Analysis of outcomes following autologous stem cell transplantation in adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia during first complete remission

The optimal treatment for adult Philadelphia chromosome-negative acute lymphoblastic leukemia [Ph(–)ALL] during first complete remission (CR1) remains a matter of debate. One treatment option for Ph(–)ALL is autologous hematopoietic stem cell transplantation (auto-SCT).[1,2] Previous studies have reported that the successful eradication of residual disease either before or after auto-SCT led to favorable clinical outcomes in patients with adult acute lymphoblastic leukemia (ALL) and yielded disease-free survival rates ranging from 57% to 77%.[3,4] Furthermore, auto-SCT was associated with a similarly increased overall survival (OS) duration to that associated with allogeneic hematopoietic stem cell transplantation (allo-SCT) in patients with lymphoblastic lymphoma,[5] a disease entity similar to ALL. However, a recent meta-analysis[1] demonstrated that the 5-year OS among adult ALL patients was significantly better in patients who underwent allo-SCT or chemotherapy alone compared to those who underwent auto-SCT. To evaluate the clinical relevance of auto-SCT for Ph(–)ALL, we conducted a retrospective study of a Japanese nationwide multicenter database to analyze the outcomes of auto-SCT for Ph(–)ALL during CR1.

A total of 155 Ph(–)ALL patients who underwent auto-SCT between 1983 and 2009 were analyzed (Table 1). Median follow-up duration was ten years (range 0.02-24 years), and the 10-year OS rate was 41% [95% confidence interval (CI): 33-49%] (Figure 1). The cumulative 10-year incidence rates of relapse and non-relapse mortality (NRM) were 47% (95%CI: 39-55%) and 10% (95%CI: 6-16%), respectively. The minimal residual disease (MRD) data could not be obtained for this study. Among patients under 45 years of age, the survival rate of adolescent/young adult (AYA; those aged ≤24 years) patients was similar to that of patients aged 25-44 years (P=0.94). A multivariate analysis revealed that age under 45 years [hazard ratio (HR): 0.60 (95%CI: 0.36-0.96); P=0.03] and the use of a total body irradiation (TBI) conditioning regimen [HR: 0.54 (95%CI: 0.30-0.98); P=0.04] were associated with increases in OS and decreases in the relapse rate, respectively (*Online Supplementary Table S1*). No significant factors were associ-

Table 1. Patients' characteristics.

Characteristic	Autologous (n=155) N.	%	Allogeneic (n=919) N.	%	*P*
Sex (Male)	86	55.5	515	56.0	0.90
Age at transplant, years					0.07
Median	25		30		
Range	16-74		16-66		
Age ≥ 45 years at transplant	33	21.3	129	14.0	0.02
Immunophenotypes					0.83
B lineage	80	51.6	588	64.0	
T lineage	21	13.6	146	15.9	
Unspecified or missing	54	34.8	185	20.1	
WBC at diagnosis, x10^9/L					0.25
<30x10^9/L	80	51.6	560	60.9	
≥30x10^9/L	26	16.8	239	26.0	
Missing	49	31.6	120	13.1	
Cytogenetics					
Normal karyotypes	69	44.5	486	52.9	0.26
t(4;11) or complex	3	1.9	49	5.3	
Others or missing	83	53.6	384	41.8	
Year of transplant, year					<0.01
≤2000	142	91.6	378	41.1	
>2000	13	8.4	541	58.9	
Conditioning regimens					<0.01
TBI regimens	42	27.1	803	87.4	
Non-TBI regimens	111	71.6	114	12.4	
Missing	2	1.3	2	0.2	
Donor source					–
Autologous	155	100.0		–	–
Related allogeneic	–	–	670	72.9	
Unrelated allogeneic	–	–	249	27.1	
HLA matching					–
Matched	–	–	630	68.6	
Class I locus-mismatched	–	–	47	5.1	
Class II locus-mismatched	–	–	61	6.6	
Class I+II locus-mismatched	–	–	13	1.4	
Missing	–	–	168	18.3	

WBC: white blood cell; TBI: total body irradiation; BM: bone marrow; PB: peripheral blood; HLA: human leukocyte antigen.

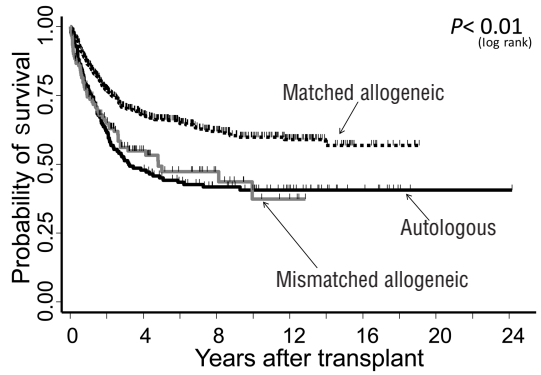

Figure 1. Overall survival according to the donor source.

ated with NRM.

