Every-2-Week Darbepoetin Alfa Is Comparable to rHuEPO in Treating Chemotherapy-Induced Anemia

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The safety and efficacy of darbepoetin alfa (Aranesp) at 3.0 µg/kg administered every 2 weeks and recombinant human erythropoietin (rHuEPO) given as 40,000 U weekly or 150 U/kg three times weekly were evaluated by

It is increasingly recognized that fatigue in cancer patients—primarily caused by anemia resulting from chemotherapy or other aspects of the disease process—is associated with debilitating effects on quality of life and functioning.[1,2] Surveys performed by the multidisciplinary Fatigue Coalition indicated that fatigue was the primary complaint in one-quarter of patients after chemotherapy (ahead of nausea at 13%), and that 61% of cancer patients felt their lives were affected more by fatigue than by pain associated with their disease.[3] Cancer-related anemia has traditionally been treated with red blood cell transfusions; however, concerns over the safety of the blood supply and potential adverse effects of transfusions in cancer patients have led to the development of erythropoietic agents as a safer alternative for increasing hemoglobin levels in these patients.

Improved understanding of the deleterious effects of anemia and the availability of recombinant human erythropoietin (rHuEPO) have led to a great deal of active investigation of the benefits of erythropoietic therapy in patients with chemotherapy-induced anemia. Most recently, with the development of darbepoetin alfa (Aranesp) and research into once-weekly therapy for rHuEPO (rHuEPO is licensed for this indication at a dose of 150 U/kg three times weekly), considerable efforts have been focused on reducing the need for frequent injections. For patients with cancer (and their caregivers), each injection can be a reminder of their disease; for those for whom self-injection is not an option, each clinic visit is an interruption of normal life and may create significant logistic challenges relating to transportation, child care, or work. For clinic staff, administrative work and time are increased. A recent study of patients with chronic renal insufficiency reported that, on average, these patients spent 90 minutes traveling to/from the clinic and waiting to be seen, and 49% relied on someone else for transportation.[4] It is likely that these findings would also be true for cancer patients. Thus, reducing the dosing frequency of erythropoietic agents given to patients with chemotherapy-induced anemia would be beneficial.

Weekly administration was shown to be effective in patients with chemotherapy-induced anemia in a large, open-label, uncontrolled study using a single subcutaneous injection of 40,000 U of rHuEPO (this dose could be increased to 60,000 U if a 1.0-g/dL hemoglobin increase had not been observed after 4 weeks).[5] With this regimen, 68% of patients achieved a hematopoietic response (a hemoglobin concentration ≥ 12.0 g/dL and/or an increase of ≥ 2.0 g/dL without preceding transfusions) by the end of the 16-week treatment period, which is comparable to the response observed with three-times-weekly dosing.[5,6] However, this dose represents an increase of approximately 33% over the more routinely studied dose and schedule of 150 U/kg three times weekly[7-9] or the dosing regimen of 10,000 U of rHuEPO three times weekly, which has also been reported.[6] Based on these results, weekly dosing is now accepted in clinical practice in the United States, although not in other regions.

Darbepoetin alfa, a unique recombinant protein produced by modifying the gene for erythropoietin, is a more potent erythropoietic agent. Darbepoetin alfa stimulates erythropoiesis through the same mechanism as endogenous erythropoietin and rHuEPO.[10] However, darbepoetin alfa was engineered to have additional carbohydrate side chains (five total N-linked glycosylation side chains with up to 22 sialic acid residues) compared with rHuEPO (three total N-linked glycosylation side chains with up to 14 sialic acid residues). Sialic acid content is directly correlated with in vivo activity, possibly due to the degree of clearance by the asialoglycoprotein receptor in the liver[11]; the increased sialic acid content of darbepoetin alfa reduces its clearance and results in an extended serum residence time.[12]
Darbepoetin alfa was initially approved for use in patients with renal failure. Pharmacokinetic studies in this indication showed that darbepoetin alfa had an approximately threefold longer terminal half-life than rHuEPO (25.3 vs 8.5 hours). An extensive clinical development program has evaluated the pharmacokinetics, efficacy, and safety of various dose and schedule combinations of darbepoetin alfa during cancer chemotherapy. Phase I and II studies explored dosing intervals ranging from weekly to every-4-week administration. These included an every-2-week dosing schedule, which appeared to be effective in alleviating anemia in patients with solid tumors receiving chemotherapy.

Comparisons between rHuEPO studies (or between rHuEPO studies and darbepoetin alfa studies) may be confounded due to differences in factors such as study design, populations, treatment duration, analytical methodologies, response definitions, or the use of analysis sets other than the intent-to-treat set. To obtain a more precise estimate of the effect of darbepoetin alfa administered at 3.0 µg/kg every 2 weeks, and to evaluate the relative effect of this dose and schedule compared with rHuEPO, data from three clinical studies of similar design have been pooled. Unlike comparisons with historical literature, this approach eliminates differences in analytical methodologies, treatment duration, and other potentially confounding factors. This report describes the results of this combined analysis.

