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The role of second transplants for leukemia

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Abstract

Management of relapsed leukemia following allogeneic transplantation is challenging. Intensive chemotherapy, donor lymphocyte infusions (DLI), or second transplantation have some value, but most reported series describe only a limited number of patients surviving beyond 2 or 3 years following relapse. Additionally, understandable selection-bias of reports describing the outcomes of intensive management approaches for relapsed leukemia confound generalizability to a broader population. However numerous reports suggest that second allogeneic transplantation for relapsed leukemia following an initial transplant may produce extended disease control and survival for patients with favorable performance status, remission at the time of second transplant, and most importantly a long interval between initial transplant and relapse. Reduced intensity conditioning for second allografts may be preferable and little data exists to suggest that a new donor will improve disease control by inducing a stronger graft-versus-leukemia effect. Improved measures to prevent the first relapse, however, may protect more patients and produce a greater fraction enjoying extended leukemia-free survival.

Keywords

Allogeneic; Allotransplant; CIBMTR; Center for International Blood and Marrow; Transplant Research; DLI; Donor lymphocyte infusion; EBMT; European Group for Blood and Marrow; Transplant; HCT; Hematopoietic cell transplantation; Leukemia; Second transplant

Introduction

The rigors of allotransplant are survivable, but only control acute leukemia for 40%–70% of allograft recipients depending on the cytogenetic and molecular risk, phenotype, and remission status of the patients. Relapse after allotransplant generally leads to poor survival with only 10%–20% of patients surviving beyond 2 years [1–7]. Notably however, patients receiving intensive chemotherapy supplemented with either donor lymphocyte infusion (DLI) or second transplants can have improved survival over those receiving supportive care alone [6,8–17]. Survival after relapse is inferior in those with circulating blasts at relapse, active infections, or other complications. Second transplant approaches using sibling,

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unrelated donor (URD), or umbilical cord blood (UCB) transplantation have been reported to have similar outcomes [1,2,9,18–28].

Second transplants are sometimes performed for incomplete donor chimerism with an additional infusion of hematopoietic stem and progenitor cells to boost engraftment. They can also be used as treatment for graft failure, but reconditioning plus a second graft infusion is essential and only successful for a minority. Most second transplants, however, are done for relapse (Table 1).

In a large Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of AML relapsing after allografts, only 23% of 1788 relapsed patients survived more than a year post relapse [1]. However, longer survival was associated with later post first transplant relapse (Fig. 1). Five-year survival from relapse was nearly 40% for those relapsing beyond 3 years and 30% for those relapsing 2–3 years after initial allograft. These results were not significantly influenced by patient age, suggesting that disease risk characteristics dominated the outcome. Multivariate analysis confirmed improved survival for those relapsing beyond 2 years, whether treated with DLI or a second allograft. Second transplant success may be similar with matched related donors or unrelated donors, but reported experience with haploidentical donor transplantation for second allografts is scant.

Same or different donor

It is often postulated that changing donors for a second allograft may be favorable with hopes of inducing a more potent graft-versus-leukemia (GVL) effect. An earlier CIBMTR and more recent European Group for Blood and Marrow Transplant (EBMT) analyses failed to support this hypothesis [19,20,27]. In the earlier CIBMTR analysis, second transplants were associated with similar risks of acute graft-versus-host disease (GVHD) (perhaps more if acute GVHD had followed the first allograft), but particularly more chronic GVHD if a different donor was used for the second transplant [19]. This did not, however, yield improved survival compared to second transplants performed using the same, original donor. The more recent, large EBMT analysis demonstrated no difference in relapse incidence, non-relapse mortality, overall survival or relapse-free survival when the same donor (N = 1884) or a different donor (N = 712) was chosen for the second transplant [27] (Fig. 2).

