leukemia is not directly derived from the presence of CD7 and CD56 antigens on leukemic cells. The poor prognosis of $CD7^+$ $CD56^+$ M1–M7 suggests that this phenotype may act as a prognostic factor for AML, but this should be confirmed in further studies.

Keywords Acute myeloid leukemia · Immunophenotyping · CD7 · CD56

1 Introduction

Acute myeloid leukemia (AML) comprises a heterogeneous group of diseases that differ in their etiology, pathogenesis, and prognosis. It was first classified by its morphology and cytochemical reactions in the French–American–British (FAB) classification [1] and the World Health Organization (WHO) classification [2]. In the past two decades, the immunological classification of AML has developed on the basis of progress on the use of monoclonal antibodies and flow-cytometric analyses [3–5]. Several phenotypic markers have been demonstrated to have clinical significance other than for diagnosis including detection of minimal residual disease [6, 7] and prognostication [8–10].

We previously identified an immunophenotypically novel AML with the $CD7^+$ $CD56^+$ myeloid $antigen^+$ phenotype and termed it "myeloid/natural killer (NK) cell precursor acute leukemia" [11]. Myeloid/NK cell precursor acute leukemia presents a similar phenotype to its normal counterpart (precursor NK cells with myeloid antigens) [12–14], but shows distinct clinicopathologic features [11, 15, 16]. Tumor cells of myeloid/NK cell precursor acute leukemia show immature blastic morphology and are positive for myeloid antigens, but are negative for the cytochemical myeloperoxidase (MPO) reaction, suggesting that this leukemia falls within the category of AML M0 according to the FAB classification. However, apart from its $CD7^+$ $CD56^+$ phenotype, its clinical presentation is quite different from those of other M0 leukemias [16]. Patients with myeloid/NK cell precursor acute leukemia frequently exhibit extramedullary involvement and lymphadenopathy with or without a mediastinal mass. Although they are responsive to AML-type chemotherapy, the prognosis is extremely poor, even for younger patients [11, 16]. In this context, it is necessary to understand whether the $CD7^+$ $CD56^+$ phenotype is responsible for these particular characteristics of myeloid/NK cell precursor acute leukemia. To clarify this issue, we collected data from patients with $CD7^+$ $CD56^+$ AML other than M0 (M1–M7), and compared their clinical characteristics with those of patients with myeloid/NK cell precursor acute leukemia [16].

2 Patients and methods

2.1 Patients

A total of 32 patients with $CD7^+$ $CD56^+$ AML other than M0 (M1–M7) were identified in the collaborating institutes of the Japan Adult Leukemia Study Group and the Japan Clinical Oncology Study Group. Data were collected with a survey form in participating institutions separately from prospective studies. The diagnosis of AML was based on the FAB and WHO classification [1, 17, 18]. Cases with extramedullary leukemia were included in this study, even though less than 20% of their bone marrow cells were leukemic [16]. The patients' records and clinical data were reviewed retrospectively. As for chemotherapeutic regimens, those containing high dose cytosine arabinoside (Ara-C) or those involving Ara-C for at least five consecutive days accompanied by anthracyclines for at least 3 days were categorized as AML-type chemotherapy. The clinical characteristics of patients with $CD7^+$ $CD56^+$ AML (M1–M7) were compared with those of patents with myeloid/NK cell precursor acute leukemia ($CD7^+$ $CD56^+$ AML M0) as previously described [16]. This study was approved by the Ethical Committee as a part of retrospective survey for NK cell-related tumors (approval #625-3).

2.2 Immunophenotyping

Flow-cytometric analyses were performed as previously described [11]. The reactivity for the following markers was analyzed: CD1, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD20, CD25, CD33, CD34, CD38, CD41, CD56, CD57, CD71, CD117, CD122, HLA-DR, T cell receptor (TCR) $\alpha\beta$, TCR $\gamma\delta$, IgA, IgG, IgM, IgD, kappa, lambda, cytoplasmic CD3 (cyCD3), cyCD22, cyCD33, cyIgM, cyMPO, and terminal deoxynucleotidyl transferase (TdT). Cytoplasmic antigens and TdT were analyzed as previously described with fixation in 50% ethanol with 1% paraformaldehyde. Leukemic cells were judged as positive for each antigen when more than 20% of the gated cell reacted with the antibody.

2.3 Cytogenetic analysis

Leukemic cells were cultured, and the chromosomes were banded. Cytogenetic abnormalities were determined according to the International System for Human Cytogenetic Nomenclature [19].

2.4 Statistical analysis

The χ^2 test and Fisher's exact test were used to examine relationships between two factors, and the Mann–Whitney

U test was used to compare graded factors. Survival curves were estimated with the Kaplan–Meier method and compared by means of the log-rank test. Data were analyzed with STATA version 9 (College Station, TX) and Fisher (Nakayama-Shoten, Tokyo, Japan) statistical software.

3 Results

3.1 Patient characteristics

A total of 49 AML patients with the CD7+ CD56+ phenotype were identified in the collaborating institutes. Of these, 17 M0 patients had previously been reported as having myeloid/NK cell precursor acute leukemia. The clinical features of the 32 patients with CD7+ CD56+ AML (M1–M7) are listed in Table 1. The CD7+ CD56+ phenotype was recognized in all FAB subtypes except M6. Notably, 6 patients were found with AML M7. No recurrent structural abnormalities were identified by chromosome examinations. One patient showed t(15;17), but none presented with t(8;21), inv(16), or 11q23 translocations. Trisomy 4 was found in 3 patients. Total or partial deletions in chromosome 7 were seen in 4 patients. A comparison of the patients' characteristics with those of patients suffering from CD7+ CD56+ M0 is shown in Table 2. The median age of the patients was 49 years, and their age distribution was not statistically different from that of the CD7+ CD56+ AML

Table 1 Patient characteristics of the CD7+ CD56+ AML (M1–M7) group

No.	Age	Sex	FAB	WBC	Blast (%)	RBC	Plt	BM blast (%)	MPO (%)	Extra-medulla	LN	Others
1	21	M	M1	91,100	86.0	298	5.8	85.5	99.9	N	–	
2	21	M	M1	17,000	97.0	250	6.2	89.2	99.9	N	–	
3	36	M	M1	39,200	77.5	480	21.0	91.6	3.0	N	–	
4	45	F	M1	43,800	98.0	278	0.6	83.5	90.0	N	–	
5	47	M	M1	4,600	56.0	325	0.8	Dry tap	99.9	N	–	
6	50	M	M1	35,800	82.0	454	3.9	89.2	5.0	Y	+	
7	53	F	M1	149,300	94.0	377	2.8	85.0	90.0	N	–	
8	54	M	M1	203,600	93.0	240	3.5	86.6	28.0	N	–	
9	70	M	M1	3,000	0	369	23.8	4.0	11.0[a]	Y	+	Spleen
10	26	F	M2	2,800	0	348	13.0	0.4	95.0[a]	Y	+	Tonsil
11	29	F	M2	31,400	75.4	439	2.0	61.9	99.2	N	–	
12	32	F	M2	1,700	0	309	23.7	55.7	61.5	N	–	
13	49	F	M2	10,100	13.0	369	1.6	53.6	50.0	N	–	
14	63	F	M2	3,600	54.0	367	3.9	48.8	100.0	N	–	
15	63	M	M2	13,200	93.5	359	1.7	87.9	90.0	Y	+	
16	70	M	M2	22,200	90.0	170	0.6	49.0	98.0	Y	–	Skin
17	74	F	M2	3,600	54.0	203	2.1	85.2	96.0	N	–	
18	76	F	M2	1,800	13.0	109	2.2	43.2	41.0	Y	–	Spleen
19	37	F	M3	4,300	90.0	213	0.4	50.0	80.0	N	–	
20	34	F	M4	3,000	14.0	104	1.7	87.6	99.0	N	–	
21	59	M	M4	55,290	39.0	246	5.7	67.4	81.5	Y	–	Skin
22	86	F	M4	211,900	60.0	264	4.2	79.0	80.0	N	–	
23	21	F	M5a	269,700	96.0	248	5.7	98.8	90.0	Y	+	Gingiva
24	23	F	M5a	540,000	98.0	210	4.4	99.0	10.0	Y	–	Meningeal
25	53	M	M5a	13,320	79.0	376	7.0	89.0	80.0	N	–	
26	17	M	M5b	3,900	20.0	409	18.8	83.5	0	N	–	
27	31	M	M7	600	20.0	344	22.2	83.0	0	N	–	
28	42	M	M7	2,100	24.0	239	11.6	81.5	18.0	N	–	
29	48	F	M7	17,000	92.0	215	37.8	70.5	2.0	N	–	
30	68	F	M7	2,800	69.0	350	2.6	54.0	10.0	N	–	
31	70	M	M7	2,600	1.5	229	9.9	20.0	0	N	–	
32	74	F	M7	3,600	32.0	400	6.0	32.4	0	N	–	

[a] Examined at the time of recurrence/progression

Table 2 Comparison of $CD7^+$ $CD56^+$ AML patient characteristics (M0 versus M1–M7)

