HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Cancer. 2017 June 01; 123(11): 2025–2034. doi:10.1002/cncr.30536.

Allogeneic Transplantation for Advanced AML: The Value of Complete Remission

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Abstract

Background—Patients with AML without complete remission (CR) or in first relapse (relapse1) can have extended leukemia control and survival following allogeneic hematopoietic cell transplantation (HCT). Transplantation in relapse1 or primary induction failure (PIF) versus

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All others report no conflicts of interest in the study design or analysis.

Author Contributions: See attached list of roles

treatment to achieve CR2 and subsequent HCT might yield similar outcomes, but available comparative data are scarce.

Methods—We studied 4682 HCT recipients, analyzing survival by disease status: PIF (N=1440), relapse1 (failing ≥1 reinduction, N=1256) and CR2 (N=1986).

Results—Patient, disease and transplantation characteristics were similar except CR2 patients more often had performance scores of 90-100, de novo AML and longer duration of CR1. Adverse cytogenetics were more common in PIF patients. 5-year survival adjusted for performance score, cytogenetic risk and donor type for CR2 was 39% (95% CI 37-41) compared to 18% (95% CI 16-20) for HCT in relapse1 and 21% (95% CI 19-23) in PIF, $p<0.0001$.

Conclusion—Although survival is superior for HCT in CR2, transplantation for selected patients in relapse1 or PIF may still be valuable. These data can guide decision-making about additional salvage therapy versus prompt HCT for patients not in CR, but also highlight intrinsically more treatable AML who have favorable risk cytogenetics, longer CR1 duration and younger patients with better performance status.

Keywords

Acute Myeloid Leukemia; Allogeneic transplantation; Complete remission; Primary induction failure; Relapse

Introduction

For patients with acute myeloid leukemia (AML) failing to achieve complete remission (CR) or in relapse after initial remission, allogeneic hematopoietic cell transplantation (HCT) can produce leukemia control and extended survival (1-4). Some reports suggest that immediate transplantation, if an available donor can be quickly identified, is a best strategy for primary induction failure (PIF) or at first relapse (relapse1) (5-8). Other data argue that additional therapy to achieve remission – whether a difficult-to-achieve CR1 or CR2, yields favorable outcomes and superior survival (9-19) noting that achieving CR may indicate intrinsically more responsive leukemia. Recognizing the limitation that our transplant registry data cannot address outcomes for those who never receive a transplant, we analyzed the comparative survival for patients proceeding to allogeneic transplantation in PIF, in relapse1 or in CR2. These data can guide decision-making about the utility of additional salvage therapy versus an alternative strategy of prompt transplant therapy, even for patients not in CR.

Subjects and Methods

Data Source

Data were obtained from the Center for International Blood Marrow Transplant Research (CIBMTR) a voluntary working group of over 350 transplant centers that report their consecutive transplantations to the CIBMTR. Data are collected on standardized data collection forms pre-transplant, at 3-, 6- and 12-months and annually thereafter until death or loss to follow-up. Compliance is ensured by on-site audits. Patients provide written

informed consent and the study was approved by the National Marrow Donor Program's Institutional Review Board.

Patients

Eligibility criteria included the following: patients aged 18 years and older with AML, in second complete remission (CR2; n=1986), first relapse (relapse1; n=1256) and primary induction failure (PIF; n=1440). Patients transplanted in relapse1 had either failed at least 1 re-induction chemotherapy cycle (n=254), were untreated (n=331; 10 treatment status unknown) while those in PIF had failed at least two induction cycles. Donor sources included HLA-matched sibling, other relative (including haploidentical), HLA-matched and mismatched unrelated donor. Recipients of cord blood grafts and second or subsequent allogeneic transplants were excluded. All transplants occurred between 2000 and 2013.

Endpoints

The primary outcome was overall survival. Death from any cause was considered an event and surviving patients were censored at last follow-up. Relapse was defined as morphologic recurrence of leukemic blasts in marrow or blood. Patients transplanted in relapse1 or PIF who relapsed within 3 months after transplantation were considered as having persistent leukemia. Measures of pre-HCT residual disease (flow cytometry, FISH or molecular) were not consistently available for the CR2 patients and were not analyzed. Non-relapse mortality (NRM) was defined as death not attributed to relapse or persistent leukemia.