Second allograft following earlier autograft

Allografting for treatment of AML relapse after an initial autograft was reported from the CIBMTR in 2013 [29]. In that analysis of 302 URD allograft recipients who had previous autologous transplantation, myeloablative conditioning was associated with excess treatment-related mortality and subsequent inferior survival while reduced intensity conditioning (RIC) was better tolerated (Fig. 3). RIC transplants thus led to improved overall survival at 1 and 5 years. Multivariate analysis identified five risk factors for mortality including: (1) relapse less than 18 months after the autograft; (2) not in complete remission (CR) at URD second transplant; (3) myeloablative conditioning; (4) Karnofsky performance status (KPS) less than 90%; and (5) cytomegalovirus (CMV) seropositive recipient. Patients with only zero to one risk factor had strikingly improved survival at 4 years (53%) vs those

with two or three risk factors (21%–25%) or those with four to five risk factors (9%). This again highlights that later relapse, better performance status, and remission at the time of the second transplant offers the best chance for benefit.

Long follow-up after second transplants

Long-term outcomes after second allotransplant for acute leukemia are rarely reported [9,19,20,24,25,27]. An EBMT series of 286 patients described 10% 10-year survival and 7% leukemia-free survival [30]. These disappointing outcomes were due to 53% relapse mortality and 35% treatment-related, non-relapse mortality. Favorable factors for long-term survival included: complete remission at second transplant, relapse more than 10 months after the first transplant, and total body irradiation (TBI) in the second transplant conditioning. Three favorable factors yielded encouraging 45% 5-year and 36% 10-year survival while only two favorable factors led to 26% 5-year and 19% 10-year survival. Survival was less than 10% survival at either time point for those with only zero or one favorable factor. Other series corroborate these same general conclusions that later relapse, achievement of complete remission before second transplant, better performance status, and reduced intensity or reduced toxicity conditioning regimens are essential for substantial benefit from a second allograft.

Limited analyses of second transplant costs have been described. Khara reported 55 patients receiving two serial allografts for hematologic malignancies [31]. While the initial hospital stay following each transplant was similar at a median of 25 and 23 days, the 100-day costs were substantially higher (first transplant median \$132,000 vs second transplant median \$151,000, $P=0.03$). Costs were substantially greater if the second transplant involved a mismatched allogeneic donor and the second graft was complicated by GVHD, lung or renal complications, or serious infections.

Conclusions

In sum, second allografts have a place, but the excess toxicity and cost associated with their application should be restricted to circumstances where favorable outcome can be anticipated. Second transplants may only be appropriate if the initial relapse was at least 1 and more favorably greater than 2 years after the first transplant; and if the patient has achieved complete remission prior to the second graft. Supplemental immunologic, small molecule or pharmacologic maintenance therapy may be beneficial to better augment the predilection of relapse following a second transplantation [8,32,33]. Available data also suggests no advantage of changing to a different donor either in augmenting the GVL effect or limiting risks of non-relapse mortality. Safer cellular, vaccine, or drug therapy to prevent initial post-transplant relapse makes much more sense and may in the long run help many more patients. Yet in selected circumstances, second transplants may be of value and even lead to long-term leukemia-free survival.

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Fig. 1.

Survival following relapse after allogeneic HCT for AML. Longer survival with later relapse (from Bejanyan et al., 2015 [1]).

Fig. 2. Survival after 2nd allogeneic HCT for AML: no advantage of changing donors in relapse (REL), non relapse mortality (NRM), overall survival (OS) or relapse-free survival (RFS). Black line same donor (n = 1884); gray line different donor (n = 712) (from Ruutu et al., 2015 [27]. Reprinted by permission from Macmillan Publishers Ltd: Bone Marrow Transplant, copyright 2015.).

Fig. 3.

Survival following URD HCT for relapse after autologous transplantation for AML. Risk factor analysis based upon one or more of the following significant risk factors [relapse < 18 months post autograft: not in CR at URD HCT; myeloablative conditioning; KPS < 90%; CMV seropositive] (from Foran et al., 2013 [29]).

Table 1

Second allogeneic transplant: settings and reasons.

Settings	Rationale
Incomplete donor chimerism	Infusion to boost engraftment
Graft failure	Reconditioning + infusion for engraftment
Relapse	Provides reconditioning and restores GVL

GVL, graft versus leukemia.