Allogeneic hematopoietic stem cell transplantation for the treatment of BCR-ABL1-negative atypical chronic myeloid leukemia and chronic neutrophil leukemia: a retrospective nationwide study in Japan

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Key words: atypical chronic myeloid leukemia, chronic neutrophil leukemia, allogeneic hematopoietic stem cell transplantation

Running title: Allo-HSCT for aCML and CNL

Text words: 2,556 words (/4,000 words)

Table: 3

Figure: 1

Reference: 49 (/50)

Abstract: 200 words (/250 words)

Supplemental Table: 1

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Abstract

Atypical chronic myeloid leukemia (aCML) and chronic neutrophilic leukemia (CNL) are rare *BCR-ABL1* fusion gene-negative myeloid neoplasms with a predominance of neutrophils. Since no standard therapeutic strategy currently exists for these diseases, we retrospectively evaluated the outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for aCML and CNL. Data from 14 aCML and 5 CNL patients as their diagnoses were collected using a nationwide survey. Allo-HSCT was performed between 2003 and 2014. Preconditioning regimens included myeloablative (n=15), reduced-intensity (n=3), and non-myeloablative (n=1) regimens. Transplanted stem cells were obtained from HLA-matched related donors (n=5) and alternative donors (n=14). Neutrophil engraftment was successfully achieved in 17 patients. One-year overall survival rates (OS) were 54.4% (95% confidence interval [CI], 24.8 to 76.7%) and 40.0% (95% CI, 5.2 to 75.3%) in patients with aCML and CNL, respectively. Among aCML patients, 1-year OS were 76.2% (95% CI, 33.2 to 93.5%) and 20.0% (95% CI, 0.8 to 58.2%) in patients with <5% myeloblasts (n=9) and ≥5% myeloblasts (n=5) in peripheral blood before allo-HSCT, respectively. These results suggest that allo-HSCT achieves long-term survival in patients with aCML and CNL. Better pre-transplant management is required to improve the outcomes of aCML patients with ≥5% blasts in peripheral blood.

Introduction

Atypical chronic myeloid leukemia (aCML) and chronic neutrophilic leukemia (CNL) are *BCR-ABL1* fusion gene-negative myeloid neoplasms with an elevated number of neutrophils [1]. Both diseases are very rare; there have been only a few cohorts of aCML patients reported, with the largest case series consisting of 65 patients [2, 3], and only approximately 150 CNL cases have been reported to date [4]. Both diseases have the overlapping clinical manifestations, such as leukocytosis, bleeding diathesis, and splenomegaly [5-11]; and share the oncogenic-drivers and disease-modifying mutations with other myeloid neoplasms (e.g. *SETBP1*, *ASXL1*, *U2AF1*, *SRSF2*, and *TET2* genes) [12-15]. Several different signatures have been identified, such as a higher frequency of colony-stimulating factor 3 receptor (*CSF3R*)-T618I mutations in CNL, and morphological dysplasia and immature granulocytosis in aCML [1, 12, 13, 16].

aCML patients have an extremely poor prognosis with a median survival time of 14-29 months [3, 7, 9], while survival times vary widely in CNL patients, ranging between 6 months and more than 20 years [5, 6]. Current treatment options for these diseases include supportive care, cytoreductive therapies, interferon-α, and intensive chemotherapies [17, 18]. The main aims of these therapies are to improve symptoms and control the proliferation of abnormal cells. Targeted therapies, such as hypomethylating agents, SRC

family kinase signaling inhibitors, JAK kinases inhibitors, and mitogen-activated protein kinase 1 inhibitors, have potential [12, 17-23]; however, few long-term observations have been conducted on aCML and CNL patients treated with these agents.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered to be a curative therapy for both diseases. Allo-HSCT for aCML is regarded as the first option for eligible patients due to its poor prognosis [18], and the utilization of allo-HSCT for CNL is recommended in the patients with the potential progression to refractory neutrophilia and leukemic transformation [17]. However, information on the post-transplant outcomes of aCML and CNL are limited due to the small numbers of patients [24-28]. Therefore, we herein conducted a nationwide retrospective cohort study to clarify the outcomes of allo-HSCT for aCML and CNL, with a focus on the impact of transplant procedures and clinical courses before transplantation.

