Figure 2

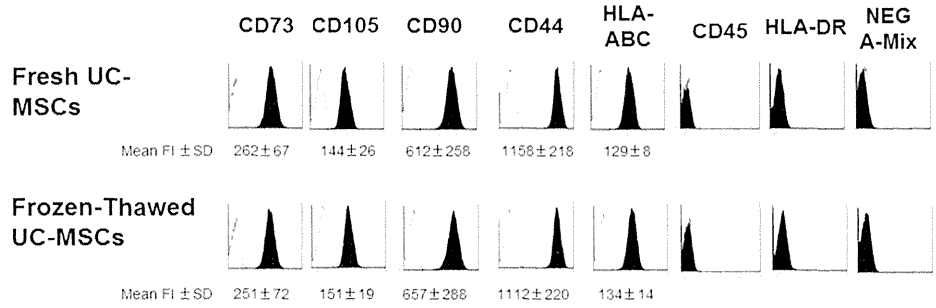


Figure 2. Characterization of umbilical cord-derived mesenchymal stem cells (UC-MSCs) isolated from frozen-thawed UC.
UC-MSCs isolated from both the fresh and frozen-thawed UC showed positive CD73, CD105, CD90, CD44, and HLA-ABC expression, and negative CD45, HLA–DR expression, and NEGA-mix containing CD34, CD14, CD19, and HLA-DR. Fluorescent intensity (FI) ± standard deviation for positive markers is indicated without significant differences between the fresh and frozen-thawed UC-MSCs (n = 3).
254x190mm (96 x 96 DPI)

Figure 3

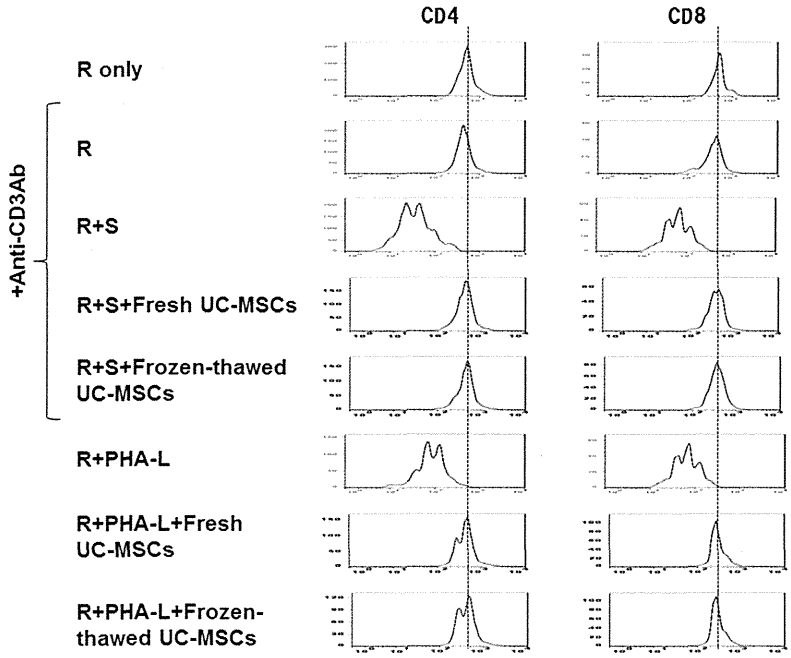


Figure 3. Immunosuppressive effect of Umbilical cord-derived mesenchymal stromal cells (UC-MSCs) derived from frozen-thawed UC.
UC-MSCs derived from the frozen-thawed UC showed inhibition of CD4- and CD8-positive T cell proliferation triggered by the allogeneic dendritic cells and PHA-L. Carboxyfluorescein succinimidyl ester (CFSE)-labeled mononuclear cells (R) were cultured in different conditions, R indicates R only, R + S indicates co-culture with allogeneic dendritic cells (S), R + S + Fresh UC-MSCs or frozen-thawed UC-MSCs indicates allogeneic stimulation and allogeneic fresh or frozen-thawed UC-MSCs of the third-party donor, respectively. The ratio of the mixture of R : S : UC-MSCs for the MLR was 10 : 1 : 1. R + PHA-L indicates R with 10 μg of PHA-L. R + PHA-L + Fresh UC-MSCs or frozen-thawed UC-MSCs indicated R + PHA-L with fresh UC-MSCs or frozen-thawed UC-MSCs from third-party donor, respectively. Data are shown as representative of three independent experiments.
254x190mm (96 x 96 DPI)