Statistical Methods

Demographic, leukemia and transplant characteristics were compared using the Chi square statistic for categorical variables. The probability of overall survival was calculated using the Kaplan Meier estimator with 95% confidence limits derived from the standard error. The duration of survival was defined as interval between date of transplantation and date of last contact. Multivariate analysis for overall mortality was performed using Cox regression model (20). Estimation of relapse and NRM were limited to patients who survived at least 100 days post-transplantation with documented CR (as a day +100 landmark analysis). The subsequent incidences of relapse and NRM were calculated using the cumulative incidence estimator and considering competing risks (21). Duration of post-transplant remission or time to death not attributed to relapse was defined as interval between day 100 post transplantation and date of event (relapse or death). Multivariate analyses for relapse and NRM were performed using the Fine and Grey regression model (22).

Factors tested in multivariate models include: disease status at HCT (CR2 versus relapse1 versus PIF) and the duration of CR1 for CR2 and relapse1, age (decade), time (in months from relapse to HCT (for relapse1 and CR2), time from diagnosis to HCT (for PIF), number of induction (or reinduction) cycles prior to HCT, performance score (90-100 versus <90), recipient cytomegalovirus (CMV) serostatus (positive versus negative), AML type (de novo versus secondary), white blood count at diagnosis (<30 versus 30-100 versus >100 × 10^9/L), cytogenetic risk (favorable versus intermediate versus poor risk according to the SWOG classification as previously reported (23)), conditioning intensity (myeloablative versus reduced intensity), donor/HLA match (HLA-matched sibling versus other related (including

haploidentical) versus HLA-matched unrelated donor (URD) versus partially matched URD), graft type (peripheral blood versus bone marrow), GVHD prophylaxis and transplant period (2000-2005 versus 2006-2013). Molecular data to define other high risk subsets were not routinely available. Flt3 ligand mutation was positive in only 3% of each HCT cohort; but was missing in the majority. Adjusted probabilities for survival, relapse and NRM were calculated considering the significant factors identified in final multivariate regression models and using left-truncation of time from diagnosis (for PIF), or from relapse (for relapse1 or CR2) to HCT. All factors met the assumptions of proportionality and there were no first order interactions between disease status at transplantation and other factors held in final multivariate models. A p-value <0.01 was considered statistically significant. The previously reported (15) CIBMTR score for HCT during relapse was also analyzed, but circulating and marrow blast counts were not reported for all patients, but the analysis was performed using all available information. All analyses were performed with SAS version 9.3 (Cary, NC).

Results

The characteristics of patients, their disease and transplant are shown in Table 1. Of the 4682 patients who met eligibility criteria 1986 (36%) were in CR2, 1256 (27%) in relapse1, and 30% in PIF at HCT. Seven percent of patients in CR2 and relapse1 had received a prior autologous HCT compared to 3% of patients in PIF. The median age in the three groups was 47, 49 and 52 years, respectively. Patient age, sex and CMV serostatus were similar across the three groups, but patients transplanted in relapse1 or PIF were more likely reported with performance scores less than 90. HCT co-morbidity index (HCT-CI) score was available after 2008; there were no differences between the groups. There were differences in disease characteristics between the groups. Patients in CR2 were less likely to have secondary AML (therapy-related or evolved from myelodysplastic or myeloproliferative syndrome) or poor risk cytogenetics compared to those in relapse1 or PIF. The duration of CR1 was < 6 months for 50% of patients transplanted in relapse1 compared to 18% for those transplanted in CR2. The duration of CR1 was > 12 months for a third of patients in CR2. Most transplants in PIF (73%) occurred within 6 months from diagnosis. The median times from relapse to HCT in relapse1 or CR2 were similar (median of 2 and 4 months, respectively) and their number of cycles from relapse to HCT (or from diagnosis to HCT for PIF) were also similar. There were no differences in regards to donor type between the groups; a third of transplants used an HLA-matched sibling donor, 40% a suitably matched URD and the remaining, mismatched URD. Only a few received non-sibling related donors (including haploidentical). There were no differences in the intensity of transplant-conditioning regimen and GVHD prophylaxis between the groups. Peripheral blood was the most common graft type. About 80% of HCTs occurred in the United States. The median follow up of patients was 5 years for patients in CR2, 7 years for those in relapse1 and 5 years for those in PIF.