Patients and methods

Data collection

Data on patients diagnosed with aCML or CNL who underwent their first allo-HSCT between January 1, 2003, and December 31, 2014 were collected by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japanese Data Center for

Hematopoietic Cell Transplantation (JDCHCT) using the Transplant Registry Unified Management Program (TRUMP) [29-31]. Data on these patients were collected and updated as of September 30, 2015. Data collected for analyses included clinical characteristics, such as age at allo-HSCT, gender, the date of transplantation, time from the initial diagnosis to transplantation, performance status (PS) according to the Eastern Cooperative Oncology Group criteria at transplantation, the source of stem cells, chromosomal abnormalities, preconditioning regimens, date alive at the last follow-up, date and cause of death, and incidence and severity of graft-versus-host disease (GVHD). Human leukocyte antigens (HLA)-A, -B, and -DRB1 were identified by serological or molecular typing in related donors, by molecular typing in unrelated bone marrow donors, and by serological typing in unrelated cord blood donors [32-34]. Additional information on clinical data at the initial diagnosis, comorbidities, detailed treatment regimens and response evaluations before allo-HSCT, and the clinical course from diagnosis to transplantation were collected using questionnaires distributed to each participating center in this study. The present study was approved by the Ethics Committee of JDCHCT (approval no.16-4) and by the Ethics Committee of Nagasaki University Hospital (approval no.16062717), at which this study was organized.

Inclusion criteria

The original dataset consisted of 4,188 patients, including 3,798 and 390 patients with *BCR-ABL1*-positive CML and -negative MPN, respectively. Data on 36 patients with aCML or CNL were submitted from this database. aCML and CNL were diagnosed according to the 2016 revised World Health Organization (WHO) classification [1]. Patients classified as neither aCML nor CNL (n=6), with detailed data missing prior to allo-HSCT (n=10), and diagnosed with acute myeloid leukemia (n=1) were excluded from the analysis. Two physicians (H.I and M.I) independently reviewed the quality of the data collected. Fourteen and 5 patients with aCML and CNL, respectively, were included in the present study.

Definitions

In this study, pre-transplant treatments included both the cytoreductive therapies (e.g. hydroxyurea, low-dose cytarabine, and busulphan) and the disease-altering therapies (intensive chemotherapy and hypomethylating agents) in order to evaluate the prognostic value of leukocytosis at allo-HSCT. Preconditioning regimens were classified as a myeloablative preconditioning (MAC), reduced intensity preconditioning (RIC), or non-myeloablative preconditioning (NMAC) regimen according to established criteria [35,

36]. Sustained engraftment was defined by absolute neutrophil counts higher than 0.5 × 10^9/L and an untransfused platelet count higher than 20 × 10^9/L for at least three consecutive days after HSCT. The diagnosis and clinical grading of acute and chronic GVHD were performed according to standard criteria [37, 38]. The responses of aCML and CNL were judged using the proposed criteria for MDS/MPN, as previously described [39].

Statistical analysis

The probabilities of overall survival (OS) were estimated by the Kaplan-Meier method. All statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichi Medical University) [40].

Results

Patient characteristics and clinical courses before transplantation

Patient characteristics are summarized in Table 1. Median age at allo-HSCT was 45 years (range, 10 to 66) and 49 years (range, 35 to 68) in the aCML and CNL groups, respectively. This study included one patient (UPN-10) younger than 16 years (i.e. 10 years old). Regarding cytogenetic abnormalities, the normal karyotype was the most

frequently observed in aCML and CNL patients.

The median intervals from the initial diagnosis to transplantation were 8.9 months (range, 2.6 to 26.7) and 10.0 months (range, 6.8 to 21.3) for aCML and CNL, respectively. The reasons for undergoing allo-HSCT were followed: the disease progression without any response to treatment in 3 aCML (UPN-05, -09, and -10) and 2 CNL patients (UPN-16 and -18); no response of neutrophilia and splenomegaly to cytoreductive agents in 3 CNL patients (UPN-15, -17, and 19). For the remaining 11 aCML patients, the utilization of allo-HSCT was considered before disease progression according to the expert recommendation [18].

Pre-transplant treatments and their responses are shown in Table 2. Five patients with aCML (UPN-02, -05, -06, -09, and -10) failed to respond to any pre-transplant treatment, and subsequently presented with ≥5% of myeloblasts in peripheral blood at the time of the preconditioning treatment. The remaining 14 patients had a stable disease status with <5% of myeloblasts in peripheral blood from the initial diagnosis to transplantation. Of 8 patients evaluable for the bone marrow status before allo-HSCT (UPN-01, -05, -12, -13, -15, -16, -17, and -18), 2 patients (UPN-16 and -18) showed the increase of blasts in bone marrow smears according to the criteria for measurement of disease progression [39]. Although 13 out of the 14 patients received pre-transplant treatments, none achieved

hematological remission. One patient (UPN-08) did not receive any pre-transplant treatment.

Transplant procedures

In 14 patients with aCML, 5, 7, and 2 patients received transplantation using an allograft from HLA-matched related, unrelated bone marrow, and unrelated cord blood donors, respectively (Table 3). All CNL patients received transplantation from alternative donors: unrelated bone marrow (n=2), unrelated cord blood (n=2), and an HLA-haploidentical sibling donor (n=1).

