

Original Article

# Clinical Outcomes after Allogeneic Stem Cell Transplantation for Adult Lymphoblastic Lymphoma

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Lymphoblastic lymphoma (LBL) is a rare subtype of non-Hodgkin lymphoma. There are limited reports on allogeneic stem cell transplantation (allo-SCT) in patients with LBL. We retrospectively analyzed the clinical outcomes of 15 adult patients with LBL who received allo-SCT at our institution. The median age at allo-SCT was 29 years (range, 18-42). Disease status at the time of transplantation was complete remission (CR), partial remission (PR), and advanced disease in 4, 4, and 7 patients, respectively. The median follow-up duration of survivors was 25 months (range, 6-106). The probabilities of overall survival (OS) and progression-free survival (PFS) at 2 years after allo-SCT were 37% and 24%, respectively. The respective 2-year OS and PFS rates of the 8 patients with CR or PR at the time of transplantation were 57% and 45%, while those with advanced disease were 14% and 0%. In conclusion, the treatment outcomes of allo-SCT in patients with LBL were unsatisfactory. Although outcomes were promising in patients with CR or PR at the time of transplantation, they were dismal in patients with progressive disease. Further advances in chemotherapy, both induction and salvage therapies, are needed to improve the clinical outcomes of patients with LBL. [*J Clin Exp Hematop* 56(1):28-33, 2016]

**Keywords:** adult, lymphoblastic lymphoma, allogeneic stem cell transplantation, disease status at the time of transplantation

## INTRODUCTION

Lymphoblastic lymphoma (LBL) is an uncommon histologic subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 2% of NHL cases.<sup>1</sup> LBL is a highly aggressive NHL but is curable if treated with intensive chemotherapy regimens for adult acute lymphoblastic leukemia (ALL).<sup>2-6</sup> Approximately 40% of patients treated with ALL-like regimens relapse even though these regimens show superior outcomes relative to CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone)-like regimens.<sup>2,3</sup> Once the disease relapses, it is difficult to cure with conventional chemotherapy.<sup>7,8</sup> Allogeneic stem cell

transplantation (allo-SCT) is considered to be a promising treatment option for these relapsed cases.<sup>9-13</sup>

There are few reports on clinical outcomes in patients with LBL who undergo allo-SCT, due to the rarity of this population. Here, we retrospectively analysed the characteristics and treatment outcomes of adult patients with LBL who received allo-SCT at our institution.

## PATIENTS AND METHODS

### Patients

We reviewed 15 adult LBL patients who received their first allo-SCT between April 2000 and April 2013 at the National Cancer Center Hospital (NCCH), Tokyo, Japan. Data were collected retrospectively by chart review. The protocol was approved by the institutional review board of the National Cancer Center.

### Clinical staging

Clinical stage was determined according to the Ann Arbor classification system.<sup>14</sup> The extent of disease was assessed by chest X-ray, computed tomography scanning from neck to

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pelvis, and bone marrow aspiration or biopsy.

### Statistical analysis

Response was assessed after completion of the initial treatment according to the International Workshop response criteria of 1999.<sup>15</sup> In patients who underwent [<sup>18</sup>F] fluorodeoxyglucose-positron emission tomography/computed tomography, the response was assessed according to the revised response criteria for malignant lymphoma published in 2007.<sup>16</sup> Overall survival (OS) was calculated from the date of transplantation to the date of death from any cause. Progression-free survival (PFS) was calculated from the date of transplantation to the date of disease progression or death from any cause. OS and PFS were evaluated by the Kaplan-Meier method. All statistical analyses were performed using Dr. SPSS II software, release 11.0.1J (SPSS Japan, Tokyo, Japan).

## RESULTS

### Patient characteristics

The demographic and clinical characteristics of 15 adult patients with LBL are shown in Table 1. Eleven patients received initial chemotherapy in other hospitals, and the remaining patients received chemotherapy at our institution. The median age at allo-SCT was 29 years (range, 18-42 years); there were 11 males (73%) and 4 females (27%). Thirteen patients (87%) had a T-cell lineage phenotype. Eleven patients (73%) received ALL-like induction regimens<sup>2,6,17</sup> at diagnosis; however, only 2 of these patients received adequate maintenance therapy after the consolidation therapy. The 4 remaining patients (27%) received CHOP-like regimens as an initial treatment.

