Darbepoetin Alfa Administered Every Three Weeks Is Effective for the Treatment of Chemotherapy-Induced Anemia

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Key Words. Chemotherapy • Anemia • Darbepoetin alfa • Hemoglobin • Cancer

ABSTRACT
Patients with cancer receiving chemotherapy often have chemotherapy-induced anemia (CIA) and reduced quality of life. Darbepoetin alfa can effectively treat CIA when administered at an extended dosing interval of once every 3 weeks (Q3W). Darbepoetin alfa administered Q3W may allow synchronization of darbepoetin alfa therapy with chemotherapy administered Q3W. This multicenter, open-label, 16-week study evaluated the effectiveness and safety of darbepoetin alfa administered as a fixed dose (300 μg) Q3W in patients with CIA. Eligible patients (≥18 years) were anemic (hemoglobin <11 g/dl), had a nonmyeloid malignancy, and were receiving multicycle chemotherapy. This analysis includes 1,493 patients who received at least one dose of darbepoetin alfa. The effect of baseline hemoglobin (<10 or ≥10 g/dl) on clinical outcomes was evaluated. Patients in the ≥10-g/dl stratum achieved the hemoglobin target range (11–13 g/dl) in less time than patients in the <10-g/dl stratum (3 weeks vs. 9 weeks). More patients in the ≥10-g/dl stratum achieved the hemoglobin target range (87% vs. 66%); however, similar proportions of patients in both strata maintained hemoglobin within the target range (73% vs. 71%). Fewer patients in the ≥10-g/dl stratum received RBC transfusions from week 5 to the end of the study (12% vs. 28%). Over 50% of patients in both strata reported clinically significant improvements (≥3-point increase) in Functional Assessment of Cancer Therapy–Fatigue score. Twenty-eight percent of patients reported serious adverse events; 3% of all patients had a venous or arterial thrombotic event. This study demonstrates that darbepoetin alfa Q3W is well tolerated and effective for treating CIA. The Oncologist 2006;11:409–417

INTRODUCTION
Chemotherapy-induced anemia (CIA) is common in patients with cancer [1] and can be treated with the erythropoiesis-stimulating agents darbepoetin alfa and epoetin alfa, which increase hemoglobin levels, reduce the requirement for RBC transfusions, and improve patients’ quality of life [2, 3]. Initially, darbepoetin alfa was evaluated using a once per week dosing schedule [3–6]. A broad range of experience has indicated that dosing of darbepoetin alfa at less frequent dosing intervals, such as once every 3 weeks (Q3W), is also effective [7–11]. Darbepoetin alfa can be administered Q3W either synchronously (the same day as...
chemotherapy) or asynchronously with chemotherapy with comparable efficacy and safety [7]. Thus, synchronous administration of darbepoetin alfa Q3W and chemotherapy Q3W potentially offers added convenience to patients and their caregivers.

In a dose-finding, placebo-controlled study of darbepoetin alfa administered Q3W, weight-based doses of 4.5–15.0 μg/kg Q3W effectively produced a lower rate of transfusion and higher percentage of patients with a hemoglobin response (i.e., an increase in hemoglobin of ≥2 g/dl from baseline in the absence of an RBC transfusion in the previous 28 days) [8]. In that trial, the minimally effective dose was 4.5 μg/kg, with some evidence of a better response observed at 6.75 μg/kg; doses above 6.75 μg/kg yielded only small incremental improvements in these endpoints. Fixed dosing of darbepoetin alfa in patients with CIA has been evaluated in clinical trials and appears to result in comparable hemoglobin, transfusion, and safety outcomes [10, 12]. Further, fixed dosing of darbepoetin alfa is common in the clinic as indicated by recent studies of current practice patterns [13, 14].

