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Is there a best graft source of transplantation in acute myeloid leukemia?

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A B S T R A C T

Only 30% of patients in the US who require an allogeneic hematopoietic cell transplant will have a fully HLA matched sibling donor. The National Marrow Donor Program/Be the Match has grown to over 25 million unrelated donors. However, a fully matched unrelated donor may not be available for many patients, particularly for patients of diverse racial and ethnic backgrounds. Over the last 10 years, considerable progress has been made in alternative donor transplant with improvements in outcomes for umbilical cord blood (UCB), haploidentical (haplo) related donor, and mismatched unrelated donor (MMUD) for patients with acute myeloid leukemia. Retrospective studies indicate comparable survival for these three graft sources. In this chapter, we review the latest results for patients receiving alternative donor transplants, and discuss strategies for choosing the optimal donor for each individual patient.

Clinical case and introduction

Mrs. X is a 38-year-old woman of French Canadian descent with fms-related tyrosine kinase 3 (FLT-3)-positive acute myeloid leukemia (AML) in second complete remission (CR 2). She is an only child, with no children, and elderly parents. She has no haploidentical (haplo) or matched unrelated donor

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(MUD) options. A 9/10 allele level human leukocyte antigen (HLA) mismatched unrelated donor (MMUD) and two 4/6 HLA matched umbilical cord blood (UCB) units of sufficient cell dose are available. After discussion of risks and benefits, she undergoes a double umbilical cord blood transplant (UCBT). She receives post transplant sorafenib on protocol due to the flt-3 positivity [1]. She has a complicated post transplant course with human herpes virus (HHV)-6 reactivation, strep mitus bacteremia, prolonged nausea, and cord colitis syndrome. She is in complete remission, back to work and with performance status of 0, now 3 years after double UCBT.

While most hematologists would agree that the best curative therapy for a young patient with AML in CR 2 is allogeneic hematopoietic cell transplantation (HCT), the graft source choice remains controversial. The same patient might be offered a MMUD in another transplant center. If she had a haplo donor, would a haplo HCT be preferred donor? How is the best donor chosen?

Given the size of most families in the US and other economically developed countries, only 30% of patients will have a matched sibling donor. In other countries where culture encourages larger families and intermarriage, the number may be significantly higher [2,3]. The National Marrow Donor Program (NMDP)/Be the Match was established in 1986 with support from the US Navy among others [4]. Despite 25 million volunteer unrelated adult donors, only 67% of White patients and 23% of Black patients will have a fully matched unrelated donor [5]. Over 5000 patients each year may be candidates for alternative donor transplant, but no randomized, prospective data are available to aid in the decision of the best graft source [6]. In this review, we address the outcome data for each approach in adults with AML, comparing differences in graft-vs-host disease (GVHD), relapse, infection, and cost. We discuss current graft selection strategies, the ongoing randomized trial, and the outlook for the future.

Umbilical cord blood transplantation

The first UCBT was performed in France in a child with Fanconi anemia in 1988 [7]. Over 35,000 UCB have been performed worldwide and over 720,000 UCB units have been donated for public use [8]. UCB is available within days, and because HLA matching does not need to be as stringent as with adult donors (due to the naïve immune system of the UCBT cells), donors may be more easily identified for a diverse group of patients; for example, Barker and colleagues have estimated that 56% of UCB recipients were of non-European descent, compared to 23% of MUD patients [9]. HLA-matching models from the NMDP suggest that suitable UCB units are available for all patients under age 20, and for more than 80% of patients 20 years and older, regardless of race or ethnicity [10].

The first UCBT were single-unit UCBT using a myeloablative preparative regimen in children. With the use of UCB units with adequate cell dose, these single UCBT were extended to adults. The Japanese groups have particularly impressive results, with a 5-year disease-free survival (DFS) of 60%–70% [11]. Double UCBT has become more popular than single UCBT for adults with AML in the US, perhaps related to the heavier weight of Americans (about 10 kg heavier than Europeans, and 15 kg heavier than Asians) [12]. There are no randomized studies in adults comparing single to double UCBT; however, the Bone Marrow Transplant Clinical Trials Network (BMT-CTN) has shown comparable survival between single and double UCBT in children [13].

The median age of patients with AML is 68 years; therefore, a reduce-intensity conditioning (RIC) or nonmyeloablative approach is an attractive option. Brunstein reported a 38% 3-year DFS for patients treated with RIC double UCBT, using a preparative regimen of fludarabine, cyclophosphamide, and low-dose total body irradiation (TBI) [14]. We have reported a 1-year DFS of 67% using an RIC regimen of fludarabine, melphalan, and rabbit antithymocyte globulin [15]. The use of sirolimus and tacrolimus for GVHD prophylaxis resulted in a very low rate (9%) of grades II-IV GVHD [16].

What is new in umbilical cord blood transplant?

Several centers have attempted ex vivo expansion and homing techniques to improve engraftment and immune recovery. A multicenter collaboration tested expansion of UCB in the presence of nicotinamide (Nicord) [17]. Median neutrophil recovery was reduced to 13 days (historical control 25 days) in a small study of 11 patients, receiving one manipulated and one unmanipulated unit. De Lima and