At the time of allo-SCT, 4 patients (27%) were in complete remission (CR), 4 (27%) were in partial remission (PR), and 7 (46%) had refractory/relapsed disease. Except for the 5 patients who received allo-SCT in CR1 or PR1, human

**Table 1.** Allogeneic stem cell transplantation for lymphoblastic lymphoma at National Cancer Center Hospital 2000-2013

Pt.	Age/Sex	Lineage	Initial treatment	Maintenance	Time of HLA typing	Disease status at transplantation	MSD	Source	Conditioning regimen	Year of ASCT	Survival (months)
1	22/M	T	LSG16*	Yes	PR1	Relapse1	No	BM	BU/CY	2000	5
2	29/M	T	JALSG-ALL93**	-	CR1	CR1	Yes	PBSC	CY/TBI	2000	58
3	25/M	T	VCAP → Hyper-CVAD	-	Refractory1	Primary refractory	Yes	PBSC	FLU/BU	2001	5
4	33/M	T	CHOP14	No	Relapse2	Relapse2	Yes	PBSC	FLU/BU	2001	7
5	24/M	NA	LSG16*	Yes	Relapse1	CR2	Yes	PBSC	BU/CY	2003	106+
6	25/M	T	THP-COP	No	Relapse1	Relapse2	No	CB	FLU/BU/TBI	2003	1
7	18/F	B	CHOP21	No	Relapse1	Relapse2	Yes	PBSC	BU/CY	2003	4
8	32/M	T	LSG16*	No	PR2	Relapse2	No	BM	BU/CY	2005	1
9	35/M	T	Hyper-CVAD/MA	No	Relapse1	PR2	Yes	PBSC	CY/TBI	2007	9
10	42/M	T	Hyper-CVAD/MA	-	PR1	PR1	No	BM	AraC/CY/TBI	2007	7
11	19/F	T	Hyper-CVAD/MA	-	PR1	PR1	No	BM	CY/TBI	2008	47
12	27/M	T	CHOP21	No	PR2	Relapse2 (CNS)	No	BM	BU/CY	2010	37+
13	31/M	T	Hyper-CVAD/MA	No	Relapse1	PR2	No	BM	CY/TBI	2012	13+
14	31/F	T	Hyper-CVAD/MA	-	CR1	CR1	No	BM	CY/TBI	2012	8
15	41/F	T	Hyper-CVAD/MA	-	CR1	CR1	No	BM	CY/TBI	2013	6+

Pt., patients; MSD, matched sibling donor; ASCT, autologous hematopoietic stem cell transplantation; JALSG, Japan Adult Leukemia Study Group; VCAP, vincristine, cyclophosphamide, adriamycin, and prednisone; CHOP, cyclophosphamide, adriamycin, vincristine, and prednisone; Hyper-CVAD/MA, cyclophosphamide, vincristine, adriamycin, and dexamethasone followed by methotrexate and cytarabine; THP-COP, pirarubicin, cyclophosphamide, vincristine, and prednisone; CR, complete remission; PR, partial remission; CNS, central nervous system; BM, bone marrow; PBSC, peripheral blood stem cells; CB, cord blood; BU, busulfan; CY, cyclophosphamide; FLU, fludarabine; TBI, total body irradiation; AraC, cytarabine. \*LSG16: Azuma T, et al.: Jpn J Clin Oncol 42:394-404, 2012; \*\*JALSG-ALL93: Takeuchi J, et al.: Leukemia 16:1259-1266, 2002

leukocyte antigen (HLA) was typed after the first relapse in 9 of the 10 patients.

Eight patients (53%) received stem cells from an unrelated donor. Six patients (40%) received stem cells from an HLA-matched related donor, and 1 patient received cord blood transplantation.

Twelve patients (80%) received a myeloablative conditioning regimen; 6 of these received cyclophosphamide (CY) plus total body irradiation (TBI), 5 received busulfan plus CY, and 1 received cytarabine plus CY followed by TBI. Due to poor performance status, 3 patients (20%) received a reduced-intensity conditioning regimen consisting of fludarabine plus busulfan with or without TBI.