The objective of this multicenter, open-label, 16-week study was to evaluate the safety and effectiveness of darbepoetin alfa administered at a fixed dose (300 μg) Q3W (roughly equivalent to a weight-based dose of 4.5 μg/kg for an average patient), with a dose increase to 500 μg, if required, in patients with cancer and CIA. We assessed the effectiveness of Q3W darbepoetin alfa in achieving and maintaining hemoglobin concentrations within the range recommended by current evidence-based guidelines (11–13 g/dl) [15–17], lowering the incidence of RBC transfusion, and improving quality of life (assessed using the Functional Assessment of Cancer Therapy–Fatigue [FACT-F] scale). Previous studies have shown that patients treated with erythropoietic agents before their hemoglobin concentration fell below 10 g/dl demonstrate greater clinical improvements than patients whose hemoglobin concentration was allowed to drop below 10 g/dl [18]. Therefore, we also evaluated the effects of baseline hemoglobin concentration (<10 and ≥10 g/dl) on clinical outcomes.

**Patients and Methods**

**Patient Population**

The study protocol was approved by the Institutional Review Board (IRB) of each of the participating sites, and all patients provided written, IRB-approved informed consent before initiation of study-related procedures.

Eligible patients were at least 18 years old, had a non-myeloid malignancy for which they were receiving at least eight additional weeks of chemotherapy, and were anemic (hemoglobin <11 g/dl) as a result of cancer and chemotherapy. Patients were excluded if they had inadequate renal and liver function, acute myelogenous leukemia, chronic myelogenous leukemia, a myelodysplastic syndrome, unstable cardiac disease, active bleeding, active systemic or chronic infection, severe active chronic inflammatory disease, any other hematologic disorder associated with anemia, uncontrolled hypertension, iron or other nutritional deficiency, HIV, history of pure red-cell aplasia, or history of positive antibody response to any erythropoietic agent. Patients were also excluded if they had previously enrolled in the study, had planned elective surgery during the study period, had an RBC transfusion within 2 weeks of screening, had erythropoietic therapy within 4 weeks of screening, had drugs or devices not approved by the U.S. Food and Drug Administration for any indication within 30 days of screening, were pregnant or lactating, or had a known hypersensitivity to mammalian cell–derived products.

**Study Design**

This was a multicenter, 16-week, single-arm, open-label study of darbepoetin alfa administered at a fixed dose of 300 μg Q3W to cancer patients with CIA. Patients received s.c. injections of darbepoetin alfa for ≤13 weeks, with a follow-up visit at week 16 on three weeks after their last dose. At any point during the study, the darbepoetin alfa dose was reduced by 25% if the hemoglobin concentration increased by more than 1 g/dl in a 2-week period. Darbepoetin alfa was withheld if the hemoglobin exceeded 13 g/dl but was reinitiated at a dose approximating 25% below the previous dose if hemoglobin fell to 12 g/dl. If after 6 weeks hemoglobin concentrations remained below 10 g/dl and the increase from baseline was less than 1 g/dl, the darbepoetin alfa dose was increased to 500 μg Q3W. Physician discretion regarding dose increases may have been exercised if the hemoglobin concentration was above 10 g/dl but below the baseline hemoglobin concentration. The dose was not increased if the hemoglobin concentration was within the hemoglobin target range (11–13 g/dl). Hemoglobin concentrations were measured weekly (before dosing with darbepoetin alfa during dosing weeks) and at the end of the study.

Patients answered 13 questions related to the FACT-F scale [19] at baseline, during each clinic visit (every 3 weeks), and at the end of the study.

**Efficacy End Points**

The objective of the study was to assess the effectiveness of darbepoetin alfa at a dose of 300 μg Q3W in achieving...
a hemoglobin concentration ≥11 g/dl and maintaining the hemoglobin concentration in the range of 11–13 g/dl, as recommended by the current evidence-based guidelines [15–17]. The primary endpoints were the percentage of patients who achieved the target hemoglobin concentration (≥11 g/dl in the absence of an RBC transfusion within the preceding 28 days) and the percentage of these patients with a mean hemoglobin concentration of 11–13 g/dl after achieving the target concentration. Secondary endpoints included the percentage of patients who had a hematopoietic response (either a 2-g/dl increase in hemoglobin from baseline or hemoglobin ≥12 g/dl in the absence of an RBC transfusion within the previous 28 days), the percentage of patients that required RBC transfusions, and the change in FACT-F score from baseline.