Figure 4

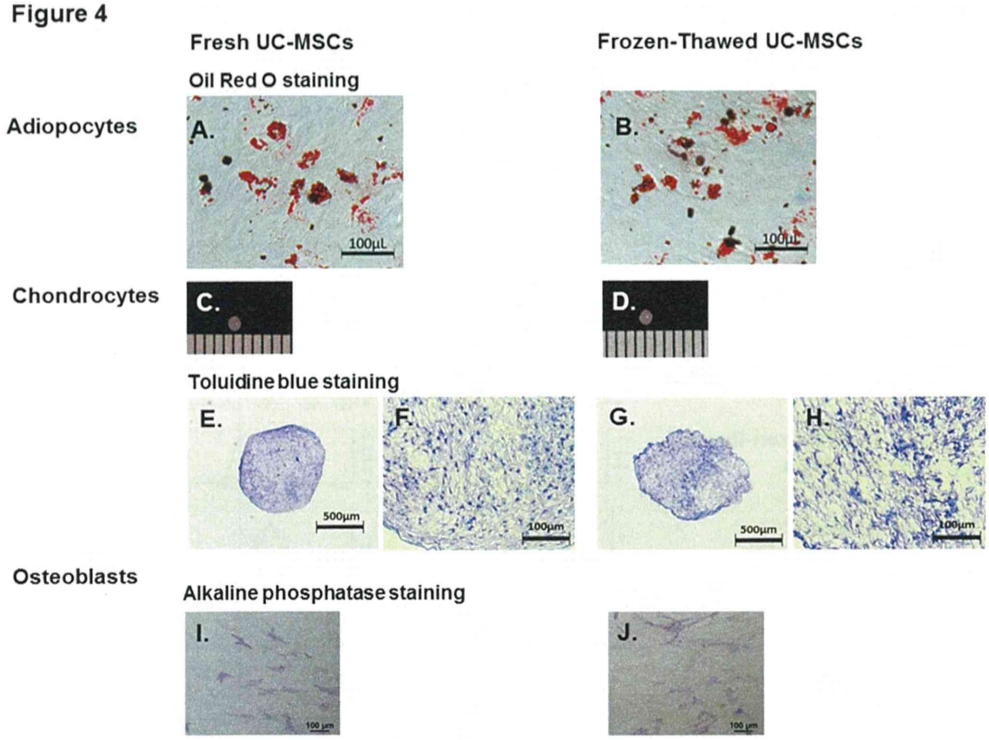


Figure 4. Adipocyte, chondrocyte, and osteoblastic differentiation ability of umbilical cord-derived mesenchymal stromal cells (UC-MSCs) derived from frozen-thawed UC.
Frozen-thawed UC-MSCs were differentiated into adipocytes (upper panel) and chondrocytes (lower panel). In adipocyte-differentiated cells (A and B), the accumulation of Oil Red O-stained lipid drops was observed in both the fresh UC-MSCs and frozen-thawed UC-MSCs (red droplets; magnification, 200X). For chondrogenic differentiation, the pellet culture system was used. The elastic firm pellet was observed in the differentiation medium after 3 weeks of culture (C and D) (magnification 40X). Toluidine blue staining revealed the presence of extracellular matrix with metachromasia in histological sections (E to H, magnification of 40X and 100X, respectively). The fresh and frozen-thawed UC-MSCs were induced into osteoblastic cells, which were positive for alkaline phosphatase (I and J) (violet cells; magnification, 200x). There was no difference in the alkaline phosphatase expression between them.
254x190mm (96 x 96 DPI)

Int J Hematol
DOI 10.1007/s12185-014-1632-9

ORIGINAL ARTICLE

# Effect of graft sources on allogeneic hematopoietic stem cell transplantation outcome in adults with chronic myeloid leukemia in the era of tyrosine kinase inhibitors: a Japanese Society of Hematopoietic Cell Transplantation retrospective analysis

**Kazuteru Ohashi · Tokiko Nagamura-Inoue · Fumitaka Nagamura · Arinobu Tojo · Kouichi Miyamura · Takehiko Mori · Mineo Kurokawa · Shuichi Taniguchi · Jun Ishikawa · Yasuo Morishima · Yoshiko Atsuta · Hisashi Sakamaki**

Received: 19 October 2013 / Revised: 1 July 2014 / Accepted: 2 July 2014


**Abstract** We retrospectively compared transplant outcomes for related bone marrow transplantation (rBMT), related peripheral blood stem cell transplantation (rPBSCT), unrelated bone marrow transplantation (uBMT), and unrelated cord blood transplantation (CBT) in 1,062 patients with chronic myeloid leukemia (CML) aged 20 years or over between January 1, 2000 and December 31, 2009 in Japan. The disease status was as follows: chronic phase 1 (CP1, $n = 531$), CP 2 or later including accelerated phase (CP2-AP, $n = 342$) and blastic crisis (BC, $n = 189$). Graft sources (GS) were rBMT ($n = 205$), uBMT ($n = 507$), rPBSCT ($n = 226$) or CBT ($n = 124$). In multivariate analysis in CP1, lower overall survival (OS) (relative risk [RR]: 6.01, 95 % confidence interval [CI]: 1.20–29.97, $P = 0.029$) and leukemia-free survival (LFS) (RR: 4.26, 95 % CI: 1.24–14.62, $P = 0.021$) were observed in uBMT compared with those in rBMT. For patients in the advanced phase of CML beyond CP1, GS had no significant impact on OS or LFS. Our results support the use of rBMT for adults with CML in CP1, but in contrast to previous reports, the superiority of rPBSCT in advanced stage of CML was not confirmed in our cohorts.

**Keywords** Chronic myeloid leukemia · Allogeneic hematopoietic stem cell transplantation · Graft sources

On behalf of Choric Myeloid Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation.

**Electronic supplementary material** The online version of this article (doi:10.1007/s12185-014-1632-9) contains supplementary material, which is available to authorized users.