**Patients and Methods**

**Study Population**
The population evaluated and the design of each of the three studies included in these analyses were similar. All study centers were in the United States. Eligible patients were men or women ≥ 18 years of age who were receiving multicycle chemotherapy and had anemia (hemoglobin concentration ≤ 11.0 g/dL). Patients were required to have adequate renal and hepatic function and could not be iron deficient (defined as both transferrin saturation < 15% and ferritin < 10 ng/mL). Patients with known cardiac disease or hematologic disorders that could cause anemia were not eligible. Each center’s independent ethics committee or central ethics committee approved the protocol, and patients provided written informed consent before any study-specific procedures were done.

The principal difference between the eligibility criteria in the three studies was tumor type (solid tumors were specified in two studies and nonmyeloid malignancies in the third). However, as most patients in both groups had solid tumors, and no difference has been noted between the effect of erythropoietic agents on patients with hematologic malignancies and those with solid tumors, this is not thought to have an impact on the validity of the conclusions from this pooled analysis.

**Study Design**
All three studies were multicenter and open-label in design. The dose of rHuEPO could be increased in both studies contributing rHuEPO data (at week 8 or week 6), and the dose of darbepoetin alfa could be increased in one of the two studies contributing darbepoetin alfa data (at week 7). The requirement for withholding drug due to reaching specified maximum hemoglobin concentrations (14 g/dL for women, 15 g/dL for men) was the same in all studies. Red blood cell transfusions were recommended if hemoglobin decreased to ≤ 8.0 g/dL or patients had symptoms.

**Statistical Analysis**
Efficacy analyses were conducted on the intent-to-treat analysis set (ie, all patients who received at least one dose of study drug). All analyses were descriptive. Baseline demographic and clinical characteristics were summarized by the mean (standard deviation) for continuous measures and number (percentage) for categorical measures (Table 2). The proportion of patients achieving a hematopoietic response during the treatment phase was estimated by subtracting the Kaplan-Meier estimate of the survivor function from 1; 95% confidence intervals (CI) were calculated by using Greenwood’s estimate of the variance (Figure 1). Time to hematopoietic response was summarized by the Kaplan-Meier estimate of the median.

Hemoglobin concentration over time was summarized by plotting the mean hemoglobin by study week (95% CI were plotted at weeks 1, 5, 9, and 13); patients missing a hemoglobin value at a particular week or who had a red blood cell transfusion within 28 days of a particular week were excluded from the mean at that week (Figure 2). In addition, the change in hemoglobin concentration after 4 weeks and at the end of treatment was summarized by the mean (95% CI); hemoglobin values that were missing or that occurred within 28 days of a transfusion were replaced with the last available value that was not within 28 days of a transfusion (Table 3). The proportion of patients with a transfusion was estimated with a crude proportion and an exact 95% CI (Table 4).
Results

Patient Demographics and Disposition
A total of 375 patients were included in this analysis. 260 darbepoetin alfa and 115 rHuEPO (Table 2). Baseline demographic characteristics were generally similar in the two groups; the mean baseline hemoglobin concentration was slightly lower for the rHuEPO group than the darbepoetin alfa group (9.89 vs 10.23 g/dL, respectively), and the proportion of patients with stage IV disease slightly higher in the rHuEPO group than the darbepoetin alfa group (68% vs 56%, respectively). Demographic and baseline characteristics were similar across the three individual studies, supporting the pooling of the data (data not shown). Patients with hematologic malignancies were enrolled in only one study (the study that allowed hematologic [nonmyeloid] tumors in addition to solid tumors).

Efficacy End Points
The effect on hemoglobin concentration during the studies was similar in the combined rHuEPO and darbepoetin alfa groups. Hematopoietic response (a ≥ 2.0-g/dL hemoglobin increase or hemoglobin value ≥ 12.0 g/dL in the absence of transfusions) was similar in the two groups, with 71% (95% CI = 65%-78%) of patients in the darbepoetin alfa group and 71% (95% CI = 61%-81%) in the rHuEPO group meeting this definition of response (Figure 1). The median duration of time required to achieve a hematopoietic response was 9 weeks (95% CI = 8-11 weeks) for darbepoetin alfa and 9 weeks (95% CI = 7-11 weeks) for rHuEPO.