	$CD7^+$ $CD56^+$ AML M1–M7 ($n = 32$)	$CD7^+$ $CD56^+$ AML M0 ($n = 17$)	P value
Age (years), median (range)	49 (17–86)	46 (15–81)	0.32
Sex (male/female)	15/17	15/2	0.002
Peripheral blood count			
WBC (/μl), median (range)	11,650 (600–540,000)	4,500 (1000–51,000)	0.04
PB blast (%), median (range)	64.5 (0–98.0)	5.0 (0–95.0)	0.0006
Hb (g/dl), median (range)	9.7 (4.1–14.2)	13.1 (5.5–17.0)	0.004
PLT ($\times 10^4$/μl), median (range)	4.3 (0.4–37.8)	12.8 (3.9–38.5)	0.002
Sites of involvement			
Bone marrow			
Median blast (%)	81.5%	80.0%	0.59
No marrow involvement	2	5	0.04
Extramedullary	9 (28%)	14 (82%)	0.0004
Lymph node	5	12	0.0002
Mediastinum	1	4	0.04
Liver and/or spleen	2	2	0.43
Skin	2	1	0.73
Others	3	3	0.34

WBC white blood cell, *PB* peripheral blood, *PLT* platelets

M0 patients. There was almost an equal sex distribution for $CD7^+$ $CD56^+$ M1–M7 (male:female = 15:17), and the male:female ratio was significantly different from that of $CD7^+$ $CD56^+$ M0 ($P = 0.006$). The peripheral blood cell count at diagnosis showed a significantly higher white blood cell count ($P = 0.04$) and higher leukemic cell percentage ($P = 0.0006$) in the $CD7^+$ $CD56^+$ M1–M7 patients than in the $CD7^+$ $CD56^+$ M0 patients. In addition, the red blood cell and platelet counts for the former were significantly lower than those for the latter (Table 2). Overall, the $CD7^+$ $CD56^+$ M1–M7 patients showed many peripheral blood count abnormalities, which is comparable to standard AML.

Two $CD7^+$ $CD56^+$ M1–M7 patients did not show bone marrow (BM) involvement at the initial diagnosis, but the other cases showed a high percentage of BM leukemic cells. However, both of the 2 cases without BM involvement at the initial presentation progressed predominantly in the BM with manifestations of acute leukemia. Extramedullary involvement was recognized in 9 patients of the $CD7^+$ $CD56^+$ M1–M7 group (28%), which was significantly lower than the number in the $CD7^+$ $CD56^+$ M0 group ($P = 0.0004$). Although lymph node involvement was the most common manifestation of the extramedullary diseases of the $CD7^+$ $CD56^+$ M1–M7 group, the absolute incidence was significantly lower than that in the $CD7^+$ $CD56^+$ M0 group ($P = 0.0002$), as was the incidence of mediastinal involvement ($P = 0.04$).

In summary, no clinical manifestations of "myeloid/NK cell precursor acute leukemia" were recognized in the $CD7^+$ $CD56^+$ M1–M7 group.

3.2 Immunophenotyping

The immunophenotypic characteristics of the patients are summarized in Table 3. By definition, all patients were positive for both CD7 and CD56 antigens. Most of the cases were positive for CD13, CD33, CD34, CD117, and HLA-DR, while all were negative for lymphoid-specific markers including CD16 and CD57. CD41 was expressed in all 6 cases of megakaryoblastic leukemia (AML M7). Several lymphoid markers that are known to be also expressed in AML, such as CD2, CD4, CD5, CD10, and TdT were expressed in some of the patients. The incidence was higher in the M1 and M7 cases.

3.3 Therapeutic response and prognosis

In the $CD7^+$ $CD56^+$ AML M1–M7 group, 20 of the 29 patients that were initially treated with AML-type chemotherapy attained complete remission (CR), whereas none of the two cases treated with CHOP chemotherapy did (Table 4). Because of the low numbers of patients, the difference was not statistically significant. Another patient could not receive any chemotherapy due to their poor condition. The CR rate was 67% (6 of 9) for M1, 56% (5 of 9) for M2, 100% (1 of 1) for M3, 67% (2 of 3) for M4, 75% (3 of 4) for M5, and 50% (3 of 6) for M7. Of the 20 patients who achieved CR, two received allogeneic hematopoietic stem cell transplantation in first CR, and both are alive without disease. Eight of the 20 patients experienced disease recurrence.

Table 3 Phenotypic characteristics of CD7+ CD56+ AML patients (M1–M7)

FAB	M1 ($n = 9$)	M2 ($n = 9$)	M3 ($n = 1$)	M4 ($n = 3$)	M5 ($n = 4$)	M7 ($n = 6$)	Total ($n = 32$)	%
CD1	0/3	0/2	ND	0/2	0/1	0/3	0/12	0
CD2	0/8	0/9	1/1	0/3	0/3	1/6	2/30	7
CD3	0/9	0/8	0/1	0/3	0/4	0/6	0/31	0
CD4	0/9	0/5	0/1	0/3	0/3	2/6	2/27	7
CD5	2/9	0/7	0/1	0/3	0/4	1/6	3/30	10
CD7	9/9	9/9	1/1	3/3	4/4	6/6	32/32	100
CD8	0/9	0/5	0/1	0/3	0/3	0/5	0/26	0
CD10	2/9	0/8	1/1	0/3	0/4	1/6	4/31	13
CD11b	1/7	0/2	1/1	1/2	1/2	4/4	8/18	44
CD13	7/9	9/9	1/1	2/3	4/4	3/6	26/32	81
CD14	0/9	0/8	1/1	1/3	0/4	1/6	3/31	10
CD15	1/5	1/3	0/1	1/2	1/2	0/4	4/17	24
CD16	0/1	0/4	ND	0/1	ND	0/5	0/11	0
CD19	0/9	0/9	0/1	0/3	0/4	0/6	0/32	0
CD20	0/9	0/9	0/1	0/3	0/4	0/6	0/32	0
CD25	0/6	0/2	0/1	0/2	0/3	0/4	0/18	0
CD33	8/9	9/9	1/1	3/3	4/4	6/6	31/32	97
CD34	9/9	7/7	1/1	2/3	4/4	4/6	27/30	90
CD41	0/7	0/4	0/1	0/3	0/2	6/6	6/17	35
CD56	9/9	9/9	1/1	3/3	4/4	6/6	32/32	100
CD57	0/3	0/2	ND	ND	ND	0/3	0/8	0
CD117	2/2	1/1	ND	ND	1/1	1/2	5/6	83
HLA-DR	7/9	8/8	1/1	2/3	4/4	4/6	26/31	84
TdT	1/3	ND	ND	ND	ND	0/2	1/5	20

ND not determined

Table 4 Therapy and response

	CD7+ CD56+ AML (M1–M7)	CD7+ CD56+ AML M0
CR rate		
AML chemotherapy	20/29 (68%)	7/9 (78%)
NHL chemotherapy	0/2[a] (0%)	0/5 (0%)
P value	0.12	0.02

CR complete remission, *AML* acute myeloid leukemia, *NHL* non-Hodgkin's lymphoma

[a] Both patients presented with extramedullary myeloid leukemia

The overall survival (OS) and disease-free survival (DFS) curves are shown in Fig. 1a. The prognosis of the CD7+ CD56+ M1–M7 patients was also poor, and no statistical difference was found from that of the CD7+ CD56+ M0 (myeloid/NK cell precursor acute leukemia) group.

4 Discussion

In this study, we demonstrated that CD7+ CD56+ AML M1–M7 does not show extramedullary leukemic involvement, which is a typical manifestation of myeloid/NK cell precursor acute leukemia, but does have a poor prognosis. The reason for the peculiar clinical manifestation of myeloid/NK cell precursor acute leukemia remains unclear, but our current results suggest that it is not caused by the expression of two key molecules, CD7 and CD56.

The low incidence of extramedullary involvement in our CD7+ CD56+ AML M1–M7 cases is consistent with the findings of previous large-scale studies that investigated CD56 expression in AML [20, 21]. We could not identify any specific features for the CD7+ CD56+ AML M1–M7 group except for a preference for FAB M7 (6 of 32 cases). The association of CD56 expression and megakaryoblastic leukemia has been documented in a study with a small number of the cases [22], but was not examined in a recent, larger study [23]. Although several similarities exist between AML M0 and M7, such as male predominance, negativity for the cytochemical MPO reaction, myeloid antigen expression, and poor prognosis [23], other clinical characteristics were different between the AML M0 and M7 CD7+ CD56+ phenotypes. This is particularly important for the correct diagnosis of myeloid/NK cell precursor acute leukemia. In the CD7+ CD56+ M1–M7 group, we

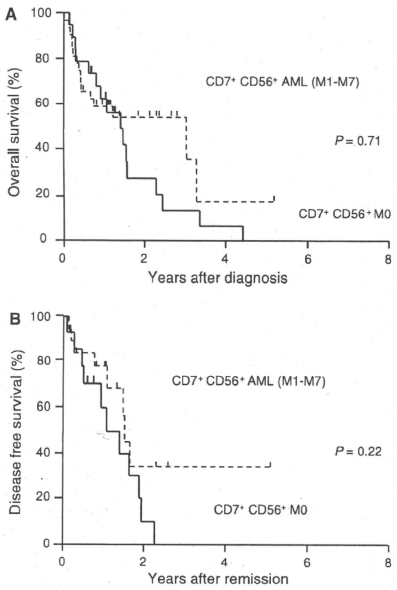

Fig. 1 Overall survival (**a**) and disease-free survival (**b**) curves of $CD7^+$ $CD56^+$ AML patients. *Thick lines* indicate survival curves of $CD7^+$ $CD56^+$ M0 and *broken lines* indicate those of $CD7^+$ $CD56^+$ AML M1–M7. No statistical differences were found between the two groups

identified one case with AML M3. This case showed the t(15;17) karyotype and responded to therapy with all-*trans* retinoic acid, indicating that the patient did not have myeloid/NK cell acute leukemia [24, 25] but typical M3.

