

Unrelated Donor Transplantation for CML

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Allogeneic stem cell transplantation (allo-STC) is used with increasing frequency to treat patients with haematological malignancies, bone marrow failure and selected congenital immunodeficiency disorders. In the 1980s transplants were performed mainly using HLA-identical sibling donors, but in the last decade there has been major increase in the number of transplants performed with HLA-‘matched’ unrelated donors. Such donors can be identified in one or other of the 40 unrelated donor registries established in 37 countries. The estimated number of registered volunteers now exceeds 5.5 million.

Today, it should be possible to identify a six-antigen matched volunteer donor for patients of Caucasian origin in approximately 75-80% of cases. Unfortunately, there is considerable racial and ethnic variation in the likelihood of identifying an HLA-A, B and DR identical donor. Amongst black recipients searching the US National Marrow Donor Program (NMDP), a suitable donor will only be identified for 50% of patients. Similar figures for patients of Hispanic and Asian origins are 65% and 55% respectively. Thus to provide donors for recipients with diverse racial and ethnic backgrounds registries of volunteer donors must be as ethnically comprehensive as possible⁽¹⁾. An alternative approach is to increase is the development of cord blood banks.

In contrast, virtually all patients will have a relative (e.g. parent, child, sibling, cousin) who is genetically identical for one HLA haplotype but mismatched for the other haplotype. The feasibility and safety of such ‘haplo-identical’ transplants has been studied by a number of groups, notably by clinicians in Perugia (Italy)⁽²⁾. They have attempted to overcome the known problems of such major HLA-disparity, i.e. graft rejection and graft-versus-host disease (GVHD), by increasing the CD34+ cell dose and improving techniques for T-cell depletion. Their preliminary results suggest that this approach may prove valuable for patients lacking HLA-identical donors.

Factors influencing the outcome of unrelated donor transplantation

The outcome of allogeneic transplantation from both sibling and alternative donors depends on a number of risk factors (**Table 1**), which can be used to aid the decision whether or not to recommend a transplant procedure in a given case. For example, for patients with CML the Chronic Leukaemia Working Party (CLWP) of the EBMT identified prognostic indicators to develop a ‘risk assessment score’⁽³⁾. Each prognostic factor was given a score of 0 to 2 according to the relative risk for transplant outcome based on analysis of results of allografting calculated from 3142 patients reported to the registry of the CLWP. The effect of

each adverse prognostic factor was cumulative for the prediction of survival and transplant-related mortality (TRM). Models such as this will prove valuable for clinicians trying to estimate the risks for an individual patient, but are necessarily oversimplified. They cannot take account of other important but less objective factors in the decision making process, i.e. patient preference, physician preference, patients’ goals, quality of life and recent advances in treatment.

Most of the known risk factors for allo-SCT for CML are common to sibling and unrelated donor transplantation and are discussed below.

Age

The increasing age of the patient is an adverse prognostic indicator of outcome for all forms of adult leukaemia and for all types of transplant. The major risk for older patients is TRM. Thus for children will ALL the clinical results of allografting with alternative donors do not differ greatly from those achieved with sibling donors. In contrast the median age of patients with CML is 55-60 years, so the majority will be too old to be safely offered a transplant using an alternative donor. However, the experience recently reported by the Seattle transplant team suggests that the risks of transplant do not change significantly between the ages of 40 and 60 years, which justifies their upper age limit of 65 years⁽⁴⁾.

An alternative approach is the so-called ‘mini-allograft’ in which the conditioning therapy is reduced to the minimum necessary to ensure a degree of donor engraftment and an anti-leukaemic effect. Continuing remission is thereafter dependent on the presence of, and supplementation with, donor-derived lymphocytes to reinforce the graft-versus-leukaemia effect⁽⁵⁾. Preliminary results suggest that this approach can achieve donor-derived haemopoiesis and re-

Table 1: Factors affecting the outcome allo-SCT for CML

Patient age
Phase of disease
Interval from diagnosis to transplant
Prior chemotherapy, incl. IFN- α
Degree of HLA-disparity with donor
Recipient/donor gender combinations
CMV serostatus
Conditioning regimen
Source of stem cells
Cell dose (CD34+ & CD3+)
Method for GVHD prophylaxis

sult in prolonged disease free survival^(6,7). If this strategy can be extended to use in the setting of T-cell depleted and/or unrelated stem cell transplantation, it may reduce the TRM associated with a conventional transplant.

Disease phase

This is the single most important determinant of transplant outcome both in HLA-identical sibling and 'HLA-matched' unrelated donor transplants. The differences in outcome are not simply due to an increased risk of relapse in patients treated for more advanced disease, but are also affected by an increase in non-relapse or (TRM).

Interval from diagnosis to transplant

Several large studies have identified decreased survival in association with increased time periods between diagnosis and transplant, particularly for those patients treated for CML. In this disease the best results in HLA-identical sibling donor transplants are seen if the transplant is performed within one year of diagnosis⁽⁸⁾. Until recently the effect of delay from diagnosis to transplant in unrelated donor procedures has been less clear. Devergie et al recently analysed the outcome of 366 recipients of unrelated donor transplants for CML who had been reported to the registry of the EBMT CLWP⁽⁹⁾. Transplant after the median duration from diagnosis to grafting of 827 days was associated with poorer outcome, an effect also recognised by McClave et al⁽¹⁰⁾ and the Seattle group⁽¹¹⁾.