Overall Survival

At a median of 5 years of follow-up, 42% of CR2, 17% of relapse1, and 20% of PIF patients are alive. The unadjusted 2-year overall survival for patients transplanted in CR2, relapse1

and PIF were 50% (95% CI 48-52), 27% (95% CI 24-29) and 29% (95% CI 27-32), respectively. The results of multivariate analysis are shown in Table 2. Compared to transplants in CR2, mortality risks were higher for transplants in relapse1 and PIF, regardless of the duration of CR1, Marrow blast % (for PIF or relapse1), or the number of cycles of induction or reinduction prior to HCT did not influence mortality risks (data not shown). The outcome of transplants in relapse1 versus PIF varied by duration of CR1 for relapse1. Mortality risks were lower for transplants in PIF than for relapse1, but only if the duration of CR1 was less than 6 months. Mortality risks were higher for transplants in PIF if the duration of CR1 was greater than 6 months for relapse1 transplants, but mortality risks were similar PIF and relapse1 when the duration of CR1 was between 6-12 months. Other factors associated with overall mortality were age (50 years or older), poor performance score (<90), intermediate and poor cytogenetic risk and mismatched related or URD transplant. The 5-year probability of overall survival after transplants in CR2, relapse1 and PIF adjusted for age, performance score, cytogenetic risk and donor type were 39% (95% CI 37-41), 18% (95% CI 16-20) and 21% (95% CI 19-23), respectively (Figure 1).

Overall there were 1159 (58%) deaths among patients transplanted in CR2, 1046 (83%) deaths among patients transplanted in relapse1 and 1145 (80%) deaths among patients transplanted in PIF. Recurrent or persistent leukemia was the most common cause of death occurring in 485 of 1159 (42%) of patients transplanted in CR2 and 567 of 1046 (54%) and 603 of 1145 (53%) of patients transplanted in relapse1 and PIF, respectively. Other predominant causes of death include GVHD, infection and organ failure.

Duval et al (15) previously reported a scoring system to predict relapse following myeloablative HCT for AML with active disease. Survival was inferior in patients with short initial remission, circulating blasts, donors other that HLA-identical siblings, performance score <90% and poor risk cytogenetics. While data was incomplete (circulating and marrow blasts were incompletely reported) a higher score was associated with inferior survival (Supplemental table S1).

Relapse and Non-relapse Mortality

The population considered for analyses of relapse and NRM are shown in Table 3. We noted in this overall high risk population that leukemia relapse was common within 100 days after HCT in CR2 (n=221; 11%) and persistent disease noted prior to day +100 was very common after HCT in relapse1 (n=577; 46%) and PIF (n=706; 49%). Thus the analyses of relapse and NRM were limited to a landmark analysis including only those patients who were alive and in CR at day 100 post transplantation. Analysis of factors associated with early (before day +100) death or relapse/persistent leukemia identified that disease status at transplant (CR2 vs. Rel1 vs. PIF) was a significant risk factor for this early treatment failure. Additionally, adverse cytogenetics, short duration of CR1 and GVHD prophylaxis also indicated higher risks of early treatment failure in all 3 cohorts while in Rel1 and PIR patients a lower KPS and year of HCT were also important (data not shown).

The results of these post day+100 landmark multivariate analyses are shown in Table 4. Compared to transplants in CR2, post day +100 relapse risks were higher for transplants in relapse1, regardless of the duration of CR1. Risks of relapse were also higher in PIF

compared to relapse1 with a CR1 duration greater than 12 months, but not with shorter CR1 duration where there were no differences in relapse risks after transplantation in either relapse1 or PIF. Compared to transplants in CR2, NRM risks were higher for transplants in relapse1, regardless of the duration of CR1. However, there were no significant differences in NRM risks following transplants in CR2 or relapse1 compared to transplants in PIF. Other factors associated with higher relapse and NRM risks were age (50 years or older), poor performance score (<90), intermediate and poor cytogenetic risk and mismatched related or URD transplant. The 5-year adjusted probabilities of relapse after transplants in CR2, relapse1 and PIF adjusted for cytogenetic risk were 32% (95% CI 29-34), 41% (95% CI 36-45) and 40% (95% CI 36-44), respectively (Figure 2). The corresponding probabilities for NRM were 23% (95% CI 21-25), 28% (95% CI 24-32) and 25% (95% CI 21-29) (Figure 3).

Discussion

Allogeneic transplantation in later stage AML can still yield long term disease control and improved survival for sizable fractions of patients, but this analysis strongly suggests that transplantation during CR2 is preferred over other approaches, including transplantation in relapse1 or PIF. This analysis has substantial, and to a large extent unquantifiable, selection bias due to inclusion of only those deemed fit for HCT during relapse and who were referred to a center accepting them for HCT. Nonetheless, the large numbers of cases, the multivariable regression adjustments and the international experience likely represent valid outcomes for patients transplanted in these three clinical situations who are selected for HCT. The favorable outcomes with HCT during CR2 suggest that additional salvage therapy to induce remission for patients in PIF or first relapse may yield a selected group who can have favorable post-transplant outcomes and improved survival. Since attaining remission with additional therapy may only identify patients with biologically less aggressive leukemia rather than rescue the outcome of those with resistant disease, the risks and benefits of repetitive remission-induction attempts must be carefully considered, particularly as new agents and reinduction regimens are being developed and tested.

