Published in final edited form as:

Best Pract Res Clin Haematol. 2013 September ; 26(3): 293–296. doi:10.1016/j.beha.2013.10.010.

Which donor or graft source should you choose for the strongest GVL? Is there really any difference

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Abstract

Patients undergoing allogeneic hematopoietic cell transplantation (HCT) face relapse of their malignancy as the most frequent cause of treatment failure. It has been postulated that the allogeneic neoplastic potency of different donor or graft sources may differ and in some situations, a particular graft source might be preferred. Data on this supposition has been reviewed here to consider HLA-matched siblings, HLA-matched or partially matched unrelated donors (URD), unrelated umbilical cord blood (UCB), and haploidentical as well as blood or marrow grafts.

Keywords

Bone marrow; graft source; graft-versus-leukemia; GVL; haploidentical; HCT; hematopoietic cell transplantation; HLA-matched donors; peripheral blood; relapse; UCB; umbilical cord blood

Introduction

Many allogeneic graft sources—whether bone marrow, peripheral blood stem cells (PBSC), or umbilical cord blood (UCB)—can produce a potent antineoplastic graft-versus-leukemia (GVL) effect. Whether the donors are matched and related, siblings, or unrelated, old, young, single or double units, all have the potential to induce valuable and essential components of the anticancer effect of an allograft. Because each graft type is associated with treatment-related mortality (TRM), the choice of which type of graft and donor to use may best be guided by graft availability and the patient's tolerance and predicted risk for TRM.

Does the donor matter?

The potency of the GVL effect was directly examined in a study from the Center for International Blood and Marrow Transplant Research (CIBMTR) [1]. The adjusted probability of relapse for chronic myeloid leukemia (CML), the disease that serves as the

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Disclosure:

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No relevant financial relationships with any commercial interest.

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poster child for being most amenable to the GVL effect, showed no advantage for an unrelated donor. The risk of relapse with an unrelated donor (URD) compared to matched siblings was similar (relative risk [RR] =0.83, 95% confidence interval, 0.6-1.5, $P=0.25$). Because allelic differences between a nonrelated and matched sibling might induce a more potent antineoplastic effect, Arora et al examined over 3,000 matched sibling donors compared to single or multiple allele mismatched unrelated donors [2]. While relapse rates were low overall (7%-14% at 5 years), in multivariate analysis there was no advantage associated with URD either allele matched or mismatched vs sibling donors in yielding better protection against relapse.

For acute myeloid leukemia (AML), the results were similar. The Ringdén analysis demonstrated higher risks of relapse (RR=1.43, 95% confidence interval, 1.11-1.85, $P=.005$) comparing URD to matched sibling after transplantation for AML [1]. A more recent update [3] addressing the same question identified similar risks of relapse comparing 8/8 allele matched URD vs matched related donors and 8/8 allele matched vs 7/8 allele matched URD. A modestly lower relapse risk (RR=0.78, 0.63-0.98, $P=.03$) was observed comparing the partial matched 7/8 URD to matched related donors, but was strongly counterbalanced by 50% greater risks of treatment-related mortality (TRM). Overall, all three groups had equivalent risks of treatment failure, the inverse of disease-free survival.

Does donor age matter?

It has been recognized in some, but not all series that younger donor age may be associated with a more cellular graft, more vigorous immune reconstitution and better survival. An earlier National Marrow Donor Program (NMDP)/CIBMTR analysis suggested 3% lower overall survival for each 15 years of greater donor age when all donors were unrelated [4]. Since siblings are usually close in age, it was postulated that older sibling donors might yield poorer transplant outcomes than younger URD or than cord blood, the youngest URD. Alousi et al recently examined donor age and recognized less relapse using matched sibling donors compared to younger URD, but only for recipients with good performance status [5]. In those with Karnofsky performance status < 80, relapse rates were similar in the older siblings (recipient over 50 years and sibling donor similar in age) compared to URD (patients older than 50 years and URD younger than 50 years). When adjusted for disease, disease status, conditioning intensity and year of transplant, a modest reduction in relapse rate led to superior survival with matched sibling donor over the age of 50 years for the patients with good performance status. Younger unrelated donors were not better.

Does graft type matter – marrow vs peripheral blood vs UCB?

Bone marrow vs peripheral blood stem cell (PBSC) grafts were formally tested in a prospective randomized trial through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), where 550 unrelated donor recipients were randomly assigned to blood or marrow grafts [6]. Relapse incidences were similar and disease-free survival, survival, and acute graft-versus-host disease (GVHD) were also similar. Chronic GVHD was more frequent in PBSC recipients, though it was not associated with any reduction in relapse. Formal comparisons with UCB and URD marrow or PBSC grafts have also been reported [7]. Relapse rates did not differ between partial matched UCB and 8/8 or 7/8 allele matched marrow transplants or 8/8 or 7/8 allele matched PBSC transplants. Relapse rates were 26%-34% in all groups ($P=0.86$). That led to similar leukemia-free survival using any of the graft sources (UCB, marrow, or PBSC matched or mismatched).

