Chemotherapy-induced anemia is common in patients who have cancer. Erythropoiesis-stimulating proteins such as epoetin alfa (Procrit) and darbepoetin alfa (Aranesp) have been shown to improve hematologic and clinical outcomes in these patients. Darbepoetin alfa has a longer serum half-life than epoetin alfa, making less frequent administration possible and offering the possibility of synchronizing the administration of erythropoietic therapy and chemotherapy. Several clinical trials have evaluated the utility of darbepoetin alfa given every 3 weeks (q3wk) in patients with chemotherapy-induced anemia. An exploratory study showed that darbepoetin alfa q3wk stabilized hemoglobin levels and reduced transfusion requirements. It was also shown that giving darbepoetin alfa q3wk at the same time as the chemotherapy produced hematopoietic benefits similar to those observed when it is given later in the chemotherapy cycle. The q3wk dosing schedule was effective in patients with mild and moderate anemia, and treatment goals were achieved in most of them. The equivalence of q3wk and qwk darbepoetin alfa has also been established. Synchronous administration of darbepoetin alfa with chemotherapy is a convenient option for patients with chemotherapy-induced anemia, with clinical trials showing it to be an effective treatment strategy.
more-frequent schedules, can increase Hgb to the target levels and reduce transfusion requirements.

The interplay between the effects of chemotherapy and erythropoiesis-stimulating proteins was explored in a randomized study that compared q3wk darbepoetin alfa given on a synchronous or asynchronous schedule relative to the chemotherapy in patients with nonmyeloid malignancies.[15] Patients treated with chemotherapy q3wk who had anemia (pretreatment Hgb level 9-11 g/dL) were randomized to darbepoetin alfa at a dosage of 6.75 µg/kg q3wk by SC injection on the same day as their chemotherapy (synchronous dosing) or on day 15 of the chemotherapy cycle (asynchronous dosing). To ensure that delays and modifications in the chemotherapy, which was given for up to 16 weeks, did not confound the study outcomes, changes in the Hgb levels were assessed at 6 weeks.

The serum levels of endogenous erythropoietin remained relatively constant during the chemotherapy cycle in the asynchronous group, but they increased by approximately fivefold in the synchronous group, peaking at day 2 and returning to near pretreatment levels by day 7 (Figure 1). Synchronous dosing was associated with a greater peak serum concentration of darbepoeitin alfa and area under the concentration-time curve than asynchronous dosing, indicating greater exposure to the study drug in the synchronous group. The serum concentrations of darbepoetin alfa declined in the synchronous group in a monophasic manner after the peak concentration had been reached, but in the asynchronous group the decline in serum concentration was interrupted for approximately 3 days after the chemotherapy (given 1 week after the darbepoetin alfa) before declining again (Figure 2).
These findings suggest that the clearance of endogenous erythropoietin and darbepoetin alfa is interrupted by chemotherapy, possibly because it suppresses receptor-bearing cells in the bone marrow that contribute to clearance. No differences between the groups were seen in the magnitude or rate of the changes in Hgb levels. The levels stabilized or declined in the week immediately after the chemotherapy in both groups, and then rose in the remainder of the chemotherapy cycle. The rates of hematopoietic responses (a 2 g/dL or greater increase in Hgb level or an Hgb level of 12 g/dL or greater in the absence of red blood cell transfusions in the previous 28 days) at the end of the study were similar in the asynchronous (69%; 95% confidence level [CI] = 52%-86%) and synchronous (81%; 95% CI = 61%-100%) groups (Figure 3). These rates compare favorably with those with more-frequent administration of darbepoetin alfa at equivalent doses (60%-66% with darbepoetin alfa at 2.25 µg/kg/wk).[4,16]
This study shows that synchronous and asynchronous dosing of darbepoetin alfa produce similar hematopoietic benefit, supporting the use of the more convenient synchronous schedule in clinical practice.

A fixed dose of darbepoetin alfa given once a week has been shown to be as effective as a weight-based weekly dose in patients with nonmyeloid malignancies and anemia.[17] The equivalence of fixed-dose darbepoetin alfa q3wk and weight-based once-weekly doses was evaluated in a large (N = 705) randomized double-blind European trial using a noninferiority design in patients treated with chemotherapy for nonmyeloid malignancies who had pretreatment Hgb levels of less than 11 g/dL.[18] Patients were randomized to darbepoetin alfa 2.25 µg/kg once a week by SC injection or to darbepoetin alfa 500 µg q3wk by SC injection. Dose modifications in accordance with the recommendations in the US prescribing information for darbepoetin alfa[19] were permitted.

Noninferiority would be achieved if the 95% CI of the difference in requirements for red blood cell transfusions between groups did not exceed 12.5%, a margin based on results from two previous placebo-controlled trials.[4,20] When adjusted for stratification factors, the difference in the proportion of patients in whom transfusions were required was 6.7% (95% CI = 0.2%-13.2%) in favor of q3wk dosing, demonstrating noninferiority between the dosages. Hemoglobin levels of 11 g/dL or higher were achieved in similar proportions of patients in both treatment groups, after adjusting for stratification factors (q3wk, 84%; qwk, 77%), and the Hgb profiles were almost identical in the groups, as were changes in their quality of life on the Functional Assessment of Cancer Therapy-Fatigue scale. There were no differences in adverse events, including cardiovascular or thrombotic adverse events, between the groups.

Summary

Giving erythropoiesis-stimulating proteins at the same time as chemotherapy is a convenient treatment option for patients who have chemotherapy-induced anemia, and it has been commonly done in clinical practice when possible. Until recently, however, there has been little understanding of the complex interaction between chemotherapy and erythropoiesis. The availability of
longer-acting darbepoetin alfa, offering the possibility of dosing once per chemotherapy cycle, brought with it a greater need to evaluate these interactions. The hematopoietic and clinical responses with q3wk of darbepoetin alfa appear indistinguishable from those with qwk dosing. Furthermore, the hematopoietic effect of darbepoetin alfa is not compromised when it is given at the same time as the chemotherapy. The use of fixed rather than weight-based dosing offers further opportunity to simplify the scheduling and administration of erythropoietic therapy.

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References:


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