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Sequential chemotherapy and myeloablative allogeneic hematopoietic stem cell transplantation for refractory acute lymphoblastic leukemia

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Running head: allo-HSCT for refractory ALL

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(KEY WORDS)
Acute lymphoblastic leukemia, allogeneic hematopoietic stem cell transplantation, non-CR, refractory leukemia, induction failure

ABSTRACT

The prognosis of patients receiving allogeneic hematopoietic stem cell transplantation (HSCT) for refractory acute lymphoblastic leukemia (ALL) is very poor. To improve survival rates, we attempted to intensify the conditioning regimen with daunorubicin, vincristine, prednisolone, medium-dose etoposide, cyclophosphamide, and total body irradiation (DNR/VCR/PSL plus medium-dose VP/CY/TBI). Four patients in relapse or induction failure of B-precursor ALL without other complications underwent allogeneic HSCT. Initially, chemotherapy comprising DNR 60 mg/m^2 for 3 days, VCR 1.4 mg/m^2 for 1 day, and PSL 60 mg/m^2 for 3 days was administered, which was followed by medium-dose VP/CY/TBI; some modifications were made for individual patients. All patients achieved engraftment and complete remission after HSCT. Regimen-related toxicities were tolerable and no patient died within 100 days. Two patients were alive without disease on days 563 and 1055. The third patient relapsed on day 951 while the fourth died on day 179 without disease. Our results indicate that intensified myeloablative HSCT should be considered for patients with refractory ALL.

1 INTRODUCTION

We previously reported that allogeneic hematopoietic stem cell transplantation (allo-HSCT) using a conditioning regimen with medium-dose etoposide, cyclophosphamide, and total body irradiation (VP/CY/TBI) was therapeutically promising for treating acute lymphoblastic leukemia (ALL) [1]. In that study, the 3-year overall survival rate was 88.6% when the patients underwent allo-HSCT in complete remission (CR). Out of the two patients who received allo-HSCT in non-CR, one is still alive and was included in the present case series.

In a recent retrospective cohort from the Center for International Blood and Marrow Transplant Research, the 3-year overall survival rate was 16% in patients who underwent allo-HSCT in relapse or primary induction failure of ALL [2]. Although we attempted to perform HSCT in CR because of its survival benefits, relapse sometimes occurs just before scheduled allo-HSCT. In such cases, there are two therapeutic options; patients either receive reinduction chemotherapies and undergo allo-HSCT after achieving CR or allo-HSCT is directly performed in relapse. Because it is unlikely that salvage chemotherapy will induce CR in early-relapsed ALL [3] as well as in primary induction failure, immediate allo-HSCT is considered for patients in relapse just before scheduled allo-HSCT. Terwey et al. [4] documented that reinduction chemotherapy may be omitted if patients meet the following criteria: available donor, ≤50% bone marrow blasts, short duration of first CR, and/or high-risk cytogenetics. In addition, some studies showed that patients with fewer bone marrow blasts at allo-HSCT have better outcomes [2,5]. We hypothesized that a low leukemia burden just before allo-HSCT was necessary even if allo-HSCT was not performed in CR. Here we present the findings for allo-HSCT in patients with relapse or primary induction failure of ALL, in whom intensified myeloablative conditioning comprising daunorubicin, vincristine, prednisolone (DNR/VCR/PSL), and medium-dose VP/CY/TBI was used.

2 CASE SERIES

Four patients with B-precursor ALL (B-ALL) in relapse or induction failure underwent allo-HSCT between July 2007 and August 2009 at Hokkaido University Hospital [2 males, 2 females; median age at HSCT 30 years (range, 18–43years)]. Patient characteristics, basic data on allo-HSCT and outcomes are summarized in Table 1. One patient had been included in our previous study [1] (Case 1). All patients received induction chemotherapy containing DNR, VCR, and PSL at least once. No patient had any history of auto- or allo-HSCT.