Preconditioning regimens were selected according to the practice and protocols available at each institute. The MAC regimen was the most frequently used for aCML (n=11, 78.6%) and CNL (n=4, 80.0%). Two and one patients with aCML and CNL were treated with anti-thymocyte globulin as part of the preconditioning regimen.

Hematopoietic recovery and chimerism

The cumulative incidence of neutrophil engraftment was 89.5%, and the median time from transplantation to neutrophil engraftment was 20 days (range, 15 to 29 days); 2 patients (UPN-09 and -17) died of sepsis (*Staphylococcus* species.) and diffuse alveolar

hemorrhage before neutrophil engraftment. All patients who achieved neutrophil engraftment demonstrated sustained complete donor chimerism tested using a short tandem repeat analysis or XY-fluorescence *in situ* hybridization analysis. The cumulative incidence of platelet recovery was 73.7%, and the median time from transplantation to platelet recovery was 35 days (range, 17 to 75 days). Three patients who achieved neutrophil engraftment, but not platelet recovery relapsed with the underlying diseases after allo-HSCT. The median relapse-free survival time of the patients who achieved neutrophil engraftment was median 1.39 years (range, 0.15 – 6.72 years).

Disease responses and survival analysis

Among patients with neutrophil engraftment, 9 out of 13 patients (76.9%) with aCML achieved CR, and one showed a marrow response (see Table 2). One patient (UPN-01) had persistent splenomegaly despite achieving an optimal marrow response and the normalization of the peripheral blood count with sustained complete donor chimerism, which was not evaluated as CR. Among CNL patients, although none of the five patients responded to pre-transplant treatments, all but one achieved complete remission after transplantation and two remained in remission at 362 and 441 days post-HSCT. The 1-year probabilities of OS after allo-HSCT were 54.4% (95% confidence interval [CI], 24.8

to 76.7%) and 40.0% (95% CI, 5.2 to 75.3%) in patients with aCML and CNL, respectively (Figure 1A).

Attempts to statistically evaluate prognostic impacts on post-transplant outcomes among patients with aCML were unsuccessful due to the small number of patients in the present study. We stratified OS after transplantation by the prognostic factors previously identified for aCML itself and MDS/MPN other than aCML [7, 41-49]: age at transplantation, the Karnofsky Performance Status (KPS), blast percentages in peripheral blood, white blood cell counts, hemoglobin levels, transfusion dependency, karyotype, the presence of splenomegaly, type of donor source, donor/recipient sex match, and the interval from the initial diagnosis to allo-HSCT. Regarding aCML, 1-year OS were 80.0% (95% CI, 20.4 to 96.9%) and 44.4% (95% CI, 13.6 to 71.9%) in patients using HLA-matched-related (n=5) and alternative donors (i.e. unrelated bone marrow and cord blood donors) (n=9), respectively; 69.3% (95% CI, 31.2 to 89.1%) and 0.0% (95% CI, 0.0 to 0.0%) in patients with KPS ≥90% (n=11) and ≤80% (n=3) at transplantation, respectively (Figure 1B and C). One-year OS were 76.2% (95% CI, 33.2 to 93.5%) and 20.0% (95% CI, 0.8 to 58.2%) for patients with <5% (n=9), and ≥5% (n=5) myeloblasts in peripheral blood at allo-HSCT, respectively (Figure 1D). We were unable to statistically evaluate the prognostic value of bone marrow status before allo-HSCT due to the small number of

aCML patients (n=4). One-year OS by other factors were shown in supplemental Table 1. Among patients who achieved CR after transplantation, 2 with aCML (UPN-05 and -06) relapsed within 1 year of transplantation.

GVHD and transplantation-related mortality

Acute GVHD was observed in 9 patients, with grades I, II, and III-IV occurring in 4, 1, and 4 patients, respectively. In the 14 patients who survived more than 100 days after allo-HSCT, chronic GVHD was observed in 4, with the limited and extensive types in 1 and 3 patients, respectively.

Before the achievement of neutrophil engraftment, 2 patients (UPN-09 and -17) died due to infectious complications and bleeding. After the achievement of neutrophil engraftment and hematological CR, 2 patients (UPN-02 and -16) died due to bleeding and sinusoidal obstruction syndrome.

