The efficacy and safety of darbepoetin alfa for treating anemia in low-risk myelodysplastic syndrome patients: results after 53/55 weeks

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Origin of Study USA

Type of Study PHASE II, SINGLE-ARM, MULTICENTER, OPEN-LABEL STUDY

Objectives Examine the efficacy of 500 μg of darbepoetin alfa (Aranesp) given every 3 weeks for treating anemia in low-risk myelodysplastic anemia patients.

Study Design Low- or intermediate-risk myelodysplastic anemia patients received 500 μg of darbepoetin alfa subcutaneously every 3 weeks for 52 weeks. Patients who did not respond by week 7 could be dosed every 2 weeks.

Dose escalation was considered after 6 weeks; the dose had to be withheld if the hemoglobin threshold was exceeded.

The study was prospectively divided into specific time points (day 1 to week 13 [test period], day 1 to weeks 27/28 [treatment period], day 1 to week 52 [extended-treatment period]). The end of the study was planned for 3 weeks after the last darbepoetin alfa dose (week 55 was the end for patients dosed every 3 weeks, and week 53 was the end for those dosed every 2 weeks).

Patient-reported outcomes were assessed with the Functional Assessment of Cancer Therapy–Fatigue (FACT–F) scale using data for patients given at least 1 dose of the drug and who completed baseline and at least one other patient-reported outcomes questionnaire.

Patients Patients were ≥ 18 years of age (50% male) and had low-or intermediate-1-risk myelodysplastic anemia and French-American-British classification of refractory anemia, refractory anemia with ringed sideroblasts, or refractory anemia with excess blasts. They underwent no previous bone marrow or stem cell transplant and had no transfusion-dependent thrombocytopenia, cardiac conditions, chronic myelomonocytic leukemia, uncontrolled hypertension, or history of malignancies other than myelodysplastic syndrome (MDS). They also had no previous or ongoing use of biologic response modifiers except erythropoiesis-stimulating agents (ESAs).

Safety and efficacy analyses were performed on 206 patients. There were 144 ESA-naive patients (50% male, 86% Caucasian; mean age, 75 years); the ESA-treated patients had similar demographics.

Results were stratified by whether patients had prior ESA therapy. Both the ESA-naive and -treated patients had a similar baseline hemoglobin level.

Observations By weeks 53/55, the percentage of patients with a major erythroid response was 59% in ESA-naive patients and 34% in ESA-treated patients. Both groups had a clinically meaningful rise in FACT–F scores from baseline.

Major responses (hemoglobin level increase ≥ 2 g/dL from baseline or transfusion independence if transfusion-dependent at baseline) were observed in 59% of patients naive to ESAs, and in 34% with prior treatment. Minor erythroid responses (hemoglobin increase ≥ 1 and < 2 g/dL over baseline or ≥ 50% decrease in transfusions) were observed in 15% and 16%, respectively. Target hemoglobin level (11 g/dL) was achieved by 82% in the naive group and by 55% in the prior treatment group at median times of 7 and 24 weeks.

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Adverse events were reported by 93% in the ESA-naive group and 89% in the ESA-treated group, with the most common events being fatigue and peripheral edema. In addition, 28% of ESA-naive patients and 34% of ESA-treated patients had serious adverse events, the most common of which included infections (eg, pneumonia) and infestations.

Death occurred in 5% of ESA-naive patients and 11% of ESA-treated patients. Of the 206 patients analyzed, 54% had a > 1.0-g/dL hemoglobin level increase within a 14-day period; 3% had a cerebrovascular accident, 3% had a myocardial infarction/coronary artery disorder, 1% had a thromboembolic event, and 4% discontinued the study because of disease progression. No anti-darbepoetin alfa-neutralizing antibodies were detected in 182 patients examined.

Conclusions

Darbepoetin alfa was well tolerated and could effectively increase hemoglobin levels in low-risk MDS patients. Most patients achieved an erythroid response by weeks 53/55. The mean change in FACT–F score at weeks 53/55 from baseline was clinically significant in ESA-naive and -treated patients.

For unclear reasons, ESA-naive patients generally showed a more robust response regarding hemoglobin parameters than did ESA-treated patients.

Discussion

Patients with MDS are often anemic, which can result in frequent red blood cell transfusions and fatigue. As an alternative to transfusion, ESAs are being tested for their ability to treat anemia in MDS patients. About 30% of MDS patients respond (with increased hemoglobin levels and the need for fewer transfusions) when treated with epoetin alfa alone, and about 40% respond when granulocyte colony-stimulating factor (G-CSF) is added *(Hellstrom-Lindberg E et al. J Haematol 2003;120:1037–1046; Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. Br J Haematol 1998;103:1070–1074)*.

Weekly darbepoetin alfa (150 or 300 μg/wk) has been shown to increase hemoglobin levels in low-risk MDS patients *(Stasi R et al. Ann Oncol 2005;16:1921–1927; Musto P et al. Br J Haematol 2005;128:204–209; Mannone L et al. Br J Haematol 2006;133:513–519)*, and treatment every 3 weeks has proven effective and especially convenient in cancer patients with chemotherapy-induced anemia *(Canon JL et al. J Natl Cancer Inst 2006;98:273–284)*. This study evaluated 500 μg given on an every-3-week schedule in 206 low- to intermediate-1-risk MDS patients. Patients were treated for 52 weeks; nonresponders at 7 weeks were treated every 2 weeks. Patients were analyzed according to whether they had or had not received prior treatment with ESAs.

By the final analysis at 53/55 weeks, most patients achieved an erythroid response. In the treatment-naive group, 39% of patients switched to every-2-week dosing, as did 55% of the group with prior treatment. Doses were increased in 25% in each group.

Treatment-naive patients generally had a more robust response with regard to hemoglobin parameters. In addition, the mean change in FACT–F score at week 53/55 was clinically significant, whether or not patients had received prior treatment.

The findings suggest that darbepoetin alfa can be administered every 3 weeks in low- or intermediate-risk MDS patients, with the schedule increased to every 2 weeks if patients do not respond within 2 months. This schedule of treatment, which requires fewer clinic visits, would be more convenient for patients.

Key Points

- Future studies must examine the efficacy of darbepoetin alfa in MDS patients and explore whether administration of an anemia therapy at an extended-dosing interval increases their quality of life.

Reference

Gabrilove J, Paquette R, Lyons RM, et al. The efficacy and safety of darbepoetin alfa for treating anemia in low-risk myelodysplastic syndrome patients: results after 53/55 weeks. Presented at the 48th Annual Meeting of the American Society of Hematology; December 9–12, 2006; Orlando, Florida. Abstract 2671.