Patients received DNR/VCR/PSL and medium-dose VP/CY/TBI sequentially (Table 2). Initially, DNR/VCR/PSL comprising DNR at a dose of 60 mg/m^2 for 3 days, VCR at 1.4 mg/m^2 (max. 2.0 mg) for 1 day, and PSL at 60 mg/m^2 for 3 days was administered as a cytoreduction chemotherapy before HSCT, but some modifications were made for individual patients; Cases 1 and 2 received a decreased dosage of DNR at 60 mg/person/day, and day 3 chemotherapy was omitted in Case 4. Medium-dose VP/CY/TBI was reported previously: briefly, VP at 15 mg/m^2 on days −7 and −6, CY at 60 mg/kg on days −5 and −4, and

fractionated TBI at 2 Gy twice daily on days −3 to −1. Median time interval between DNR/VCR/PSL and VP/CY/TBI was 7 days (range, 0–11 days). Tacrolimus and short-term methotrexate for GVHD prophylaxis, granulocyte-colony stimulating factor (G-CSF), and antibiotic prophylaxis were routinely administered. MRD status was monitored by PCR amplification of immunoglobulin DNA rearrangement, as previously reported [6], or by RT-PCR of the minor *BCR-ABL* fusion gene (Case 2, see Table 1).

Median nucleated cell count was 153,500/mm^3 (range, 47,000–634,000/mm^3) and median percentage of blasts was 67.0% (range, 7.2%–95.0%) at the time of diagnosis of relapse or primary induction failure of ALL. Two patients underwent bone marrow examination between administration of DNR/VCR/PSL and VP/CY/TBI. Nucleated cell counts and blast percentage were 700/mm^3 and 35.0% in Case 1, and 23 000/mm^3 and 35.7% in Case 3, respectively, indicating that the leukemia burden was reduced. All patients achieved engraftment at a median of day 14.5 after HSCT (range, 14–15 days). Median duration of neutropenia was 24.5 days (range, 18–29 days). Febrile neutropenia was observed in Cases 2 and 3, and both were treated with intravenous antibiotics. Grade 3 and 4 non-hematological toxicities as determined by Common Terminology Criteria for Adverse Events version 3 were also seen in these 2 patients. Stomatitis and diarrhea were the most common regimen-related toxicities (RRT). All patients developed acute GVHD (3 grade I-II and 1 grade III-IV) and chronic GVHD (3 limited and 1 extensive).

Median follow-up was 816 days (range, 179–1420 days). All patients achieved CR after allo-HSCT. Case 2 achieved molecular CR that was sustained until final follow-up. Day-100 mortality rate was 0%. Only 1 patient (Case 1) developed a late CNS relapse (on day 951). At final follow-up, two patients were alive without disease on days 563 and 1055, respectively, one was alive with disease on day 1420, and one (Case 3) died on day 179 without disease.

3 DISCUSSION

To achieve optimal outcomes in patients with acute leukemia undergoing allo-HSCT, disease status at HSCT is critical. Relapse rate in patients with relapsed ALL undergoing allo-HSCT is higher than that for CR [7]. Duval et al. [2] investigated risk factors for undergoing allo-HSCT in relapse or induction failure, with the following factors being associated with a poor prognosis: second/greater relapse or primary refractory, ≥25% bone marrow blasts, cytomegalovirus-seronegative donor, and age of ≥10 years. Three-year survival rate in patients with ALL varied between 10% and 46% according to the predictive score. Similarly, Oyekunle et al. [5] demonstrated that ≤20% bone marrow blasts at allo-HSCT was beneficial for survival. In our study, 3 patients had >30% bone marrow blasts (Table 1), and all patients were considered to have a poor prognosis according to the criteria of Duval et al.

Few studies have investigated survival in refractory acute leukemia after sequential treatment with chemotherapy and a myeloablative or non-myeloablative conditioning regimen for allo-HSCT [8-10]; however, high frequencies of relapse and treatment-related toxicities present major obstacles to survival. To overcome these drawbacks, we decided to administer DNR/VCR/PSL in anticipation of debulking of

leukemia, followed by allo-HSCT using a conditioning regimen with VP/CY/TBI. While combination chemotherapies consisting of vincristine and steroids (as key drugs for ALL) and anthracyclines have been incorporated in many studies since the 1960s [11-14], these have rarely been administered as a conditioning regimen. Bone marrow blasts were reduced as expected by DNR/VCR/PSL, so that the leukemia burden could be minimized at allo-HSCT. Administration of DNR/VCR/PSL did not apparently increase the number of severe toxicities, as compared with our previous study [1]. The high CR rates, tolerable toxicities and long-term survival rates in our study are encouraging compared with results of previous studies. Improvements in supportive care might contribute to reduction in toxicity [15].

Reinduction chemotherapy followed by allo-HSCT in CR is another therapeutic option, which rarely leads to CR in early-relapsed ALL [3] or primary induction failure. Furthermore, longer reinduction schedules might lead to more infectious events during multiple neutropenic periods. In our present case series, all patients with the exception of Case 4 (primary induction failure) experienced relapse just before the scheduled allo-HSCT, indicating it was rare to predict CR with conventional chemotherapy. The duration of neutropenia was less than 1 month and no microbiologically documented infections were seen in our study, suggesting that our therapeutic approach has some advantages in reducing adverse events.

