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Annotations

Bone marrow transplantation for leukaemia

Over 10 years have passed since the classic paper from Seattle showed that a small proportion of patients with end stage leukaemia could be cured by total body irradiation, cyclophosphamide, and infusion of bone marrow from an HLA identical sibling donor.[1] Since that time bone marrow transplantation has become safer and more widely available, and thanks to relentless media interest forms the subject of endless enquiries from parents and relatives. Yet the decision to perform bone marrow transplantation, particularly in first remission of acute leukaemia, is a difficult one and involves careful assessment of the possible risks and benefits. This annotation will focus on the present indications for bone marrow transplantation in leukaemia and the expected results, but some appreciation of the possible complications is essential. The indications will, of course, change in the future as more effective chemotherapy regimens develop or bone marrow transplantation, or both, become safer.

Risks and complications of bone marrow transplantation

The most widely used preparative regimens for bone marrow transplantation involve high doses of cyclophosphamide and fractionated or unfractionated total body irradiation. This treatment causes profound myelosuppression for at least two to four weeks and long term immunosuppression. The infective risks associated with bone marrow transplantation have been extensively reviewed and include both bacterial and fungal sepsis.[2] Cytomegalovirus infection may cause pneumonitis and long term immunosuppression exacerbated by graft versus host disease may predispose to pneumococcal infection. Allogeneic bone marrow transplantation with a sibling donor who is HLA identical carries a significant risk of graft versus host disease and measures to prevent this complication either by treatment of the recipient, or the donor bone marrow, are essential.[3]

Despite these problems bone marrow transplantation is in general well tolerated by a fit child in remission and perhaps the main concern for the paediatrician lies in the late effects of treatment. Assessment of growth and endocrine function in children who have received total body irradiation and cyclophosphamide shows gonadal failure, thyroid dysfunction, spinal shortening, and particularly in those who have received previous cranial irradiation, abnormal hypothalamic-pituitary function and learning problems.[4 5] Many of these late effects are attributable to total body irradiation. There are alternative preparative regimens using chemotherapy alone such as the combination of busulphan and cyclophosphamide,[6 7] but both the efficacy and late toxicity of such treatment have been less well studied.

Choice of a donor

A major limitation to the use of bone marrow transplantation is that only about one in three children in the United Kingdom will have an HLA identical sibling donor. Transplantation from a non-identical family member increases the risk of graft versus host disease and failure of engraftment.[8] There are now reports of the successful use of matched unrelated donors in chronic leukaemia but the search for these is time consuming and expensive.[9]

Autologous marrow transplantation is less hazardous than allogeneic transplantation, and in theory more freely available, but carries a higher risk of relapse which may be due to the reinfusion of leukaemic cells or the loss of any graft versus leukaemia effect. Despite these considerations it is unclear at present whether attempts to purge the marrow of possible residual leukaemic cells are necessary.[10]

Chronic myeloproliferative disease

Chronic myeloid leukaemia in childhood resembles the disease in adults with a median survival of three to four years. Two transplant groups have reported actuarial survival of 49%[11] and 72%[12] after bone marrow transplantation from sibling donors, the latter report had a median follow up time of two years. Successful bone marrow transplantation has also been reported in juvenile chronic myeloid leukaemia and the monosomy 7 syndrome.[13 14] Allogeneic bone marrow transplantation is the treatment of choice for these rare disorders and, in patients where no sibling donor is available and the

pace of the disease permits, a search for a matched unrelated donor seems appropriate.[9]

Acute myeloid leukaemia

Advances in the treatment of acute myeloid leukaemia have been recently reviewed and children have been among the major beneficiaries.[15] The outlook for paediatric acute myeloid leukaemia has improved from the previous appalling 12% event free survival rate both for children receiving bone marrow transplantation and those treated with chemotherapy alone.[16] With modern intensive chemotherapy and full supportive care over 85% of children with acute myeloid leukaemia should achieve remission. The best overall results from chemotherapy protocols have been in unrandomised, often single centre studies with event free survival of 30–40%.[17–19] Survival rates in small series of children with acute myeloid leukaemia from the time of marrow transplantation in first remission are in the order of 65%.[20 21]

