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Risks and benefits of intensive treatment of acute leukaemia

Over 90% of children with acute lymphoblastic leukaemia will achieve remission with simple induction treatment. Given treatment to prevent overt leukaemic infiltration of the central nervous system (central nervous system prophylaxis) and continuing moderate dose (so called maintenance) chemotherapy, many will remain in remission for 3 to 4 years. Yet experience over the past 15 years has shown that this approach will cure only a minority of children. If leukaemic relapse occurs, particularly in the bone marrow during treatment, the outlook is very poor with few patients surviving more than a further 1 to 2 years. Remission is now achieved in most children with the rarer acute myeloid leukaemia but using conventional maintenance treatment the long term relapse free survival rate is not greater than 15%.

Classification and risk groups

The past few years have seen increasing emphasis on identification of prognostic factors in acute lymphoblastic leukaemia, as determined by clinical features at presentation, initial leucocyte count, and the morphological, immunological, and cytogenetic features of the leukaemic blast cell.[1] This approach has made it possible to stratify patients into 'risk groups' with the aim of identifying those who might benefit from more intensive treatment and those in whom treatment might perhaps be reduced. This stratification is necessary to select patients for different treatment regimens but it should be noted that the importance of individual prognostic factors (for example, sex) may well vary with the individual treatment protocol. Moreover, even the most optimistic selection of a 'good risk group' does not predict greater than 75 to 80% disease free survival, thus assuming treatment failure in 25%.

The treatment of acute myeloid leukaemia has not progressed to the point where risk groups can be identified with confidence, although certain associations have been noted, for example the prevalence of monocytic leukaemia and central nervous system involvement in infants.

Does more mean better?

Does more intensive treatment in patients with acute leukaemia, particularly those at high risk of treatment failure, improve the proportion of patients achieving long term remission and perhaps cure? The most widely publicised form of intensive treatment is the use of high dose chemotherapy, usually with total body irradiation followed by subsequent infusion of bone marrow. The safety of bone marrow transplantation will almost certainly be improved by measures to reduce the incidence of graft verus host disease and this may increase the number of potential recipients by permitting widespread use of haploidentical donors or donors from a registry. The use of autologous bone marrow for rescue obviates the risk of graft versus host disease but complete success probably requires removal of residual leukaemic cells while preserving sufficient normal haemopoietic progenitors to enable the graft to take. Ultimately, however, the success of this form of short term intensive treatment depends on the ability of chemotherapy or total body irradiation, or both, to eradicate the leukaemia. Thus bone marrow transplantation as a form of treatment must be assessed in direct comparison with alternative strategies, not only with respect to the cure rate but also to short and long term morbidity.

Lymphoblastic leukaemia

Measures to prolong marrow remission. The hypothesis that early intensification of treatment in children with acute lymphoblastic leukaemia reduces the subsequent risk of bone marrow relapse remains unproved, although there is increasing circumstantial evidence to support it. Certainly many studies purporting to show no benefit could be criticised on the grounds of choice or dose of drugs administered.[1]

The best published reports on prolongation of haematological remission in acute lymphoblastic leukaemia are those of the West German study group whose protocols comprise an intensive eight week induction schedule with additional treatment for patients deemed at high risk of relapse, and fairly simple maintenance treatment. Unfortunately the components of this treatment were not evaluated in a prospective randomised study and so the value of each phase remains uncertain.[2] It is likely that this approach involves overtreatment of an appreciable proportion of patients since a high long term survival rate can be achieved in good risk

patients (defined by age and leucocyte count), by three drug induction treatment and simple maintenance.[3]

It is apparent in retrospect that the previous generation of Medical Research Council trials, using one week of L-asparaginase only and reduced chemotherapy during and after cranial irradiation, did not comprise sufficiently intensive treatment for many patients. The introduction, in the Medical Research Council's UKALL VIII, of prolonged L-asparaginase and strict criteria for maximum drug dosage throughout treatment seems to have halved the marrow relapse rate in comparison with previous schedules. It is planned that the next trial (UKALL X) should investigate the value of further early intensification of treatment.

There is no evidence, however, that more complicated maintenance (continuing treatment) schedules improve prognosis in standard or high risk patients.[1 4] The optimum length of treatment in acute lymphoblastic leukaemia clearly depends on the type and intensity of previous treatment (for example the lack of maintenance after bone marrow transplantation) but it may be that increased intensity of early treatment will allow the subsequent duration of treatment to be curtailed.

Bone marrow transplantation. Bone marrow transplantation is the treatment of choice for children with acute lymphoblastic leukaemia, in second marrow remission, who have a suitable donor.[5 6] Nevertheless, like all forms of treatment it is attended by a considerable risk of leukaemic relapse. Patients who fare best are those with long first remissions: children relapsing within the first year or so of treatment are less likely to be cured. It remains to be seen whether more intensive conditioning regimens or fractionation of total body irradiation, or both, will provide more effective control of leukaemia.

