Resistance to Recombinant Human Erythropoietin in a Child with Renal Failure, Cystinosis and β -Thalassaemia Minor

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and 6.5 g/dl. Investigations revealed: normal plasma ferritin, vitamin B₁₂, folate, haptoglobin; negative direct Coombs' test; normal G-6-PD activity; normal bone marrow. Stool samples for occult bloods were repeatedly negative. Because of a decline in renal function, peritoneal dialysis was commenced at the age of 10 years 3 months, and continued until renal transplantation at the age of 11 years 4 months. As there was a continuing transfusion requirement, erythropoietin was commenced (fig. 1) but despite increasing

Dear Sir,

The use of recombinant human erythro-poietin (rhEPO) has greatly improved the quality of life for patients with end-stage renal failure, but it is widely recognised that a small number of patients do not normalise their haemoglobin levels. Failure to show a response to rhEPO may be due to an inadequate dose of rhEPO, intercurrent infection, low iron stores, aluminium toxicity or occult blood loss [1, 2]. Rarely, folate deficiency or vitamin B₁₂ deficiency have been implicated, while the role of hyperparathyroidism remains controversial [3]. All these are remediable causes and usually account for the majority of patients who do not respond to rhEPO. We wish to report a child who showed a marked resistance to the action of rhEPO, presumably because of pre-existing conditions, rather than from remediable causes.

The child, 11.5 years of age at the time of this study, first came to the attention of the community health service at the age of 9 months when she was noted to have decreased weight gain; she was subsequently referred to this center at the age of 1 year because of continuing failure to thrive. She was the first child of consanguineous Asian parents, and there was no neonatal history of note. Initial investigations at 14 months of age revealed a mild iron deficiency anaemia, β -thalassaemia trait, a normal jejunal biopsy and biochemical and radiological evidence of rickets. She was initially treated with conventional doses of vitamin D, but was noted to have persisting rickets and hypophosphat-aemia despite increasing vitamin D. A diagnosis of cystinosis was made following re-investigation at 2 years and 10 months of age and she was subsequently referred to the ne-
Transplantation

400 600

Days

Fig. 1. Subcutaneous rhEPO dose (U/kg/week) and haemoglobin values.

phrology department. The child was treated with cysteamine, electrolyte and base supplementation, but because of recurrent vomiting, white cell cystine levels were not consistently low. Following a change to phospho-cysteamine, there was an improvement in compliance and white cell cystine levels were maintained in the desired range for much of the time. From the age of 6 years, despite good biochemical control, her renal function declined and coincident with this was a decline in the level of haemoglobin to between 4.5

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dosage, the response remained unsatisfactory with a reticulocyte count no higher than 2-3%. Repeat estimations of plasma ferritin, vitamin B₁₂ and folate were normal. Following renal transplantation, haemoglobin values have remained between 8 and 9 g/dl without rhEPO or blood transfusions.

In cystinotic patients, cystine crystals are known to accumulate in bone marrow cells and may well render them less responsive to the action of rhEPO. Furthermore, patients with haemoglobinopathies have been demonstrated to have a resistance to the action of rhEPO, and doses up to 1,500 U/kg/week have been used [4,5]. It is notable that in both reports a reticulocyte response was noted, a finding which differs from our patient. We therefore postulate that our patient's requirement for large doses of rhEPO could be explained by the shortened erythrocyte half-life as a consequence of the combination of β -thalassaemia trait and chronic renal failure, together with resistance to the action of rhEPO as a consequence of cystinosis. This latter point appears evident from the lack of a reticulocyte response. Whether larger doses

of rhEPO should have been used in our patient is unclear. It is interesting that our patient has maintained adequate haemoglobin levels since transplantation as a comparison between the pharmacokinetics of subcutaneously administered rhEPO [6] and previously reported post-transplantation EPO levels [7] suggests the dosage used should have been adequate. It may be that the correction of uraemia following transplantation has improved red-cell longevity; unfortunately, appropriate studies were not undertaken prior to transplantation.

References

Macdougall I, Hutton RD, Cavell I, Coles GA, Williams JD: Treating renal anaemia with recombinant human erythropoietin: Practical guidelines and a clinical algorithm. *Br Med J* 1990; 300:655.

Rosenlof K, Fyhrquist F, Tenhunen R: Erythropoietin, aluminium and anaemia in patients on haemodialysis. *Lancet* 1990; 335:247.

Grutzmacher P, Ehmer B, Messinger D, Scigalla P: Effect of aluminium overload and hyperparathyroidism on bone marrow response to recombinant human erythropoietin therapy. *Nephrol Dial Transplant* 1989; 4:474.

Panel discussion at International Workshop on Treatment of Anaemia with Recombinant Human Erythropoietin, Cologne, 1989. *Contrib Nephrol. Basel, Karger, 1989, vol 76, p 216.*

Tomson CRV, Edmunds ME, Chambers K, Bricknell S, Feehally J, Walls J: Effect of recombinant human erythropoietin on erythropoiesis in homozygous sickle-cell anaemia and renal failure. *Nephrol Dial Transplant* 1992;7:817.

Macdougall IC, Roberts DE, Neubert P, Dhar-masena AD, Coles GA, Williams JD: Pharmacokinetics of intravenous, intraperitoneal, and subcutaneous recombinant erythropoietin in patients on CAPD. *Contrib Nephrol. Basel, Karger, 1989, vol 76, pp 12.*
Eckardt KU, Kurtz A, Scholz H, Bauer C: Regulation of erythropoietin formation in vivo. *Contrib Nephrol. Basel, Karger, 1989, vol 76, p 33.*

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