

Successful Treatment of T-cell Prolymphocytic Leukemia With Full-intensity Conditioning Followed by Matched Unrelated Donor Allogeneic Stem Cell Transplantation

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T-cell prolymphocytic leukemia (T-PLL) is an uncommon aggressive malignancy of mature postthymic T cells. In recent years, the anti-CD52 monoclonal antibody alemtuzumab (Campath, Bayer) has been used to treat T-PLL.^{1,2} Although alemtuzumab improves response rates and survival duration, this therapy has not changed the incurable nature of T-PLL. However, there have been several reports of long-term remission and potential cure in T-PLL patients treated with allogeneic stem cell transplantation (SCT),²⁻⁸ the majority of whom underwent matched-sibling transplantation. We report the fourth T-PLL patient treated successfully with full-intensity conditioning followed by matched unrelated donor (MUD) SCT.

In February 2005, a 43-year-old man with seizure disorder presented for neurologic follow-up. Routine bloodwork showed a white blood cell count of $36.9 \times 10^9/L$ with 81% lymphocytes; hemoglobin level and platelet count were normal. The patient was referred to our oncology clinic and diagnosed with T-PLL. After receiving alemtuzumab, he entered complete remission and was referred for MUD SCT. In May 2006, the patient received myeloablative conditioning with cyclophosphamide, busulfan, and rabbit antithymocyte globulin. Cyclosporine and methotrexate were used initially for graft-versus-host disease (GVHD) prophylaxis. The patient's course was remarkable for grade 4 mucositis

requiring short-term intubation and grade 3 renal failure necessitating temporary hemodialysis. Because of renal dysfunction, tacrolimus was substituted for cyclosporine, and methotrexate was discontinued. After 10 months, the patient is clinically well, with stage 2 chronic kidney disease being his major post-transplant medical problem. The patient has not experienced GVHD and remains in complete remission from his T-PLL.

Despite improved survival duration with alemtuzumab, T-PLL remains incurable with conventional therapy. Only allogeneic SCT has yielded prolonged complete remissions; however, SCT for T-PLL is not universally accepted and only 13 cases have been reported (Table 1). Of these, 4 patients received myeloablative MUD transplants, including our patient. Among all reported cases, 10 patients have survived and achieved complete remission with varying durations of follow-up (range, 2–48 months); the 3 deaths thus far were due to myocardial infarction 3 years after transplant, transplant-related mortality, and relapsed disease following nonmyeloablative conditioning. The latter patient did not experience GVHD.

The role of a graft-versus-leukemia (GVL) effect in T-PLL remains unanswered. De Lavallade and colleagues described a patient who achieved complete remission following allogeneic SCT, despite progressive disease at the time of transplantation.⁹ They noted that remission occurred simultaneously with chronic GVHD onset. Others have also described success with SCT in the setting of progressive disease.^{3,7,10} Given the resistance of T-PLL to chemotherapy, one may postulate that allogeneic SCT

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Table 1. Thirteen Reported Cases of Patients With T-PLL Who Underwent Allogeneic SCT

Age/Sex	Status	Graft Source	Conditioning	Acute GVHD	Chronic GVHD	Outcome	Reference
57/M	First CR	Matched sibling	CY/TBI	NR	NR	Died, TRM (3 weeks)	Dearden et al ²
40/M	First CR	Matched sibling	CY/TBI	NR	NR	Alive, CR (24+ mo)	Dearden et al ²
51/M	PR	Matched unrelated	FDR/alemtuzumab/melphalan (nonablative)	NR	NR	Alive, CR (2+ mo)	Dearden et al ²
50/M	PR	Matched sibling	FDR/alemtuzumab/melphalan (nonablative)	NR	NR	Alive, CR, DLI (16+ mo)	Dearden et al ²
54/M	Prog	Matched sibling	FDR/melphalan (nonablative)	Grade 2	NR	Alive, CR (48+ mo)	Curtin and Schwarzer ³
43/F	PR	Matched unrelated	CY/TBI	Yes (Grade NR)	Yes (Grade NR)	Died, MI (36+ mo)	Ghobrial et al ⁴
47/M	First CR	Matched sibling	CY/TBI	Grade 2	Limited	Alive, CR (11+ mo)	Collins et al ⁵
28/M	PR	Matched unrelated	CY/busulfan	No	No	Alive, CR (16+ mo)	Murase et al ⁶
53/M	Prog	UCB	CY/TBI	Grade 1	No	Alive, CR (9+ mo)	Tanimoto et al ⁷
52/F	PR	Matched sibling	FDR/busulfan (nonablative)	No	No	Died, relapse (5+ mo)	Garderet et al ⁸
30/M	Prog	Matched sibling	FDR/busulfan/ATG	Grade 3	Extensive	Alive, CR (38+ mo)	de Lavallade et al ⁹
34/F	Prog	Matched unrelated	CY/TBI	Grade 2	NR	Alive, CR (22+ mo)	Okamura et al ¹⁰
43/M	First CR	Matched unrelated	CY/busulfan/ATG	No	No	Alive, CR (10+ mo)	Present case