K. Ohashi (✉) · H. Sakamaki
Hematology Division, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan
e-mail: k.ohashi@cick.jp

T. Nagamura-Inoue
Department of Cell Processing and Transfusion, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

T. Nagamura-Inoue
Japan Cord Blood Bank Network, Tokyo, Japan

F. Nagamura
Division of Clinical Trial Safety Management, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

A. Tojo
Department of Hematology/Oncology, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

K. Miyamura
Department of Hematology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan

T. Mori
Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

M. Kurokawa
Department of Cell Therapy and Transplantation Medicine, The University of Tokyo, Tokyo, Japan

S. Taniguchi
Department of Hematology, Toranomon Hospital, Tokyo, Japan

J. Ishikawa
Department of Hematology and Chemotherapy, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Y. Morishima
Division of Epidemiology/Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

Published online: 02 August 2014

## Introduction

According to the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the number of transplants reported annually for the treatment of CML was 306 in 2000, but drastically dropped to 46 transplants in the year 2009. Unsurprisingly, the drop in transplant activity was observed in Japan after imatinib (IM) became available as an experimental drug in 2000 and subsequently as a frontline treatment for CML in 2001. Thus, the excellent outcomes demonstrated by tyrosine kinase inhibitors (TKIs) argue against the use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) as an upfront therapy for CML in CP1; allo-HSCT is currently recommended for patients with a T315I mutation, or who failed TKIs and progress to advanced phase disease [1–6]. Moreover, the newly launched third generation TKI, ponatinib, having a unique binding mechanism allowing inhibition of BCR-ABL kinases, including those with the T315I mutation may further narrow the range of transplant indication [7, 8]. Therefore, those CML patients who undergo allo-HSCT represent a selection of high-risk patients due to more advanced disease with high rates of accelerated or blast phase. To improve transplant outcomes, comprehensive approaches in transplant strategies including timing, choice of conditioning and GS, maintenance therapy might be needed for those CML patients being selected nowadays for allo-HSCT. The main purpose of this study was to analyze the impact of GS on transplant outcome for patients with CML in the era of TKIs, particularly the role of GS in each disease status. We also clarified the prognostic factors for transplant outcomes in each disease status. We herein report our analysis of 1,062 patients, whose complete registry-based clinical data which were provided by the JSHCT.

## Patients and methods

### Patients

Data on a total of 1,143 patients of at least 20 years of age who had undergone allogeneic bone marrow, peripheral blood, or cord blood transplantation for CML between January 1, 2000 and December 31, 2009 were initially collected through the Transplant Registry Unified Management Program (TRUMP). Eighty-one patients were excluded from the analysis, because one or two critical data such as alive, relapse, and engraftment status with or without date of onset were missing. Other missing data were dealt as missing data in the study and the analysis numbers in each variable were described, respectively. This included data from the Japan Cord Blood Bank Network (JCBBN), the Japan Marrow Donor Program (JMDP), and JSHCT. These are the 3 largest allo-HSCT registries in Japan, and their roles have been described previously [9]. The study was approved by the data management committees of JSHCT, as well as by the ethical committee of Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital (Tokyo, Japan), where this study was organized.

### Statistical analysis

The outcome endpoints were neutrophil recovery, platelet recovery, acute and chronic GVHD, relapse, transplantation-related mortality (TRM), overall survival (OS), and leukemia-free survival (LFS). The definitions of the statistical models used were in accordance with the statistical guidelines of the European Group for Blood and Marrow Transplantation (EBMT) (http://www.ebmt.org/1WhatisEBMT/whatisebmt2.html). Neutrophil recovery was defined by an absolute neutrophil count (ANC) of at least $0.5 \times 10^9$/L for 3 consecutive days, with the first day considered as the recovery day. Platelet recovery was defined by a non-transfused platelet count of at least $20 \times 10^9$/L for 3 consecutive days. Deaths occurring before day 90 or day 180 were considered as competing risks for neutrophil or platelet recovery, respectively. The graft failure rate for neutrophils was calculated for patients living without relapse for more than 30 days. Acute and chronic GVHD were diagnosed and graded at each center according to the standard criteria [10–12]. Relapse was defined on the basis of the reappearance of the blast or Philadelphia chromosome (Ph) or *BCR-ABL1* transgene by cytogenetic and/or molecular analysis, including polymerase chain reaction and fluorescence in situ hybridization. TRM was considered a sole cause of non-leukemic deaths occurring after transplantation; OS was defined as the time between transplantation and death due to any cause; LFS was defined as the time interval from allo-HSCT to a first event, either relapse or death, in patients achieving complete remission. HLA antigen disparities were categorised as either GVHD or rejection direction. Low-resolution antigens of HLA-A and HLA-B were identified for all patients by serologic typing or low-resolution molecular typing methods. While, HLA-DRB1 alleles were

Y. Morishima
Japan Marrow Donor Program, Tokyo, Japan

Y. Atsuta
Department of HSCT Data Management/Biostatistics, Nagoya University Graduate School of Medicine, Nagoya, Japan

Y. Atsuta · H. Sakamaki
Japanese Society of Hematopoietic Cell Transplantation, Nagoya, Japan

determined by high-resolution molecular typing using the sequence-based HLA typing method. In rBMT, HLA-DRB1 alleles were counted as identical, if the low-resolution antigens of HLA-A, B, and DR were identical. Data on HLA-DRBI allele were not fully available; there were 2 lacking data in CP1, 4 lacking data on CP2-AP and 2 lacking data in BC. Detail of HLA disparity toward either rejection or GVHD are noted in Table 1 and Supplementary Table 1.

