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Darbepoetin Alfa

A Viewpoint by Anatole Besarab

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Erythropoietin is critical for the multiplication, differentiation and sustenance of committed erythroid progenitors. These cells undergo apoptosis if erythropoietin levels fall below the critical level (produced by a low mean residence time) required to maintain them throughout their maturation. The average half-life of the first-generation epoetins when given intravenously is short (8 hours) compared with the usual dosage interval in patients (2 to 3 days). Subcutaneous administration produces more consistent and sustained levels of erythropoietin which in turn reduces the inefficient erythropoiesis associated with apoptosis. Subcutaneous administration permits a 33% dose reduction compared with the intravenous route for equivalent pharmacodynamic effects.

The route of administration would become less important if the half-life of epoetin could be extended, because administration via either route would then minimise apoptosis. Darbepoetin alfa, a super-sialated analogue of epoetin alfa, thus represents the next step in the development of the epoetins. The major pharmacokinetic difference between darbepoetin alfa and the first-generation epoetins is a prolongation of the half-life from 8.4 to 25.3 hours when given intravenously and still further to 48.8 hours when given subcutaneously. The increased residence time of darbepoetin alfa permits equivalent pharmacodynamic effects to epoetin (i.e. increase in haemoglobin levels) after less frequent administration. It is therefore not surprising that equivalent increases in haemoglobin levels were noted with dosing intervals 2- to 3-fold longer for darbepoetin alfa than for epoetin. Although not studied directly, it is expected that the route of administration of darbepoetin alfa will have less effect on the haemoglobin response because of the prolonged half-life.

Less frequent administration (weekly or every other week) will be of great importance to patients with renal anaemia from chronic kidney disease, particularly those not on dialysis. It will also benefit those with chemotherapy- or cancer-related anaemias. The development of darbepoetin alfa will result in fewer office visits, less interruption to patient's schedule, fewer injections and reduced demand on staff time. These are all important in terms of cost effectiveness and maintenance of quality of life. We must now develop methods to deliver darbepoetin alfa using 'needleless' systems which will minimise the discomfort to patients and reduce the need for professional staff. ▲