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ASH evidence-based guidelines: is there a role for second allogeneic transplant after relapse?

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A 35-year-old male with a FLT3$^+$ AML underwent allogeneic peripheral blood stem cell transplant using a myeloablative non-total body irradiation (TBI) conditioning regimen from his HLA-matched sibling donor. Following transplantation, he developed grade II acute graft-versus-host disease (GVHD) that resolved with increasing immunosuppression. The medications were subsequently discontinued, and he did not develop any evidence of chronic GVHD. Eighteen months after transplant, while off all immunosuppression, he developed fatigue and a blood count showed circulating blasts consistent with relapse of his disease. Among the various therapeutic questions is whether there is a role for a second allogeneic transplant to treat his disease and if so, at what time, with what conditioning, and with which type of donor.

Options to treat relapse after allogeneic transplantation include the choice of no further therapy, withdrawal of immunosuppression to elicit a therapeutic graft-versus-tumor (GVT) response, reinduction chemotherapy with the same or different agents, donor lymphocyte infusions with or without preceding chemotherapy, and second transplants with or without preceding chemotherapy. Clinical nuances, including the presence of antecedent GVHD, organ function, willingness of the donor (sibling or unrelated), time between transplant and relapse, and the specific characteristics of the leukemia contribute to the difficulty of the decision. As allogeneic transplant is performed with curative intent, the question is whether patients who relapse and then undergo second allogeneic transplant can be cured of their disease.

To examine the current evidence-based literature evaluating the efficacy of second allogeneic transplant after relapse, we performed a comprehensive literature review using Ovid Medicine from 1996 to the present time. The MESH terms "hematopoietic cell transplantation" (10,254 hits) and "relapse" (12,744 hits) were combined and yielded 498 hits. When combining "second hematopoietic cell transplantation" (854 hits) and "relapse" we had a more reasonable result of 34 articles. After narrowing these articles to those relevant to the question and excluding single case reports, in addition to adding relevant studies gleaned from the reference lists of these articles, 16 studies were chosen as the basis for this mini-review. These articles described a variety of malignant hematopoietic disorders, disease status at the time of second transplant, conditioning regimens, and donor sources. These items and selected outcomes of specific interest are listed in **Table 1** of this review.

Despite the apparent heterogeneity of these studies, several principles have emerged that are relevant to the question. As a practical matter, most centers tended to use the same donor for both the first and second transplant. Most patients underwent reinduction treatment with chemotherapy in order to reduce the disease burden, knowing that the outcome for any transplant is improved if the patient is in remission. However, there are exceptions to this rule, as described by one study in this review where some patients transplanted with active disease remained alive and disease free after transplant.[2] In addition, although numerous different conditioning regimens were employed, typically patients who underwent a TBI-based regimen for initial transplant would undergo a non-TBI myeloablative regimen for their second transplant. Recently, with increased appreciation of the role of the graft-versus-leukemia effect in facilitating cure of leukemia, several studies reported patients who underwent transplant using a reduced-intensity transplant regimen with some favorable outcomes, almost exclusively in those patients who underwent transplant in remission. In this review, overall survival ranged anywhere between 0 and 67% for the studies described herein, although, admittedly, for some studies the follow-up is short.

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Table 1. Selected articles from 1996 onward using second allogeneic hematopoietic cell transplantation (HCT) to treat relapse.