### Survival analysis and causes of death

The median follow-up duration of the survivors was 25 months (range, 6-106). The respective probabilities of 2-year OS and 2-year PFS were 37% and 24% (Fig. 1a & 1b). The respective probabilities of 2-year OS and 2-year PFS in the 8 patients with CR or PR at the time of allo-SCT were 57% and 45%, while those in the remaining patients were 14% and 0% (Fig. 1c & 1d). In the 5 patients who received allo-SCT in CR1 or PR1, the respective probabilities of 2-year OS and 2-year PFS were 50% and 27%, compared with 30% and 20% in the remaining patients (Fig. 1e & 1f). In the 12 patients who received a myeloablative conditioning regimen, the respective probabilities of 2-year OS and 2-year PFS were 47% and 30%. Three patients who received a reduced-intensity conditioning regimen died of disease progression within 6 months of undergoing allo-SCT (Fig. 1g & 1h).

Eleven patients died after allo-SCT; 6 of these died of lymphoma progression. Two patients died of regimen-related toxicity during the salvage therapy performed after the first allo-SCT. One patient died of toxicity experienced during the third allo-SCT performed at another hospital. Two patients

died of non-relapse mortality; 1 died of bacterial meningitis on day 30, and the other died of bronchiolitis obliterans.

## DISCUSSION

The aim of the present study was to assess the patient characteristics and treatment outcomes of adult patients with LBL who underwent allo-SCT. Most of these patients had unfavorable treatment outcomes, with the most frequent cause of death being relapse/progression of LBL. This may indicate that the clinical benefit of allo-SCT for LBL is limited in patients with refractory/progressive disease, and should be used only after careful deliberation. In contrast, the patients in CR or PR at the time of allo-SCT had promising clinical outcomes, suggesting that favorable disease control at the time of allo-SCT is an important factor for better treatment outcomes.

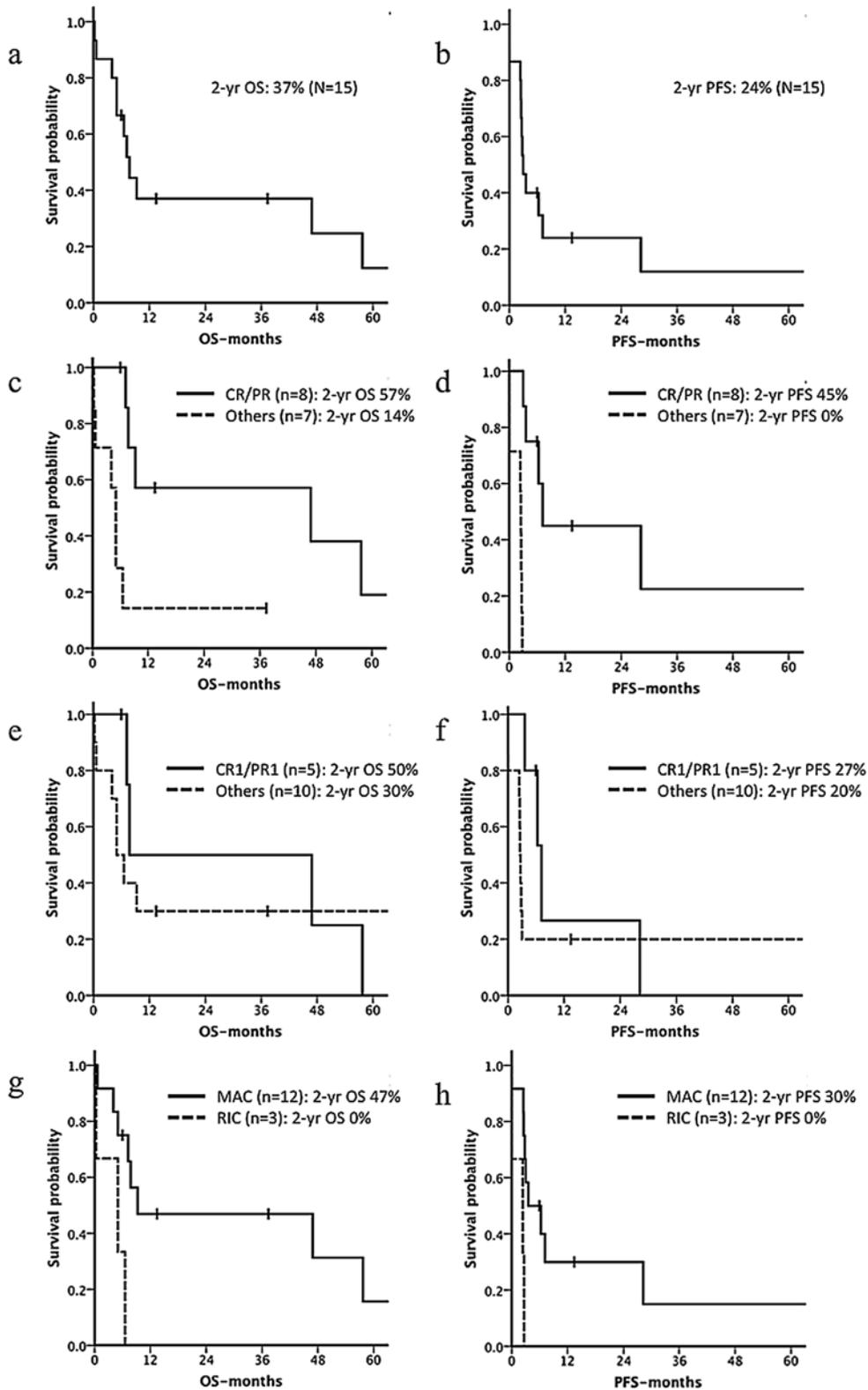
Previous reports on allo-SCT in LBL are listed in Table 2. Levine *et al.*<sup>9</sup> and Lazarevic *et al.*<sup>10</sup> demonstrated treatment outcomes that were very similar to those in the present study. Bouabdallah *et al.*<sup>11</sup> and Sweetenham *et al.*<sup>12</sup> reported better outcomes than those in the present study. However, all the patients in these prior studies were in CR at the time of allo-SCT. In contrast, van Besien *et al.* conducted a study in refractory cases and showed poorer 2-year OS and PFS of 21% and 17%, respectively.<sup>13</sup> Kim *et al.* analyzed nationwide survey data in Japan to determine the treatment outcomes of allo-SCT in patients with non-Hodgkin lymphoma, including 84 with LBL, but the detailed characteristics of the patients with LBL, such as disease status at the time of allo-SCT, were unclear.<sup>18</sup>