**Safety End Points**
Only data on serious adverse events were collected. Serious adverse events and serious treatment-related adverse events that occurred on or after the first dose of darbepoetin alfa and on or before the end of the study were summarized according to the affected body system and by the preferred term within the body system using the Medical Dictionary for Regulatory Activities (MedDRA, version 6.1). Patients were assessed for the presence of antibodies to darbepoetin alfa at the beginning and end of the study.

**Statistical Analysis**
This analysis included all patients who were correctly consented and who received at least one dose of darbepoetin alfa. Patients were stratified according to their baseline hemoglobin concentration of <10 g/dl and ≥10 g/dl. Baseline demographics and clinical characteristics were summarized by number and percentage for categorical variables and mean (standard deviation [SD]) for continuous variables. Hemoglobin-based end points were calculated using two approaches: the last value carried forward (LVCF) approach (missing hemoglobin values or values within 28 days of an RBC transfusion were imputed using the previous value) and an available data approach (not imputation). The number and percentage of patients who achieved the target hemoglobin concentration, who had a hematopoietic response by the end of the study and who received at least one RBC transfusion were calculated (with a 95% confidence interval [CI]). Time to target hemoglobin response was summarized using the Kaplan-Meier (KM) method.

The number and percentage of patients who had a ≥1-g/dl rise in hemoglobin during the first 4 weeks of treatment were also calculated to explore if this end point was a clinically meaningful predictor of response. The sensitivity and specificity of a ≥1-g/dl rise in hemoglobin during the first 4 weeks to the incidence of RBC transfusion and the proportion of patients who achieved the target hemoglobin were determined. Sensitivity was defined as the proportion of patients with a ≥1-g/dl increase in hemoglobin that also had a positive clinical response (either achieved the target hemoglobin or did not receive an RBC transfusion). Specificity was defined as the proportion of patients without a ≥1-g/dl increase in hemoglobin that also had a negative clinical response (either did not achieve the target hemoglobin or did receive an RBC transfusion).

FACT-F scores were calculated using available data from patients who received at least one dose of darbepoetin alfa and who completed both the baseline and one subsequent FACT-F questionnaire.

All statistical analyses were done using SAS version 8.2.

**RESULTS**

**Patient Demographics and Baseline Characteristics**
A total of 1,501 patients from 230 sites was enrolled in this study. Of these, 1,493 patients were properly consented, received at least one dose of darbepoetin alfa, and were included in the primary analysis set. Patient disposition is shown in Figure 1. The reasons for discontinuation of darbepoetin therapy were similar for patients in both hemoglobin strata.

The demographic and baseline clinical characteristics of the two baseline hemoglobin strata were similar except that there were 8% more women in the ≥10-g/dl stratum, and 8% more patients had stage IV disease in the <10-g/dl stratum (Table 1). Nearly all (96%) of the patients had received at least one cycle of prior chemotherapy, and 47% had received at least three cycles of prior chemotherapy. Thirty-three percent of patients in both groups received platinum-based chemotherapy during the study. In addition, 10% of the subjects had received prior radiation therapy.

**Darbepoetin Alfa Dosing**
Darbepoetin alfa use was similar for patients in the two hemoglobin strata (Table 2). When compared with patients in the <10-g/dl stratum, 8% more patients in the ≥10-g/dl stratum had at least one dose of darbepoetin withheld, 4% more had a dose decrease, and 8% less had a dose increase, possibly because of higher baseline hemoglobin values. Eight percent of patients in both strata received at least one extra dose of darbepoetin alfa. Despite the dose adjustments, the average weekly dose administered to the total study population was 105.4 μg.
Efficacy End Points

**All Patients**

In this study of darbepoetin alfa administered at a dose of 300 μg Q3W, 79% of patients achieved the target hemoglobin level by the end of the study (Table 3). The KM estimated median time to achieve the target hemoglobin was 4 weeks, and 73% of patients maintained their hemoglobin levels within the target hemoglobin range after achieving it (Table 3). Eighteen percent of patients required RBC transfusions from week 5 to the end of the study, and the incidence of RBC transfusion was reduced from 12% in month 1 to 3% by month 4. A clinically significant improvement (≥3-point change [20]) in FACT-F score (Table 3) was seen in 55% of patients by the end of the study.