Adjusted probabilities of OS and LFS were analyzed using Cox proportional-hazards regression model. The variables used were patients' age at HSCT, patients' sex, body weight at HSCT, time from diagnosis to HSCT, ABO mismatch, conditioning regimen, imatinib administration, kind of GVHD prophylaxis, and year of HSCT. Variables with more than two categories were dichotomized for the final multivariate analyses. Variables were dichotomized as the followings: patient's age at HSCT younger or older than median; patient's body weight at HSCT lighter or heavier than median; time from diagnosis to HSCT <1 year or >1 year. ABO major mismatch or others; myeloablative conditioning regimen or others; cyclosporine-based GVHD prophylaxis regimen or tacrolimus-based; year of HSCT before or after 2004. The endpoints of neutrophil and platelet recovery, acute GVHD and chronic GVHD, relapse and TRM were analyzed using cumulative incidence curves that estimated incidence according to the Fine and Gray models, in which we first used univariate models that contained each of the variables one at a time. Then all variables with a $P < 0.05$ by the likelihood-ratio test were included in a multivariate model.

Cause-specific hazard ratios were estimated with 95 % confidence intervals (CIs). Statistical analysis was performed with the R Foundation statistical computing package, version 2.12.2 (http://www.r-project.org/).

**Table 1** Characteristics of patients with CML in CP1, CP2-AP, and BP

| | CP1 ($n = 531$) | CP2-AP ($n = 342$) | BP ($n = 189$) |
|---|---|---|---|
| Graft source rBMT/uBMT/rPBSCT/CBT | 138/258/125/10 | 43/176/59/64 | 24/73/42/50 |
| Gender | 338/193 ($P < 0.001$) | 215/127 ($P < 0.001$) | 123/66 ($P < 0.001$) |
| Male/female | | | |
| Median age at transplantation (range) | 40 (20–67) | 43 (21–69) | 43 (20–74) |
| GVHD prophylaxis CyA + MTX/CyA based/FK + MTX/FK based/ others | 331/27/144/12/14[a] | 148/17/145/19/9[a] | 88/22/58/17/2[a] |
| Pre-transplant IM | 133/249[b] | 187/108[b] | 94/95 ($P = 0.94$) |
| Yes/no | ($P < 0.001$) | ($P < 0.001$) | |
| Duration from diagnosis to transplantation, months median (range) | 12.5 (0.8–169.0) | 18.2 (1.6–255.3) | 15.5 (2.4–322.7) |
| Duration from diagnosis to transplantation ≤1 year/> 1 year | 248/258[c] ($P = 0.65$) | 135/195[c] | 80/100[c] ($P = 0.14$) |
| | | ($P < 0.001$) | |
| Patient's body weight, kg Median (range) | 61 (40–104) | 60 (34–104) | 58.5 (34–96) |
| Conditioning regimen Myeloablative/reduced intensity | 475/53[d] ($P < 0.001$) | 289/53 ($P < 0.001$) | 161/28 ($P < 0.001$) |
| Years at transplantation 2000–2004/2005–2009 | 447/84 ($P < 0.001$) | 211/131 ($P < 0.001$) | 116/73 ($P < 0.01$) |
| ABO mismatch No/yes | 189/161[e] ($P = 0.13$) | 132/156[e] ($P = 0.16$) | 64/91[e] ($P = 0.03$) |
| HLA disparities (rejection direction)[g] 0–1/> 2 | 510/19[f] ($P < 0.001$) | 281/57[f] ($P < 0.001$) | 145/42[f] |
| | | | ($P < 0.001$) |
| HLA disparities (GVHD direction)[g] 0–1/> 2 | 507/22[f] ($P < 0.001$) | 285/53[f] ($P < 0.001$) | 140/47[f] |
| | | | ($P < 0.001$) |

*CP* chronic phase, *AP* accelerated phase, *BP* blastic phase, *rBMT* related bone marrow transplantation, *rPBSCT* related peripheral blood stem cell transplantation, *uBMT* unrelated bone marrow transplantation, *CBT* unrelated cord blood transplantation, *GVHD* graft-versus-host disease, *CyA* cyclosporine, *MTX* methotrexate, *FK* tacrolimus, *IM* imatinib mesylate, *HLA* human leukocyte antigen

[a] Data on GVHD prophylaxis were not fully available; there were 3 missing data in CP data, 4 missing data on CP2-AP and 2 missing data in BC

[b] Data on pre-transplant imatinib administration were not fully available; 149 data and 47 data were not retrieved in CP1 and in CP2-AP, respectively

[c] Loss of data on duration from diagnosis to transplantation (≤ 1 year/> 1 year) was noted; 25 data in CP, 12 data in CP2-AP, and 9 data in BP were not retrieved

[d] Three data regarding conditioning regimen in CP were not retrieved

[e] Loss of data on ABO mismatch was noted; 181 data in CP, 54 data in CP2-AP, and 34 data in BP were not retrieved

[f] Data on HLA-DRBI allele were not fully available; there were 2 lacking data in CP, 4 lacking data on CP2-AP and 2 lacking data in BC

[g] More detail of HLA disparity toward either rejection or GVHD is noted in supplementary Table 1