Taken together, the results of these studies and our own support the idea that disease status at the time of allo-SCT is an important prognostic factor for treatment outcome. We believe that in our cases, poor response to conventional chemotherapy, inadequate maintenance therapy, and the timing

**Table 2.** Reports on allogeneic stem cell transplantation in lymphoblastic lymphoma

Study	Country	Year of transplantation	Disease status	No. of patients (Total)	DFS/PFS	OS
van Besien <i>et al.</i> <sup>13</sup>	U.S.	1981-1994	Rel1/Refractory disease	25	17% (2-yr)	21% (2-yr)
Bouabdallah <i>et al.</i> <sup>11</sup>	France	1980-1992	CR1/CR2	11/1 (12)	-	78% (5-yr)
Sweetenham <i>et al.</i> <sup>12</sup>	Europe	1992-1997	CR1	12	-	59% (3-yr)
Levine <i>et al.</i> <sup>9</sup>	IBMTR	1989-1998	CR1/CR2/Less than CR	24/16/36 (76)	46% (1-yr), 36% (5-yr)	49% (1-yr), 39% (5-yr)
Lazarevic <i>et al.</i> <sup>10</sup>	Sweden	1987-2005	CR1/CR2/PR2/Refractory	9/4/4/2 (19)	32% (5-yr)	30% (5-yr)
Kim <i>et al.</i> <sup>18</sup>	Japan	1990-2001	-	84	-	41% (2-yr)
Present study	Japan	2000-2013	CR/PR/Less than PR	4/4/7 (15)	24% (2-yr)	37% (2-yr)

DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; IBMTR, International Bone Marrow Transplant Registry; Rel1, relapse; CR, complete remission; PR, partial remission



**Fig. 1.** Overall survival (OS) and progression-free survival (PFS) of all 15 patients with lymphoblastic lymphoma (*1a*, *1b*), the 8 patients with complete remission (CR) or partial remission (PR) at the time of transplantation and the remaining patients (*1c*, *1d*), the 5 patients with first CR or PR at the time of transplantation and the remaining patients (*1e*, *1f*), and the 12 patients who received myeloablative conditioning regimen (MAC) and the 3 patients who received reduced-intensity conditioning regimen (RIC) (*1g*, *1h*).

of HLA typing contributed to poor disease status at the time of allo-SCT.