The reason for the difference in extramedullary involvement between myeloid/NK cell precursor acute leukemia and $CD7^+$ $CD56^+$ AML M1–M7 remains unclear. Because CD56 was expressed in every case by definition, the extramedullary tumorigenesis does not directly derive from the hemophilic adhesion by CD56. Other adhesion molecules or chemokine/chemokine receptor might be responsible for this difference, which needs further investigations. Another hypothesis is that differentiation status of these leukemias is different. Since the origin of myeloid/NK cell precursor acute leukemia has been speculated as myeloid antigen-positive T/NK bi-potential progenitor [12, 13], the leukemic cell may retain affinity to lymph node or mediastinum.

The appropriate therapeutic approach for $CD7^+$ $CD56^+$ M1–M7 patients remains unknown. Expression of CD56 has been documented in various types of AML [20, 21], including specific subtypes, i.e., AML M2 with t(8;21) [26], AML M3 [27–29]. It is currently accepted as a marker of poor prognosis in AML [30–32]. Furthermore, the prognosis for NK cell malignancies, which are generally positive for CD56, is mostly poor [33–35], as is that for anaplastic large cell lymphoma [36], but not for those of peripheral T cell lymphoma, unspecified [37] or diffuse large B cell lymphoma. In this context, CD56 does not seem to cause the poor prognosis, but is rather a surrogate marker of poor prognosis. Hematopoietic stem cell transplantation, which was performed in several of our cases, is a treatment option [38], but this approach needs to be examined further in prospective studies. New agents such as CD56 monoclonal antibody conjugated with toxin or radio isotope are also good candidates [39, 40].

In summary, we found that $CD7^+$ $CD56^+$ M1–M7 shows a low incidence of extramedullary involvement, which is different from $CD7^+$ $CD56^+$ M0 or myeloid/NK cell precursor acute leukemia, but it still has a poor prognosis.

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Appendix

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ORIGINAL ARTICLE

Imatinib for newly diagnosed chronic-phase chronic myeloid leukemia: results of a prospective study in Japan

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Abstract Although imatinib has become the current standard treatment for chronic myeloid leukemia (CML), there is limited information regarding its efficacy and safety among Japanese patients. We therefore conducted a prospective multi-center open-label study of imatinib for Japanese patients with newly diagnosed chronic-phase CML (CP-CML). A total of 107 patients were enrolled and treated with imatinib at an initial daily dose of 400 mg. Eighty-three patients completed 3 years of study treatment. The cumulative rates of major cytogenetic response and complete cytogenetic response (CCyR) were 90.9 and 90.2% at 3 years, respectively. The safety profile was not very different from that reported in the IRIS study, although grade ≥3 neutropenia occurred relatively frequently (31.8 vs. 14.3%). Only seven patients discontinued the study due to adverse events, as did four patients due to

T. Nagai and J. Takeuchi contributed equally to this study, and the order in which they are listed should be considered arbitrary.

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insufficient efficacy. The 3-year probabilities of overall survival and progression-free survival were 93.2 and 91.4%, respectively. Higher average daily doses (i.e., ≥350 mg) were significantly associated not only with higher rates of achieving CCyR, but also with longer duration of CCyR. These findings confirm the clinical utility of imatinib in Japanese patients with newly diagnosed CP-CML, and suggest detrimental effect of low average daily dose on treatment results.

Keywords Chronic myeloid leukemia · Chronic phase · Newly diagnosed · Imatinib

1 Introduction

Imatinib is a molecule-targeting drug that inhibits BCR-ABL tyrosine kinase and exerts a selective proliferation-inhibitory effect in chronic myeloid leukemia (CML) [1, 2]. Several international trials have documented excellent clinical efficacy of imatinib in patients with chronic-phase CML (CP-CML) [3–5], as well as in patients in accelerated phase (AP) [6] and blast crisis (BC) [7]. Based on those studies along with Japanese phase I and phase II studies [8], imatinib was approved in Japan in November 2001, and has been available in clinical practice since December 2001. However, there is very limited information regarding efficacy and safety of imatinib among Japanese patients. We therefore conducted a post-marketing study to confirm clinical utility of imatinib in Japanese patients with newly diagnosed CP-CML.

2 Patients and methods

2.1 Study design

This was a prospective, multi-center, non-controlled study to evaluate efficacy and safety of imatinib in Japanese patients 15–74 years of age with Philadelphia chromosome positive (Ph+) CP-CML. Eligible patients were those with Eastern Cooperative Oncology Group performance status 0–3 who had been previously untreated with interferon (IFN) or imatinib. Patients were excluded if serum bilirubin or serum creatinine levels were ≥3 times the upper limit of the normal range, if serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were ≥5 times the upper limit of the normal range, if they received hydroxycarbamide within a week prior to enrollment or any other antileukemic drug within 2 weeks, or if there was any evidence of AP or BC in association with any of the following conditions: ≥15% blasts in the peripheral blood or bone marrow; ≥30% blasts plus promyelocytes in the peripheral blood or bone marrow; ≥20% basophils in the peripheral blood; or extramedullary leukemic infiltrates with the exception of spleen or liver. Women who were pregnant or possibly pregnant were also excluded.

Patients were treated with imatinib at a daily dose of 400 mg. Dose escalation to 600 mg was implemented if they had failed to achieve complete hematologic response (CHR) at 3 months or major cytogenetic response (MCyR) at 6 months. If the patient had failed to achieve MCyR at 9 months, IFN was started at a daily dose of 300 million unit per body two or three times a week while on imatinib. Dose modification of imatinib was generally based on the following guidelines. For grade ≥3 liver dysfunction (elevated bilirubin, AST, or ALT), administration was interrupted until recovery to grade <2, and then resumed at 300 mg/day. For grade ≥3 neutropenia or thrombocytopenia, administration was interrupted until recovery to grade <2, and then resumed at 400 mg/day. If grade ≥3 toxicity recurred after resuming, dose reduction to 300 mg/day was implemented. The study was discontinued in the event of failure to achieve CHR at 6 months, intolerance to imatinib, disease progression to AP or BC, death, patient request, and lost to follow-up, or at the discretion of the investigator. Patients were followed up to 3 years from the day of starting imatinib.

2.2 Endpoints

The primary endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the day of first dose of imatinib to death or last follow-up, and PFS was defined as the time from the day of first dose of imatinib to progression to AP or BC, death or last follow-up. Secondary endpoints were hematologic, cytogenetic and molecular response, and adverse events. Cytogenetic response was assessed by using bone marrow cells every 3 months until 12 months and every 6 months thereafter until 36 months. Complete cytogenetic response (CCyR) was defined as complete disappearance of the Philadelphia chromosome. MCyR was defined as decrease in Philadelphia chromosome to 35% or lower. Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Cumulative rates of hematologic and cytogenetic response, PFS, event-free survival (EFS), and OS were evaluated in accordance with the IRIS study reports [3, 9]. EFS was defined as the time from the day of first dose of imatinib to death, progression to AP or BC, loss of CHR, loss of MCyR, increase in white blood cell count to 20000/μL, or last follow-up.

This study was conducted in compliance with the Declaration of Helsinki and was approved by local Institutional Review Boards. All patients provided written informed consent prior to initiation of study medication.

2.3 Statistical methods

OS, PFS, and EFS were estimated by using the Kaplan–Meier method. Efficacy endpoints were compared by patient age (≥60 years and <60 years), and by average daily dose of imatinib (i.e., ≥350 mg/day, 250 to <350 mg/day and <250 mg/day). The Wilcoxon two-sample test was used to compare the average daily dose between the age groups. In patients who had achieved CCyR, CCyR duration was compared by average daily dose of imatinib after achieving CCyR. Average daily dose was calculated as cumulative dosage divided by the total days on study.

