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Transplants in Adult ALL—? Allo for Everyone

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The large MRC/ECOG adult acute lymphoblastic leukemia (ALL) study establishes the value of sibling donor allogeneic transplant in standard-risk patients demonstrating superior outcome to conventional chemotherapy. The small but significant number of patients having matched unrelated donor (MUD) transplants on this study protocol appear to do well, and may establish the value of such an approach for those without a sibling. Reduced-intensity conditioning (RIC) conditioning might begin to address the transplant-related mortality problems of the older patients. The youngest adults may not need a transplant at all. If they are now treated on pediatric chemotherapy protocols, their outcome appears to improve significantly. The MRC/ECOG study, the emerging MUD and RIC data all help establish allogeneic transplant more widely in this disease.

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INTRODUCTION

We know that, in general, adult acute lymphoblastic leukemia (ALL) has a very poor outcome compared to that in children. It is clear, however, that the disease is curable but only in a minority of patients. Approximately one-third are cured. This is despite the fact that CR is very high, close to 90% in some studies [1]. The problem is that few remain in remission despite the fact that, as in pediatric ALL, the treatment is initially very intensive throughout induction and consolidation, and maintenance treatment typically goes on for 2 further years or more. Thus, the evidence is that many patients must be undertreated in that relapse rates are high, yet it appears difficult to conceive how chemotherapy could contribute any more without the introduction of new drugs. The promise of a range of effective new ones is not very great presently.

This disease is unusual compared to adult acute myelogenous leukemia (AML) in that a significant proportion of patients in complete remission (CR) die in CR. This is not just in the group receiving allogeneic transplant but also includes the group not having a transplant. The level of nonrelapse mortality (NRM) in the high-risk "no-donor" group in UKALL 12/ECOG 2993 is around 12% [1]. This is a level considerably higher than that usually seen in AML protocols. It means that the net treatment-related mortality (TRM) associated with transplant might be considered less unattractive than initially thought; for instance, if 25% of a particular group have a TRM associated with transplant but would have had a 12% TRM anyway without it, then the net *incremental* TRM of transplant of $25 - 12 = +13\%$. In adult ALL where the CR rate is very high, we have few totally new agents available, although there is a possibility that anti-CD 20 and other monoclonal antibodies, for example, anti-CD22, may improve the freedom from relapse in some patients already in remission. At this stage, however, until we have totally novel agents available, careful risk-benefit analysis is the only way to assign current therapies appropriately. This raises the possibility that the graft-versus-leukemia (GVL) effect, well recognized in this disease [2] can be harnessed in more patients safely to reduce the amount of relapse without losing the patient to the problems of NRM frequently associated with allogeneic transplantation and unrelated donor transplantation in particular. The value of unrelated transplants of potentially reduced toxicity will need to be assessed [3].

In addressing the issue of how widespread the applicability of allogeneic transplant is in adult ALL the following questions need to be addressed:

1 Is there a GVL effect in adult ALL?
2 Is there evidence from large studies of a "donor versus no-donor" effect beneficial in favor of sibling allogeneic transplantation in adult ALL?
3 Is the constituency for allogeneic transplantation extended by the use of matched unrelated donors—is there any evidence in favor of this?
4 Could the older and higher risk patients benefit from allogeneic transplant—is there any evidence

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for the use of reduced-intensity conditioning (RIC) in this disease?
5 Are there any clues as to who might be eligible particularly for a matched unrelated donor transplant?
6 Are young adults eligible for this approach, because after all, their transplant-related mortality will be low?
7 Is allogeneic transplant still relevant for Ph+ve patients in the era of Tyrosine Kinase Inhibitors?

The best way to approach this debate is to address these questions 1 by 1.

1. Is There a GVL Effect in Adult ALL?

Classical studies such as that as far back as Wieden et al. 1979 [2] show that there is a GVL effect in this disease. This is clearly demonstrated in many other studies, but particularly in the large MRC/ECOG study that shows significant reduction in relapse from the allogeneic effect in both standard and high-risk groups.

