
Palliative	58	94.9	37.7

Discussion

The results presented demonstrate that darbepoetin α is an effective and well-tolerated treatment for patients receiving anti-cancer chemotherapy who develop anemia. Darbepoetin α elicited a response rate of 72%, achieved with dose escalation to 300 μg in only 16.7% of responders. This is in agreement with the results of previous studies that have shown darbepoetin α to be an effective treatment option in cancer patients [11]. Patients also benefited markedly in terms of control of chemotherapy treatment-related symptoms, reinforcing the results of other groups [12]. Our data show that while at the start of treatment 93.3% of all patients were suffering from profound symptoms of anemia, this dropped substantially to 26% at the end of follow-up, underlining darbepoetin α's efficacy in the treatment of anemia.

In the light of ongoing world-wide pharmacoeconomics discussions, we evaluated whether there is a difference in response rates in patients receiving therapy with baseline Hb < 10 g/dl or Hb ≥ 10 g/dl. As demonstrated in our study, patients on chemotherapy with Hb < 10 g/dl showed a higher response rate with darbepoetin α than the group with Hb ≥ 10 g/dl. These results were surprising and are contrary to those presented by other groups [13]. The reasons for these differences should be further investigated.

There are a number of possible explanations for these results. First, in the current study, the relatively small

number of patients could have biased the results. Another possible explanation is that with response to chemotherapy, bone marrow infiltration by malignant cells could have been reduced, thereby increasing normal bone marrow function, again influencing the results. As bone marrow biopsies were not routinely performed in this study, such a bias cannot be excluded. It is also reasonable to assume that patients with metastatic disease and low Hb levels have more advanced disease than patients with higher Hb levels. If these patients show a response to chemotherapy, the underlying reasons for tumor-associated anemia as described above (e.g. a relative erythropoietin deficiency) may change, leading to a higher response rate to erythropoietic treatment.

A potential explanation we were able to rule out was the dependence of response on the bone marrow toxicity of the different anti-cancer therapies. We were able to show that more patients in the Hb < 10 g/dl group required G-CSF support than in the Hb ≥ 10 g/dl group (13 versus six patients, respectively). The number of blood transfusions in the two groups showed the expected pattern. In those patients with a lower baseline Hb level, more blood transfusions were required than in those with higher baseline Hb levels.

An important factor that has been shown in other studies and is again highlighted here is the fact that therapy with darbepoetin α is virtually side-effect free, something of special importance in cancer patients.

In conclusion, this study shows darbepoetin α to be effective and well tolerated in patients with chemotherapy-associated anemia, both in terms of increased Hb levels and improved quality of life. The novel molecular design renders it an attractive alternative to the other currently available erythropoietins.

The results showing a better response in patients with lower Hb levels are open to question, and this phenomenon should be further evaluated in larger phase II and III trials. Nonetheless, it is necessary to increase the use of erythropoietic treatment, both in the adjuvant and palliative setting in cancer patients, in order to improve their quality of life. However, in the light of pharmacoeconomic pressures, it will be necessary to identify patients who will profit most from erythropoietic treatment as early as possible.

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