Who is the best alternative allotransplant donor?

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Abstract

Assuming that most physicians will chose an HLA-identical sibling as the best allotransplant donor, the question arises who is the best alternative donor when an HLA-identical sibling is unavailable? The most commonly used alternative donors are HLA-identical or -mismatched unrelated donors, HLA-matched or -mismatched umbilical cord blood donor or a related, HLA-haplotype-matched related donor. Each alternative donor option has advantages and disadvantages. We discuss selected aspects of these issues based on data from randomized clinical trials and observational databases. However, because there are limited data to address specific clinical settings, quantification of expert opinion is sometimes needed.

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Introduction

In a person slated for an allotransplant, most physicians will choose an HLA-identical sibling. However, when such a donor is unavailable who is the next best donor: an HLA-matched unrelated donor (URD), an HLA-matched or -mismatched umbilical cord blood (UCB) donor or an HLA-

haplotype-matched related donor? Unfortunately, this question cannot be simply answered or perhaps not answered at all. For example, many subject-, disease- and transplant-related variables beside donor availability enter the calculus. Examples include donor and recipient age, gender, mass (or body surface area), co-morbidity and frailty, disease and disease state, prior therapy(ies), relapse risk, proposed pre-transplant conditioning, type of graft (such as blood vs. bone marrow cells), post-transplant immune suppression, risk of GVHD and others.

Background

Data from the Center for International Blood and Marrow Research (CIBMTR) indicate ~ 4300 URD transplants in the US in 2012; substantially greater than the number of related donor transplants. In ~ 70% of transplants the graft was blood cells. Approximately 15% of each of the remaining URD grafts were bone marrow or UCB. The age distribution of URD in adults in ~ 40% of each ages 18–50 and 50–65 years and 20% age >65 years. Amongst UCB transplant ~ 50% are <16-years old[1].

Outcomes

Global unadjusted data reported by the CIBMTR on 1-year survival of URD transplants in 2011 was ~ 60% and was significantly better in recipients <50 years vs those >50 years. In each age cohort the result was significantly, although not substantially, worse than results of transplants from HLA-identical siblings. Causes of death after URD transplants were predominately disease persistence/ recurrent (~35%) and GVHD and infection (~15%) [1]. Outcomes in different diseases varied. In persons with AML, disease state was a strong determinant of 5-year survival: ~ 45% in persons with early and intermediate state disease vs 20% in those with advanced disease in unadjusted analyses. In persons with ALL <20 years old, 5-year survivals were ~ 60, 50 and 30% in early, intermediate and advanced disease states. In persons >20 years parallel outcomes were about 10% less in each cohort. Age similarly negatively impacted 5-year survivals in persons with aplastic anemia with 5-year survivals of 70 and 60% in those < or >20 years. Five-year survivals in Hodgkin lymphoma (30%), mantle cell lymphoma (35%) and plasma cell myeloma (20%) were in each setting worse than the outcomes of transplants from HLA-identical siblings in unadjusted analyses[1].

Comparison of alternative donors

To compare options we need to consider several issues including, but not limited to, which type of alternative donor is best and how outcomes compare between different alternative donors. But the overwhelmingly important question is when is an alternative donor transplant appropriate? Because we have difficulty answering this question even with an HLA-identical sibling donor, it is unlikely we can answer this question precisely in the context of an alternative donor. (Harried readers can skip to the summary).

A fundamental issue in analyzing these questions is what criteria should be used to evaluate validity of data-based conclusions. We suggest the following: strength of the evidence; consistency of results; a consideration of alternative explanations; clinical, statistical and biological plausibility of the conclusion; and applicability of the conclusion and coherence of analyzable data. The sum of these considerations influences the credibility we should accord conclusion or the sum of data such as in meta-analyses.

With these rules in mind we can now consider which variables operate in the alternative donor transplants including the subject, donor, graft, disease and disease state, pre-transplant conditioning and post-transplant immune suppression (mostly GvHD prevention). Obviously many of these variables are confounded, a factor which is often ignored in studies of small sample size and especially when multivariate analyses are not done or not reliable (such as <100 subjects). For example, frailer recipients are more likely to receive a reduced-intensity vs. conventional pre-transplant conditioning. In this discussion we focus on leukemia-free survival (LFS) because most alternative donor transplants are for leukemia and the object of most transplants is cure. Others might argue for a survival endpoint.