The failures in the chemotherapy reports are largely due to relapse, and those in the series of bone marrow transplantation due to transplant related deaths. There is a continuing debate, reviewed elsewhere,[15] between the proponents of bone marrow transplantation in first remission for children with acute myeloid leukaemia and a donor, and chemotherapy with bone marrow transplantation at the first sign of relapse. All published studies directly comparing bone marrow transplantation and chemotherapy in first remission favour the former,[22–25] however, and at present it must be the preferred option for children with acute myeloid leukaemia who have a donor.

There is great interest in the use of autologous bone marrow transplantation as a form of intensive treatment in first remission. This approach has been pioneered in adults with acute myeloid leukaemia, using regimens with and without total body irradiation.[26] The results of the reported uncontrolled studies are encouraging but open to the criticism that the patients are a selected group who have survived past the risk of early relapse. The new Medical Research Council trial for children and adults with acute myeloid leukaemia (AML 10) will address this important question and starts this spring. All patients will receive intensive induction and consolidation and those with an HLA identical sibling donor will be eligible for allogeneic bone marrow transplantation. All those without a donor will undergo marrow harvest and storage and will then be randomised to receive chemoradiotherapy and autologous marrow transplantation or no further treatment. Patients relapsing after chemotherapy alone will be eligible for autologous marrow transplantation in second remission.

Lymphoblastic leukaemia

The prognosis of children with acute lymphoblastic leukaemia who relapse during treatment remains poor.[27] Long remissions may be obtained in children relapsing after elective cessation of treatment or even, according to one recent report, relapsing more than 18 months from diagnosis.[28] In our experience, after long term follow up, however, many such patients may still eventually again relapse.[27] Actuarial disease free survival in children receiving allogeneic transplantation in second remission is reported as ranging from 27–40%[29–32]; the major cause of treatment failure is further leukaemic relapse. A much higher survival rate of an estimated 64% at five years has recently been reported in children prepared for transplant with hyperfractionated total body irradiation preceding cyclophosphamide.[33]

While there is no doubt that children with acute lymphoblastic leukaemia who relapse during treatment, and probably off treatment as well, should be offered a transplant if they have a compatible sibling donor, in our experience the impact of such a programme has been small because of the small number of children with donors and the instability of second remission in many children.[34] A recent report showed a disease free survival rate of 20% in patients with relapsed acute lymphoblastic leukaemia after autologous transplantation,[32] and the time seems ripe for a trial comparing autologous bone marrow transplantation with chemotherapy in children with acute lymphoblastic leukaemia in second marrow remission.

Isolated central nervous system relapse has a poor prognosis[35 36] and bone marrow transplantation should be considered in suitable patients and in those with an overt testicular relapse during treatment.[37] Boys with testicular relapse after treatment has been stopped are curable by conventional chemotherapy and radiotherapy.[27] The most controversial area lies in the selection of children with acute lymphoblastic leukaemia for bone marrow transplantation in first remission. There are a small number of children with an unquestionably poor prognosis, for example those in whom the leukaemia is associated with certain cytogenetic abnormalities for whom such treatment is justified on an uncontrolled basis.[38] For others, such as children with a very high initial leukocyte count, bone marrow transplantation should be investigated in the context of a clinical trial. In the present Medical Research Council UKALL X trial

allogeneic transplantation may be offered to children with a presenting leukocyte count of greater than 100×10^9/l who have a compatible sibling. It is thus hoped to obtain a comparison with the outcome of children receiving intensive chemotherapy.

Conclusion

Chemoradiotherapy and transfusion of allogeneic or autologous marrow is the most intensive short term treatment available for childhood leukaemia. It is becoming increasingly available as regional transplant units open in the United Kingdom. Paediatricians have an excellent record of collaboration in treatment of childhood leukaemia and it is essential that this collaboration is extended to include critical evaluation of bone marrow transplantation as a form of treatment.

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