

Occasional articles

Bone marrow transplantation for thalassaemia major

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Introduction

Bone marrow transplantation is at present the only cure for thalassaemia major. The alternative is a life long regimen of blood transfusions and chelation with regular subcutaneous injections of desferrioxamine. The treatment is familiar, but of limited effectiveness. Without transfusion, patients remain severely anaemic. As babies they fail to thrive, are prone to infection, and may die before they reach 12 months of age. Those who survive show growth failure with bone changes and fractures, massive hepatosplenomegaly and hypersplenism, leg ulcers and other complications. These changes can be prevented by regular blood transfusions; but for those who are regularly transfused, iron overload leads to hepatic, cardiac, and endocrine damage such as growth retardation, delayed or absent puberty, diabetes mellitus, cirrhosis and cardiac failure. In a United Kingdom series, before regular iron chelation was introduced, patients died predominantly in their late teens, and no patient survived beyond the age of 24.¹

The standard drug used for chelation is desferrioxamine. It is poorly absorbed by mouth. When given intramuscularly, some is excreted before it has bound all the iron it is capable of chelating, and its relative insolubility limits the size of the dose. It is best given intravenously or by what is now the customary route, subcutaneously, using a battery powered syringe driver, usually for eight to 10 hours overnight, several nights a week.

This is a traumatic and expensive regimen to follow for the whole of one's life. In many underdeveloped countries where thalassaemia is common it is not available and in developed countries compliance can be poor. So, although regular iron chelation can reduce iron stores,² in practice many do not achieve this ideal.

Blood transfusion problems

Most of the world's patients live in underdeveloped countries. Good blood supplies are only available in the West, where donors' blood groups reflect the indigenous population, and few donors come from the same racial group as the patients. Minor incompatibilities develop, and sometimes it is very difficult to find compatible blood. In the East, where family and friends form the usual donor pool, enough donors for the life long transfusion of thalassaemic children may simply not be available.

Post-transfusion hepatitis and iron overload increase the risk of hepatic cirrhosis. In Italy portal fibrosis of moderate or severe type was present in 10% of cases under 4 years old, and 50% of those between 8 and 11 years, rising to 85% in cases aged over 16.³ The risk of liver disease should be reduced by better screening of blood products. The recent introduction of testing for hepatitis C should reduce the long term risk of chronic hepatitis. In the United Kingdom blood is now screened for hepatitis B and hepatitis C. Transaminase screening is not practised. Fevers due to leucocyte reactions are common, but are preventable and treatable.

New alternatives

Much discussion has centred on the possibility of alternative new treatments. It seems likely that iron chelating drugs that are active by mouth may be available before long. One such product, L1 (1,2-dimethyl-3-hydroxy-pyrid-4-one), has been evaluated in the United Kingdom.³ However, the problem with all iron chelation treatment is that a drug is prescribed over many years for prophylaxis, and there is no immediate effect on the child's well being. It is difficult for many parents to understand the importance of continuing with treatment designed to prevent complications that may not appear for 10 years or more. Oral treatment is clearly less traumatic than subcutaneous injection; but experience with prescribing oral penicillin for patients with other haemolytic anaemias such as sickle cell anaemia, or with rheumatic fever, is not encouraging, because compliance is poor.^{4,5} So it does not follow that because oral drugs are easier to take, compliance will be improved. Fortunately, L1 is not difficult to manufacture and should not be expensive; the problem is that no Western company has yet taken up production.

Insertion of DNA sequences in to the human β -globin gene locus was described six years ago⁶ but gene therapy still remains only a theoretical possibility. As the Red Queen said to Alice in Wonderland, "Jam tomorrow . . ."

Bone marrow transplantation

Standard treatment is clearly far from perfect. How do the results of bone marrow transplantation compare? The single largest series has come from Pesaro, Italy, where over 450 patients have now received transplantations.⁷ A successful transplantation is a complete cure: but it is only available for patients with a

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fully matched sibling donor. For the 17 children who received transplantations in Pesaro from family members who were not fully matched, the results were very poor. Only four (24%) survive free of disease. Seven died of transplant complications, and in six the graft was rejected and thalassaemia recurred.⁷ For other disease, mismatched transplants have fared poorly in other centres, so there is no reason to suspect that alternative regimens might be more successful. For those who have a fully matched donor, the results seem to depend on the previous quality of care. Patients with high iron stores, pronounced hepatomegaly, and portal fibrosis fare worse.