Beyond disease status, outcomes were superior for those with intrinsically more treatable leukemia, including those who have favorable risk cytogenetics and longer duration of CR1 prior to relapse. Additionally, patient characteristics including age younger than 50 and good performance status (90 or 100) also led to better survival. Transplant was recognized as useful and yielding extended disease control in this broad array of patients with persistent, relapsed, or second-remission AML. This echoes reports from the earliest experience of transplant where a fraction of advanced AML patients could be salvaged using myeloablative conditioning and allografts (7-15). Several decades ago, untreated first relapse and second remission patients were reported as having similar outcomes after allogeneic transplantation (9, 10). In more recent series, including an earlier report from the CIBMTR, disease burden manifest as bone marrow blast percentage or circulating blasts, high-risk phenotype (adverse cytogenetics), as well as age and performance status influenced the outcome of transplantation with active disease (11-15). Molecular or flow cytometric measures of detectable disease, even for those in CR prior to HCT (24) might further refine the prognosis following HCT although such data were not available for this analysis.

Limited more recent experience incorporating re-induction with fludarabine, cytarabine and amsacrine followed immediately by a reduced intensity allotransplant yielded reasonable outcomes for a fraction of patients with otherwise persistent disease (19). Novel approaches however are still required. More effective, yet less toxic conditioning regimens to deplete detectable residual tumor (25, 26), enhanced immunologic surveillance of residual disease (27) or post-transplant maintenance therapy (28) may all be required to produce effective leukemia control for such high-risk patients.

Additionally, measures of physiologic fitness to tolerate intensive conditioning and transplantation are needed. Patients may be particularly vulnerable to complications after extended, though unsuccessful therapy to induce remission, along with its attendant period of extended neutropenia. This will require careful patient selection, aggressive supportive care techniques and vigorous infection prophylaxis to identify patients most likely to benefit from transplantation with active disease. Early referral and prompt donor identification remain essential to avoid delays which put patients at risk for early disease progression or relapse or clinical deterioration further compromising post-HCT outcomes. Nonetheless, these data, even recognizing the limits of selection evident in a transplant registry-based report, still demonstrate that inherent leukemic sensitivity and achievement of second remission by conventional or novel approaches still yields better and curative outcomes for a larger fraction of patients. Thus, if added therapy can attain remission without compromising HCT eligibility, transplantation during remission remains a preferred goal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful to the patients and to the medical and data management staff at the transplant centers who provided the data for this analysis.

CIBMTR Support List: The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement 5U24-CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-15-1-0848 and N00014-16-1-2020 from the Office of Naval Research; and grants from Alexion; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US; AstraZeneca; Be the Match Foundation; *Bluebird Bio, Inc.; *Bristol Myers Squibb Oncology; *Celgene Corporation; Cellular Dynamics International, Inc.; *Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd.; Genentech, Inc.; Genzyme Corporation; *Gilead Sciences, Inc.; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals, Inc.; Jeff Gordon Children's Foundation; The Leukemia & Lymphoma Society; Medac, GmbH; MedImmune; The Medical College of Wisconsin; *Merck & Co, Inc.; Mesoblast; MesoScale Diagnostics, Inc.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; Neovii Biotech NA, Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Otsuka America Pharmaceutical, Inc.; Otsuka Pharmaceutical Co, Ltd. – Japan; PCORI; Perkin Elmer, Inc.; Pfizer, Inc; *Sanofi US; *Seattle Genetics; *Spectrum Pharmaceuticals, Inc.; St. Baldrick's Foundation; *Sunesis Pharmaceuticals, Inc.; Swedish Orphan Biovitrum, Inc.; Takeda Oncology; Telomere Diagnostics, Inc.; University of Minnesota; and *Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

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The study was performed at the CIBMTR with partial financial support from Sunesis who had no independent part in the data collection, analysis or publication. One co-author (P. Hyare) is a Sunesis employee.