Discussion

The primary objective of the present study was to evaluate post-transplant outcomes among patients with aCML and CNL. The TRUMP database was introduced in >99% of approximately 250 transplant centers in Japan; thus, the cohort of this study included a

relatively large number of patients with aCML and CNL using a nationwide survey. Mittal et al. reported 7 post-transplant patients with Philadelphia chromosome-negative CML for whom detailed data at the initial diagnosis were not sufficient to differentiate aCML or CNL [24]. In terms of the diagnosis of aCML and CNL, we used the 2016 revised WHO classification in the present study. Since neither aCML nor CNL patients achieved CR by pre-transplant treatments, our analyses provide a clearer insight into the feasibility of allo-HSCT for patients with aCML and CNL.

In the present study, various types of preconditioning regimens were employed for aCML. In two case series reported by Koldehoff et al. and Lim et al., 9 and 2 aCML patients, respectively, underwent allo-HSCT, which was mostly conditioned using busulfan with cyclophosphamide or total body irradiation and cyclophosphamide as the MAC regimen [25, 28]. The present study included 7 patients with aCML treated with a fludarabine-based preconditioning regimen (i.e. fludarabine with busulfan or melphalan), which reflected currently used, real-world regimens. Three out of the 7 patients treated with the fludarabine-based regimen have survived without relapse for more than 2.5 years after transplantation, suggesting that a fludarabine-based regimen is a promising therapeutic option for aCML. Due to the small number of cases with the RIC regimen using fludarabine (UPN-03 and -07), difficulties are associated with evaluating its

efficacy for this disease.

The choice of donor source remains a controversial issue for rare myeloid neoplasms. Based on our results and previous findings on the successful outcomes of transplantation with the use of unrelated bone marrow or peripheral blood stem cells [25], the application of these allografts needs to be considered as an option if available in a timely manner. Furthermore, it is important to note that 3 out of 4 patients (aCML, n=2; CNL, n=2) with the use of unrelated cord blood were alive without relapse more than 340 days after transplantation in the present study. These results indicate that unrelated cord blood transplantation is a feasible treatment for these diseases. More definitive conclusions on the role of unrelated cord blood grafts as a therapeutic option will be obtained from larger studies with longer follow-ups.

Another important result of the present study was that a difference may exist in OS based on the myeloblast percentage (i.e. <5% or ≥5%) in peripheral blood before allo-HSCT for aCML. The myeloblast percentage in peripheral blood was previously identified as a significant prognostic factor for CML in the accelerated phase [43]. Our results suggest that patients with a higher percentage of myeloblasts were more difficult to treat, even with allo-HSCT, than those with a lower percentage of myeloblasts. In order to maximize the benefits of allo-HSCT for aCML, management, including the application of novel

agents before allo-HSCT, needs to be optimized according to the risk stratification of this disease [18-22].

Our study has several limitations due to its retrospective nature. The number of patients examined was too small to demonstrate a significant contribution of GVHD to disease control (e.g. the presence of the graft-versus-leukemia effect). There were insufficient number of patients to evaluate the prognostic value of bone marrow status before allo-HSCT. Future studies are warranted to assess the impact of pre-transplant bone marrow status on post-transplant outcomes. Furthermore, we were unable to evaluate the impact of genetic mutations on post-transplant outcomes due to the lack of the required data. It will be of interest to investigate whether information on mutations in several genes, such as *CSF3R*, Janus kinase 2 (*JAK2*), and SET binding protein 1 (*SETBP1*), will be useful for estimating the risk stratification of post-transplant outcomes and assessing minimal residual disease after allo-HSCT [12-15].

In conclusion, the present results suggest that allo-HSCT offers the best opportunity for hematological remission and prolonged survival in patients with aCML and CNL. Prospective studies need to be conducted in order to clarify the role of allo-HSCT in the treatment algorithm of aCML and CNL, and the development of supportive care to minimize fatal complications will be crucial for post-transplant patients.

Authorship

Contribution

H.I. and Y.M. designed the research, organized the project, collected data from TRUMP, analyzed data, and wrote the manuscript. H.I., Y.M., S.O., T. Ikeda, H.T., I.A., Y.H., T. Ichinohe, T.F., Y.A., A.T., and T.K. interpreted data, and reviewed and approved the final manuscript.

Appendix

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of Fukui: Dr. A Tanizawa; Keio University School of Medicine: Dr. H. Shimada; Osaka Women's and Children's Hospital: Dr. M Yasui; Ehime Prefectural Central Hospital: Dr. Y Ishida; Okayama University Hospital: Dr. A. Shimada; Saitama Children's Medical Center: Dr. M. Mori.

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Acknowledgments

This work was supported in part by the Practical Research Project for Allergic Diseases and Immunology (Research Technology of Medical Transplantation) from the Japan Agency for Medical Research and Development, AMED.