HLA-identical siblings vs unrelated donors

A few examples: in a large observational database analysis from the CIBMTR of persons with AML in all disease states and receiving diverse pre-transplant conditioning regimens, use of an URD was associated with worse adjusted LFS compared

with HLA-identical sibling transplant[2]. Hazard ratios (HR) for failure to achieve LFS increased parallel to the degree of HLA-disparity of the URD: 8/8 HLA-matched, HR = 1.26 (95% confidence interval, 1.14–1.30; P =10^{-3}), 7/8 HLA-matched, HR = 1.42 (1.29–1.58; P = 10 × $10E^{-3}$) and < 7/8 HLA-matched, HR = 1.81 (1.58–2.06; P =10^{-3}). Other studies report comparable outcomes using HLA-identical sibling donors and URDs. For example, in another CIBMTR study in adults with AML in the first remission and poor-risk features at diagnosis, adjusted 3-year LFS was comparable in 8/8 HLA-matched URD transplants but inferior in < 8/8 HLA-matched URD transplants (HR for failure = 1.38 (1.02–1.87); P = 3.8 × $10E^{-3}$)[3]. Another CIBMTR study of adults >50 years with AML in the first remission compared LFS after HLA-matched and –mismatched URD trans-plants and HLA-matched UCB transplants. Here HRs for LFS for HLA-matched and -mismatched URD transplants were similar but the HLA-mismatched UCB transplants had poorer survival (HR = 1.35 (1.16–1.76); P = 8 × $10E^{-4}$)[4]. A reasonable conclusion of these data in AML is HLA-identical sibling transplants and 8/8 HLA-matched URD transplants results in approximately comparable or only slightly worse outcomes for URD transplants whereas transplants from <8/8 HLA-matched URDs and from UCB donors have slightly worse LFS. We cannot exclude the possibility this gap is narrowing.

HLA-haplotype-mismatched transplants

We now move from the unrelated to the related donor, but first we need to resolve some nomenclature. Although these transplants are referred to as HLA-haplotype-mismatched, this is not always an accurate descriptor. For example, some recipients who share an HLA-haplotype with their donor are also matched (not necessarily identical) for one or more HLA-antigens on other HLA haplotype. A detailed discussion of the implications of these HLA-matches/-mismatches and whether they arise from either parent is beyond the scope of this report, in which we consider these variations under the heading HLA-haplotype-mismatched transplants. This seems reasonable because there are few clinical trials outcomes data to accurately sort out these variations.

Some comparisons of outcomes of HLA-haplotype-mismatched transplants use as a control transplants from HLA-matched URDs. It is therefore necessary to know if a graft of blood vs bone marrow cells is important in the URD setting and needs adjustment before comparing the outcomes. In the Blood and Marrow Transplant Clinical Trials Network study 0201, results of blood vs bone marrow grafts from HLA-matched URDs had comparable outcomes[5]. Consequently, we grouped these types of grafts. Likewise, in a recent meeting outcomes of HLA-haplotype-matched transplants with in vitro modification of the graft or with no in vitro modification but with post-transplant immune suppression with cyclophosphamide had similar outcomes. Consequently we grouped these approaches. Whether these approaches will be shown to have different outcomes awaits randomized comparisons; these are unlikely to be done. Other perturbations such as using blood and/or bone marrow collected after treating the donor with molecularly-cloned hematopoietic growth factors (such as G-CSF) and/or posttransplant immune suppression with methotrexate and cyclosporine also seem to have similar outcomes. Grouping of these approaches seems reasonable presently because of the lack of high-quality observational database analyses of the impact of these variables on transplant outcomes and the lack of similar randomized trials addressing these issues.

Another comparator cohort for HLA-haplotype-mismatched transplants are recipients of UCB donor transplants. Consequently, we need to know whether using one or two cord blood cell units affects transplant outcomes. Analyses of randomized trials in children and observational databases in adults suggest no substantial difference in LFS. Consequently, we also grouped these approaches.

Results of two modest size (N = 50) phase-2 studies of UCB transplants (Blood and Marrow Transplant Clinical Trials Network 0603) and of HLA-haplotype-mismatched transplants (Blood and Marrow Transplant Clinical Trials Network 0604) are shown in Figure 1. Entry criteria were comparable and outcomes appear similar[6].