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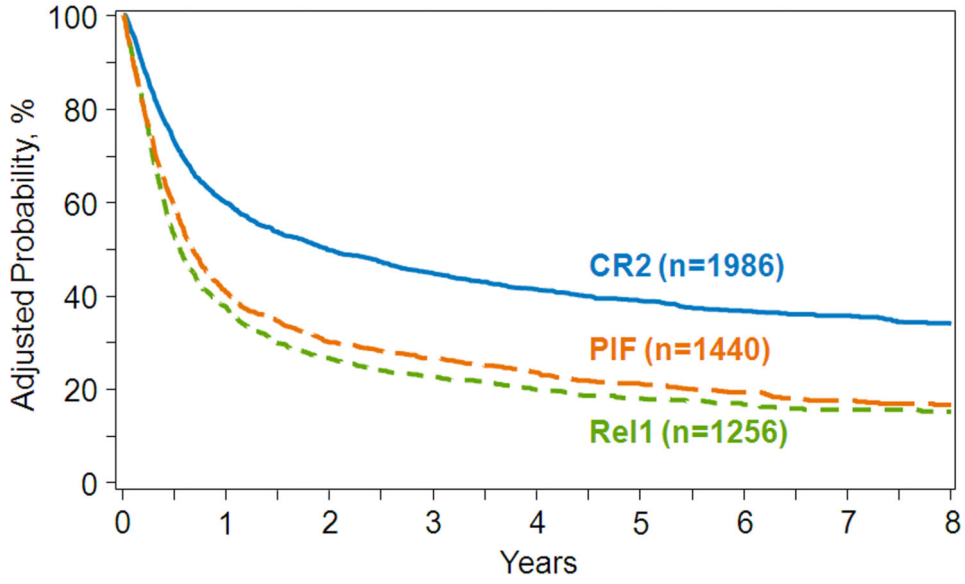

Figure 1.

The 5-year probability of overall survival by disease status at transplantation, adjusted for age, performance score, cytogenetic risk and donor type.

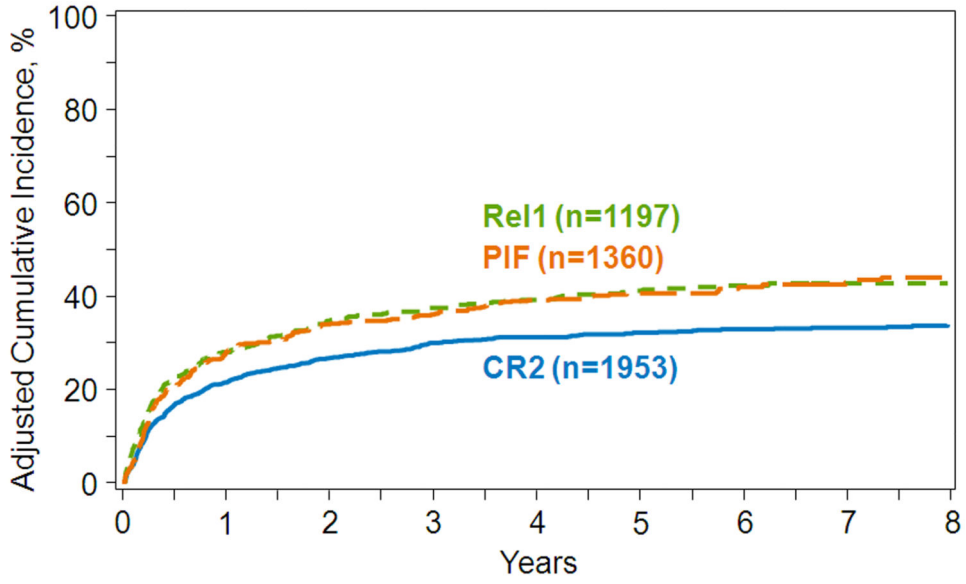

Figure 2.

Amongst 100 day survivors in CR, the 5-year probability of relapse by disease status at transplantation, adjusted for age, performance score, cytogenetic risk and donor type.