3 Results

3.1 Patients

A total of 107 patients were enrolled in the study between November 2002 and June 2004, and administered imatinib. All patients were evaluable for efficacy and safety, and the median duration of imatinib exposure was 1091 days (range, 82–1156 days). Among these patients, 83 completed 3 years of study treatment, whereas 24 discontinued the study due to adverse events ($n = 7$), withdrawal of consent ($n = 5$), insufficient efficacy ($n = 4$), allogeneic bone marrow transplantation ($n = 4$), and other reasons ($n = 4$). Demographic characteristics of patients in the full analysis set are summarized in Table 1. The median age was 47 years (range, 16–74 years), with 71 males and 36 females. Prior therapies for CML included hydroxycarbamide ($n = 7$), and leukapheresis ($n = 1$). The median time from diagnosis of CML to initiation of imatinib was 8.0 days (range, 1–1526 days).

The initial dose of imatinib was 400 mg/day for all patients. The mean (±standard deviation) dose administered during the study was 343 (±90) mg/day. Dose modification was required in 70.1% of patients mainly due to adverse events. Details of dose modification are summarized in Table 2. There were no patients in whom IFN was added to imatinib. Average daily doses were ≥350 mg, 250 to <350 mg, and <250 mg in 68 (63.6%), 21 (19.6%) and 18 patients (16.8%), respectively. As shown in Table 3, the percentage of patients who continued imatinib at 400 mg/day without any dose modification was 48.6% during week 1–13, 57.5% during week 14–26, and was around 60% thereafter.

3.2 Treatment results

The cumulative rate of CHR was 99.1% at 1 year, and the cumulative rates of MCyR and CCyR were 90.9 and 90.2% at 3 years, respectively (Fig. 1). The median time to CHR

Table 1 Patient characteristics

Characteristics	Category	Number of patients
Total number of subjects		107
Sex	Male	71 (66.4)
	Female	36 (33.6)
Age	10s	4 (3.7)
	20s	10 (9.3)
	30s	24 (22.4)
	40s	18 (16.8)
	50s	26 (24.3)
	60s	19 (17.8)
	70s	6 (5.6)
	Mean ± SD	47.1 ± 14.7
	Minimum–maximum	16–74
	Median	47.0
Body weight	40 to <50 kg	13 (12.1)
	50 to <60 kg	34 (31.8)
	60 to <70 kg	40 (37.4)
	70 to <80 kg	13 (12.1)
	80 to <90 kg	5 (4.7)
	≥90 kg	2 (1.9)
	Mean ± SD	61.66 ± 10.88
	Minimum–maximum	43.0–103.0
	Median	61.50
Body surface area	1.2 to <1.4 m^2	5 (4.7)
	1.4 to <1.6 m^2	31 (29.0)
	1.6 to <1.8 m^2	53 (49.5)
	1.8 to <2.0 m^2	15 (14.0)
	≥2.0 m^2	3 (2.8)
	Mean ± SD	1.6705 ± 0.1670
	Minimum–maximum	1.307–2.151
	Median	1.6800
Previous CML therapy	No	99 (92.5)
	Yes	8 (7.5)
	Hydroxycarbamide	7 (6.5)
	Leukapheresis	1 (0.9)
ECOG performance status	0	95 (88.8)
	1	10 (9.3)
	2	2 (1.9)
Time elapsed from the first day of CML diagnosis to the start of study treatment	<4 weeks	92 (86.0)
	4 to <13 weeks	14 (13.1)
	≥52 weeks	1 (0.9)
	Mean ± SD	27.0 ± 146.9
	Minimum–maximum	1–1526
	Median	8.0

Values within parenthesis are given in percentage

SD standard deviation, *CML* chronic myeloid leukemia, *ECOG* Eastern Cooperative Oncology Group

and CCyR were 92.5 days (range, 75–207 days) and 179.5 days (range, 70–589 days), respectively. In 92 patients who had achieved CCyR, 77 patients remained in CCyR until the end of 3 years of imatinib treatment. All of the 15 patients who hadn't achieved CCyR discontinued the study. Among them, 4 patients progressed to AP or BC, and 5 patients proceeded to hematopoietic stem cell transplantation.

Of 107 patients, progression to AP or BC and death occurred in nine and seven patients, respectively. One death, which was because of pneumonia, was reported during the study and the remaining six deaths were reported after patients discontinued the study. The probabilities of OS, PFS and EFS at 3 years were 93.2% [95% confidence interval (CI) 88.3–98.1%), 91.4% (95% CI 86.1–96.8%), and 81.9% (95% CI 74.6–89.3%), respectively (Fig. 2).

3.3 Response and survival by average daily dose

Next, we evaluated cumulative CCyR rate, OS, PFS, and EFS according to the average daily dose of imatinib (≥350 mg/day, 250 to <350 mg/day, and <250 mg/day). As shown in Figs. 3, 4, CCyR and EFS were significantly associated with the average daily dose ($p < 0.001$, respectively). In particular, patients with the average daily dose <250 mg had low rates of CCyR and EFS. CCyR duration was also significantly different according to the average daily dose ($p < 0.001$, Fig. 5). OS and PFS seemed lower in those with lower average daily dose, although the differences did not reach statistical significance.

The average daily doses were significantly different by age group, with 360 (±81) mg in patients aged <60, and 287 (±97) mg in patients aged ≥60 years ($p < 0.001$). Patients aged <60 had statistically non-significant better EFS than those aged ≥60 years (85.3 vs. 70.6% at 3 years, $p = 0.101$). In terms of OS or PFS, there were no significant differences between the age groups.

Table 2 Summary of dose modification

	n	%
No dose change	32	29.9
Dose change	75	70.1
Reduction only	7	6.5
Reduction and interruption	43	40.2
Reduction and increase	1	0.9
Increase only	1	0.9
Increase and interruption	4	3.7
Interruption only	19	17.8
Total	107	100.0

3.4 Adverse events

Adverse events were reported in all of the 107 patients. Serious adverse events which developed in ≥2 patients included neutropenia ($n = 4$), blast crisis ($n = 3$), anemia, intestinal obstruction, gastric antral vascular ectasia, appendicitis, herpes zoster, thrombocytopenia, and leukocytopenia ($n = 2$, each). Grade ≥3 adverse events were reported in 31 patients (29.0%, 47 episodes). As listed in Table 4, grade ≥3 adverse events reported in >5% of patients were neutropenia (31.8%), leukocytopenia (19.6%), lymphocytopenia (17.8%), thrombocytopenia (14.0%), and rash (8.4%). When frequencies of adverse events were compared between this study and the IRIS study [3], nasopharyngitis, rash, upper respiratory tract infection, pyrexia, and grade ≥3 neutropenia seemed more frequent, while nausea, muscle cramp, joint pain seemed less frequent in our study.

4 Discussion

Although it is widely accepted that imatinib is the standard treatment for CP-CML, published experiences of imatinib

Table 3 Average daily dose of imatinib over time

Week:	1–13		14–26		27–39		40–52		53–78		79–104		105–130		131–156	
No. of patients (*n*):	107		106		102		95		92		90		88		88	
Average daily dose (mg)	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
<200	3	2.8	12	11.3	9	8.8	7	7.4	6	6.5	4	4.4	3	3.4	1	1.1
200 to <300	24	22.4	16	15.1	11	10.8	7	7.4	9	9.8	9	10.0	9	10.2	14	15.9
300 to <350	13	12.1	12	11.3	14	13.7	18	18.9	12	13.0	12	13.3	16	18.2	12	13.6
350 to <400	15	14.0	4	3.8	4	3.9	0	0.0	5	5.4	5	5.6	4	4.5	6	6.8
400	52	48.6	61	57.5	61	59.8	61	64.2	58	63.0	58	64.4	54	61.4	52	59.1
>400	0	0.0	1	0.9	3	2.9	2	2.1	2	2.2	2	2.2	2	2.3	3	3.4

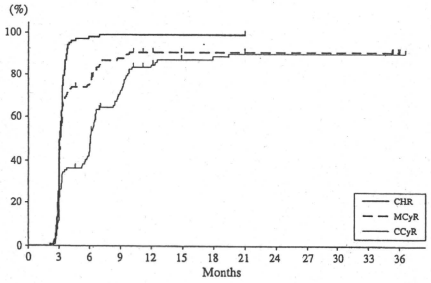
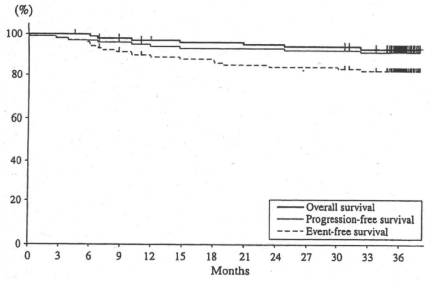


Fig. 1 Kaplan–Meier curves of cumulative rates of complete hematologic response (*CHR*), major cytogenetic response (*MCyR*) and complete cytogenetic response (*CCyR*)



	No. of Events	Estimated 3-year rate (%)
OS	7	93.2
PFS	9	91.4
EFS	19	81.9

Fig. 2 Kaplan–Meier curves of overall survival, progression-free survival and event-free survival of all patients