## Results

### Patient characteristics

Of 1,062 patients (676 men, 386 women; median age, 41 years; range, 20–74), 414 patients (39 %) had a clear history of pre-transplant IM use. Disease status was as follows: CP1 ($n = 531$), CP2-AP ($n = 342$) and BC ($n = 189$). GS were related rBMT ($n = 205$), uBMT ($n = 507$), rPBSCT ($n = 226$) and CBT ($n = 124$). The unrelated PBSCT has not been allowed in Japan until 2012 and, therefore, our data included only unrelated BMT, not PBSCT. In addition, during the study period, there were no related CBTs at all. The other variables, including GVHD prophylaxis, pre-transplant IM, body weight at allo-HSCT, duration from diagnosis to transplant, conditioning intensity, years at transplantation (2000–2004 vs. 2005–2009), ABO mismatch, HLA mismatch in either GVHD or rejection direction, are shown in Table 1.

### Overall survival and leukemia-free survival

The median follow-up period was 914 days after transplantation (range 2–3,902) and 1,914 days after diagnosis (range 29–9,120). Three-year OS was 70.6 % (95 % CI, 66.8-74.7 %) for patients in CP1 at the time of transplantation, 58.9 % (95 % CI, 53.7–64.7 %) for those with CP2-AP, and 26.9 % (95 % CI, 20.9–34.6 %) for those in BC. The probability of 3-year LFS for patients in CP1, CP2-AP and BC was 64.6 % (95 % CI, 60.4–68.6 %), 46.1 % (95 % CI, 40.9–51.9 %) and 19.2 % (95 % CI, 14.1–26.1 %), respectively (data not shown).

OS and LFS according to GS in CP1, CP2-AP, and BC are shown in Fig. 1a–c, and d–f, respectively. In view of OS and LFS according to GS, 3-year OS after rBMT, rPBSCT, uBMT, and CBT in CP1 was 84.4, 70.0, 64.4, and 48.0 %, respectively (Fig. 1a). Three-year LFS after rBMT, rPBSCT, uBMT, and CBT in CP1 was 76.3, 64.3, 59.3, and 30 %, respectively (Fig. 2d). Multivariate analysis for OS identified the following factors as adverse prognostic factors for

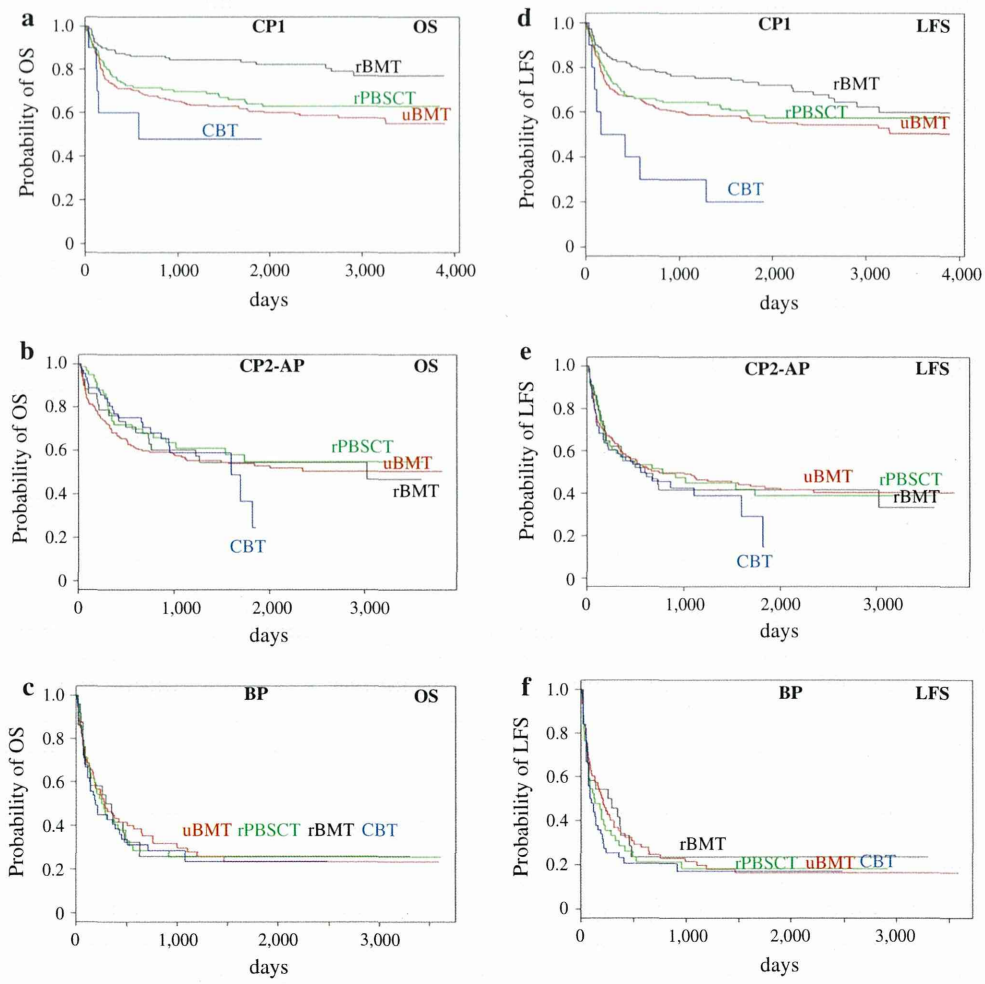


**Fig. 1** Kaplan–Meier estimate of overall survival (OS) for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and leukemia-free survival (LFS) for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)