Patients who had undergone myeloablative preparative regimens[6] followed by allo-SCT were selected for comparison (Table 1). With a median follow up of 4.9 years, allo-SCT yielded a better OS rate than auto-SCT (63% *vs.* 48% at 4 years; $P<0.01$). The cumulative incidence of relapse at four years was higher among patients who underwent auto-SCT than among those who underwent allo-SCT [46% (95%CI: 37-54%) *vs.* 23% (95%CI: 20-26%); $P<0.01$]. The NRM rates at four years after auto-SCT and allo-SCT were 9% (95%CI: 5-14) and 16% (95%CI: 14-19), respectively ($P=0.04$). With respect to the donor source, matched allo-SCT yielded a better OS than did auto-SCT, whereas auto-SCT and mismatched allo-SCT showed similar outcomes (Figure 1). In a multivariate analysis, autologous graft use was identified as a risk factor for relapse; however, this factor was not a significant risk factor for OS.

This study demonstrated that auto-SCT during CR1 could produce favorable outcomes in a proportion of Ph(–)ALL patients who exhibited long-term survival plateaus. The multivariate analysis revealed that the donor source (autograft *vs.* allograft) was not a prognostic factor for OS. These findings appear to be encouraging. However, the current strategy has uncovered a strong trend toward omitting auto-SCT. With advances in allo-SCT methods and the improved transplant success rate, many physicians have placed the highest priority on allo-SCT as consolidation when a suitable donor is available during CR1. Besides, given the near 100% health insurance system coverage, the improved co-ordination of the Japan Marrow Donor programs,[7] and improved outcomes from the use of pediatric-based chemotherapy regimens in adult ALL, the number of patients undergoing auto-SCT decreased rapidly in the 2000s. Approximately half of the cases in our study population were patients aged 24 years or under. The prognosis of younger patients, especially AYA patients, could be improved by the current intensive pediatric protocols.[8] Further studies are needed to compare the consolidative role of auto-SCT to that of chemotherapy alone.

A high relapse rate is among the main factors leading to the poorer clinical outcomes of ALL patients.[1] One important factor that has been associated with subsequent relapse is the conditioning regimen selected. TBI has been widely used as a component in the conditioning regimens of ALL patients undergoing allo-SCT.[9] In the present study, we identified TBI as a potential prognostic factor associated with reduced relapse rates in Ph(–)ALL patients who underwent auto-SCT, a finding that was consistent with those reported in earlier studies.[10] TBI might be a powerful tool for disease control along with both allo-SCT and auto-SCT. However, among mature lymphoid malignancies, the Dana-Farber group documented secondary malignancy rates of 16% at ten years and 38% at 15 years in patients who underwent auto-SCT with TBI-based conditioning during CR1.[11] Physicians should be careful when applying TBI regimens, especially to younger patients.

Ph(–)ALL adults who benefit from allo-SCT are primarily those who present with post-induction positive MRD, whereas patients with negative MRD fare equally well with conventional chemotherapy.[12] Whether auto-SCT would be beneficial compared to chemotherapy for patients with high post-induction MRD and no suitable donor is a matter of debate. A recent meta-analysis[1] showed a lack of benefit from auto-SCT compared to treatment with chemotherapy alone. Nevertheless, no prospective studies have compared auto-SCT with chemotherapy alone in adult Ph(–)ALL patients while stratifying according to MRD status. Recent advances in MRD detection technologies might lead to a more precise selection of transplant candidates; moreover, the use of novel agents could reduce MRD at transplantation[13-15] which might help to expand the indications for auto-SCT. Auto-SCT might reduce the treatment duration and, in addition, would provide relatively easily available grafts. As the optimal post-remission therapy timing is sometimes critical for adult Ph(–)ALL patients, auto-SCT during CR1 might represent a rational treatment option for some adult ALL patients. However, high relapse rates remain a well-described and significant problem among ALL patients who have undergone auto-SCT, and the prognosis of relapsed ALL is usually extremely poor. To re-define the role of auto-SCT, further investigations that compare the results of auto-SCT with those of intensive chemotherapy without stem cell transplantation and that take into account MRD status will be needed.

Harumi Kato,[1] Takakazu Kawase,[2] Shinichi Kako,[3] Shuichi Mizuta,[4] Mineo Kurokawa,[5] Takehiko Mori,[6] Kazuteru Ohashi,[7] Koji Iwato,[8] Koichi Miyamura,[9] Michihiro Hidaka,[10] Hisashi Sakamaki,[7] Ritsuro Suzuki,[11] Yasuo Morishima,[12] and Junji Tanaka[13]; on behalf of the Adult Acute Lymphoblastic Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT)

[1]Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; [2]Program in Immunology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]Division of Hematology, Saitama Medical Center, Jichi Medical University, Japan; [4]Department of Hematology, Fujita Health University Hospital, Toyoake, Aichi, Japan; [5]Department of Hematology and Oncology, Graduate School of Medicine, The University of Tokyo, Japan; [6]Division of Hematology, Keio University School of Medicine, Tokyo, Japan; [7]Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japan; [8]Internal Medicine, Hiroshima Red Cross and Atomic-Bomb Survivals Hospital, Japan; [9]Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Aichi, Japan; [10]Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan; [11]Department of HSCT Data Management and Biostatistics, Nagoya University School of Medicine, Nagoya, Aichi, Japan; [12]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Aichi, Japan; and [13]Department of Hematology, Tokyo Women's Medical University, Tokyo, Japan.

Correspondence: hkato@aichi-cc.jp
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