The authors would like to thank all the physicians and data managers at the various institutes who contributed valuable data on transplantation to the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and all the members of the data management committees of JSHCT; a complete membership list of the "Adult and Child Chronic Myeloid Leukemia/Myeloproliferative Neoplasms Working Group of the JSHCT" appears in the "Appendix".

We especially thank the doctors who responded to the questionnaire: Osaka Medical Center and Research Institute for Maternal and Child Health: Dr. M Inoue; Tokai University School of Medicine: Dr S. Machida: Nara Medical University Hospital: Dr. I. Amano: Aichi Cancer Center Hospital: Dr. H. Taji; Shizuoka Cancer Center: Dr. T. Ikeda; University of Tsukuba: Dr. Y. Hasegawa; Sapporo Hokuyu Hospital: Dr. S. Ota and Dr. A. Imai; Tokushima University Graduate School: Dr. K. Kagawa; Kurume University: Dr. K. Nagafuji; Tenri Hospital: Dr. T Akasaka; Hyogo College of Medicine: Dr. K Ikegame; Yokohama Minami Kyousai Hospital: Dr. Tajika K; Hamanomachi Hospital: Dr. T. Eto;

Kanagawa Cancer Center: Dr. T. Tachibana; National Center for Global Health and Medicine: Dr. M. Takeshita; Shinshu University School of Medicine: Dr. H. Nakazawa; Akita University Graduate School of Medicine: Dr. M. Nara; National Hospital Organization Kumamoto Medical Center: Dr. M. Hidaka; Kanagawa Children's Medical Center: Dr. S. Hamanoue; Nagoya University Graduate School of Medicine; Dr. M. Murata.

Conflicts of interest

The authors state that they have no conflicts of interest.

Table Legends

Table 1. Patient characteristics

Abbreviations: aCML, atypical chronic myeloid leukemia; CNL, chronic neutrophilic leukemia; HSCT, allogeneic hematopoietic stem cell transplantation; KPS, Karnofsky Performance Status; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; Hb, hemoglobin; WBC, white blood cell count; PB, peripheral blood; PLT, platelet count.

Table 2. Clinical responses to pre-transplant treatments

* Disease progression was diagnosed by an increase in the blast count.

Abbreviations: CBC, complete blood count; PB, peripheral blood; aCML, atypical chronic myeloid leukemia; CNL, chronic neutrophil leukemia; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count; CR, complete remission; SD, stable disease; PR, progressive disease; AraC, cytarabine arabinoside; DNR, daunorubicin; IDR, idarubicin; MIT, mitoxantrone; ETP, etoposide.

Table 3. Transplant procedures and outcomes

*The preconditioning regimen included anti-thymocyte globulin.

†The systemically administered steroid (i.e. methylprednisolone and/or prednisolone) was used to treat GVHD.

‡ This patient received transplantation from a HLA haploidentical related donor.

Abbreviations: GVHD, graft-versus-host disease; HLA, human-leukocyte-antigen; OS, overall survival; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; NMAC, non-myeloablative conditioning; TBI, total body irradiation; Cy, cyclophosphamide; Flu, fludarabine; ivBu, intravenous busulphan; AraC, cytosine arabinoside; Mel, melphalan; ETP, etoposide; Tac, tacrolimus; CsA, cyclosporine; sMTX, short-term methotrexate; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide; R-BM, related bone marrow; R-PBSC, related peripheral blood stem cell; UR-BM, unrelated bone marrow; UR-CB, unrelated cord blood; CR, complete remission; SOS, sinusoidal obstruction syndrome.

Figure Legends

Figure 1. Overall survival after allo-HSCT

(A) Overall survival (OS) in aCML and CNL. (B) OS by the type of donor source in aCML. (C) OS by KPS before allo-HSCT in aCML. (D) OS by myeloblast percentages in peripheral blood before allo-HSCT in aCML.

Table 1. Patient characteristics

	Disease type	
	aCML (n=14)	CNL (n=5)
Sex of recipient, n		
Male	7	3
Female	7	2
Median age at HSCT (range), y	45 (10 - 66)	49 (35 - 68)
Interval from diagnosis to HSCT (range), mo	8.9 (2.6 - 26.7)	10.0 (6.8 - 21.3)
KPS before HSCT, n		
≥90%	11	5
≤80%	3	0
HCT-CI, n		
0	11	3
1-2	2	2
≥3	1	0
Cytogenetic abnormality, n		
Normal karyotype	8	4
+8	3	0
t(8;22)(p12;q11.2)	1	0
i(18)(q10)	1	0
inv(8)(p21q22)	1	0
t(7;11)(p15;p15)	0	1
Median Hb (g/dL) before HSCT (range)	8.5	9.4
Median WBC ($\times 10^9$/L) before HSCT (range)	9.5 (0.9 - 71.2)	11.1 (3.4 - 16.5)
≥25.0×10^9/L	4	0
≥13.0×10^9/L, <25.0×10^9/L	2	1
<13.0×10^9/L	8	4
Median myeloblasts in PB (%) before HSCT (range)	1.0 (0.0 - 25.0)	0.0 (0.0 - 1.0)
≥5%	5	0
<5%	9	5
Median PLT ($\times 10^9$/L) before HSCT (range)	46 (3 - 1073)	61 (21 - 371)
Palpable hepatomegaly before HSCT, n		
Yes	3	3
No	11	2
Palpable splenomegaly before HSCT, n		
Yes	9	5
No	5	0

