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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.

20%, and 39%, respectively. Multivariate analyses suggested that TRM was significantly higher with HLA mis-matched donors and T cell depletion. In common with other studies that appear to show the outcome from matched unrelated donors (MUDs) to be little different from that with sibling donors in this disease [3]. There is considerable encouragement that unrelated donor transplant could be extended to those who do not have a matched sibling, and this would significantly shorten the overall treatment length for these patients to around 6 months from diagnosis to transplant from the 2 to 2.5 years required to give induction consolidation and maintenance chemotherapy for those not receiving a transplant.

4. What About the Older and High-Risk Patients—Is There Any Evidence for Use of Reduced-Intensity Consolidation?

We can see from the above data, particularly the MRC/ECOG data, that the problem is that the TRM in the high-risk patients, with age as probably the most significant factor, is such to abrogate the overall benefit from transplant, so that with the MUDs as with the sibling donors the age distribution of the MRC/ECOG study and its relevance to OS is clearly shown in the enclosed figure. Patients over the age of 40 years have only a 23% survival in the whole study, and those over the age of 50 years, 15% at 5 years. For patients over 6- years, not studied by MRC/ECOG, the OS is worse still. Because adult ALL has a median age incidence of 60 years, the problem is that by conventional therapy the majority of patients, that is, those over 40, have a very poor outcome indeed for treatments not involving transplant. With allogeneic transplant there is clearly evidence in that age group of a GVL effect, but of a high TRM. It is possible that reduced-intensity conditioning (RIC) in the older patient may represent a way forward with the garnering of the allogeneic effect and a reduction of the TRM. There are several early studies of small groups of patients that might point to this approach being useful (see Figure 2).

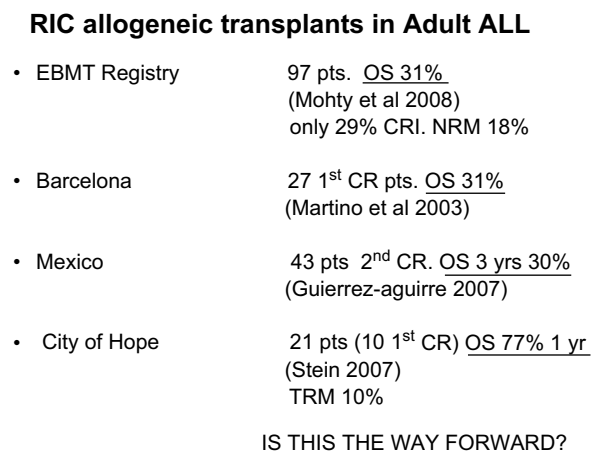

Figure 2. RIC allogeneic transplants in adult ALL.

5. Are There Any Clues As to Who Might Be Eligible for a MUD?

Obviously, the prime candidates would be those without a matched sibling, but still of an age group able to tolerate any form of allogeneic transplant without too much treatment-related risk. A greater risk might be taken in those patients who have very high-risk disease or who respond poorly to treatment when it is initiated. There are some suggestions that any delay in reaching first remission beyond 4 weeks might be indicative of poor prognosis, but this was not substantiated in the MRC/ECOG trial [7]. It appears that for patients who are still MRD positive after 2 courses, it may yet be worth while to go forward with a less well-matched donor, understanding the risk, but considering that the outcome is still likely to be better than with conventional therapy.

6. Are Young Adults Eligible for This Approach?

It may be that the 1 group who should not be considered for allogeneic transplant are adolescents and young adults with ALL. There have been a plethora of publications recently by pediatric groups of apparently superior outcome for adolescents and young adults treated on typical paediatric regimens [8-12]. We are probably in a position where for adolescents and young adults we cannot prospectively study the apparent superiority of pediatric protocols to adult protocols, and have therefore adopted pediatric protocols despite the fact that all comparisons have been retrospective and recognize the difficulty in comparing adolescents and young adults treated in adult settings, with those treated in pediatric units. Pediatric protocols are rather generally more intensive with more Asparaginase and perhaps fewer gaps in therapy. Keeping to time adherence and adherence to dose schedules may also be more common in paediatric approaches.. It is also quite clear that the biology of the disease changes radically between 15 and 20 years and the distribution of these young adults between apparently similar paediatric and adult protocols is never identical. For the young adults, however, in the large MRC/ECOG study those with a donor still had a superior outcome compared to those who did not have a donor. Although it seems likely that we will adapt for the adolescents and young adults to the apparently superior paediatric protocols, it is too early to state unequivocally that an allogeneic transplant approach should be abandoned in this group of patients, especially among adolescents and young adults at high risk.

7. Is Allogeneic Transplantation Still Relevant in Ph+ve Adult ALL in the Era of Tyrosine Kinase Inhibitors?

It has been true for some considerable time that allogeneic transplant represented the best and the only likely way to cure Ph+ve ALL. The results of early allograft have been not unpromising, and some time ago led to the greater use of MUD transplants for those without a matched sibling. These outcomes, too, in the younger recipients, have been encouraging.

However, Imatinab and newer variants have increased the CR rate in this subgroup and reduced the amount of MRD after 1 to 2 months of treatment. It seems likely that the combination of chemotherapy and Imatinab will mean that the risk of an unrelated donor transplant is not worth taking for some patients who might be cured by Imatinab and chemotherapy alone. However, so far, data is inconclusive, and allogeneic transplant cannot be said to have outlived its usefulness.

CONCLUSION

The allogeneic effect clearly reduces relapse in Adult ALL. Very large studies analysed on a "donor versus no-donor" basis and meta-analysis are the only types of data that can adequately address these issues. Smaller studies will inevitably give "*P*" values that do not infer significance and often seemingly give an incorrect "steer" to tentative conclusions are the utility of allogeneic transplant.

Although allogeneic transplant may well have less of a role for the young adult under 25 years, between 25 years and 60+ years encouraging data is emerging of its value in those with and without a sibling donor.

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