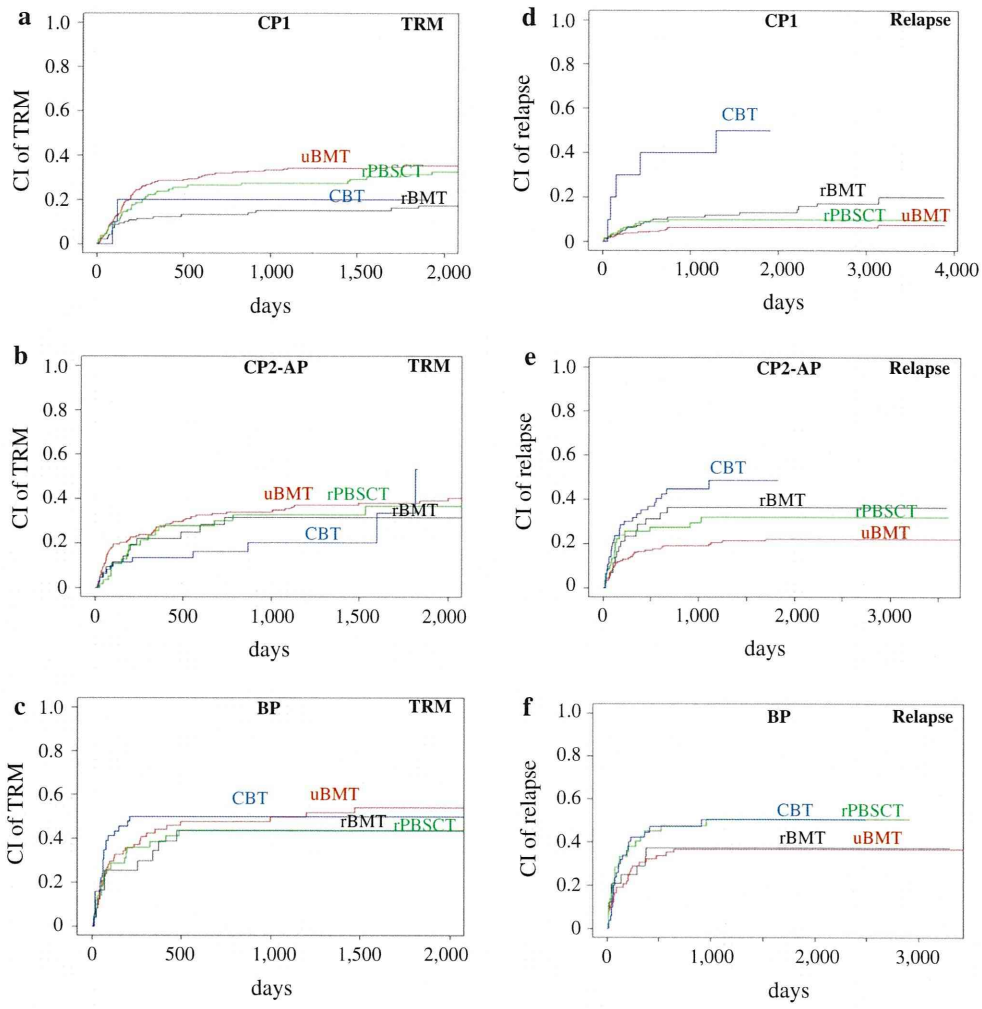


**Fig. 2** The cumulative incidence of transplantation-related mortality (TRM) for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and relapse for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)

patients in CP1: older age (>median age, 40 years: HR 1.67, 95 % CI, 1.15–2.41, $P = 0.007$), ABO mismatch (HR 1.44, 95 % CI, 1.003–2.06, $P = 0.048$) (Table 2), and uBMT (RR 6.01, 95 % CI, 1.20–29.97, $P = 0.029$) (Table 3). In CP2-AP, older age (> median age, 43 years: HR 1.74, 95 % CI, 1.25–2.43, $P < 0.001$) was the only factor an adverse prognostic factor (Table 2). In BC, pre-transplant IM (HR 0.61, 95 % CI, 0.49–0.89, $P = 0.011$) was the only factor for better OS (Table 2). Concerning LFS, multivariate analysis showed that uBMT (RR 4.26, 95 % CI, 1.24–14.62, $P = 0.021$) and older age (>median age, 40 years: HR 1.43, 95 % CI, 1.02–1.99, $P = 0.038$) were adverse risk factors in CP1 (Table 2, 3). For patients in CP2-AP and BC, no significant factor for OS or LFS was found. Thus, for patients in CP1, GS could have a significant impact on survival outcomes. While, for patients in the advanced phase of CML of beyond CP1, GS could have no significant impact on OS or LFS (Table 3).

## TRM and relapse

The 1-year cumulative TRM rate by disease stage was 23.1 % (95 % CI, 19.5–26.7 %) in CP1, 24.2 % (95 % CI, 19.5–28.9 %) in CP2-AP, and 43.2 % (95 % CI, 35.9–50.5 %) in BC. TRM by GS is shown in Fig. 2a–c. The TRM rate appeared low in rBMT compared with uBMT or rPBSCT in CP1 (Fig. 2a). Multivariate analysis showed that uBMT (RR 2.49, 95 % CI 1.02–6.10, $P = 0.046$) and older age (>median age, 40 years: HR 1.69, 95 % CI, 1.19–2.39, $P = 0.003$) were factors associated with a significantly increased risk of TRM in CP1 (Table 2, 3).