First, conventional salvage chemotherapies are ineffective in patients with relapsed/refractory LBL; the CR rates are approximately 30-50%.<sup>7,8,19,20</sup> Strategies using novel agents should be considered. Nelarabine, a newly approved nucleoside analogue, has significant activity in patients with relapsed or refractory T-ALL/LBL, and the CR rate was 38% for T-LBL and the OS was 41% for T-ALL/LBL.<sup>21</sup> The proteasome inhibitor bortezomib,<sup>22</sup> the mTOR (mammalian target of rapamycin) inhibitor everolimus,<sup>23</sup> and a gamma-secretase inhibitor<sup>24</sup> have also been shown to be potent novel agents for refractory LBL/ALL.

Second, not all patients in this study received an adequate initial ALL-like chemotherapy regimen consisting of induction, consolidation, and maintenance therapies. In the present study, excluding 1 primary refractory patient and 5 patients who received allo-SCT at CR1 or PR1, only 2 of the 9 patients received maintenance therapy after induction and consolidation therapies. The 7 patients who did not receive maintenance therapy experienced recurrence of LBL and consequently received allo-SCT with poor disease control. In general, maintenance therapy is the standard of care in patients with ALL. Omitting maintenance therapy was previously shown to lead to inferior long-term outcomes, with PFS of 18-28%.<sup>25</sup> The standard initial chemotherapy for LBL may not be widely known in part because of the rarity of the disease.

Third, the timing of HLA typing in Japan is rather late compared to that in Western countries.<sup>26</sup> In the present study, HLA typing was not performed in any patients at the time of initial diagnosis because we could not identify patients who were at high risk of subsequent relapse without allo-SCT. In contrast, in the European Group for Blood and Marrow Transplantation (EBMT) centers, HLA typing is performed in 64% of acute leukemia patients at initial diagnosis and in 24% when they achieve CR1. Early HLA typing and initiation of donor coordination are mandatory for proper timing of allo-SCT, particularly in the setting of unrelated SCT.

Although chemo-sensitivity seems to be important for achieving favourable outcomes, allo-SCT at CR1 or PR1, so called 'up-front allo-SCT,' remains controversial because no clinical trials have yet compared the treatment outcomes between up-front allo-SCT and standardised ALL-like chemotherapy. Further prospective studies should be conducted to determine the role of allo-SCT in patients with chemo-sensitive LBL. Novel prognostic factors, such as minimal residual disease, cytogenetics, and molecular abnormalities, are also required to distinguish higher-risk patients who need allo-SCT from the remaining patients with chemo-sensitive curable disease.

Further refinement of first-line treatments is also an important issue with regard to reducing the number of

relapsed/refractory patients who need allo-SCT. Children and adolescents with T-LBL are treated with more intensive ALL-like chemotherapy than adults, and were shown to achieve better treatment outcomes.<sup>27,28</sup> A prospective clinical trial for untreated adult T-ALL/LBL is currently being conducted by the Japan Adult Leukemia Study Group to assess the combination regimen of nelarabine and more intensive ALL-like chemotherapy, such as that administered during childhood (UMIN000010642).

The limitations of the present study should be clarified. First, this was a single-institution, retrospective study, and selection biases may be associated with this type of design. Second, this study enrolled a small number of patients. However, to our knowledge, there have been no reports on allo-SCT in adult LBL cases over the past decade.

In conclusion, we demonstrated unfavourable treatment outcomes in adult patients with LBL who received allo-SCT. Our results suggest that good disease control at the time of allo-SCT is an important factor for better treatment outcomes after allo-SCT. The decision to perform allo-SCT in patients with poor disease control should be carefully deliberated. Improving the treatment outcomes of LBL will require further chemotherapeutic advances of both initial and salvage therapies.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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