ATG=antithymocyte globulin; CR=complete remission; CY=cyclophosphamide; DLI=donor lymphocyte infusion; FDR=fludarabine; GVHD=graft-versus-host disease; MI=myocardial infarction; NR=not reported; PR=partial remission; Prog=progressive disease; SCT=stem cell transplantation; TBI=total body irradiation; T-PLL=T-cell prolymphocytic leukemia; TRM=treatment-related mortality; UCB=unrelated cord blood.

offers benefit beyond high-dose chemotherapy, perhaps mediated by a GVL effect.

Based on favorable results among the small population of T-PLL patients treated with allogeneic SCT, this modality should be considered for selected patients. We believe that eligible patients in first complete or partial remission should be referred for transplant evaluation. Our success and that of others with MUD SCT for T-PLL indicates that this option may be appropriate, given the otherwise incurable nature of this disease.

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Review

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T-cell prolymphocytic leukemia (T-PLL) is an extremely rare malignancy accounting for less than 2% of all lymphocytic leukemias. The disease generally follows an aggressive clinical course with poor response to conventional chemotherapy and death within 1–2 years of diagnosis. The introduction of the anti-CD52 monoclonal antibody alemtuzumab has facilitated a marked improvement in complete remission rates—of 60% and 80% in previously treated and therapy-naïve patients, respectively—and has improved median survival to more than 2 years.^{1,2} However, these improved results have not translated into cure and patients inevitably relapse, ultimately dying from disease progression. Although high-dose therapy with autologous stem cell support prolongs remission duration, this strategy is also not curative.

Kruspe and colleagues report a single case of successful full-intensity matched unrelated donor (MUD) stem cell transplantation (SCT) for T-PLL.³ This patient fulfilled many of the criteria associated with favorable outcome: younger age, limited disease at presentation (lymphocytosis alone), and rapid achievement of complete remission. Sadly, for many patients with T-PLL, older age, poor performance status, and extensive disease mean that allogeneic SCT is not a feasible approach and other strategies, such as maintenance alemtuzumab, need to be explored.

Because of the rarity of T-PLL, many of the data regarding treatment strategies have been derived from

small series or single case reports. Kruspe and colleagues have reviewed previous such reports to assemble a series of 13 patients with T-PLL who have undergone allogeneic SCT.³ This type of review can be misleading, as unreported cases with unsuccessful outcome tend to be underrepresented. The full extent of transplant-related mortality (TRM), for example, may not be appreciated. My institution's experience of allogeneic SCT in 9 patients with T-PLL (5 sibling and 4 MUD) suggests that the TRM in patients receiving full-intensity conditioning is approximately 50% compared to no deaths with reduced-intensity conditioning.⁴ In addition, even within a single center, transplant conditioning regimens may not be consistent, making the optimal strategy difficult to determine.

The most important question is whether or not allogeneic SCT is a curative approach in T-PLL. Two patients in our series (one who underwent full-intensity and one reduced-intensity conditioning) subsequently relapsed and died after 2–3 years in remission. In contrast, 1 patient who achieved only a partial response to initial alemtuzumab therapy is in continued complete remission more than 7 years after a reduced-intensity MUD allograft, suggesting a GVL effect, at least in this case. The patient reported by Kruspe and colleagues is only at 10 months follow-up and it is therefore too early to predict cure.³ Nevertheless, allogeneic SCT, with full- or reduced-intensity conditioning, is currently the only therapy for this disease likely to be curative and should therefore be considered early (in first remission) for all eligible patients.

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