These data are the background for a definitive comparison of these approached in adults with leukemia who will be randomly-assigned to receive an UCB transplant (two units) or a HLA-haplotype-mismatched transplant.

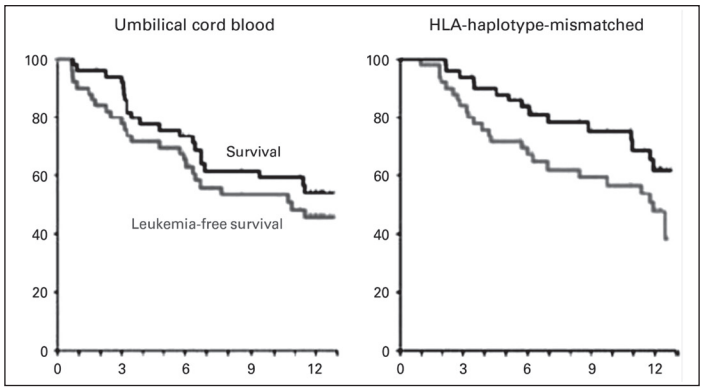

Figure 1. *CIBMTR Clinical Trial Network Trials 603 and 604.6*

Table 1. Comparison of alternative donors

	URD	*UCB*	*HLA-haplotype*
Available	++	++	++++
Graft-failure	+	++++	++
GVHD	++	+	++++
Infection	++	++++	+++
Relapse	++	++++	++
LFS	+++	++	++

Abbreviations: HLA-Haplotype, HLA-haplotype-matched related donor; URD, HLA-matched unrelated donor; UCB, HLA-matched umbilical cord blood donor. Comparison of alternative donors for allotransplants. Arbitrary scoring events and outcomes on an ordinal scale of + (least likely) to ++++ (most likely).

However, we also need to admit limitations even of randomized trials. First, most subjects who might in the future receive an alternative donor transplant will not have the study-entry features as persons entered into the randomized trial. This means conclusions of the trial need not apply to them. Second, randomized trials inform us of the relative outcomes of therapies applied to a cohort, not to a person. There are many examples where the outcome of an intervention in a cohort is better than the controls but where one can prospectively identify subjects in the cohort, intervention is unnecessary. Third, progress in technology may affect 1 or both arms of a randomized trial such that the conclusion of data from today may not inform a decision 5 or 10 years later. Fourth, although the therapy-intervention of interest may be randomly-assigned, many subsequent therapy-interventions are not specified, cannot be controlled and may occur nonrandomly. In this regard many, if not most, randomized trials with a long-term end point evolve into an observational database. Fifth, randomized trial cannot simulate the diversity of subject-, disease- and transplant-related variable which a physician must consider when recommending a therapy or therapy-strategy[7].
A summary of relative benefits and risks of different alternative donors is shown in **Table 1**.

Who should receive an alternative donor transplant
This is, of course, the key question. If no one should receive an alternative donor transplant we do not need to worry which alternative donor is best. But if everyone without an HLA-identical sibling needs an alternative donor transplant we face a huge challenge. Judging who needs an alternative donor transplant depends predominately on our ability to accurately predict how a person (not a cohort) will do without a transplant. For example, although it is widely believed a transplant is needed in everyone with AML who relapses, several prognostic scoring systems can accurately identify a cohort with a 50% likelihood of 5-year LFS after relapse[8]. When one takes the variables used to develop prognostic scoring systems in AML at diagnosis and uses them in a receiver–operator characteristic curve which more accurately defines the ability of a test to predict outcome in a person (vs a cohort) we find these prognostic systems only slightly better than a coin-

flip[9]. This is especially so when such prognostic system are applied to persons with AML achieving CR and not relapsing in the first 3–6 months when transplant decisions are typically made.
The bottom line is absent variables or tests which are more sensitive and specific for predicting the outcome, quantification of expert opinion may be our best tool. Results of genetic analyses and testing for so-called minimal residual disease (better termed measurable residual disease) are unlikely to substantially improve this calculus[10].

Summary

Although the purpose of this typescript is to identify who is the best alternative donor, we admit to not knowing the answer. Nor do we know precisely who should receive an alternative donor transplant. We hope the reader is not disappointed but, trust us, no one else knows; beware of the false Messiahs and we beg the reader's mercy to consider this remark from Voltaire: 'Judge a man by his questions rather than by his answers."

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Declaración de conflictos de interes:

Los autores declaran no poseer conflictos de Interés.

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