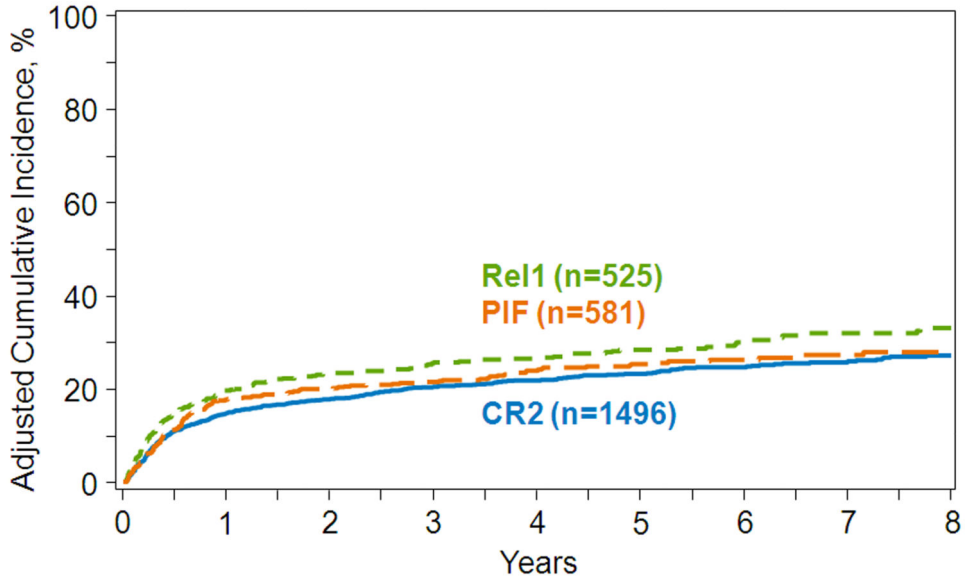

Figure 3.

Amongst 100 day survivors in CR, the 5-year probability of non-relapse mortality (NRM) by disease status at transplantation, adjusted for age, performance score, cytogenetic risk and donor type.

Table 1
Patient, disease and transplant characteristics

Variable	CR2 N (%)	Relapse1 N (%)	PIF N (%)
Number of patients	1986	1256	1440
Patient age at transplant, in years			
18-29	360 (18)	172 (14)	163 (11)
30-39	317 (16)	200 (16)	184 (13)
40-49	483 (24)	292 (23)	289 (20)
50-59	539 (27)	351 (28)	466 (32)
60-69	264 (13)	218 (17)	307 (21)
≥70	23 (1)	23 (2)	31 (2)
Gender			
Male	1050 (53)	641 (51)	814 (57)
Female	936 (47)	615 (49)	626 (43)
Recipient CMV status			
Negative	711 (36)	400 (32)	481 (33)
Positive	1261 (63)	848 (68)	947 (66)
Missing	14 (<1)	8 (<1)	12 (<1)
Performance score			
<90%	531 (27)	566 (45)	696 (48)
≥90%	1337 (67)	616 (49)	672 (47)
Missing	118 (6)	74 (6)	72 (5)
HCT-CI			
0	426 (21)	215 (17)	327 (23)
1	197 (10)	86 (7)	99 (7)
2	21 (1)	12 (<1)	15 (1)
3	3 (<1)	2 (<1)	2 (<1)
Missing or not collected (before 2008)	1339 (67)	941 (75)	997 (69)
White blood cell count at diagnosis, $\times 10^9$/L			
<30	1007 (51)	724 (58)	955 (66)
30-100	414 (21)	225 (18)	207 (14)
>100	203 (10)	120 (10)	111 (8)
Missing	362 (18)	187 (15)	167 (12)
Cytogenetic risk group			
Favorable	307 (15)	65 (5)	21 (1)
Intermediate	1187 (60)	766 (61)	796 (55)
Poor/adverse	222 (11)	280 (22)	449 (31)
Not tested/missing	270 (14)	145 (12)	174 (12)
Time from relapse to HCT (CR2 and Rel1 only)			
<2 months	141 (7)	595 (47)	N/A
2-4 months	769 (39)	394 (31)	
4-6 months	582 (29)	143 (11)	