Children present for transplantation with differing diseases and have less risk of GVHD, potentially altering the balance between the hazards of GVHD and the antineoplastic

benefits of GVL. Relapse risks in sibling vs URD vs UCB transplants in children with ALL were recently compared [8]. Relapse risks in all three groups were similar with no statistical advantage for either. The greater alloreactivity associated with URD marrow (HLA-matched or mismatched) or UCB compared to sibling transplants did not alter relapse rates, which were 29%-37% in all four groups.

An earlier report [9] observed reduction in relapse risks for pediatric leukemia recipients of UCB compared to URD marrow (HLA-matched or mismatched). In this report, a lower adjusted relapse risk (0.54-0.68) was observed in all UCB transplants and was statistically significantly lower compared to URD matched marrow using either high cell dose UCB grafts matched at 5/6 HLA-loci or 4/6 matched grafts with any UCB dosing. Because of concerns that early treatment-related, non-relapse mortality could prevent observation of later relapse protection, landmark analyses at 6 and 12 months in the leukemia-free survivors were repeated. They similarly showed statistically significant lower relapse rates in UCB 4/6 matched transplants compared to URD bone marrow (RR=0.41-0.50, $P<.004$).

Double vs single UCB

Double cord transplants, pioneered at the University of Minnesota, were recognized to yield lower relapse risks than single cord grafting [10]. In this report, significantly lower relapse risks were seen in double UCB recipients of transplants for either acute lymphoblastic leukemia (ALL) or AML, even considering the more frequent use of double cord grafting in adults and single cord grafting in children. To address this more directly, a combined University of Minnesota and Fred Hutchinson Cancer Research Center (Seattle) research study evaluated matched or mismatched URD grafts and matched sibling donor transplants, all using myeloablative conditioning with cyclophosphamide plus fractionated total body irradiation (TBI) [11]. In this study, the matched siblings from both centers had equivalent outcomes representing an internal control for study validity. Double cord recipients (mostly from Minnesota) had the lowest relapse rates (<20% at 5 years) compared to the other three groups including the URD recipients (mostly from Seattle). This translated to the best survival and leukemia-free survival for recipients of double UCB and matched URD transplants. Similar observations were presented at European Group for Blood and Marrow Transplantation (EBMT) by Rocha et al describing Eurocord data, where adults with acute leukemia transplanted in first complete remission had 15% relapse at 3 years following double cord, but higher 25% relapse rates after single cord grafting ($P=0.03$). The results were confirmed in adjusted multivariate analysis.

The BMT CTN, however, found different results in Protocol 0501: A Randomized Trial Comparing Double vs. Single Cord Grafting in Children with Acute Leukemia (recently presented at the American Society of Hematology meeting, December 2012, abstract 359). While low rates of relapse were observed in the double cord recipients (approximately 14% at 1 year), this was identical to the 12% relapse risk in the single cord recipients and other outcomes were similar in both cohorts. Other series including mostly adults with double cord grafting [12] associated with reduced relapse risks, were not reproduced in this series with only children. Surprisingly, in the BMT CTN trial, it was observed that relapse rates in children are strikingly low, even after large single cord unit transplants. Results in adults for whom single cord grafting uses only a smaller unit may differ from children because of different diseases being treated, higher risk populations in the adult recipients, and more frequent HLA-mismatch in adults receiving cord blood grafts. It is also possible that the higher frequency of GVHD following double cord grafting in adults may be associated with more potent GVHD associated GVL, but that hypothesis remains speculative.

Reduced intensity grafting where GVL is critical: Does the graft matter?

Brunstein et al compared double cord transplants and unrelated peripheral blood transplants following reduced intensity conditioning [13]. The data were separated by double cord transplants using the Minnesota protocol of low dose TBI, cyclophosphamide and fludarabine (TCF) vs other reduced intensity cord blood regimens, which have been associated with twice the rate of TRM. When analyzed for relapse risk, however, double cord grafting with the Minnesota regimen or other regimens had similar relapse rates compared to 8/8 allele matched PBSC URD transplants or 7/8 allele matched URD transplants. In this setting, double cord grafting did not have the strongest GVL, but was equivalent to URD PBSC.

What about haploidentical transplants?

Lots of recent interest has rekindled enthusiasm for haploidentical transplantation, particularly using the technique of posttransplant cyclophosphamide developed at Johns Hopkins University to blunt alloreactivity and limit the hazards of GVHD[14]. While little formal comparative data is available, Bashey recently reported comparative outcomes of matched related, matched URD, and haploidentical transplantation, all using a similar posttransplant cyclophosphamide technique[15]. Relapse rates in all three groups (33%-34%) were similar. Survival and disease-free survival outcomes were similar as well.

Is there a bottom-line?

Many allogeneic graft sources can produce potent antineoplastic GVL. Bone marrow, PBSC, and UCB from matched related donors, siblings, URD, UCB, single or double, old or young, can all induce valuable and essential components of the anticancer effect of an allograft. Because associated TRM and competing morbidities may differ with the different grafts, their availability and the patient's tolerance and predicted risk for TRM may better guide the choice of graft and donor option to yield the best transplant outcome. All allogeneic donor options induce GVL and thus all still have their place in the armamentarium.

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