Drugs 2003; 63 (11): 1075-1077
0012-6667/03/0011-1075/$33.00/0

Darbepoetin Alfa

A Viewpoint by Michael Hedenus

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The use of recombinant human erythropoietin (rHuEPO) in the treatment of anaemia in patients with cancer is expensive, the recommended dosing schedule is inconvenient (three times weekly), the time to onset of response is relatively long, and no clear dose-response relationship has been established.

Darbepoetin alfa represents the second generation of supersialated epoetin analogues, conferring a longer serum half-life and increasing the haematocrit more efficiently in animal models than rHuEPO. After a single subcutaneous injection of darbepoetin alfa in cancer patients with anaemia, darbepoetin alfa demonstrates slow absorption, with a peak concentration after ≈72 hours, and a prolonged residence time. However, there is no evidence of drug accumulation after multiple weekly administration or when given once every 2 or 3 weeks. Thus, compared with the first generation epoetins, darbepoetin alfa has several potential advantages: shorter time to response, a dose-response effect and less frequent dosing. All these issues are being addressed in an extensive and ongoing clinical development programme for the drug, which may provide a better cost-effective profile and an improved convenience for patients.

With the exception of a placebo-controlled, phase III trial in lung cancer patients with anaemia receiving chemotherapy, currently available data are derived from phase II trials. In all trials, development of antibodies against darbepoetin alfa has not been detected and the tolerability profile of the drug has been shown to be similar to that of rHuEPO. Darbepoetin alfa 2.25 μg/kg once weekly, has recently been approved in the US and the European Union for the treatment of anaemia in patients with non-haematological malignancies receiving chemotherapy.

Most of the dose-finding studies have been performed in patients with solid tumours and anaemia receiving chemotherapy. Haemoglobin (Hb) correction and response, as well as the need for RBC transfusion, seemed to be dose-dependent at darbepoetin alfa dosages of 1.0–4.5 μg/kg once weekly. Moreover, there was no apparent loss in efficacy after increasing the dosing interval from 1 to 2 weeks. The time to onset of response with darbepoetin alfa ≥4.5 μg/kg once weekly was shorter than with a standard dosage of rHuEPO. In a phase II 'front-loading' study, patients receiving a darbepoetin alfa loading dose of 4.5 μg/kg once weekly, followed by a maintenance dose of 1.5 or 2.25 μg/kg once weekly or 3.0 μg/kg once every 2 weeks, appeared to have higher Hb response rates and greater increases in Hb levels than patients receiving a standard treatment regimen of rHuEPO. This 'front-loading' concept of administration of darbepoetin alfa is currently being tested in a large-scale comparative phase III trial. This regimen may be more cost-effective by identifying non-responders to epoetins at an early stage.

A dose-finding, placebo-controlled study in patients with solid tumours and anaemia receiving chemotherapy has been conducted using darbepoetin alfa 4.5–18 μg/kg administered once every 3 or 4 weeks. There appears to be a dose-response relationship with dosages of up to 15 μg/kg administered once every 3 or 4 weeks.

Results from a small phase II study in patients with lymphoproliferative malignancies and anaemia receiving chemotherapy demonstrated that increasing dosages of darbepoetin alfa produced identical response rates to those achieved in studies in patients with solid tumours and anaemia. A phase III trial in this setting is currently underway.

In conclusion, phase II/III trials clearly indicate that the prolonged elimination half-life of darbepoetin alfa offers the potential for a more flexible and convenient dosing schedule and a potentially better cost-effective profile than rHuEPO; higher dosages are associated with higher response rates and a shorter time to response. No tolerability concerns have been reported thus far. Ongoing phase III trials are further evaluating the optimal dosing of this new drug in the treatment of anaemia in patients with cancer. ▲