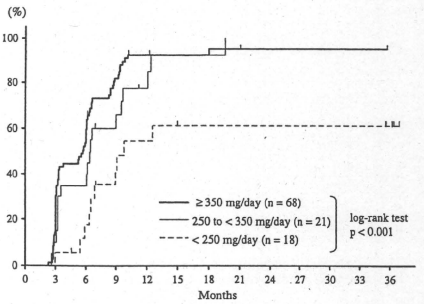


Fig. 3 Kaplan–Meier curves of cumulative rates of complete cytogenetic response (CCyR) by average daily dose of imatinib

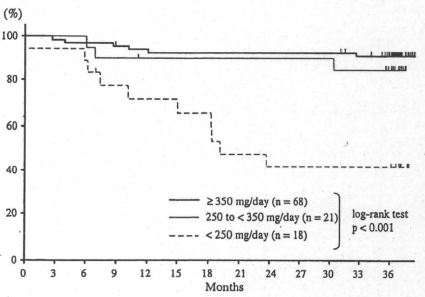


Fig. 4 Kaplan–Meier curves of event-free survival by average daily dose of imatinib

in Japanese patients are limited [8, 10–16]. Under such circumstances, a nationwide registration system for CML has been established by the Japanese Society of Hematology since 2003, and early results were published [15]. To further clarify the clinical utility of imatinib among Japanese patients, we conducted a prospective study of imatinib in 109 patients with newly diagnosed CP-CML. MCyR and CCyR rates at 12 months were 90.9 and 84.8%, which were comparable or even superior to those in the IRIS study (85 and 69%, respectively) [9]. Likewise, long-term outcomes were not different between both studies, because the OS rate in our study was 93.2% at 3 years, whereas, in the IRIS study, it was reported to be 97.2% at 18 months and 89% at 5 years [3, 9]. The safety profile observed in our study was almost comparable with that of the IRIS study, although grade ≥3 neutropenia occurred relatively frequently in our study than in the IRIS study (31.8 vs. 14.3%), while the incidences of neutropenia of all grades were not different (53.3% in our study versus 60.8% in the IRIS study). In both studies, imatinib was initiated at a daily dose of 400 mg and interrupted in the event of grade ≥3 neutropenia or thrombocytopenia until the toxicity resolved to grade <2. The reason for this observation was not clear; however, the finding that only seven of our patients discontinued the study due to adverse events showed feasibility of the treatment. Some non-hematological adverse events like nausea, muscle cramp, and joint pain were less frequent in Japanese than in Caucasians. These efficacy and safety results, taken together, confirmed the clinical utility of imatinib in Japanese patients with newly diagnosed CP-CML.

Based upon observations in a relatively small number of Japanese patients, some authors have suggested the possibility that the daily dose of imatinib could be reduced to less than 400 mg without significant disadvantage, partly

due to smaller body size as compared with Caucasians [12, 13]. Analyses of cumulative rate of CCyR and EFS by average daily dose in our study showed that patients given higher average daily doses of imatinib (≥350 mg) not only achieved higher CCyR rate but also had longer CCyR duration than those given lower average daily doses. EFS was also superior among patients who were treated with higher average daily doses of imatinib. Matsuo et al. [10] reported similar findings of a clear dose–response relationship between imatinib daily dose and treatment results. In that study, CCyR rate at 30 months was higher in patients receiving daily dose of imatinib >300 mg than in those receiving 250–300 mg, or <250 mg. Sugita et al. [16] also reported that mean daily doses of ≥300 mg led to higher CCyR rate, longer CCyR duration, and improved OS as compared to 200–300 mg. These results, taken together, suggest detrimental effect of low average daily dose on treatment results. Our observation that EFS was relatively lower in patients aged ≥60 years than in those aged <60 years might be explained partly by the difference in the average daily dose. To achieve and maintain better response, it would be beneficial to avoid excessive dose

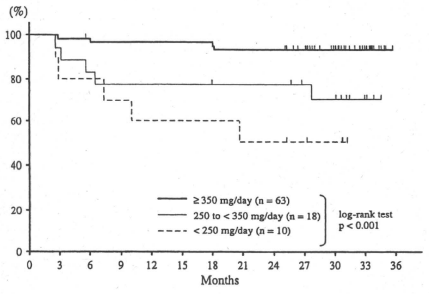


Fig. 5 Kaplan–Meier curves of duration of complete cytogenetic response (CCyR)

Table 4 Comparison of adverse events between this study and the IRIS study

	This study (n = 107)				IRIS study (n = 533) [3]			
	All grades		Grade 3/4		All grades		Grade 3/4	
	n	%	n	%	n	%	n	%
Hematological								
Neutropenia	57	53.3	34	31.8	324	60.8	76	14.3
Leukocytopenia	51	47.7	21	19.6	NR	NR	NR	NR
Lymphocytopenia	48	44.9	19	17.8	NR	NR	NR	NR
Thrombocytopenia	44	41.1	15	14.0	302	56.6	42	7.8
Anemia	33	30.8	3	2.8	238	44.6	17	3.1
Nonhematological								
Surficial edema	71	66.4	0	0.0	296	55.5	5	0.9
Nasopharyngitis	70	65.4	0	0.0	117	22.0	0	0.0
Rash	64	59.8	9	8.4	181	33.9	11	2.0
Diarrhea	44	41.1	3	2.8	175	32.8	10	1.8
Gastroenteritis	37	34.6	3	2.8	NR	NR	NR	NR
Nausea	35	32.7	0	0.0	233	43.7	4	0.7
Malaise	29	27.1	0	0.0	184	34.5	6	1.1
Myalgia	27	25.2	2	1.9	114	21.4	8	1.5
Upper respiratory tract infection	27	25.2	0	0.0	77	14.5	1	0.2
Muscle cramps	26	24.3	0	0.0	204	38.3	7	1.3
Pyrexia	26	24.3	0	0.0	70	13.1	4	0.7
Headache	23	21.5	0	0.0	166	31.2	2	0.4
Dizziness	17	15.9	0	0.0	77	14.5	5	0.9
Vomiting	16	15.0	0	0.0	90	16.9	8	1.5
Joint pain	14	13.1	0	0.0	151	28.3	13	2.4
Cough	13	12.1	0	0.0	77	14.5	1	0.2
Anorexia	11	10.3	0	0.0	28	5.3	0	0.0
Pruritus	11	10.3	0	0.0	39	7.3	1	0.2

NR not reported

reduction and interruption with careful monitoring of safety in individual patients. A similar concept was advocated by a study reported by Kanda et al. [14].

In summary, this prospective study confirmed remarkable efficacy and safety of imatinib in Japanese patients with newly diagnosed CP-CML. It also suggested a clear relationship between higher daily doses of imatinib (i.e., ≥350 mg) and better treatment results.

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Allogeneic stem cell transplantation for adult Philadelphia chromosome negative acute lymphocytic leukemia: comparable survival rates but different risk factors between related and unrelated transplantation in first complete remission

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Allogeneic stem cell transplantation for adult Philadelphia chromosome–negative acute lymphocytic leukemia: comparable survival rates but different risk factors between related and unrelated transplantation in first complete remission

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To identify factors to improve the outcomes of related and unrelated allogeneic stem cell transplantations (allo-SCT) for Philadelphia chromosome–negative acute lymphocytic leukemia (Ph⁻ ALL) in the first complete remission (CR1), we retrospectively analyzed 1139 Ph⁻ ALL patients using the registry data, particularly the details of 641 patients transplanted in CR1. Overall survival was significantly superior among patients transplanted in CR1, but no significant difference was observed between related and unrelated allo-SCTs (related vs unrelated: 65% vs 62% at 4 years, respectively; $P = .19$). Among patients transplanted in CR1, relapse rates were significantly higher in related allo-SCT compared with unrelated allo-SCT, and multivariate analysis demonstrated that less than 6 months from diagnosis to allo-SCT alone was associated with relapse. On the other hand, nonrelapse mortality (NRM) was significantly higher in unrelated allo-SCT compared with related allo-SCT, and multivariate analysis demonstrated that 10 months or longer from diagnosis to allo-SCT, human leukocyte antigen mismatch, and abnormal karyotype were associated with NRM. In conclusion, our study showed comparable survival rates but different relapse rates, NRM rates, and risk factors between related and unrelated allo-SCTs. After a close consideration of these factors, the outcome of allo-SCT for adult Ph⁻ ALL in CR1 could be improved. (*Blood.* 2010;116(20):4368-4375)

Introduction

The indication of allogeneic stem cell transplantation (allo-SCT) for Philadelphia chromosome–negative acute lymphocytic leukemia (Ph⁻ ALL) is still controversial.[1,2] As for related allo-SCT, one prospective study suggested that related allo-SCT for Ph⁻ ALL in first complete remission (CR1) could provide the most potent antileukemic therapy and considerable survival benefits.[3] As for unrelated allo-SCT, the largest retrospective study of Ph⁻ ALL patients in CR1 showed worse overall survival (OS) rates because of higher incidences of nonrelapse mortality (NRM) than those in related allo-SCT,[4] whereas another reported that there were no differences in OS rates and NRM rates between related and unrelated allo-SCTs for adult ALL in CR1.[5] These data indicated that unrelated allo-SCT could also be a treatment option for adult Ph⁻ ALL patients in CR1 if NRM rates were low enough, although it is not yet routinely performed.