Another reinduction chemotherapy using novel anti-leukemic agents is considered in early relapse or refractory disease. Some clinical studies have been conducted in patients with relapsed or refractory ALL to assess the safety and efficacy of novel anti-leukemic agents, including nucleotide analogs [16-18] and molecular targeted agents [19, 20]. While these agents were tolerable, responses were not completely satisfactory. A few studies have suggested that these novel agents are possible candidates for a conditioning regimen [21]. It is clear that further studies are needed to determine the optimal use of these agents.

In conclusion, an intensified conditioning regimen incorporating DNR/VCR/PSL plus medium-dose VP/CY/TBI followed by allo-HSCT should be administered for selected patients. Note that intensified allo-HSCT should only be considered under clinical research programs because our findings are based on our small retrospective case series.

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Table 1. Patients characteristics, basic information on HSCT, and outcomes.

		Case 1	Case 2	Case 3	Case 4
Age/Sex		28/F	32/F	18/M	43/M
Disease		B-ALL	Ph+ ALL (with T315I)	B-ALL	B-ALL
Cytogenetics		46,XX,t(5;13)(q13;q14)[3]/46,XX[17]	46,XX,t(5;9;22),−7,del9,add12,−17,+der(22)t(9;22),+mar[12]/46,XX[12]	46,XY,add(3)(q?),del(6)(q15q23),−10,add(20)(q13),+mar[6]	46,XY[20]
Status		Rel 2	Rel 1	Rel 2	induction failure
HCT-CI		0	0	1 (mild liver dysfuction)	0
Administration of DNR/VCR/PSL		day −21 to −19	day −10 to −8	day −15 to −13	day −18 to −17
Stem cell sourse		U-BMT	U-BMT	U-BMT	R-BMT
HLA		6/6	5/6 (−DR)	5/6 (−DR)	5/6 (−A)
GVHD prophylaxis		TAC+sMTX	TAC+sMTX	TAC+sMTX	TAC+sMTX
NCC ($\times 10^4/mm^3$) (blast %)	Before administration of DNR/VCR/PSL	4.7 (95%)	63.4 (91.2%)	25.8 (40.5%)	4.9 (7.2%)
	After administration of DNR/VCR/PSL	0.07 (35%)	N.D.	2.3 (35.7%)	N.D.
Day of neutrophil engraftment		Day 15	Day 15	Day 14	Day 14
Duration of neutropenia (days)		29	18	21	28
Regimen-related toxicity		Diarrhea (G1)	Stomatitis (G3), Diarrhea (G1)	Stomatitis (G3), Diarrhea (G3)	Stomatitis (G1), Diarrhea (G1)
Grade of acute GVHD (Skin, liver, intestine)		1 (1, 0, 0)	2 (3, 0, 1)	3 (3, 3, 1)	1 (1, 0, 0)
Chronic GVHD		Extensive	Limited	Limited	Limited
Best response		CR	CR	CR	CR
Relapse		Yes, day 951	No	No	No
Outcome		Alive with disease	Alive without disease	Died without disease (hemorrhagic cystitis)	Alive without disease
Last follow-up		Day 1420	Day 1055	Day 179	Day 563

F: female, M: male, Rel: relapse, HCT-CI: hematopoietic cell transplantation-specific comorbidity index, U-BMT: unrelated bone marrow transplantation, R-BMT: related bone marrow transplantation, GVHD: graft-versus-host disease, TAC: tacrolimus, MTX: methotrexate. N.D.: not determined, G: grade (CTCAE v3.0), CR: complete remission.

Table 2. Sequential treatment with chemotherapy and myeloablative stem cell

Drug	Dose	day	1’	2’	3’	…	−7	−6	−5	−4	−3	−2	−1	0
DNR	60 mg/m^2/day *		●	●	●									
VCR	1.4 mg/m^2/day		●											
PSL	60 mg/m^2/day		●	●	●									
VP	15 mg/kg/day						●	●						
CY	60 mg/kg/day								●	●				
TBI	12 Gy/6fr/3days										●	●	●	
HSCT														●

C: Case, DNR: daunorubicin, VCR: vincristine, PSL: prednisolone, VP: etoposide, CY: cyclophosphamide, TBI: total body irradiation, HSCT: hematopoietic stem cell transplantation. * see manuscript.