The 3-year cumulative relapse rate by disease stage was 9.0 % (95 % CI, 3.9–7.9 %) in CP1, 28.2 % (95 % CI, 23.3–33.1 %) in CP2-AP, and 43.6 % (95 % CI, 36.3–50.9 %) in BC. Relapse rate by GS is demonstrated in Fig. 2d–f. For patients in CP1, the relapse rate after CBT appeared to be higher than that after other GS (Fig. 2d). In multivariate analysis by the effect of GS in CP1, CBT (RR

**Table 2** Multivariate analysis of risk factors for the main outcomes after allo-HSCT for CML in CP1, CP2-AP, and BP

| Main outcomes | Factors | CP1 | | | | CP2-AP | | | | BP | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Factors | HR | (95 % CI) | *P* value | Factors | HR | (95 % CI) | *P* value | Factors | HR | (95 % CI) | *P* value |
| OS | Age | ≤40 | 1 | | | ≤43 | 1 | | | | | | |
| | | >40 | 1.67 | 1.15–2.41 | 0.007 | >43 | 1.74 | 1.25–2.43 | < 0.001 | | | | |
| | ABO mismatch | No | 1 | | | | | | | | | | |
| | | Yes | 1.44 | 1.003–2.06 | 0.048 | | | | | | | | |
| | Pre-transplant IM | | | | | | | | | No | 1 | | |
| | | | | | | | | | | Yes | 0.61 | 0.41–0.89 | 0.011 |
| LFS | Age | ≤40 | 1 | | | | | | | | | | |
| | | >40 | 1.43 | 1.02–1.99 | 0.038 | | | | | | | | |
| TRM | Age | ≤40 | 1 | | | | | | | | | | |
| | | >40 | 1.69 | 1.19–2.39 | 0.003 | | | | | | | | |
| Relapse | HLA mismatch (rejection) | | | | | | | | | 0, 1 | 1 | | |
| | | | | | | | | | | ≥2 | 1.7 | 1.04–2.76 | 0.033 |
| | HLA mismatch (GVHD) | | | | | 0, 1 | 1 | | | | | | |
| | | | | | | ≥2 | 3.57 | 1.55–8.21 | 0.003 | | | | |
| Acute GVHD (all grades[a]) | Pre-transplant IM | No | 1 | | | | | | | | | | |
| | | Yes | 0.75 | 0.57–0.99 | 0.04 | | | | | | | | |
| | BW | | | | | ≤60 kg | 1 | | | | | | |
| | | | | | | >60 kg | 1.35 | 1.01–1.82 | 0.045 | | | | |
| Acute GVHD | BW | | | | | ≤60 kg | 1 | | | | | | |
| (≥grade 2) | | | | | | > 60 kg | 1.53 | 1.05–2.24 | 0.028 | | | | |
| Chronic GVHD (extensive[b]) | BW | | | | | ≤60 kg | 1 | | | | | | |
| | | | | | | >60 kg | 1.75 | 1.06–2.73 | 0.028 | 0 | | | |

*OS* overall survival, *LFS* leukemia-free survival, *TRM* transplantation-related mortality, *ANC* absolute neutrophil count, *GVHD* graft-versus-host disease, *IM* imatinib, *HLA* human leukocyte antigen, *BW* body weight, *HR* hazard ratio, *CI* confidence interval, *CP* chronic phase, *AP* accelerated phase, *BP* blastic phase, *imatinib* imatinib mesylate

[a] Overall grade of acute GVHD assigned according to the Center for International Blood and Marrow Transplant Research (CIBMTR) severity index

[b] Chronic GVHD was graded as limited or extensive based on the Seattle criteria