**Effect of Baseline Hemoglobin**

The mean hemoglobin concentration (using available data) of patients in the ≥10-g/dl stratum was within the target range at week 7 (Fig. 2). In contrast, the mean hemoglobin level of patients with baseline hemoglobin <10 g/dl was lower than 11 g/dl at week 7 (Fig. 2). At week 16, the mean hemoglobin concentration for patients in both strata was within the target range (Fig. 2). Patients in the ≥10-g/dl stratum achieved the target hemoglobin concentration in a median time of 3 weeks (Fig. 3), whereas patients in the <10-g/dl stratum had a median time to target of 9 weeks. The percentage of patients who achieved the target hemoglobin level was approximately 20% greater for patients with baseline hemoglobin ≥10 g/dl (Table 3, Fig. 3). However, once target was achieved, similar percentages of patients in both groups (71% and 73% in the <10-g/dl and ≥10-g/dl strata) maintained their hemoglobin levels within the target range.
### Table 1. Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Baseline hemoglobin &lt;10 g/dl (n = 462)</th>
<th>Baseline hemoglobin ≥10 g/dl (n = 918)</th>
<th>All patients (n = 1,493)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>258 (56)</td>
<td>583 (64)</td>
<td>906 (61)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>360 (78)</td>
<td>721 (79)</td>
<td>1,178 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>66 (14)</td>
<td>115 (13)</td>
<td>192 (13)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20 (4)</td>
<td>56 (6)</td>
<td>80 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (3)</td>
<td>26 (3)</td>
<td>43 (3)</td>
</tr>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>62.9 (13.0)</td>
<td>62.5 (13.5)</td>
<td>62.6 (31.3)</td>
</tr>
<tr>
<td><strong>Geriatric (≥65 years old) age group, n (%)</strong></td>
<td>224 (48)</td>
<td>453 (49)</td>
<td>724 (48)</td>
</tr>
<tr>
<td><strong>Primary tumor type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>124 (27)</td>
<td>290 (32)</td>
<td>439 (29)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>100 (22)</td>
<td>229 (25)</td>
<td>360 (24)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>77 (17)</td>
<td>114 (12)</td>
<td>216 (14)</td>
</tr>
<tr>
<td>Lung</td>
<td>58 (13)</td>
<td>103 (11)</td>
<td>171 (11)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>48 (10)</td>
<td>74 (8)</td>
<td>135 (9)</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>23 (5)</td>
<td>39 (4)</td>
<td>68 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>32 (7)</td>
<td>69 (8)</td>
<td>104 (7)</td>
</tr>
<tr>
<td><strong>Disease stage, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (3)</td>
<td>43 (5)</td>
<td>60 (4)</td>
</tr>
<tr>
<td>II</td>
<td>67 (15)</td>
<td>149 (16)</td>
<td>232 (16)</td>
</tr>
<tr>
<td>III</td>
<td>86 (19)</td>
<td>227 (25)</td>
<td>339 (23)</td>
</tr>
<tr>
<td>IV</td>
<td>243 (53)</td>
<td>409 (45)</td>
<td>706 (47)</td>
</tr>
<tr>
<td><strong>Patients receiving platinum-based chemotherapy, n (%)</strong></td>
<td>151 (33)</td>
<td>307 (33)</td>
<td>499 (33)</td>
</tr>
<tr>
<td><strong>Baseline hemoglobin, g/dl, mean (SD)</strong></td>
<td>9.3 (0.6)</td>
<td>10.5 (0.3)</td>
<td>10.1 (0.7)</td>
</tr>
</tbody>
</table>

*aSixty-six patients (4%) had a missing hemoglobin value at baseline, and 47 patients (3%) had baseline hemoglobin levels measured within 28 days of an RBC transfusion.*

*bMay include acute and chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, Hodgkin’s disease, multiple myeloma, and other lymphoma.*

*cMay include bone sarcoma, soft tissue sarcoma, melanoma, head and neck cancer, and other tumors.*

dExcludes small cell lung cancer patients.

Abbreviation: SD, standard deviation.