Author	Diseases	Status at 2nd HCT	2nd HCT conditioning	2nd HCT donor	Same donor used	NRM or TRM	DFS	OS	Comments
Chiang 1996[1] n = 23	CML (11); acute leukemia (7); lymphoma (4); MDS (1)	Not stated	Bu/Cy (23)	MRD (18); MMURD (4); Auto (1)	13 (57%)	12 of 23	38% at 3 y	43% at 3 y	8 of 23 pts received autos for 1st HCT.
Bosi 1997[2] n = 38	AML (21); ALL (17)	CR (24); Relapse (14)	TBI-based (14); non-TBI based (24)	MRD (38)	34 (89%)	11 of 38 (28% at 3 y)	42% at 3 y	Not stated	13 Italian BMT centers; Remission after 2nd HCT longer than 1st; AML did better.
Kishi 1997[3] n = 66	ANLL (29); ALL (27); CML (6); MDS (4)	CR (30); NR (24)	Multiple high-dose regimens (Cy, TBI, Bu, Ara-C, VP16, Mel)	Sibs (59); syngeneic twin 3); other relatives (4)	55 (83%)	14 of 66 at 3 mo	28% 2 y; 15% at 4 y CR/NR: 38/23% 1 y; 34/23% 2 y; 30/0% 4 y	Not stated	Survey sent to 24 centers in Japan
Mehta 1997[4] n = 23	Acute leukemias (23)	CR (7); PR (5); Untreated relapse (8); Refractory (3)	Mel ± TBI (6); Bu/Cy (1); Cy/TBI (16)	Unknown	22 (96%)	38.3% at 2 y	0 of 23	1 of 23	23 of 114 pts relapsed after primary HCT. 17 of 23 pts relapsed after 2nd HCT.
Blau 2000[5] n = 27	AML (17); ALL (6); CML (4)	CR (5); PR (7); Refractory relapse (7); Untreated relapse (8)	TBI/Cy(11); Bu/VP16 (8); Bu/Cy (6); Cy/MP/ATG (2)	MRD (11); URD (16)	11 (41%)	7 of 27 200 d	8 of 27 (7 pts had prior auto; 1 pt with prior allo)	29% (43% for pts with 1st with auto)	16 of 27 pts received autos for 1st HCT
Michallet 2000[6] n = 150	AML (61); ALL (47); CML (42)	CR (60); Chemosensitive (8); Untreated relapse (27); Refractory relapse (13); CP (17); accelerated (13); blast (12)	TBI-based (25%); Non-TBI (75%)	Syngeneic twin (7); MRD (133); MMRD (3); Pheno-identical donor (2); URD (5)	83%	45±9%	30±8% at 5 y	32±8% at 5 y	Survey sent to 31 centers in France. Risk of relapse 44±12%
Bosi 2001[7] n = 170	AML (85); ALL (83); AUL (2)	CR (81); Relapse (86); Primary refractory (3)	TBI-based (38); Non-TBI (130)	MRD (154); Syngeneic twin (7); MMRD (6); URD (3)	154 (91%)	68 of 170 (46% at 5 y)	25% at 5 y (20% if relapsed; 13% if refractory)	26% at 5 y (16% if relapse/ refractory)	Retrospective review of 56 European centers; Relapse rate 59% at 5 y
Keil 2001[8] n = 5	AML (4); ALL (1)	CR (1); Untreated relapse (3); Refractory relapse (1)	Not stated	Not stated	Not stated	5 of 5	3 of 5 with initial CR	0%	5 of 47 pts were given 2nd HCT. The remaining 42 underwent other therapies (DLI, chemo, withdrawal IS)

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Table 1 continued from previous page.

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Pawson 2001[9] n = 14	AML (7) ALL (5) RAEBt(2)	CR (3); Relapse (11)	FLAG ±Ida	MRD (13); 1 ant MM sib (1)	14 (100%)	0 of 14	26% at 58 mo	60% at 58 mo	10 of 14 pts relapsed (4 despite ceGVHD)
Tomonari 2002[10] n = 16	AML (7) ALL (8) CML (1)	CR (7); Relapse (7); Aplasia (2)	Dauno (1), Bu/Cy±VP16 (7); TBI/Ara-C (4); TBI/VP16 (2); Cy/VP16 (1); none (1)	MRD (13); MM sib (2); URD (1)	14 (88%)	4 of 16 100 d	5 of 16	44% 1 y 31% 4 y (14% OS 4 y if in relapse at 2nd HCT)	3 pts received DLI after 2nd HCT
Meshinchi 2003[11] n = 25	AML (25)	CR (10) Relapse (15)	Cy/TBI ± ATG	MRD (12), MMR (9), URD (4)	Not stated	5 of 25	44% 10 y (70% if in remission; 27% if in relapse)	88% 100 d 56% 1 yr 48% 10 y	11 of 25 pts received autos for 1st HCT
Chang 2004[12] n = 5	JMML (5)	Relapse (5)	TBI-based (3); non-TBI (1); unknown (1)	MRD (3); 1 ant MM sib (1); Unknown (1)	4 (1 unknown)	1 of 5	3 of 5	3 of 5	Case (1) + lit search (4)
Eapen 2004[13] n = 279	AML (125); ALL (72); CML (82)	CR (144); Relapse (135)	Myeloablative with TBI (90) and w/o TBI (144); RIT with TBI (1) and w/o TBI (44)	Unknown	238 (85%)	26% 1 y; 30% 5 y	38% 1y; 28% 5 y	41% 1 y; 28% 5 y	IBMTR study; 36% relapse at 1 y, 42% 5 y; no advantage seen when using different MRD
Duus 2005[14] n = 6	CML (2); CLL (1); AML (1); MDS (1); NHL (1)	CR (1); PR (1); CP (1); AP (1); Refractory relapse (1); Untreated relapse (1)	Bu/Cy (2); Cy/TBI ±VP16 (3); TBI 2Gy/ATG (1)	MRD (1); URD (4); 5/6 MRD (1)	0 (0%)	0 of 6	5 of 6 achieved CR	67% median 23 months	
Pollyea 2007[15] n = 13	AML (12) MDS(1)	Unknown due to no eval after re-induction (4); CR (2); Relapse (7)	Thio/Bu/Cy ±Alem; Bu/Cy; 2CDA; T BI/Thio/Flu; Flu/Bu/Alem	MRD (14); URD (11) [No more than 1 antigen/allele MM]	13 (100%)	2 of 13	10 of 13 with initial CR 2 of 13 with durable CR	2 of 13	1 pt received DLI after 2nd HCT
Shaw 2008[16] n = 71	AML (26); ALL (14); MDS (9); CML (7); MPD (3); MM (2)	CR/PR (33); Relapse (36); Unknown (2)	FLAG±Ida (26) Flu/Mel or Bu (25); Flu/low-dose TBI (6); Other Flu (4); Other non-Flu (8); Unknown (2)	MRD (49); URD (18); Other related (4)	56 (80%)	15% 100 d; 23% 1 y	33% 1 y 22% 2 y	42% 1 y 28% 2 y	UK Study-all received RIT conditioning for 2nd HCT; 48% relapse at 1 yr, 56% relapse at 2 yrs