Although the analyses of the outcome of allo-SCT alone have some biases, such as excluding death during chemotherapy, and there may be potential differences in the baseline characteristics of patients between related and unrelated allo-SCTs, the comparison of transplantation outcomes and risk factors between related and unrelated allo-SCTs for adult Ph⁻ ALL could indicate strategies to improve transplantation outcomes for this disease. We particularly focused on allo-SCT in CR1 because this is the area of controversy.

Methods

Collection of data and data sources

The recipients' clinical data were provided by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japan Marrow Donor Program (JMDP). Both JSHCT and JMDP collect recipients' clinical data at 100 days after allo-SCT. The patient's data on survival, disease status, and long-term complications, including chronic graft-versus-host disease (GVHD) and second malignancies, are renewed annually by follow-up forms. More than 99% of unrelated allo-SCT in Japan was captured in the JMDP database, and approximately 75% of related allo-SCT was captured in the JSHCT database. This study was approved by the data management committees of JSHCT and JMDP. Informed consent was obtained from both recipients and donors in accordance with the Declaration of Helsinki.

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Patients

Data of 1976 patients who underwent their first allo-SCT for Ph⁻ ALL between 1993 and 2007 were available in the registration database of JSHCT and JMDP. Excluding 662 patients whose age was 15 years or younger, 67 patients without data of GVHD prophylaxis and the interval from diagnosis to allo-SCT, 22 patients who underwent 2 or more human leukocyte antigen (HLA) loci mismatched related allo-SCT, and 86 patients who received reduced-intensity conditioning regimens, we analyzed 1139 adult Ph⁻ ALL patients (499 related and 640 unrelated). We particularly analyzed details of 641 patients transplanted in CR1, according to donor types (310 related and 331 unrelated). All but 4 patients were donated from Japanese donors harvested in Japanese harvest centers. Only bone marrow grafts were used in unrelated allo-SCT because peripheral blood stem cell donation from unrelated donors is not yet approved in Japan. HLA high-resolution molecular typing methods were performed for HLA-A, -B, -Cw, and -DRB1 for all patients in JMDP. Donor and recipient pairs were considered matched when HLA was matched at -A, -B, and -DRB1 loci in related allo-SCT and at -A, -B, -Cw, and -DRB1 loci in unrelated allo-SCT. Mismatches were defined as at least one disparity of these loci.

Definition

Neutrophil recovery was defined by an absolute neutrophil count of at least 0.5×10^9/L for 3 consecutive days; platelet recovery was defined by a count of at least 50×10^9/L without transfusion support. Acute and chronic GVHD was diagnosed and graded according to consensus criteria.[6,7] Relapse was defined as hematologic leukemia recurrence. NRM was defined as death during continuous remission. For analyses of OS, failure was death from any cause, and surviving patients were censored at the date of last contact. The date of allo-SCT was the starting time point for calculating all outcomes. Patients were classified at diagnosis by the Japan Adult leukemia Study Group (JALSG) risk stratification: low risk was defined as less than 30 years at diagnosis and white blood cell count less than 30 000/μL at diagnosis, high risk as 30 years or more at diagnosis and white blood cell count 30 000/μL or more at diagnosis, and intermediate risk as other.[8] To determine the cut-off for the upper limit of tolerability by age, we analyzed the cumulative incidence of NRM by categorizing the patients' age every 5 years. Because NRM rates of 45- to 49-year-old and 50-year-old or older categories showed higher incidences compared with other categories, we determined the best cut-off point as 45 years old.

Statistical analysis

The 2-sided χ^2 test was used for categorical variables. OS rates were estimated by the Kaplan-Meier method, and P values were calculated using a log-rank test.[9,10] Cumulative incidences of relapse, NRM, and GVHD were calculated by the Gray method.[11,12] Death without relapse was considered as a competing event for relapse, and relapse as a competing event for NRM. Univariate and multivariate analyses were performed using Cox proportional hazard regression model.[13] A significance level of P less than .05 was used for all analyses.

Results

Patient characteristics

Of 1139 patients, 641 received allo-SCT in CR1 (310 related and 331 unrelated), 199 in subsequent remission (56 related and 143 unrelated), and 299 in nonremission (133 related and 166 unrelated). The characteristics of the patients transplanted in CR1 are shown in Table 1. The frequencies of HLA mismatched donor and tacrolimus-based GVHD prophylaxis were higher, and the interval from diagnosis to allo-SCT was longer among patients who underwent an unrelated allo-SCT than among those who underwent a related allo-SCT. There was no significant difference in the age at allo-SCT, the white blood cell counts at diagnosis, JALSG risk stratification, and year of allo-SCT between related and unrelated allo-SCTs.

Survival

Median follow-up periods among survivors were 47.7 months (range, 1.3-162 months). OS rates at 4 years were 64% in CR1, 39% in subsequent CR, and 16% in non-remission ($P < .0001$). Although OS rates were significantly different among disease stages at allo-SCT, there were no significant differences in OS rates at 4 years between related and unrelated allo-SCTs in any disease stage (related vs unrelated: 65% vs 62% in CR1, $P = .19$; 44% vs 38% in subsequent CR, $P = .66$; and 17% vs 16% in non-remission, $P = .59$; respectively; Figure 1). There was no statistical difference in OS rates and NRM rates over transplantation years (data not shown). Among 641 patients transplanted in CR1, JALSG risk stratification did not have a significant impact on the OS after allo-SCT (68% in low risk, 62% in intermediate risk, and 58% in high risk, at 4 years, respectively; $P = .31$). To address our main issue, we performed the following analyses among patients transplanted in CR1 according to donor types.

Among 310 patients who underwent a related allo-SCT in CR1, multivariate analysis showed that age at allo-SCT and less than 6 months from diagnosis to allo-SCT were significant risk factors for OS. Among 331 patients who underwent an unrelated allo-SCT in CR1, multivariate analysis showed that abnormal karyotype [except for t(4;11) and t(1;19)], HLA mismatch, and 10 months or longer from diagnosis to allo-SCT were significant risk factors for OS (Table 2).

Relapse and NRM among patients transplanted in CR1

The cumulative incidence of relapse was significantly higher in patients who underwent a related allo-SCT compared with those who underwent an unrelated allo-SCT (related vs unrelated: 32% vs 22% at 4 years, $P = .03$; Figure 2A). Multivariate analyses according to donor type showed that less than 6 months from diagnosis to allo-SCT alone was associated with relapse among 310 patients who underwent a related allo-SCT in CR1, whereas only abnormal karyotype [except for t(4;11) and t(1;19)] was associated with relapse among 331 patients who underwent an unrelated allo-SCT in CR1 (Table 3).

The cumulative incidence of NRM was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 14% vs 27% at 4 years, $P = .0002$; Figure 2B). Multivariate analyses according to donor type showed that age only 45 years or older at allo-SCT was associated with NRM among 310 patients who underwent a related allo-SCT in CR1, whereas abnormal karyotype [except for t(4;11) and t(1;19)], HLA mismatch, and 10 months or longer from diagnosis to allo-SCT were associated with NRM among 331 patients who underwent an unrelated allo-SCT in CR1 (Table 4).

Acute and chronic GVHD among patients transplanted in CR1

The cumulative incidence of grade II-IV acute GVHD was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 30% vs 42% at day 100; $P = .0003$). The cumulative incidence of grade III-IV acute GVHD was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 7% vs 16% at day 100; $P = .0006$).