### Table 2. Darbepoetin alfa dosing

<table>
<thead>
<tr>
<th></th>
<th>Baseline hemoglobin &lt;10 g/dl (n = 462)</th>
<th>Baseline hemoglobin ≥10 g/dl (n = 918)</th>
<th>All patients (n = 1,493)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of weeks of dosing, mean (95% CI)</strong></td>
<td>10.9 (10.5–11.2)</td>
<td>11.4 (11.2–11.6)</td>
<td>11.2 (11.0–11.3)</td>
</tr>
<tr>
<td><strong>Average weekly dose administered, μg/week, mean (95% CI)</strong></td>
<td>109.8 (107.4–112.1)</td>
<td>102.9 (101.1–104.6)</td>
<td>105.4 (104.0–106.7)</td>
</tr>
<tr>
<td><strong>Average Q3W dose administered, μg/dose, mean (95% CI)</strong></td>
<td>331.1 (325.8–336.3)</td>
<td>319.0 (315.5–322.6)</td>
<td>323.6 (320.8–326.4)</td>
</tr>
<tr>
<td><strong>No. of doses received, mean (95% CI)</strong></td>
<td>4.2 (4.1–4.4)</td>
<td>4.3 (4.2–4.3)</td>
<td>4.2 (4.2–4.3)</td>
</tr>
<tr>
<td><strong>No. of patients with at least one dose withheld (%)</strong></td>
<td>52 (11)</td>
<td>175 (19)</td>
<td>242 (16)</td>
</tr>
<tr>
<td><strong>No. of patients who had a dose increase (%)</strong></td>
<td>207 (45)</td>
<td>336 (37)</td>
<td>585 (39)</td>
</tr>
<tr>
<td><strong>No. of patients who had a dose increase because of an extra dose of darbepoetin alfà (%)</strong></td>
<td>36 (8)</td>
<td>77 (8)</td>
<td>116 (8)</td>
</tr>
<tr>
<td><strong>No. of patients who had a dose decrease (%)</strong></td>
<td>85 (18)</td>
<td>206 (22)</td>
<td>308 (21)</td>
</tr>
</tbody>
</table>

*aThe hemoglobin threshold of 13g/dl was reached in these patients.*

*bIncluding patients who received an extra dose at week 15 or 16 probably because of scheduling or administration errors.*

Abbreviations: CI, confidence interval; Q3W, every 3 weeks.
Table 3. Summary of hemoglobin, transfusion, and quality-of-life end points

<table>
<thead>
<tr>
<th>成就目标血红蛋白（≥11 g/dl）a</th>
<th>基线血红蛋白 &lt;10 g/dl (n = 462)</th>
<th>基线血红蛋白 ≥10 g/dl (n = 918)</th>
<th>全体患者 (n = 1,493)</th>
</tr>
</thead>
<tbody>
<tr>
<td>实现目标血红蛋白百分比（95% CI）[n]</td>
<td>66 (61–70) [462]</td>
<td>87 (85–90) [891]</td>
<td>79 (77–81) [1464]</td>
</tr>
<tr>
<td>KM时间至目标血红蛋白，周（95% CI）[n]</td>
<td>9 (8–10) [462]</td>
<td>3 (NE, NE) [891]</td>
<td>4 (4–5) [1464]</td>
</tr>
<tr>
<td>维持目标血红蛋白</td>
<td>11.5 (0.8) [304]</td>
<td>11.6 (0.8) [803]</td>
<td>11.6 (0.8) [1178]</td>
</tr>
</tbody>
</table>

a患者在基线时的血红蛋白值未达到目标值。b百分比基于实现目标血红蛋白的患者。c基线FACT-F分数的±1周窗口。d≥3点变化的FACT-F分数具有临床意义[20]。粗百分比表示实际患者数。

图2. 基线血红蛋白（Hb）浓度在基线、第7周和第16周。Darbepoetin alfa在每3周300 μg的剂量下，基线血红蛋白<10 g/dl或≥10 g/dl。第16周，患者在两个血红蛋白亚组中实现了基线血红蛋白浓度，这些浓度在推荐范围内由现有证据支持的指导方针（11–13 g/dl，阴影区域）。平均血红蛋白使用可用数据方法计算。条形图代表95%置信区间（CI）。

图3. 目标血红蛋白所需时间。目标血红蛋白（Hb）水平所需时间对于基线血红蛋白<10 g/dl的患者更长。95%置信区间由未删失时间点到第16周的未删失时间点确定。
strata, respectively) maintained hemoglobin concentrations within it; few patients (5% vs. 3%, respectively) had hemoglobin levels that exceeded the target range (Table 3).