**Table 3** Impact of graft sources on main outcomes after allo-HSCT for CML in CP1, CP2-AP, and BP

| Main outcomes | Graft sources | CP1 | | | CP2-AP | | | BP | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | RR | (95 % CI) | *p* value | RR | (95 % CI) | *p* value | RR | (95 % CI) | *p* value |
| OS | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 6.01 | (1.20–29.97) | 0.029 | 1.12 | (0.33–3.79) | 0.851 | >99 | (0.00–99.99) | 0.999 |
| | rPBSCT | 1.76 | (0.77–4.04) | 0.180 | 0.84 | (0.21–3.43) | 0.809 | 1.13 | (0.56–2.30) | 0.727 |
| | CBT | 1.00 | (0.00–99.99) | 1.000 | NA | NA | NA | NA | NA | NA |
| LFS | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 4.26 | (1.24–14.62) | 0.021 | 1.61 | (0.55–4.74) | 0.383 | 0.00 | (0–99.99) | 0.999 |
| | rPBSCT | 1.72 | (0.95–3.11) | 0.073 | 0.42 | (0.14–1.31) | 0.135 | 0.67 | (0.31–1.44) | 0.299 |
| | CBT | 1.00 | (0.00–99.99) | 1.000 | NA | NA | NA | NA | NA | NA |
| TRM | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 2.49 | (1.02–6.10) | 0.046 | 1.36 | (0.60–3.09) | 0.47 | 2.71 | (0.74–9.96) | 0.13 |
| | rPBSCT | 1.03 | (0.52–2.07) | 0.93 | 0.94 | (0.52–1.70) | 0.83 | 1.43 | (0.64–3.22) | 0.39 |
| | CBT | 0.33 | (0.04–2.63) | 0.29 | 0.98 | (0.60–1.60) | 0.94 | 1.26 | (0.82–1.92) | 0.29 |
| Relapse | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 0.33 | (0.12–0.95) | 0.041 | 0.66 | (0.29–1.55) | 0.34 | 2.23 | (0.28–17.61) | 0.45 |
| | rPBSCT | 1.13 | (0.62–2.07) | 0.68 | 1.17 | (0.64–2.14) | 0.6 | 1.06 | (0.44–2.54) | 0.9 |
| | CBT | 25.16 | (1.76–369.10) | 0.018 | 1.15 | (0.74–1.80) | 0.53 | 0.77 | (0.39–1.60) | 0.49 |
| ANC recovery | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 0.82 | (0.55–1.23) | 0.35 | 0.83 | (0.53–1.31) | 0.43 | 0.58 | (0.27–1.26) | 0.17 |
| | rPBSCT | 1.31 | (1.02–1.69) | 0.036 | 1.2 | (0.90–1.59) | 0.21 | 0.91 | (0.33–2.52) | 0.86 |
| | CBT | 2 | (0.67-5.98) | 0.22 | 0.53 | (0.42–0.67) | <0.001 | 0.55 | (0.37–0.82) | 0.003 |
| Platelet recovery | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 0.75 | (0.46–1.21) | 0.24 | 0.89 | (0.51–1.56) | 0.68 | 0.21 | (0.07–0.61) | 0.0039 |
| | rPBSCT | 0.93 | (0.69–1.26) | 0.65 | 0.91 | (0.61–1.35) | 0.63 | 0.67 | (0.28–1.57) | 0.35 |
| | CBT | 1.07 | (0.35–3.28) | 0.9 | 0.78 | (0.62–0.99) | 0.049 | 0.44 | (0.26–0.74) | 0.0018 |
| Acute GVHD (all grades[a]) | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 3.35 | (1.50–6.22) | <0.001 | 1.67 | (0.92–3.02) | 0.09 | 1.22 | (0.46–3.25) | 0.69 |
| | rPBSCT | 1.49 | (0.94–2.37) | 0.091 | 0.86 | (0.51–1.44) | 0.56 | 0.94 | (0.32–2.73) | 0.91 |
| | CBT | 1.67 | (0.68–4.11) | 0.26 | 0.76 | (0.58–1.01) | 0.054 | 1.05 | (0.56–1.96) | 0.87 |
| Acute GVHD (≥grade 2) | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 4.28 | (1.92–9.53) | <0.001 | 2.14 | (0.93–4.94) | 0.075 | 1.34 | (0.39–4.61) | 0.65 |
| | rPBSCT | 1.5 | (0.82–2.72) | 0.19 | 1.53 | (0.82–2.86) | 0.18 | 2.23 | (0.36–1.39) | 0.39 |
| | CBT | 1.00 | (0.00–99.99) | 1.000 | 0.84 | (0.58–1.22) | 0.36 | 1.45 | (0.55–3.81) | 0.45 |
| Chronic GVHD | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 0.95 | (0.53–1.70) | 0.86 | 1.1 | (0.45–2.68) | 0.84 | 0.27 | (0.06–1.33) | 0.11 |
| | rPBSCT | 1.37 | (0.97–1.92) | 0.075 | 1.24 | (0.70–2.19) | 0.47 | 0.84 | (0.22–3.20) | 0.8 |
| | CBT | 8.52 | (0.64–11.43) | 0.11 | 0.8 | (0.52–1.25) | 0.33 | 0.73 | (0.32–1.66) | 0.46 |
| Chronic GVHD (extensive[b]) | rBMT | 1.00 | | | 1.00 | | | 1.00 | | |
| | uBMT | 1 | (0.49–2.04) | 1 | 0.84 | (0.33–2.15) | 0.72 | 0.69 | (0.14–3.46) | 0.65 |
| | rPBSCT | 1.31 | (0.87–1.96) | 0.19 | 1.19 | (0.60–2.34 | 0.62 | 1.08 | (0.27–4.24) | 0.92 |
| | CBT | 6.61 | (0.22–200.8) | 0.28 | 0.63 | (0.36–1.09) | 0.097 | 0.77 | (0.31–1.88) | 0.56 |

*OS* overall survival, *LFS* leukemia-free survival, *TRM* transplantation-related mortality, *ANC* absolute neutrophil count, *GVHD* graft-versus-host disease, *RR* relative risk, *CI* confidence interval, *CP* chronic phase, *AP* accelerated phase, *BP* blastic phase, *rBMT* related bone marrow transplantation, *rPBSCT* related peripheral blood stem cell transplantation, *uBMT* unrelated bone marrow transplantation, *CBT* unrelated cord blood transplantation, *NA* not available

[a] Overall grade of acute GVHD assigned according to the Center for International Blood and Marrow Transplant Research (CIBMTR) severity index

[b] Chronic GVHD was graded as limited or extensive based on the Seattle criteria