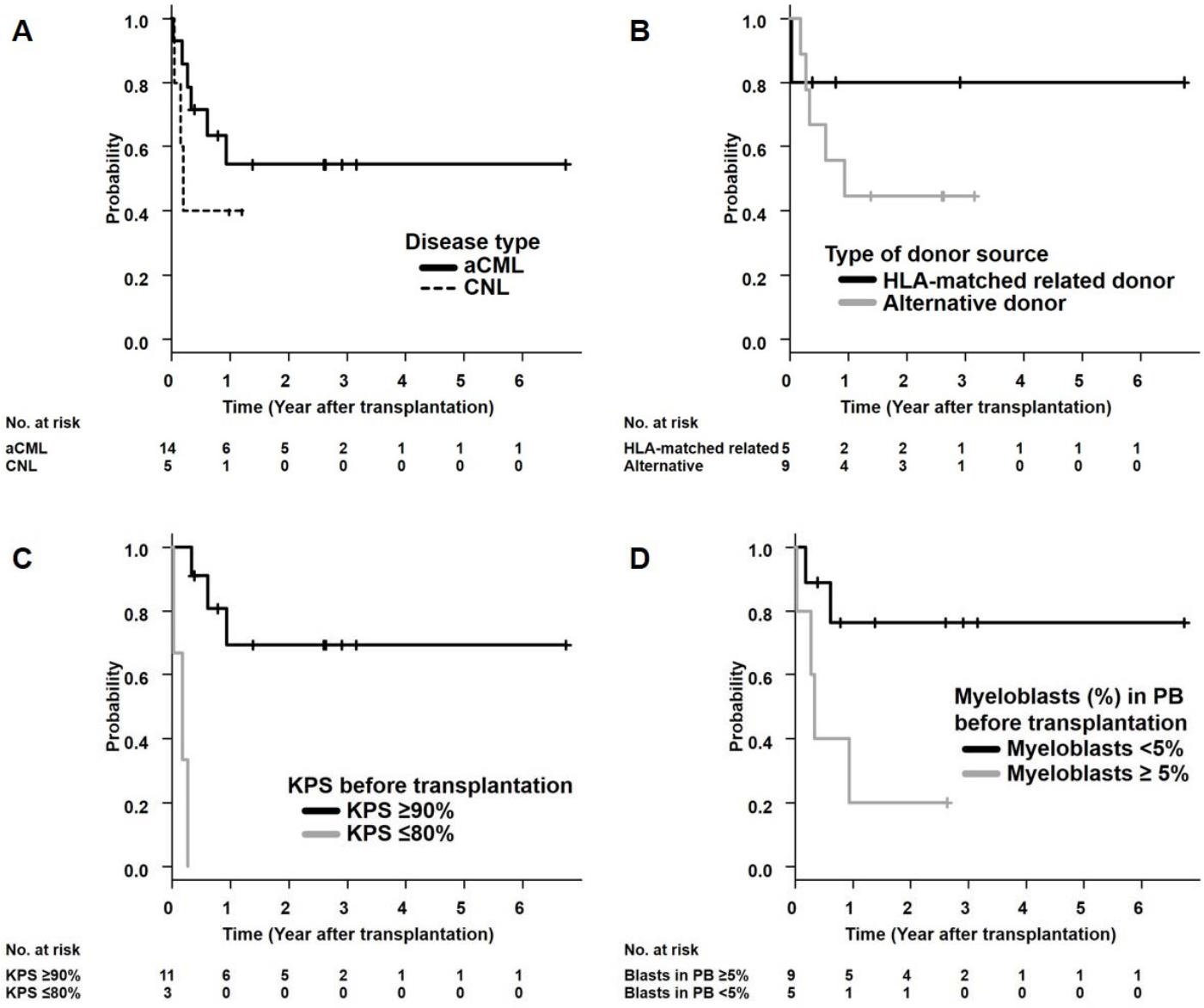
Table 2. Clinical responses to pre-transplant treatments