The mean baseline hemoglobin level was 1.2 g/dl lower in the <10-g/dl stratum than in the ≥10-g/dl stratum (9.3 vs. 10.5 g/dl, respectively). The absolute increase in hemoglobin concentration from baseline to week 16 was higher in the <10-g/dl stratum (2.1 g/dl vs. 1.2 g/dl for the <10-g/dl and ≥10-g/dl strata, respectively, using available data). In both strata, the mean change in hemoglobin was lower using the more conservative LVCF approach (1.5 g/dl vs. 0.9 g/dl for the <10-g/dl and ≥10-g/dl strata, respectively). A higher percentage of patients with a baseline hemoglobin level ≥10 g/dl achieved a hematopoietic response (Table 3).

Fewer patients in the ≥10-g/dl stratum than in the <10-g/dl stratum required transfusions during the study. A lower proportion of patients in the ≥10-g/dl stratum received transfusions from week 5 to the end of the study compared with the <10-g/dl stratum (12% vs. 28%, respectively). In the first month of the study, the percentages of patients who received transfusions were 5% (95% CI, 4%–6%) and 22% (95% CI, 18%–26%), for the ≥10-g/dl and <10-g/dl strata, respectively (Fig. 4). By the last month of the study (month 4), the transfusion requirements were further reduced: 3% (95% CI, 1%–5%) versus 3% (95% CI, 2%–4%) (Fig. 4).

Improvement in FACT-F score from baseline to the end of the study was associated with increased hemoglobin concentration. By week 16, patients in both hemoglobin strata had clinically significant improvements in their mean FACT-F score (Table 3). By week 7, 47% and 43% of patients in the <10.0-g/dl and the ≥10.0-g/dl strata, respectively, reported clinically significant improvements in FACT-F score (Table 3). By week 16, clinically significant improvements in FACT-F scores were reported by more than 50% of patients (58% and 53%, respectively) (Table 3).

Predictors of Clinical Response
Fifty percent (95% CI, 47%–53%) of patients had a ≥1-g/dl rise in hemoglobin concentration during the first 4 weeks of treatment: 53% (95% CI, 48%–57%) in the <10-g/dl stratum and 49% (95% CI, 45%–52%) in the ≥10-g/dl stratum. Sensitivity and specificity were calculated to determine if a ≥1-g/dl rise in hemoglobin during the first 4 weeks of darbepoetin alfa therapy was predictive of whether patients required an RBC transfusion or achieved the target hemoglobin concentration. Sensitivity and specificity were 56.2% and 80.4% for RBC transfusions, and 58.0% and 90.4% for achievement of the target hemoglobin concentration. The relatively low sensitivity suggests that a ≥1-g/dl rise in hemoglobin during the first 4 weeks is a poor predictor of clinically meaningful patient end points.

Safety
A total of 420 patients (28%) reported at least one serious adverse event, including 168 patients (36%) in the <10-g/dl stratum and 220 patients (24%) in the ≥10-g/dl stratum. No obvious differences in any given system organ class were observed between the two strata. The most commonly reported serious adverse events were febrile neutropenia (2%), pneumonia (1%), and pyrexia (1%); none of these were reported to be related to darbepoetin alfa use. In addition, 3% of patients reported a venous or arterial thrombotic event. Ten patients reported at least one treatment-related serious adverse event: four patients with deep vein thromboses, two patients with pulmonary emboli, and one patient each with phlebothrombosis, cerebral artery occlusion, cerebrovascular accident, and acute myocardial infarction.

A total of 387 patients (26%) did not complete the study. Of these, 78 (5%) died, including 34 (7%) in the <10-g/dl stratum and 36 (4%) in the ≥10.0-g/dl stratum. The primary reasons for death were the underlying tumor, disease progression, or complications such as sepsis or pneumonia.