The mean change in hemoglobin concentration was calculated for all patients after 4 weeks and after 12 weeks of treatment. The results were comparable for rHuEPO and darbepoetin alfa in each case (Table 3). The mean change was 0.38 g/dL (95% CI = 0.24 -0.52 g/dL) and 0.46 g/dL (95% CI = 0.20-0.72 g/dL) after 4 weeks, and was 1.48 g/dL (95% CI = 1.28-1.68 g/dL) and 1.31 g/dL (95% CI = 0.97-1.64 g/dL) after 12 weeks for darbepoetin alfa and rHuEPO, respectively. The rise in hemoglobin concentration over time for the two groups followed a nearly superimposable course (Figure 2).

Reports have indicated that red blood cell transfusion requirements may not be affected until after 4 weeks of rHuEPO treatment,[8,9,23] so we evaluated transfusions from week 5 to the end of treatment (Table 4). Seven percent (95% CI = 4%-11%) of darbepoetin alfa patients and 14% of rHuEPO patients (95% CI = 8%-22%) required a transfusion during this period.

Safety
Adverse events were comparable between the darbepoetin alfa and rHuEPO patients in the completed studies. The most frequently reported events were nausea, fatigue, vomiting, and diarrhea, consistent with a population of patients undergoing chemotherapy. Interim data from the ongoing study suggested no important deviations from previous reports establishing the safety profile of darbepoetin alfa. Analysis of serum samples collected at various intervals has revealed no evidence of neutralizing antibodies to darbepoetin alfa.

Discussion
Patients undergoing cancer chemotherapy are faced with frequently overwhelming challenges in managing the debilitating effects of chemotherapy, as well as the physical and psychological aspects of their disease. Among the factors affecting the quality of life for these patients, fatigue resulting from chemotherapy-induced anemia has been demonstrated to have a significant negative impact.[1-3] Even patients who are only mildly or moderately anemic have been shown to benefit from treatment with rHuEPO in terms of improved energy and activity levels and overall quality of life.[7] However, the three-times-weekly dosing schedule indicated for rHuEPO can be burdensome to patients who may require a clinic visit for each injection. A weekly dosing schedule, which is commonly used in the United States, though not in other regions, offers some improvement, but further decreases in dosing frequency would benefit patients, caregivers, and health-care providers alike.

Because of its longer serum residence time, darbepoetin alfa has allowed extended dosing in the renal disease setting, and has now been approved for use in patients with chemotherapy-induced anemia. Presented here are data from three studies undertaken in the clinical development of darbepoetin alfa for this indication. The data were combined to obtain a more robust analysis with a larger number of patients. Because the three studies enrolled a broadly similar population (ie, one representative of the currently approved label for darbepoetin alfa), were all conducted in the United States where medical practice is relatively consistent for this patient population, and had similar treatment durations/design characteristics, it was considered appropriate to combine the data from these studies. Minor differences in eligibility criteria are not expected to have had an effect on the
conclusions from the analysis. One study enrolled patients with nonmyeloid malignancies while the others specified solid tumors; however, results from the individual studies did not suggest a difference in response, nor does the literature suggest a differential response between patients with solid tumors or those with hematologic malignancies.\cite{5,6} One of the studies allowed a dose increase for inadequate early hemoglobin increase in patients receiving darbepoetin alfa, whereas dose increases were permitted in all rHuEPO groups; any effect on the results due to this difference would be to rHuEPO’s advantage.

The combined analysis included a total of 375 patients with chemotherapy-induced anemia. The dose of 3.0 µg/kg darbepoetin alfa given every 2 weeks produced increases in hemoglobin concentration similar in both magnitude and time course to those obtained with rHuEPO. Hematopoietic response, which has become a commonly accepted measure of hemoglobin increase as reported in the literature,\cite{5,6} was achieved by 71% of darbepoetin alfa patients and 71% of rHuEPO patients, consistent with other reports for rHuEPO.\cite{5,6} In terms of clinical consequences of the increase in hemoglobin, only 7% (95% CI = 4%-11%) of darbepoetin alfa patients received red blood cell transfusions during the second and third months of treatment (ie, from week 5 onward), compared with 14% (95% CI = 8%-22%) of rHuEPO patients.

In a comprehensive clinical development program in cancer patients with chemotherapy-induced anemia, darbepoetin alfa demonstrated a tolerable level of adverse events:\cite{14-21} few serious, treatment-related events, no unmanageable rapid increases in hemoglobin, and no confirmed neutralizing antibodies.\cite{14-21} The results from the three studies analyzed here are consistent with this safety profile.

The ability to restore normal hemoglobin levels with one dose of darbepoetin alfa every 2 weeks represents an important advance for patients undergoing chemotherapy. In all of the analyses performed, the impact of darbepoetin alfa at 3.0 µg/kg every 2 weeks was similar to that observed with rHuEPO either after 12 weeks of treatment or evaluated over the treatment time course. The early and sustained erythropoietic effect obtained with darbepoetin alfa given at 3.0 µg/kg every 2 weeks permits effective control of anemia with minimal disruption to patients’ daily lives.

References:
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