UPN	Disease	CBC in PB at the initial diagnosis				1st-line treatment		2nd-line treatment		3rd-line treatment		CBC in PB before allo-HSCT			
		Hb (g/dL)	WBC ($\times 10^9$/L)	Myeloblast (%)	PLT ($\times 10^9$/L)	Regimen	Response	Regimen	Response	Regimen	Response	Hb (g/dL)	WBC ($\times 10^9$/L)	Myeloblast (%)	PLT ($\times 10^9$/L)
UPN-01	aCML	14.0	22,990	0.5	2.2	Hydroxyurea	Marrow response	-	-	-	-	12.5	7,900	0.0	3.9
UPN-02	aCML	6.8	48,600	5.3	2.3	Hydroxyurea	PD*	-	-	-	-	7.8	13,000	25.0	1.1
UPN-03	aCML	13.5	23,100	3.0	10.2	Hydroxyurea	SD	AraC, DNR	SD	-	-	5.6	52,800	1.0	5.4
UPN-04	aCML	9.9	23,300	1.0	15.9	Hydroxyurea	Marrow response	-	-	-	-	9.1	6,200	0.0	15.1
UPN-05	aCML	10.5	15,150	0.0	28.4	AraC, IDR	CR	Hydroxyurea	PD*	Low-dose AraC	SD	5.7	30,340	16.5	0.7
UPN-06	aCML	8.9	85,900	6.0	14.8	Hydroxyurea	SD	Busulphan	SD	-	-	7.2	7,900	7.0	3.0
UPN-07	aCML	9.8	62,600	0.5	10.3	Hydroxyurea	SD	Busulphan	SD	-	-	7.3	71,200	0.0	2.3
UPN-08	aCML	4.8	17,090	2.0	9.0	-	-	-	-	-	-	6.4	36,720	4.0	8.3
UPN-09	aCML	6.9	14,700	15.0	0.6	ETP, DNR	PD*	-	-	-	-	10.2	1,700	39.0	2.0
UPN-10	aCML	7.6	43,900	1.0	66.7	Low-dose AraC	CR	Azacitidine	PD*	AraC, MIT	SD	11	10,600	12.0	107.3
UPN-11	aCML	10.0	153,400	0.4	13.0	Hydroxyurea	SD	Ranimustine	SD	-	-	9.2	14,800	0.0	4.6
UPN-12	aCML	15.2	29,400	4.0	13.0	Hydroxyurea	SD	AraC, DNR	Marrow response	-	-	11.7	2,250	0.0	8.9
UPN-13	aCML	14.4	22,300	2.0	41.9	Hydroxyurea	CR	-	-	-	-	13.4	8,400	0.0	16.8
UPN-14	aCML	13.2	18,710	1.5	24.4	Hydroxyurea	SD	Mercaptopurine	SD	ETP, DNR	SD	6.5	930	0.0	0.3
UPN-15	CNL	12.0	27,400	0.0	85.5	Hydroxyurea	SD	-	-	-	-	13.2	11,100	0.0	37.1
UPN-16	CNL	12.7	37,000	0.0	23.8	Hydroxyurea	PD	-	-	-	-	11.9	3,400	1.0	6.5
UPN-17	CNL	11.9	23,000	0.0	22.5	Hydroxyurea	SD	Azacitidine	SD	-	-	7.1	12,900	1.0	2.3
UPN-18	CNL	13.2	38,760	0.0	25.3	AraC, DNR	SD	-	-	-	-	9.4	7,340	0.0	2.1
UPN-19	CNL	7.2	58,700	0.0	34.2	Dasatinib	SD	Hydroxyurea	SD	-	-	8.6	16,500	0.0	6.1