2CDA indicates cladribine; Alem, alemtuzumab; Ara-C, cytarabine; ATG, antithymocyte globulin; Auto, autograft; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ANLL, acute nonlymphocytic leukemia; ceGVHD, chronic extensive GVHD; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; Dauno, daunorubicin; FLAG, fludarbine/cytarabine/granulocyte colony stimulating factor; Flu, fludarabine; IBMTR, International Bone Marrow Transplant Registry; Ida, Idarubicin; IS, immunosuppression; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; Bu, busulfan; Cy, cyclophosphamide; Mel, melphalan; MMRD, HLA-mismatched related donor; MP, methylprednisolone, MPD; myeloproliferative disease; MRD, HLA-matched related donor; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, Not in remission; PR, partial response; RAEBt, refractory anemia with excess blasts in transformation; RIT, reduced-intensity transplant; thio, thiotepa; URD, HlA-matched unrelated donor; VP16, etoposide

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In general, patients with chemo-sensitive disease in remission who had a long initial remission (> 6 to 12 months) after first transplant and who never developed any GVHD are those who benefited with long-term control of their disease after a second transplant. Conversely, those patients who had a short remission and who did not achieve a beneficial response with reinduction chemotherapy were unlikely to benefit and probably should not be considered for second allogeneic transplant. In those patients who undergo second transplant and had no significant chronic GVHD, an attempt is generally made to taper the immunosuppression more quickly in order to harness a therapeutic GVT effect in the post-transplant setting. Additionally, patients who had acute and chronic GVHD without a GVT effect during the first transplant are less likely to benefit from a second transplant from the same donor.

Based on this mini-review, we conclude a second allogeneic hematopoietic cell transplant does have an important potential role in treating relapse after failing allogeneic transplant in selected patients. Those patients who have an early relapse, high tumor burden, or chemo-resistant disease are not patients who should undergo second transplant, as the literature does not support the clinical benefit for these selected patients. Thus the decision to undergo a second transplant should be weighed against the associated co-morbidities that can contribute to transplant-related mortality, for which a reduced-intensity approach can certainly be considered, with earlier tapering of immunosuppression. With regard to the donor, under most circumstances the same donor is used, but if there is a different HLA-matched sibling or unrelated donor, this also could be considered, especially if there was no antecedent GVHD. As randomized-controlled trials are non-existent to answer the question of the role of second allogeneic transplant to treat relapse, multi-institutional observational studies were used in this mini-review to make these recommendations. Given that relapse after transplant can be a lethal situation and that select patients can remain alive and disease-free after second allogeneic transplant, we are giving our recommendations a score of 1B.[17]

Disclosures

Conflict-of-interest disclosures: SJF is employed by City of Hope; MST declares no competing financial interests. Off-label drug use: None disclosed.

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