Variable	CR2 N (%)	Relapse1 N (%)	PIF N (%)
≥6 months	258 (18)	109 (9)	
Missing	136 (7)	15 (1)	
Time from diagnosis to HCT (PIF only)			
<3 months	N/A	N/A	372 (26)
3-6 months			670 (47)
≥6 months			395 (27)
Missing			3 (<1)
Duration of CR1 (CR2 and Rel1 only)			
<6 months	357 (18)	632 (50)	N/A
6-12 months	511 (26)	281 (22)	
>12 months	759 (38)	173 (14)	
Missing	359 (18)	170 (14)	
Number of cycles of induction/reinduction			
≤2	1053 (53)	623 (50)	403 (28)
>2	54 (3)	49 (4)	81 (6)
Missing	120 (6)	92 (7)	473 (33)
Not collected *	759 (38)	492 (39)	483 (34)
Number of cycles of consolidation			
0	39 (2)	92 (7)	N/A
1	496 (25)	307 (24)	
≥2	461 (23)	185 (15)	
Missing	231 (12)	180 (14)	
Not collected *	759 (38)	492 (39)	
Extramedullary disease any time pre-HCT			
No	1919 (97)	1168 (93)	1367 (95)
Yes	67 (3)	88 (7)	73 (5)
Prior autologous HCT **			
No	1855 (93)	1167 (93)	1400 (97)
Yes	131 (7)	89 (7)	40 (3)
Conditioning regimen intensity			
Myeloablative	1362 (69)	871 (69)	978 (68)
RIC/NMA	623 (31)	381 (30)	458 (32)
Missing	1 (<1)	4 (<1)	4 (<1)
Donor-recipient gender match			
Female donor, male recipient	340 (17)	241 (19)	261 (18)
Other	1557 (78)	958 (76)	1108 (77)
Missing	89 (4)	57 (5)	71 (5)
Donor/recipient CMV serostatus			
+/+	636 (32)	412 (33)	473 (33)
+/-	229 (12)	119 (9)	148 (10)
-/+	609 (31)	414 (33)	450 (31)
-/-	468 (24)	275 (22)	326 (23)

Variable	CR2 N (%)	Relapse1 N (%)	PIF N (%)
Missing	44 (2)	36 (3)	43 (3)
Donor			
HLA identical sibling	536 (27)	377 (30)	455 (32)
Other relative	77 (4)	50 (4)	67 (5)
Well-matched unrelated or 8/8 allele matched	935 (47)	548 (44)	643 (45)
Partially-matched unrelated or 7/8,6/8	349 (18)	223 (18)	205 (14)
Mismatched unrelated or 5/8	80 (4)	55 (4)	64 (4)
Unrelated (matching uncertain)	9 (<1)	3 (<1)	6 (<1)
Graft source			
Bone marrow	508 (26)	309 (25)	298 (21)
Peripheral blood	1478 (74)	947 (75)	1142 (79)
GVHD prophylaxis			
Tacrolimus containing	1042 (52)	709 (56)	786 (55)
Cyclosporine containing	749 (38)	427 (34)	491 (34)
CD34 selection or ex-vivo T-cell depletion	131 (7)	80 (6)	97 (7)
Other[a]	43 (2)	24 (2)	42 (3)
Missing	21 (1)	16 (1)	24 (2)
ATG/Alemtuzumab			
Yes	1315 (66)	824 (66)	889 (62)
No	561 (28)	329 (26)	428 (30)
Missing	110 (6)	103 (8)	123 (9)
Year of transplant			
2000-2005	962 (48)	704 (56)	697 (48)
2006-2013	1024 (52)	552 (44)	743 (52)
Median follow-up of survivors (range), months	72 (2-174)	83 (1-170)	71 (3-171)

[a]Other GVHD prophylaxis: Cyclophosphamide (n=59), MTX + MMF (n=1), MTX ± others (n=19), MMF ± others (n=21), palifermin (n=1), sirolimus alone (n=2), ATG alone (n=1), corticosteroids alone (n=4), other not specified (n=1)

*Not collected – for URD before 2008;

**autologous transplant for disease other than AML

Table 2

Factors associated with overall survival

	N	Hazard Ratio (95% confidence interval)	P-value
Disease status at transplantation			
Relapse1 vs. CR2	1256 vs. 1986	1.65 (1.51 – 1.81)	<0.0001
PIF vs. CR2 (CR1 <6 months)	1440 vs. 357	1.26 (1.13 – 1.41)	<0.0001
PIF vs. CR2 (CR1 6-12 months)	1440 vs. 511	1.60 (1.43 – 1.80)	<0.0001
PIF vs. CR2 (CR1 >12 months)	1440 vs. 759	2.24 (2.01 – 2.50)	<0.0001
PIF vs. Relapse1 (CR1 <6 months)	1440 vs. 632	0.76 (0.70 – 0.84)	<0.0001
PIF vs. Relapse1 (CR1 6-12 months)	1440 vs. 281	0.97 (0.86 – 1.09)	0.60
PIF vs. Relapse1 (CR1 >12 months)	1440 vs. 173	1.36 (1.20 – 1.54)	<0.0001
Age: ≥50 vs. 18 – 49 years	2222 vs. 2460	1.15 (1.07 – 1.23)	<0.0001
Performance Score: 90-100	2625	1.00	<0.0001
<90	1793	1.28 (1.19 – 1.37)	<0.0001
Cytogenetic risk: Favorable	393	1.00	<0.0001
Intermediate/Poor	3700	1.50 (1.29 – 1.74)	<0.0001
Donor type: HLA-matched sibling	1368	1.00	<0.0001
Other Relative	194	1.52 (1.27 – 1.81)	<0.0001
Matched Unrelated	2126	1.05 (0.97 – 1.14)	0.24
Mismatched Unrelated	976	1.31 (1.19 – 1.45)	<0.0001

