

A phase II, randomized, open-label study to assess the efficacy of extended-dose schedule administration of darbepoetin alfa in cancer patients with chemotherapy-induced anemia

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Origin of Study	USA, Canada
Type of Study	MULTICENTER, RANDOMIZED, CONTROLLED, OPEN-LABEL, NONINFERIORITY STUDY
Objectives	Evaluate the efficacy and safety of darbepoetin alfa (Aranesp) administered using an extended-dose schedule versus a weekly schedule in treating patients with chemotherapy-induced anemia.
Study Design	<p>Patients were assigned randomly 1:1 to receive darbepoetin alfa given once weekly, every 2 weeks, or every 3 weeks. The drug was given the same day as chemotherapy (before chemotherapy, if possible). Randomization was stratified based on screening hemoglobin level (< 10 vs ≥ 10 g/dL), tumor type (lung/gynecologic vs other nonmyeloid malignancies), and length of chemotherapy cycle.</p> <p>During the correction phase, patients in the weekly arm received 150 μg weekly regardless of chemotherapy schedule. Patients in the extended-dose schedule arm received either 300 μg every 2 weeks when given chemotherapy weekly or every 2 or 4 weeks or 500 μg every 3 weeks if given chemotherapy every 3 weeks.</p> <p>During the maintenance phase, if the hemoglobin level was ≥ 11 g/dL for the first time or increased ≥ 2 g/dL in 4 weeks (≥ 2 g/dL in 3 weeks for the every-3-week arm), the dose was reduced to 100 μg, 200 μg, or 300 μg for the weekly, every-2-week, and every-3-week arms, respectively. If the hemoglobin level increased ≥ 2 g/dL in 4 weeks (≥ 2 g/dL in 3 weeks for the every-3-week arm) for a second time, the dose was reduced further to 75 μg, 150 μg, or 250 μg for the weekly, every-2-week, and every-3-week arm respectively.</p> <p>If the hemoglobin level was ≥ 13 g/dL at the time of the next dose, the dose was withheld until it fell to ≤ 12 g/dL and was restarted at 100 μg, 200 μg, or 300 μg for the weekly, every-2-week, and every-3-weeks arm, respectively. For a second or third increase in hemoglobin level ≥ 13 g/dL, the dose was withheld until the hemoglobin level fell to ≤ 12 g/dL and was restarted at 75 μg, 150 μg, or 250 μg for the weekly, every-2-week, and every-3-week arm, respectively.</p> <p>Patients could receive red blood cell (RBC) transfusions when the hemoglobin level fell to ≤ 8 g/dL or if medically indicated.</p> <p>The primary endpoint was the change in hemoglobin level from baseline to week 13; secondary endpoints were the percentage of patients needing at least one RBC transfusion and change in Functional Assessment of Cancer Therapy–Fatigue (FACT–F) score over this period.</p>
Patients	Patients were ≥ 18 years of age, diagnosed with nonmyeloid malignancies, anemic from chemotherapy, and scheduled to receive at least 8 additional weeks of chemotherapy given on a weekly, every-2-week, or every-3-week basis. In all, 374 patients were in the weekly darbepoetin arm and 378 were in the extended-dosing arms.
Observations	In the weekly darbepoetin group, 27% maintained a mean hemoglobin level < 11 g/dL, 71% maintained a mean hemoglobin level between 11–13 g/dL, and 2% maintained a mean hemoglobin level > 13 g/dL. In the extended-dose schedule group, 12%, 85%, and 4% maintained these mean hemoglobin levels, respectively.

Study to assess the efficacy of extended dose schedule administration of darbepoetin alfa

According to Kaplan-Meier percentages, 24% of patients receiving weekly darbepoetin alfa and 20% of those given extended-dose schedules required an RBC transfusion from baseline to week 13. A Kaplan-Meier estimate showed that patients in the weekly and extended-dose-schedule groups needed a median of 7 weeks to achieve the target hemoglobin level.

The upper limit of the 95% confidence limits for the difference in the change in hemoglobin level at week 13 was within the prespecified noninferiority margin. In all, 34% of the weekly darbepoetin alfa group and 40% of the extended-dose-schedule group had a ≥ 3 -point increase in FACT-F score from baseline to week 13.

An adverse event occurred in 92% of the weekly darbepoetin alfa group and 93% of the extended-dose schedule group; 4% and 3% of these, respectively, were related to treatment; 30% and 25%, respectively, were serious; and 5% and 3%, respectively, were life-threatening. Further, 4% of the weekly darbepoetin alfa group and 3% of the extended-dose schedule group experienced thromboembolic events; 1% of each group experienced cerebrovascular accidents. Six deaths occurred among the weekly darbepoetin alfa group and among the extended-dose schedule group during the study or within 30 days of the last dose.

No neutralizing antibodies to darbepoetin alfa were detected in patients with available results.

Conclusions

Neither regimen was considered inferior to the other in this study.

The RBC transfusion requirements and change in FACT-F scores were similar for both groups.

The incidence and nature of adverse events were similar between the groups.

Discussion

Because of its long half-life, darbepoetin alfa is an effective treatment for chemotherapy-induced anemia when given weekly, every 2 weeks, or every 3 weeks. This flexibility allows darbepoetin alfa to be synchronized with a variety of chemotherapy schedules. "Although chemotherapy is traditionally given every 3 weeks, many patients are now receiving chemotherapy weekly or every 2 weeks," said Dr. Schwartzberg. "We thought it was important to show flexibility with a supportive care agent that allows dosing at the same time the chemotherapy was being delivered. This avoids additional patient visits and saves on patient and clinic resources."

"We started at slightly higher doses than have been used conventionally, and when patients corrected to a target of 11 g/dL or greater they went to a lower maintenance dose," Dr. Schwartzberg continued. "We achieved good hemoglobin responses whether we gave darbepoetin weekly or with extended dosing. The time to hitting the target hemoglobin was the same between weekly and extended dosing, as was the need for transfusion. All the endpoints were virtually identical between the dosing schedules."

Approximately 75% of each dosing group achieved target hemoglobin levels. Median time to target was 7 weeks. Transfusions were given to 24% of weekly patients and 20% of extended-dose patients.

"We believe that you can simplify the dosing of erythropoietic therapy," concluded Dr. Schwartzberg. "You can give it with chemotherapy, whatever the schedule."

Key Points

- Darbepoetin alfa apparently is effective and similarly tolerated when given on a weekly, every-2-week, or every-3-week schedule. Such flexibility may allow synchronization of darbepoetin alfa administration with most chemotherapeutic schedules.
- Further analyses to explore the possibility of synchronous use of darbepoetin alfa and chemotherapy are planned.

Reference

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