Gender

Several analyses have reported that the use of female donors adversely affects the results of HLA-identical sibling transplantation, because of an enhanced risk of GVHD. This is clearly a complex issue. If a patient has a choice of donors then gender may be a valuable guide to donor choice. For male patients at increased risk of TRM (e.g. older age, HLA-disparity) female donors should be avoided. For female patients at high risk of relapse (e.g. advanced phase disease) female donors may be more appropriate.

Cell dose

Two recent publications have highlighted the importance of high stem cell dose in determining transplant outcome. Sierra et al have shown that nucleated cell doses in excess of $3.65 \times 10^8/\text{kg}$ were associated with improved survival in recipients of unrelated donor allo-SCT for acute leukaemia⁽¹²⁾. Similarly, the Genoa transplant group identified this effect in HLA-identical sibling transplants⁽¹³⁾. With an increasing trend towards the use of peripheral blood derived stem cells (PBSC) in sibling grafts, which seem not to increase the incidence and severity of acute GVHD, maximising nucleated cell doses may prove a simple but effective way of reducing TRM. If the lack of an increased incidence of both acute and chronic GVHD and the safety of recombinant growth factors can be confirmed, then it is likely that clinicians will favour the use of PBSC for unrelated donor transplants as well as for sibling transplants.

Degree of HLA-disparity

Although the influence of increasing degrees of HLA-disparity on transplant results is well recognised, in practice it is an extremely difficult area of analysis. A number of methodologies of varying levels of sophistication are now available to identify HLA-antigens, e.g. serology, isoelectric focusing and high resolution DNA analysis, and functional compatibilities, eg: mixed lymphocyte culture (MLC), cytotoxic and helper T-cell precursor frequencies (CTLp and HTLp) (reviewed in ref 14). The consequence of the availability of improved matching techniques is that a 'perfect' match is rarely found. Moreover, the search for the perfect match delays the transplant, thereby increasing the risks of disease progression and TRM.

Whilst accepting the difficulties inherent in donor identification, the effects of disparity are clear. Several large series have identified the adverse effects of HLA-DRB1 and DQB1 mismatching^(9,11,15). Mismatches at these loci are associated with an increased incidence of severe GVHD and lower survival rates. Mismatches for class I HLA-antigens also result in lower survival. The presence of high frequencies of cytotoxic T-cell precursors (which reflect mainly HLA class I disparities) predicts an increased incidence and severity of GVHD. However, the outcome for patients transplanted in chronic phase from donors identical for HLA class I by serology and for class II by high resolution DNA typing is now approaching that of patients transplanted from HLA-identical sibling donors⁽¹¹⁾.

T-cell depletion

Although T-cell depletion of donor stem cells can effectively reduce the incidence and severity of GVHD, the technology is associated with increased risks of graft failure and disease recurrence and has largely been abandoned in HLA-identical sibling transplantation. T-cell depletion is, however, frequently used in unrelated donor allografting. The Seattle transplant team do not employ T-cell depletion and recent reports from this group and that of the Hammersmith Hospital in London (where in vivo T-cell depletion is routine practice) have allowed a comparison of the two approaches in patients transplanted for CML. Hansen et al analysed 196 patients transplanted in first chronic phase and found an overall survival at 5 years of 57% and a relapse risk of 10%⁽¹¹⁾. In patients aged less than 50 years, who received marrow from donors well matched for HLA-A, -B and -DRB1 within 12 months of diagnosis, the 5-year survival rate was 74%. The authors acknowledged the effects, not only of known risk factors, but also of improved supportive care with anti-fungal prophylaxis and pre-emptive treatment for CMV reactivation. The 5-year survival rate of patients transplanted in first chronic phase at the same centre is 77%, thus confirming the close approximation of results from related and unrelated donors. However, the incidence of acute GVHD of grades II-IV was 77% in recipients of well matched stem cells and 89-95% for patients receiving mismatched marrow. Extensive chronic GVHD occurred in 67% of survivors.

In contrast, the use of T-cell depletion by the Hammer-smith group results in a much reduced incidence of acute and chronic GVHD but a lower overall survival. The results of transplant are, however, significantly affected by the CMV serostatus of the recipient. The 5-year survival of CMV-seronegative patients transplanted in first chronic phase from donors compatible by high resolution HLA-DR typing is also 75%, whereas the outcome of CMV seropositive patients is much poorer at 17%. The incidence of acute GVHD of grades III and IV in the entire population is 18% and of extensive chronic GVHD, 36%. The combined influence of CMV status and CTLp frequency has previously been shown by this group to be an extremely powerful predictor of outcome. There were no survivors in the group with both CMV seropositivity and high frequency CTLp. For CMV-seronegative patients with well-matched donors the outcome is equivalent to that seen in Seattle with an acceptably low incidence of severe acute and chronic GVHD. For CMV seropositive patients the use of T-cell depletion in its current form must now be reconsidered.

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