Table 3
Survival and Disease status by day 100 post transplantation

	Disease status at transplantation		
	CR2	**Relapse1**	**PIF**
Number Evaluable			
At transplant	1986	1256	1440
Persistent disease after HCT	--	534	660
Relapse within 100 days after HCT	221	43	46
Death within 100 days after HCT	254	154	153
Follow up < 100 days	15	--	--
Alive and in CR by 100 days after HCT	1496 (75%)	525 (42%)	581 (40%)

Table 4
Factors associated with Non-relapse mortality and Relapse

Non-relapse mortality	**N**	**Hazard Ratio (95% confidence interval)**	**P-value**
Disease status at transplantation			
Relapse1 vs. CR2	525 vs. 1496	1.32 (1.09 – 1.61)	0.005
PIF vs. CR2 (CR1 < 6 months)	581 vs. 237	0.99 (0.76 – 1.27)	0.92
PIF vs. CR2 (CR1 6–12 months)	581 vs. 379	1.18 (0.91 – 1.52)	0.21
PIF vs. CR2 (CR1 >12 months)	581 vs. 615	1.30 (1.04 – 1.63)	0.02
PIF vs. Relapse1 (CR1 < 6 months)	581 vs. 215	0.75 (0.58 – 0.96)	0.02
PIF vs. Relapse1 (CR1 6–12 months	581 vs. 133	0.89 (0.68 – 1.17)	0.40
PIF vs. Relapse1 (CR1 >12 months)	581 vs. 103	0.98 (0.75 – 1.29)	0.91
Age:			
18– 49 years	1422	1.00	<0.0001
50+ years	1180	1.48 (1.27 – 1.73)	<0.0001
Performance score:			
90-100%	1605	1.00	0.002
<90%	834	1.30 (1.10 – 1.53)	0.002
Cytogenetic risk:			
Favorable	300	1.00	0.10
Intermediate/Poor	1986	1.34 (1.01 – 1.78)	0.05
Donor type:			
HLA-identical sibling	715	1.00	0.004
Other relative	75	1.42 (0.88 – 2.29)	0.15
Matched Unrelated	1266	1.14 (0.94 – 1.38)	0.19
Mismatched Unrelated	538	1.51 (1.22 – 1.89)	0.0002
Relapse	N	Hazard Ratio (95% confidence interval)	P-value
Disease status at transplantation			
Relapse1 vs. CR2	525 vs. 1496	1.34 (1.13 – 1.58)	0.001
PIF vs. CR2 (CR1 < 6 months)	581 vs. 237	1.11 (0.90 – 1.38)	0.33
PIF vs. CR2 (CR1 6–12 months)	581 vs. 379	1.18 (0.96 – 1.45)	0.11
PIF vs. CR2 (CR1 >12 months)	581 vs. 615	2.01 (1.64 – 2.46)	<0.0001
PIF vs. Relapse1 (CR1 < 6 months)	581 vs. 215	0.83 (0.67 – 1.03)	0.09
PIF vs. Relapse1 (CR1 6–12 months)	581 vs. 133	0.89 (0.71 – 1.11)	0.29
PIF vs. Relapse1 (CR1 >12 months)	581 vs. 103	1.50 (1.19 – 1.91)	0.001
Age:			
18 – 49 years	1422	1.00	
≥50 years	1180	1.09 (0.96 – 1.25)	0. 19

Non-relapse mortality	**N**	**Hazard Ratio (95% confidence interval)**	**P-value**
Performance score:			
90-100%	1605	1.00	
<90%	834	1.14 (0.99 – 1.32)	0.06
Cytogenetic risk:			
Favorable	300	1.00	0.03
Intermediate/Poor	1986	1.38 (1.09 – 1.76)	0.008
Donor type:			
HLA-identical sibling	715	1.00	0.13
Other relatives	75	1.62 (1.13 – 2.32)	0.009
Matched Unrelated	1266	1.09 (0.93 – 1.27)	0.31
Mismatched Unrelated	538	1.07 (0.88 – 1.30)	0.48