Three years after transplantation, of those with both hepatomegaly and portal fibrosis, only 61% survived and 16% had rejected the graft. For those with only one of these findings, 80% survived and 9% rejected the graft. Of those with none, 94% survived and none rejected the graft.⁸ Of 12 children of median age 6 years in Taiwan, none of whom had received desferrioxamine, only six survived.⁹

At the Westminster Children's Hospital, London, 24 cases have received transplantations. Seven (29%) died, all of transplant complications. Although the results do not reach significance, 83% of the children of Mediterranean origin survived, compared with only 64% of the Asian children. (Vellodi 1991; personal communication). The Asian children had higher serum ferritin concentrations, attributed to poorer compliance with chelation. In Manchester we transplanted 14 cases, all Asian. Four died, three of transplant complications and one of sepsis after removal of the spleen, giving a survival of 71%. Two twin brothers rejected a graft from a single donor but now function as thalassaemia intermedia. The patients who died all had a heavy iron overload.

Arguments for and against bone marrow transplantation

In 1985 the Pesaro group reported their results of transplanting 24 thalassaemic children aged 6 months to 7 years, prepared with 14 mg/kg busulphan and 200 mg/kg cyclophosphamide.¹⁰ One died without engrafting, four had a recurrence of thalassaemia, and 19 (79%) survived without thalassaemia. Three had chronic graft versus host disease over a year after transplantation. These results were very encouraging. Two years later, 40 patients aged 8 to 15 years of age were reported.¹¹ Twenty eight (70%) were alive and disease free, thalassaemia recurred in two and 10 (25%) patients died. This second article provoked a response from several well known experts from New York, Philadelphia, Boston, Oxford and Bethesda, who pointed out that the prognosis for the disease was improving with a median survival of 30 years.¹² The one in four chance of death was unacceptable. Prospects for new and better forms of treatment lay ahead. However, four years later, there is still little sign of these improved prospects becoming reality. Bone marrow transplantation, however, has moved on. For cases with poor prognosis

the new Pesaro regimen, using a lower dose of cyclophosphamide and adding anti-lymphocyte globulin, produced 91% survival, with a 37% risk of rejection and 60% disease free survival.⁷ In Pescara another Italian series of 52 patients showed 92% survival with 85% disease free survival and 2% graft failures, 6% late rejections, and 12% with acute graft versus host disease.¹³ The results of adult transplant recipients are encouraging too. Six of seven adult cases were alive and well up to 35 months after transplantation.¹³

It is recognised that there may be long term endocrine after-effects in patients treated for leukaemia and aplastic anaemia, but little is known about the long term after-effects of bone marrow transplantation for thalassaemia. It is, however, a disease predisposed to endocrine damage as a result of treatment. The Pesaro group reported normal thyroid and parathyroid function in 58 children at least one year after transplantation. Three of six with impaired glucose tolerance before transplantation became normal afterwards, and two girls showed improved gonadotrophin concentrations¹⁴; so bone marrow transplantation may allow recovery to occur in cases where iron overload has caused only slight tissue damage.

It is stressful and bad for staff morale for a transplant centre to treat substantial numbers of cases with a poor prognosis. If poor risk thalassaemic patients are to be accepted on a transplant programme, not only must the family understand the management and prognosis, but so must all the transplant unit staff who have to care for the patients hour by hour. Most will be happy to accept young patients without excess iron overload and with the best prognosis. When resources are in short supply, the major effort should be directed at these younger children. As Slavin and Rachmilewitz concluded, transplantation is most probably the treatment of choice for young minimally transfused patients.¹⁵ Weatherall, who at one time considered that transplantation was too dangerous,¹² now agrees that it must be considered a serious option.¹⁶

The treatment of thalassaemia is expensive. Our figures for 1989 in the North Western Region showed an average of £6421 per patient per year. The figure is high because most are treated in hospitals where overnight admission for transfusion is usual. Day case transfusion is cheaper. However, although the cost of bone marrow transplants for thalassaemia is high, it is much cheaper than life long conservative care. So on purely financial grounds, transplantation must be the treatment of choice.