Table 3. Transplant procedures and outcomes

UPN	Preconditioning regimen	GVHD prophylaxis	Source of stem cells	No. of HLA mismatches	Neutrophil engraftment (day)	Platelet recovery (day)	Response after HSCT	Acute GVHD grade	Chronic GVHD severity	Relapse of disease (day)	OS (day)	Cause of death
UPN-01	TBI 12 Gy/Cy	Tac/sMTX	UR-BM	1	18	32	No	I †	Extensive (Skin, liver)	non-CR	225	Underlying disease
UPN-02	TBI 12 Gy/Cy	Tac/sMTX	UR-BM	0	17	24	CR	III †		No	123	Bleeding
UPN-03	Flu/ivBu 6.4 mg/kg	CsA/sMTX	R-BM	0	26	42	CR			No	+140	
UPN-04	Flu/ivBu 12.8 mg/kg/AraC	CsA/sMTX	R-BM	0	29	20	CR		Extensive † (Skin, liver)	No	+2456	
UPN-05	TBI 12 Gy/Cy	Tac/sMTX	UR-BM	0	21	No	Marrow response			63	104	Underlying disease
UPN-06	Flu/Cy/TBI 2 Gy	CsA/MMF	UR-CB	2	15	75	CR	I		343	343	Underlying disease
UPN-07	Flu/Mel 140 mg/m^2	Tac/sMTX	UR-BM	0	21	17	CR		Extensive † (Mouth, liver)	No	+1151	
UPN-08	TBI 12 Gy/Cy	CsA/sMTX	R-BM	0	16	36	CR	I		No	+1063	
UPN-09	Flu/ivBu 12.8 mg/kg	CsA/sMTX	R-PBSC	0	No	No	No			No	15	Infection
UPN-10	Flu/Mel 210 mg/m^2/ETP*	Tac/sMTX/Steroid	UR-BM	1	16	35	CR	III †		No	+961	
UPN-11	TBI 12 Gy/Cy	CsA/sMTX	UR-BM	0	16	30	CR	I		No	+947	
UPN-12	TBI 12 Gy/Cy/AraC	CsA/sMTX	UR-CB	2	20	40	CR	III †		No	+509	
UPN-13	TBI 12 Gy/Cy	CsA/sMTX	R-PBSC	0	17	30	No	III †		non-CR	+290	
UPN-14	Flu/ivBu 12.8 mg/kg*	Tac/sMTX	UR-BM	0	25	No	No	III		non-CR	71	Underlying disease
UPN-15	TBI 12 Gy/Cy/AraC	Tac/sMTX	UR-CB	2	26	30	CR			No	+441	
UPN-16	TBI 12 Gy/Cy	Tac/sMTX	UR-BM	0	16	21	CR			No	56	SOS
UPN-17	Flu/Mel 140 mg/m^2/TBI 2 Gy	Tac/sMTX	UR-CB	2	No	No	No			No	19	Bleeding
UPN-18	Flu/ivBu 12.8 mg/kg*	Tac/sMTX	UR-BM	0	15	17	CR	II	Limited (Skin)	No	+362	
UPN-19	Flu/ivBu 12.8 mg/kg/TBI 4 Gy	PTCy/Tac/MMF	R-BM‡	2	20	No	No			non-CR	76	Underlying disease

Figure 1. Overall survival after allo-HSCT



Supplemental Table 1. Overall survival rate 1 year after transplantation

Factor		aCML patients	
		No. of patients	OS at 1 year (%) (95% CI)
Age at allo-HSCT*	≥ 45 yrs.	8	41.7% (7.2 - 74.7%)
	< 45 yrs.	6	66.7% (19.5 - 90.4%)
Karnofsky Performance Status at allo-HSCT	≥ 90%	11	69.3% (31.2 - 89.1%)
	≤ 80%	3	0.0% (0.0 - 0.0%)
White blood cell count before transplantation	≥ 10.0×10^9/L	7	71.4% (25.8 - 92.0%)
	< 10.0×10^9/L	7	38.1% (6.1 - 71.6%)
Myeloblasts (%) in peripheral blood before allo-HSCT	≥ 5%	5	20.0% (0.8 - 58.2%)
	< 5%	9	76.2% (33.2 - 93.5%)
Hemoglobin level before allo-HSCT	≥ 10 g/dL	5	60.0% (12.6 - 88.2%)
	< 10 g/dL	9	53.3% (17.7 - 79.6%)
Transfusion dependency before allo-HSCT	Yes	6	83.3% (4.6 - 67.6%)
	No	8	68.6% (21.3 - 91.2%)
Karyotype	Normal	8	58.3% (18.0 - 84.4%)
	Other	6	50.0% (11.1 - 80.4%)
The presence of splenomegaly before allo-HSCT	Yes	9	48.6% (12.8 - 77.6%)
	No	5	60.0% (20.4 - 96.9%)
Conditioning regimen	MAC	11	54.5% (22.9 - 78.0%)
	RIC / NMAC	3	50.0% (0.6 - 91.0%)
Type of donor source	Matched-related	5	80.0% (20.4 - 96.9%)
	Alternative	9	44.4% (13.6 - 71.9%)
Donor/recipient sex match	Match	10	50.0% (18.4 - 75.3%)
	Mismatch	4	66.7% (5.4 - 94.5%)
Interval from the initial diagnosis to allo-HSCT	≥ 12 months	5	40.0% (5.2 - 75.3%)
	< 12 months	9	66.7% (28.2 - 87.8%)

*The median age at allo-HSCT was 45 years among patients with aCML.

Abbreviations: MAC, myeloablative conditioning regimen; RIC, reduced-intensity conditioning regimen; NMAC, non-myeloablative conditioning regimen; OS, overall survival rate; 95% CI, 95% confidential incidence.