2. Is There Evidence from Large Studies of a Donor versus No-Donor Effect Beneficial in Favor of Sibling Allogeneic Transplantation in Adult ALL?

I think that the answer is, that, yes there is indeed a benefit for sibling allogeneic transplant on a donor versus no-donor basis. This is clearly shown in the large MRC/ECOG study [1]. It is not clearly shown in smaller studies such as that of Sebban et al. 1994 [4]. If one looks at the trends across a variety of studies, then the significance of the superiority of transplants on a donor versus no-donor basis seems to be clearly related to the size of individual studies, and therefore will probably be confirmed and reflected in a meta-analysis, bringing together the appropriate data.

Does the evidence in favor of donor versus no-donor for survival in relation to sibling allograft occur for all groups of patients? The answer is that this is far from clear. Standard and high-risk patients are defined differently in different studies. In the MRC/ECOG study, for instance, all patients above 35 years are high risk, all those with B cell disease or a white count of $>30 \times 10^9$L or T cell disease with a white count of $>100 \times 10^9$L with the Philadelphia chromosome or with T4 11, T8 14, complex karyotype, or low hypodiploidy or triploidy. With any one of these factors a patient becomes high risk. With none of them a patient is standard risk. The large MRC/ECOG study again clearly shows a benefit on a donor versus no-donor basis for allogeneic sibling transplanted standard risk groups. It shows it less clearly for high-risk groups. The standard-risk groups do show a benefit for transplant of significance, whereas the high-risk group do not. In a later trial by the French group for high-risk patients, standard risk patients receiving only chemotherapy, on a donor versus no-donor basis there is significantly better disease-free survival (DFS) in the high-risk group with a donor. In the Spanish PETHEMA group [5], high-risk patients, defined slightly differently, did not show a superiorority of transplants on a donor versus no-donor basis, even when Ph+ve ALL patients were excluded.

These results in high-risk patients emphasize the following problems. There is undoubtedly a significant reduction in relapse seen in all these studies via the allogeneic effect, but there are 2 problems. First, the TRM in high-risk patients is such as to abrogate the overall beneficial effect on survival in some studies, and second, many of the studies are powered with too small a number of patients to be able to show significant differences between 1 group and the other.

3. Could Allo Be Extended by the Use of MUD Donors?

In the MRC/ECOG study close to 70 patients had an unrelated donor transplant (see Figure 1). For those under 35 years the overall survival (OS) for a transplant was 58%, and was much superior to that for those over 35 years, which was, in fact, 28%, but the small numbers mean that the *P* value was only 0.1. Relapse-free survival (RFS) from transplant was 78% for the younger group versus 61% for the older group; *P* value here was 0.3. If looked at in terms of Ph status, Ph+ve patients had a survival of 37% and the Ph−ve patients an encouraging outcome with an OS of 58% ($P = 0.2$). In terms of RFS from transplant it was 63% for the Ph+ve patients and 83% for the Ph−ve patients, with a significant *P* value here of 0.04. There is quite clearly other corrobative data here, suggesting encouraging outcomes for the use of matched unrelated donors in adults with this disease. Marks et al. [6] described unrelated donor transplants in 169 adult patients with a median age of 33 years. The TRM, RFS, and OS are 42%,

MRC/ECOG Study

Outcome in MUD transplant patients by selected variables
Outcome given as % at 5 years (standard error)

	Number of patients	Number of deaths	Overall survival from transplant %	Number of relapses	Relapse free survival from transplant %
Overall	67	35	46.2 (6.5)	14	71.4 (6.6)
Patient age at entry					
<35 years	42	18	58.1 (7.8)	7	77.6 (7.6)
≥ 35 years	25	17	27.9 (10.0) p=0.1	7	60.6 (11.8) p=0.3

Figure 1. MRC/ECOG study.