Table 1. Characteristics of patients transplanted in CR1, according to donor type

	Related (n = 310)		Unrelated (n = 331)		
No. of patients	**No.**	**%**	**No.**	**%**	***P***
Median WBC count at diagnosis/μL (range)	10 250 (109-328 000)		11 000 (700-892 000)		.43
Median patient age at allo-SCT, y (range)	30 (16-66)		31 (16-59)		.95
16-20	66	21.3	77	23.3	
21-30	93	30.0	82	24.8	
31-40	71	22.9	86	26.0	
41-50	58	18.7	68	20.5	
51 or older	22	7.1	18	5.4	
Sex					.09
Male	157	50.6	190	57.4	
Female	153	49.4	141	42.6	
Source					< .0001
BM	212	68.4	331	100.0	
PB	98	31.6	0	0.0	
Lineage					.01
T	50	16.1	54	16.3	
B	218	70.3	203	61.3	
Other	42	13.5	74	22.4	
Cytogenetics					.07
Normal	193	62.3	208	62.8	
t(4;11)	11	3.5	5	1.5	
Other MLL/11q23 translocations	1	0.3	3	0.9	
t(1;19)	10	3.2	6	1.8	
t(8;14)	3	1.0	3	0.9	
14q32 translocations	1	0.3	0	0.0	
del(6q)	3	1.0	1	0.3	
del(7p)	2	0.6	1	0.3	
−7*	5	1.6	2	0.6	
+8*	2	0.6	0	0.0	
+X*	0	0.0	1	0.3	
del(9p)	3	1.0	9	2.7	
abnormality of 11q	0	0.0	3	0.9	
del(12p)	2	0.6	1	0.3	
del(13q)/−13	1	0.3	2	0.6	
del(17p)	0	0.0	1	0.3	
Complex	10	3.2	15	4.5	
Low hypodiploidy/near triploidy	2	0.6	0	0.0	
High hyperdiploidy	16	5.2	12	3.6	
Other abnormality (no t(9;22))†	45	14.5	58	17.5	
JALSG risk stratification					.21
Low	39	12.6	45	13.6	
Intermediate	163	52.6	192	58.0	
High	108	34.8	94	28.4	
HLA matching					< .0001
* Match	285	91.9	192	58.0	
Class I 1 locus-mismatch	18	5.8	53	16.0	
Class II 1 locus-mismatch	7	2.3	32	9.7	
2 or more loci mismatch	0	0.0	54	16.3	
Time from diagnosis to transplantation, mo (range)	5.7 (1.9-36.6)		10.0 (4.0-43.0)		< .0001
< 6	169	54.5	23	6.9	
6-9	109	35.2	143	43.2	
10 or longer	32	10.3	165	49.8	
Preparative regimen					.004
CY + TBI	140	45.2	156	47.1	
CA + CY + TBI	66	21.3	84	25.4	
BU + CY + TBI	17	5.5	15	4.5	
VP + CY + TBI	23	7.4	32	9.7	
Other TBI myeloablative regimens	39	12.6	32	9.7	
BU + CY	17	5.5	12	3.6	
Other non-TBI myeloablative regimens	8	2.6	0	0.0	
GVHD prophylaxis					< .0001
Cyclosporine A with or without other	283	91.3	171	51.7	
Tacrolimus with or without other	27	8.7	160	48.3	

Table 1. Characteristics of patients transplanted in CR1, according to donor type (continued)

No. of patients	Related (n = 310)		Unrelated (n = 331)		P
	No.	%	No.	%	
Years of allo-SCT					.26
1993-1997	48	15.5	55	16.6	
1998-2002	132	42.6	120	36.3	
2003-2007	130	41.9	156	47.1	

WBC indicates white blood cell; BM, bone marrow; PB, peripheral blood; related HLA match, identical HLA-A, -B, and -DRB1 loci; unrelated HLA match, HLA-A, -B, -Cw, and -DRB1 loci; HLA mismatch, at least one disparity at one of these loci; CY, cyclophosphamide; TBI, total body irradiation; CA, cytarabine; BU, busulfan; and VP, etoposide.

*These groups exclude cases with low hypodiploidy and high hyperdiploidy.

†Abnormal karyotypes excluding those with any of the aforementioned abnormalities.

Among evaluable patients who survived at least 100 days after allo-SCT, no significant difference was observed between related and unrelated allo-SCTs in the incidence of chronic GVHD (related vs unrelated: 41% vs 41% at 2 years; $P = .76$). Extensive disease was observed in 60 (55%) of 109 with chronic GVHD after related allo-SCT and in 80 (74%) of 118 after unrelated allo-SCT ($P = .048$).

Causes of death among patients transplanted in CR1

Although relapse was the leading cause of death in both related and unrelated allo-SCTs, the proportion of relapse was significantly lower in those transplanted from unrelated donors ($P = .01$). Infection, GVHD, and organ failure were the major causes of NRM, and the incidence of interstitial pneumonia was higher in patients transplanted from unrelated donors ($P = .06$; Table 5).

Discussion

This study reports the largest series of adult Ph⁻ ALL patients who underwent allo-SCT. There was no significant survival difference between related and unrelated allo-SCTs in any disease stage. Among patients who underwent a related allo-SCT in CR1, a shorter interval from diagnosis to allo-SCT was associated with relapse, and age at allo-SCT was associated with NRM. On the other hand, among patients who underwent an unrelated allo-SCT, abnormal karyotype was associated with both relapse and NRM, and a longer interval from diagnosis to allo-SCT and HLA mismatch were associated with NRM. These results indicated that factors affecting transplantation outcomes were different according to donor type.

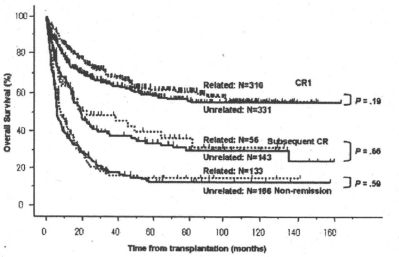

Figure 1. OS according to disease status and donor type. OS rates were significantly superior among patients transplanted in CR1. There was no significant difference between related and unrelated allo-SCTs (related vs unrelated: 65% vs 62% in CR1, $P = .19$; 44% vs 38% in subsequent CR, $P = .66$; and 17% vs 16% in nonremission, $P = .59$; respectively).

In our study, unrelated allo-SCT resulted in OS rates similar to those from related allo-SCT, which was compatible with the result of one prospective study for standard-risk hematologic malignancies.[14] The rates of OS, relapse, and NRM among patients who underwent a related allo-SCT in CR1 were 65%, 32%, and 14%, respectively, which were compatible with those observed in the United Kingdom Medical Research Council UKALL XII/Eastern Cooperative Oncology Group E2993 trial (53%, 24%, and 18%, respectively).[3] Some patients were transplanted from a 1-locus mismatched related donor because it was reported that the outcome of allo-SCT from a 1 locus-mismatched related donor was similar to that of matched unrelated allo-SCT in the Japanese population.[15] On the other hand, the rates of OS, relapse, and NRM among patients who underwent an unrelated allo-SCT were 62%, 22%, and 27%, respectively, which were better than those reported from the Center for International Blood and Marrow Transplant Research (39%, 20%, and 42%, respectively).[4] These differences in NRM could be explained by the lower incidence of acute GVHD in our population, which possibly resulted from the genetic homogeneity in the Japanese population.[16,17] Interestingly, abnormal karyotype was associated with NRM. This could be explained by the possibility that patients with abnormal karyotype received intensive chemotherapy before allo-SCT because of persistent minimal residual disease, which might result in increased NRM rates. Another possibility is that rapid taper of immunosuppressive treatment might also cause GVHD leading to NRM.

In this study, NRM rates were higher in unrelated allo-SCT compared with related allo-SCT, whereas comparable NRM rates were reported in some recent reports,[18] suggesting that NRM rates after unrelated allo-SCT could be reduced with further efforts, such as better HLA matching. Because HLA-C was not routinely typed before 2003, most of the HLA-C data in this study were examined retrospectively, revealing that considerable numbers of patients had received class I allele-mismatched unrelated allo-SCT. Better HLA matching might reduce NRM after unrelated allo-SCT in the future. Although slower hematopoietic recovery after bone marrow transplantation compared with peripheral blood stem cell transplantation might affect the timing of deaths, there was no statistical difference in early mortality between the grafts (data not shown).

There was no statistical difference in the incidence of chronic GVHD between related and unrelated allo-SCTs, although acute GVHD was observed more frequently in unrelated allo-SCT. This was compatible with a past report in which the incidence of chronic GVHD was similar between related and unrelated allo-SCTs, whereas acute GVHD was observed more frequently in related allo-SCT.[14]

It was noteworthy that the interval from diagnosis to allo-SCT revealed a different effect on related and unrelated allo-SCTs. In Japanese clinical practice, the JALSG protocols have been common, where 1.5-month induction chemotherapy was followed by

Table 2. Univariate and multivariate analyses of factors influencing OS among patients transplanted in CR1, according to donor type