Assay results for neutralizing antibodies to darbepoetin alfa were available for 1,169 patients; none developed neutralizing antibodies to darbepoetin alfa during the study.
**Discussion**

This study showed that administration of darbepoetin alfa at a fixed dose (300 μg) Q3W appears to be well tolerated and effective for the treatment of cancer patients with CIA. A high proportion of the total patient population (79%) achieved the target hemoglobin concentration (≥11 g/dl), and the median time to target hemoglobin was 4 weeks. Treatment with darbepoetin alfa at a dose of 300 μg Q3W also reduced the requirement for RBC transfusion and led to clinically significant improvements in FACT-F scores.

The results of this study emphasize the benefits of initiating erythropoietic therapy when patients’ hemoglobin concentrations are ≥10 g/dl rather than <10 g/dl. Intervening in the treatment of CIA while hemoglobin was ≥10 g/dl, that is, on-time intervention, resulted in more patients achieving the target hemoglobin by week 16, rather than waiting until hemoglobin was <10 g/dl, that is, late intervention (a 20% difference: 66% with late intervention vs. 87% with on-time intervention). The median time to achieve the target hemoglobin range when intervening on time was threefold shorter than when intervening late (3 weeks vs. 9 weeks). Patients receiving on-time intervention required fewer RBC transfusions between week 5 and the end of study than patients receiving late intervention. By study month 4, however, similar percentages of patients in the two groups (3%) received transfusions.

As mean hemoglobin concentration increased from week 7 to the end of the study, there was an increase in the percentage of patients in both baseline-hemoglobin strata who reported a clinically meaningful improvement (≥3-point change) in FACT-F score, with >50% of patients in both strata reporting clinically meaningful improvements in FACT-F scores. These observations are consistent with previous studies that demonstrated an association between hemoglobin level and patient-reported quality-of-life outcomes [8, 21, 22].

More than 50% of patients in each baseline-hemoglobin strata had a ≥1-g/dl rise in hemoglobin concentration during the first 4 weeks of treatment, similar to the incidence reported for epoetin alfa administered weekly [23]. Others have suggested that this end point is a useful predictor of clinically meaningful response to erythropoietic therapy in patients with CIA [23]. However, in the present study, sensitivity and specificity analyses suggest that a ≥1-g/dl rise in hemoglobin during the first 4 weeks is not a good predictor of the requirement for RBC transfusion or achievement of target hemoglobin in patients with CIA. This finding agrees with previously published data on predictors of response from trials using epoetin alfa [24].

The dose titration rules employed in this study were effective in achieving and maintaining hemoglobin concentrations within the range recommended by current evidence-based guidelines [15–17]. More than 70% of patients who achieved the target hemoglobin maintained an average hemoglobin level within this range; only 4% of patients had a mean hemoglobin concentration that exceeded the threshold (13 g/dl). This result is important given recent safety concerns over adverse survival outcomes for clinical studies using epoetin alfa [25, 26] and epoetin beta [27], in which hemoglobin levels were allowed to exceed 13 g/dl. In the present study, darbepoetin alfa at a dose of 300 μg Q3W was well tolerated; there was a low incidence of treatment-related serious adverse events and no treatment-related deaths.

In summary, administration of darbepoetin alfa Q3W may simplify the treatment of CIA in the oncology practice and minimize disruption to the lives of patients and their caregivers by synchronizing erythropoietic therapy with chemotherapy.

**Acknowledgments**

We wish to thank the investigators, study coordinators, and participants at each of the institutions for their contributions to this study. We thank Kathryn Boorer, Ph.D., for assistance in writing this manuscript; Joe Murray, M.S., and Hung Lam, Ph.D., for statistical assistance; and Ben Frierson, M.B.A., and Wen Kung, M.A., for programming support. This study was sponsored by Amgen Inc. (Study No. 20030206).

**Disclosure of Potential Conflicts of Interest**

Peter Silberstein has acted as a consultant for Amgen; Drs. Ralph Boccia, Tom Lillie, and Dianne Tomita have a financial interest in Amgen; and Drs. Tom Lillie and Dianne Tomita are employees of Amgen.


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