

The Emerging Role of Darbepoetin Alfa in the Management of Patients With Cancer

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The use of hematopoietic growth factors has significantly affected the manner in which physicians treat and manage patients with cancer. In the past, patients with chemotherapy-induced anemia

would typically be managed with periodic red blood cell (RBC) transfusions to alleviate symptoms of anemia, without a significant outlook for actually improving hemoglobin levels long-term. With the clinical introduction of recombinant erythropoietic agents (epoetin alfa and epoetin beta) for treating chemotherapy-induced anemia, the need for RBC transfusions was significantly reduced. This success led to further exploration of their potential to maintain or normalize hemoglobin levels during chemotherapy or as a result of cancer-related causes. Because the incidence of RBC transfusions decreases with increasing hemoglobin concentration, new parameters for measuring success, such as improvement in health-related quality of life and the critical endpoint of increased survival, are being explored.

Less-Frequent Dosing

The most recent development in erythropoietic support was the approval by the US Food and Drug Administration (FDA) of darbepoetin alfa for the treatment of chemotherapy-induced anemia. Darbepoetin alfa is a recombinant version of erythropoietin with additional sialic acid residues, which results in a longer terminal half-life. As a consequence, darbepoetin alfa can be administered on an every-2-week basis, as opposed to the weekly or thrice weekly regimens needed for epoetin alfa therapy.

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Receiving therapy less frequently is potentially beneficial to many patients. Moore et al assessed just how much of a benefit was to be gained by interviewing cancer patients and their caregivers about their perceptions regarding medical office visits (page 4). Typically, multiple office visits were viewed negatively by patients and their families because of the burden the extra visits placed on family members and the way the visits reinforced patients' perceptions of themselves as "cancer patients," adding to their anxiety and depression. The results of this study suggest that the less-frequent dosing schedule of newer erythropoietic agents has a potential value beyond that of mere convenience.

Equivalence to Epoetin Alfa

Having been approved by the FDA for the treatment of chemotherapy-induced anemia, darbepoetin alfa is increasingly being used in this clinical setting. A series of studies and medical chart reviews by Boccia et al (page 6), Schwartzberg et al (page 8), and Reeves et al (page 10) have all arrived at much the same conclusion: a substantial share of erythropoietic therapy for chemotherapy-induced anemia is now represented by darbepoetin alfa, and its efficacy is similar to that of epoetin alfa in terms of hematopoietic response and a reduction in the need for RBC transfusions.

One of the perceived benefits of this transition from epoetin alfa to darbepoetin alfa is the less-frequent dosing of darbepoetin alfa. In addition, Thames et al performed a chart review in several US Oncology practices indicating that hematopoietic responses to darbepoetin alfa are seen not only in growth factor-naïve patients but also in those who are switched from epoetin alfa to the usual starting dose of darbepoetin alfa (page 12). This suggests that even patients receiving higher doses of epoetin alfa may benefit from conversion to the less frequently required doses of the newer agent.

Comparative trials assessing the ability of darbepoetin alfa given once every 2 weeks to produce hematopoietic responses similar to those expected from epoetin alfa have been conducted. Mirtsching

et al (page 14) reported preliminary results from their ongoing trial comparing darbepoetin alfa at a standard weight-based dose of 3.0 µg/kg every 2 weeks with epoetin alfa administered either weekly (40,000 U) or thrice weekly (150 U/kg). The results of this study and those of Schwartzberg et al (page 16), in which fixed-dose darbepoetin alfa (200 µg every 2 weeks) was compared with weekly doses of epoetin alfa (40,000 U), consistently demonstrated similar outcomes in terms of hematopoietic response and reduction in RBC transfusions. In both settings, darbepoetin alfa produced clinical outcomes similar to those achieved with epoetin alfa but with less-frequent dosing. These findings provide additional clinical evidence for the seeming equivalence of the two erythropoietic agents and are supported by the large community-based trial of Blayney et al (page 18), which demonstrated findings similar to those in the large epoetin community trials with regard to improvement in hemoglobin values and quality of life.

Optimizing Administration

Some of the more exciting research over the past several years has focused on maximizing or optimizing the dose and schedule of darbepoetin alfa. Hesketh et al assessed the role of fixed versus weight-based dosing in an initial weekly phase of therapy, followed by extension of the same doses every 3 weeks for maintenance (page 20). Regardless of how the dose was chosen, both regimens produced similar response rates, with hematopoietic responses in the mid-80% range. Maintenance of these doses was achieved with every-3-week dosing, indicating that darbepoetin alfa dosing at this interval has adequate hematopoietic activity.

To address issues of the timing of a weekly dose of darbepoetin alfa relative to that of a chemotherapy cycle, Glaspy et al assessed prechemotherapy dosing versus dosing on the day of chemotherapy (page 22). Comparable clinical results emerged from these two treatment arms, although differences in pharmacokinetics were seen, suggesting that darbepoetin alfa's clearance may be mediated, at least in part, by the bone marrow compartment.

Timing of the initiation of erythropoietic ther-

apy has been a hotly discussed topic. Whether to wait until a patient's hemoglobin value has fallen to the point where the patient is at risk for transfusion (< 10 g/dL) or to start earlier and prevent a reduction in the patient's quality of life has emerged as a point of interest. Rearden et al assessed the ability of every-3-week dosing of darbepoetin alfa to maintain a hemoglobin level ≥ 10.5 g/dL in mildly anemic patients (early intervention) and patients who became moderately to severely anemic before erythropoietic treatment (late intervention). Compared with late intervention, early intervention resulted in fewer transfusions and greater symptom improvement (page 24).

Newer Indications

The use of darbepoetin alfa in a variety of newer settings is attracting significant interest. Charu et al assessed the role of darbepoetin alfa in patients with cancer-related anemia who were not receiving chemotherapy and demonstrated a significant hematopoietic response rate compared with a control group not receiving growth factor therapy (page 26). Additional studies by Schriber et al in allogeneic bone marrow transplant recipients (page 28) and Singer et al in thalassemia intermedia patients (page 30) highlight the potential use of erythropoietic agents, in general, in settings other than chemotherapy-induced anemia.

Finally, better ways of understanding and assessing early indicators of response to erythropoietic therapy are being developed, as evidenced by the work of Vadhan-Raj et al (page 32) and Cleeland et al (page 34).

In summary, we are facing a period of significant growth and evolution in our understanding of the optimal use of erythropoietic agents. The flexibility of darbepoetin alfa's dosing schedule allows for exploration of new regimens to optimize clinical efficacy. Depending on the patient and his or her particular situation, physicians may have a series of alternative regimens from which to select, depending upon the desired endpoint. We anxiously await the next generation of clinical results, as well as the studies to which the emerging pilot data will lead.