	Related (n = 310)					Unrelated (n = 331)				
		Univariate		Multivariate			Univariate		Multivariate	
Covariates	N	HR (95% CI)	P	HR (95% CI)	P	N	HR (95% CI)	P	HR (95% CI)	P
WBC count at diagnosis										
< 30 000/μL	224	1.00		—		230	1.00		—	
30 000/μL or more at diagnosis	86	1.19 (0.78-1.82)	.42	—		101	0.83 (0.56-1.25)	.38	—	
Lineage										
B	218	1.00		—		203	1.00		—	
T	50	0.73 (0.34-1.77)	.52	—		54	0.81 (0.44-1.48)	.35	—	
Other	42	0.94 (0.54-1.64)	.84	—		74	1.08 (0.70-1.67)	.72	—	
Karyotype										
Normal	193	1.00		—		208	1.00		—	
t(4;11) or t(1;19)	21	0.51 (0.14-1.54)	.19	—		11	1.49 (0.54-4.09)	.44	1.59 (0.58-4.36)	.37
Other (no t(9;22))	96	1.03 (0.67-7.14)	.89	—		112	1.49 (1.03-2.17)	.04	1.43 (1.13-2.40)	.01
JALSG risk stratification										
Low	39	1.00		—		45	1.00		—	
Intermediate	163	1.36 (0.87-2.12)	.18	—		192	1.06 (0.71-1.59)	.77	—	
High	108	1.77 (0.95-3.31)	.07	—		94	1.02 (0.56-1.88)	.94	—	
Age at allo-SCT										
< 45 y old	255	1.00		—		281	1.00		—	
45 y old or older at allo-SCT	55	2.04 (1.30-3.13)	.002	2.13 (1.36-3.34)	.0009	50	1.05 (0.63-1.73)	.86		
HLA										
Match	285	1.00		—		192	1.00		—	
Mismatch	25	0.95 (0.46-1.96)	.90	—		139	1.44 (1.01-2.06)	.04	1.45 (1.01-2.07)	.04
Stem cell source										
Bone marrow	212	1.00		—					—	
Peripheral blood	98	1.43 (0.94-2.13)	.09	1.40 (0.93-2.11)	.11					
Time from diagnosis to allo-SCT										
6 mo or longer	169	1.00		—		23	1.00		—	
< 6 mo	141	1.75 (1.16-2.63)	.007	1.80 (1.19-2.71)	.005	308	0.33 (0.10-1.04)	.06	—	
< 10 mo	278	1.00		—		166	1.00		—	
10 mo or longer	32	0.56 (0.26-1.20)	.14	—		165	1.54 (1.07-2.21)	.02	1.62 (1.12-2.34)	.01
Preparative regimen										
Non-TBI regimens	25	1.00		—		12	1.00		—	
TBI regimens	285	0.72 (0.38-1.35)	.30	—		319	0.59 (0.27-1.26)	.17	—	
GVHD prophylaxis										
Cyclosporine A with or without other	283	1.00		—		171	1.00		—	
Tacrolimus with or without other	27	2.02 (1.15-3.56)	.01	—		160	1.38 (0.96-1.97)	.08	—	

HR indicates hazard ratio; CI, confidence interval; WBC, white blood cell; —, not applicable; and TBI, total body irradiation.

6-month consolidation chemotherapy and 16-month maintenance chemotherapy.[8] Therefore, a shorter interval from diagnosis to allo-SCT, which was more common in related cases, might result in insufficient consolidation chemotherapy and worse survival because of increased relapse rates in related allo-SCT. Alternatively, effects from insufficient consolidation chemotherapy might be more prominent in related allo-SCT because graft-versus-leukemia effects might be weaker after related allo-SCT than unrelated allo-SCT.[19] On the other hand, a longer interval from diagnosis to allo-SCT, which was more common in unrelated cases, might result in the cumulative toxic sequelae of chemotherapy responsible for interstitial pneumonia indicated in the past reports.[20-25] Because the JALSG protocols do not define the timing of allo-SCT, it is possible that chemotherapy before allo-SCT might be prolonged because of persistent minimal residual disease. However, we could not confirm this because there were no data concerning minimal residual disease in the registry database.

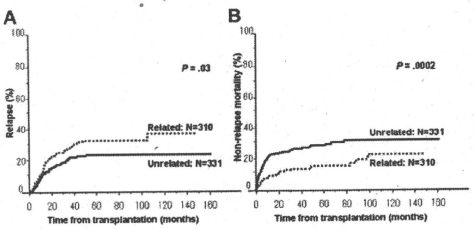

Figure 2. Cumulative incidence of relapse and NRM in patients transplanted in CR1 according to donor type. (A) Cumulative incidence of relapse among patients transplanted in CR1 was significantly higher in patients who underwent a related allo-SCT compared with those who underwent an unrelated allo-SCT (related vs unrelated: 32% vs 22% at 4 years, $P = .03$). (B) Cumulative incidence of NRM among patients transplanted in CR1 was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 14% vs 27% at 4 years, $P = .0002$).

Table 3. Univariate and multivariate analyses of factors influencing relapse among patients transplanted in CR1, according to donor type

	Related (n = 310)					Unrelated (n = 331)				
		Univariate		Multivariate			Univariate		Multivariate	
Covariates	N	HR (95% CI)	P	HR (95% CI)	P	N	HR (95% CI)	P	HR (95% CI)	P
WBC count at diagnosis										
< 30 000/μL	224	1.00		—		230	1.00		—	
30 000/μL or more at diagnosis	86	0.88 (0.52-1.47)	.62	—		101	1.11 (0.62-1.98)	.72	—	
Lineage										
B	218	1.00		—		203	1.00		—	
T	50	0.54 (0.22-1.37)	.09	—		54	1.31 (0.57-3.02)	.62	—	
Other	42	1.21 (0.66-2.21)	.54	—		74	1.06 (0.53-2.11)	.87	—	
Karyotype										
Normal	193	1.00		—		208	1.00		—	
t(4;11) or t(1;19)	21	0.64 (0.19-2.12)	.36	—		11	1.97 (0.46-8.35)	.91	—	
Other (no t(9;22))	96	1.11 (0.68-1.82)	.67	—		112	2.15 (1.24-3.73)	.01	2.15 (1.24-3.73)	.01
JALSG risk stratification										
Low	39	1.00		—		45	1.00		—	
Intermediate	163	0.96 (0.59-1.55)	.87	—		192	1.04 (0.57-1.91)	.90	—	
High	108	0.81 (0.35-1.84)	.61	—		94	1.04 (0.43-2.52)	.94	—	
Age at allo-SCT										
< 45 y old	255	1.00		—		281	1.00		—	
45 y old or older at allo-SCT	55	0.82 (0.41-1.64)	.57	—		50	0.74 (0.42-1.32)	.08	—	
HLA										
Match	285	1.00		—		192	1.00		—	
Mismatch	25	0.82 (0.33-2.02)	.66	—		139	0.74 (0.42-1.32)	.31	—	
Stem cell source*										
Bone marrow	212	1.00		—					—	
Peripheral blood	98	1.07 (0.65-1.76)	.79	—					—	
Time from diagnosis to allo-SCT										
6 mo or longer	169	1.00		—		23	1.00		—	
< 6 mo	141	1.68 (1.05-2.69)	.03	1.68 (1.05-2.69)	.03	308	0.47 (0.11-1.92)	.29	—	
< 10 mo	278	1.00		—		166	1.00		—	
10 mo or longer	32	0.49 (0.18-1.34)	.16	—		165	0.92 (0.54-1.58)	.76	—	
Preparative regimen										
Non-TBI regimens	25	1.00		—		12	1.00		—	
TBI regimens	285	0.62 (0.31-1.25)	.18	—		319	0.47 (0.15-1.52)	.21	—	
GVHD prophylaxis										
Cyclosporine A with or without other	283	1.00		—		171	1.00		—	
Tacrolimus with or without other	27	1.62 (0.81-3.26)	.18	—		160	1.39 (0.81-2.38)	.24	—	

HR indicates hazard ratio; CI, confidence interval; WBC, white blood cell; —, not applicable; and TBI, total body irradiation.
*Stem cell source (peripheral blood) was not a significant risk factor for relapse in the multivariate analysis.

Although we mainly focused on patients in CR1, our results also indicated that some, but not all, patients with refractory disease could be rescued by allo-SCT. These patients could not have survived long with chemotherapy alone, and complete unresponsiveness, even to allo-SCT, was often assumed. These results were compatible with some reports showing that long-term survival could be achieved for patients receiving allo-SCT, even in refractory disease.[26-28]

Our study has several limitations. First, there might be some selection biases between related and unrelated allo-SCTs. It was possible that eligibility was more stringent in patients who received unrelated allo-SCT, and they might have had better pretransplantation conditions. Second, a time-censoring effect might impact the outcome. The longer interval from diagnosis to unrelated allo-SCT eliminates the effect of patients who die during that period. This bias might improve the outcome of unrelated allo-SCT. Third, we could not make the comparison between chemotherapy and allo-SCT in this study.

The time-censoring effect could be the major bias in this study, which resulted in lower relapse rates, especially in patients transplanted from unrelated donors. We tried to correct this bias by the previously described method.[29] In the JALSG ALL study, it was reported that approximately 80% and 75% of patients were alive 6 months and 10 months after enrollment, respectively.[8] Because 6 months and 10 months were the median interval from diagnosis to related and unrelated allo-SCTs, respectively, a crude way to apply a correction factor for the survival seen in our study is to lower the survival estimate at any given time point by 20% for related allo-SCT and 25% for unrelated allo-SCT, respectively. Thus, the corrected OS rates at 4 years were 52% ± 5% for related allo-SCT and 47% ± 4% for unrelated allo-SCT, which showed no statistical difference between related and unrelated allo-SCTs. Time-censoring effects would not change the results.

The change of transplantation indication for adolescents through the observation period might affect the outcome. In the JALSG protocol ALL202 (from September 2002), we treated patients less than 25 years old with a similar protocol performed for pediatric patients. Because allo-SCT was recommended only for high-risk patients, such as those with t(4;11) or MLL-rearrangement in the pediatric protocol, the outcome of young patients might be affected by the difference in the indication for allo-SCT between pediatric and adult protocols after 2002. However, the effect of this small population would not be so large.