Although children with central nervous system relapse as a first event survive longer, there is a high risk of subsequent marrow relapse even in patients receiving further systemic intensification, and the role of bone marrow transplantation in treatment merits evaluation.[7] Treatment of boys with occult testicular leukaemia or isolated relapse off treatment with local irradiation and chemotherapy is effective in many cases but bone marrow transplantation should be considered in those who develop overt testicular disease during chemotherapy, since their prognosis is poor.[8]

The role of bone marrow transplantation or autologous bone marrow transplantation in first remission is not determined. High dose chemotherapy and total body irradiation may afford more effective control of leukaemia than longer term low dose chemotherapy (although preliminary reports suggest it is attended by a substantial relapse rate.[9] Transplantation should be considered for patients known to have a very poor prognosis such as Ph'+ve acute lymphoblastic leukaemia, the more recently described $t^4/11$, and the rare B-acute lymphoblastic leukaemia. Multivariate analysis of prognostic factors in acute lymphoblastic leukaemia does not suggest that any other immunological subtype carries independent prognostic importance so that selection of high risk cases should be based on a risk scoring system or the initial leucocyte count, which remains in most studies the strongest determinant of prognosis.[1] We are presently considering transplantation in first remission for patients who present with a leucocyte count in excess of $100\times10^9/1$ and comparing the outcome with that in patients with no available donor who receive early intensification treatment.

Acute myeloid leukaemia

The most encouraging results in the treatment of acute myeloid leukaemia have hitherto been reported in patients receiving bone marrow transplantation in first remission from an HLA identical sibling donor: overall disease free survival rates of up to 50 to 60% have been reported in children.[10] Meanwhile, however, the results of chemotherapy have improved, again particularly in young patients. There are now several published reports of series of patients, usually treated at single centres, with projected long term disease free survival of the order of 30 to 40%. These protocols all include a period of very intensive post remission chemotherapy, but in one series at least, treatment comprised only six courses of cytotoxics.[11–13] There is little evidence that conventional maintenance treatment has any role in the treatment of acute myeloid leukaemia and further long term follow up is needed to determine whether this short term intensive chemotherapy will prove as effective as bone marrow transplantation. The level of supportive care required by these protocols is equivalent to or greater than that for bone marrow transplantation.

The price of more intensive treatment

Increasing the intensity of chemotherapy inevitably produces more profound myelosuppression, involving a longer stay in hospital, higher risk of bacterial and fungal infection, and increased demand for blood products. Many cytotoxic regimens produce gut toxicity with additional problems of nutrition

necessitating nasogastric and intravenous feeding, a problem most noticeable in intensive protocols for acute myeloid leukaemia. The period of continuing treatment in all patients is one of risk for non-bacterial infection, notably measles, *Varicella zoster*, and *Pneumocystis carinii* pneumonia.[14] Marrow transplantation in remission entails the same need for early supportive care with the additional hazards of graft versus host disease and late immunosuppression.[15] The psychosocial and financial strains for the child and his family are considerable, as are the strains on the hospital service in an era of constraint.

Late effects of treatment. The late effects of conventional chemotherapy for childhood leukaemia have been recently reviewed[16] and perhaps the area of greatest concern is the effect of central nervous system prophylaxis. It is clear that children who receive intrathecal chemotherapy and cranial irradiation at a young age have the highest risk of subsequent learning problems. These considerations have led to a reduction in the recommended dose of cranial irradiation from 2400 to 1800 rads and deferring radiotherapy in children under 2 years. It is probable that further modifications of central nervous system prophylaxis will be made in the next few years.

A recent review of the late effects of bone marrow transplantation gives some indication of the complications of total body irradiation.[15] Children receiving total body irradiation before puberty have impaired growth, with primary ovarian failure in girls and delayed puberty in some boys. There is no information yet about the effect on cognitive function and learning ability and this is urgently needed; at present we feel hesitant to recommend irradiation for children under the age of 2 years. There are alternative conditioning regimens which do not use irradiation but in view of the high rate of central nervous system relapse in acute lymphoblastic leukaemia it seems probable that, for this form of leukaemia at least, it will be an essential component of any conditioning regimen.

Conclusions

Prolonged survival is now achieved in many children with acute leukaemia so that long term follow up is needed to determine the precise value of any specific therapeutic innovation. Although bone marrow transplantation has clearly given some children with relapsed leukaemia a second chance, only time will tell whether transplantation in first remission is a passing phase or becomes a permanently established form of treatment. Meanwhile, the risks and benefits of this and all forms of intensive treatment can be properly determined only by prospective studies with full evaluation of prognostic factors.

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