Conclusion

Physicians' opinions have been taken into account, but the patients' views have not been reported, and few families are happy with the present conservative management of thalassaemia. Even if children are given treatment by their parents in the best possible way, they often rebel as adolescents, and there is no guarantee that young adults will continue with

their desferrioxamine injections. Unfortunately, the evidence shows that patients with lower iron stores do better after transplantation than those with severe iron overload, so a transplantation is not an "easy" alternative for the patient who will not or cannot tolerate a regular chelation regimen.

Most families now ask about the possibility of transplantation. It is the physician's responsibility to discuss the pros and cons with them, and allow them to decide. In Manchester most families originate from Pakistan and Gujerat in India. They know that their children cannot, at present, receive satisfactory treatment in their home country, and the parents cannot look forward to returning there. Even a holiday must be brief, unless they live within reach of a reliable hospital centre, or one of the branches of the Fatimid Foundation in Karachi, Peshawar, or Lahore. Furthermore, their compliance with standard treatment may be sub optimal. They are not happy with the prospect of life long treatment, with eventual premature death in the mid-30s, perhaps preceded by a prolonged period of incapacity. They want a cure and many prefer to take the risk of losing their child early rather than face years of treatment without cure.

The Fatimid Foundation is an Islamic group set up originally to provide an emergency blood transfusion service in Karachi. It now has branches elsewhere in Pakistan, and provides blood and blood products for patients with haemophilia and thalassaemia. The contact in England is Mrs MS Daroo, Blessings, 16 Little Potters, Bushey Heath, Herts WD2 3QT.

- 1 Modell B, Letsky EA, Flynn DM, Peto R, Weatherall DJ. Survival and desferrioxamine in thalassaemia major. *Br Med J* 1982;284:1081-4.
- 2 Hoffbrand AV, Gorman A, Laulich M, et al. Improvement in iron status and liver function in patients with transfusional iron overload with long-term subcutaneous desferrioxamine. *Lancet* 1979;i:947-9.
- 3 Bartlett AN, Hoffbrand AV, Kontoghiorghes GJ. Long term trial with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one(LI) II. Clinical observations. *Br J Haematol* 1990;76:301-4.
- 4 Cummins D, Heuschkel R, Davies SC. Penicillin prophylaxis in children with sickle cell disease in Brent. *Br Med J* 1991;302:989-90.
- 5 Gordodis L, Markovitz M, Lilienfeld AM. Why patients don't follow medical advice : a study of children on long term antistreptococcal prophylaxis. *J Pediatr* 1969;75:957-68.
- 6 Smithies O, Gregg RG, Boggs SS, et al. Insertion of DNA sequences into the human chromosomal beta-globin locus by homologous recombination. *Nature* 1985;317:230-4.
- 7 Lucarelli G. For debate: Bone marrow transplantation for severe thalassaemia. The view from Pesaro. *Br J Haematol* 1991;78:400-1.
- 8 Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassaemia. *N Engl J Med* 1991;322:417-21.
- 9 Lin K-M, Lin K-S. Allogeneic bone marrow transplantation for thalassaemia in Taiwan: factors associated with graft failure. *Am J Ped Hem Oncol* 1989;11:417-23.
- 10 Lucarelli G, Polchi P, Galimberti M, et al. Marrow transplantation for thalassaemia following busulphan and cyclophosphamide. *Lancet* 1985;i:1355-7.
- 11 Lucarelli G, Galimberti M, Polchi P, et al. Marrow transplantation in patients with advanced thalassaemia. *N Engl J Med* 1987;316:1050-5.
- 12 Piomelli S, Lerner N, Cohen A, et al. Bone marrow transplantation for thalassaemia. *N Engl J Med* 1987;317:964.
- 13 Di Bartolomeo P, Di Girolamo G, Angrilli F, et al. Bone marrow transplantation for adult patients with thalassaemia major. *Bone Marrow Transplant* 1991;7 suppl 2:73.
- 14 Galimberti M, De Sanctis V, Lucarelli G, et al. Endocrine function after bone marrow transplantation for thalassaemia. *Bone Marrow Transplant* 1991;7 suppl 2:74.
- 15 Slavin S, Rachmilewitz EA. Bone marrow transplantation in thalassaemia. *Bone Marrow Transplant* 1986;1:11-5.
- 16 Weatherall DJ. For Debate: Bone marrow transplantation for severe thalassaemia (2). To be or not to be. *Br J Haematol* 1991;78:301-30.