Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia with Hyperdiploid Complex Karyotype

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Article

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Abstract

Allogeneic hematopoietic cell transplantation (allo-HCT) remains the best consolidation strategy for acute myeloid leukemia (AML) with complex karyotype (CK). However, CK is a heterogenous and highly diverse entity. Numerical abnormalities have been associated with a controversial prognosis and AML with only multiple numerical abnormalities known as pure hyperdiploid karyotype (HDK) may have a distinct prognosis after allo-HCT compared to non-pure HDK CK AML.

A total of 236 patients were identified within the EBMT registry as having HDK comprising 95 pure (pHDK) and 141 with other cytogenetic abnormalities (HDK+). The 2-year probability of leukemia-free survival (LFS) was 50% for pHDK and 31% for HDK+ (p=0.003). The 2-year probability of overall survival (OS) was 57% for pHDK and 36% for HDK+ (p=0.007). The 2-year cumulative incidence of relapse (RI) was 22% for pHDK and 44% for HDK+ (p=0.001). The 2-year probability of graft-versus-host disease (GvHD)-free and relapse-free survival (GRFS) was 36% for pHDK and 21% for HDK+ (p=0.01). On multivariate analysis, pHDK remained associated with significantly better LFS, OS and GRFS and lower RI (all p-values<0.004).

pHDK AML constitutes probably a distinct cytogenetic entity from HDK+ or other non-hyperdiploid CK AML with better outcomes after allo-HCT.

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is now a standard approach recommended for patients with high-risk acute myeloid leukemia (AML) in remission [1,2]. High-risk AML is mainly defined by the presence of determined poor-risk cytogenetic abnormalities at diagnosis together with specific mutational events [3–6]. In general, conventional post-remission high-dose chemotherapy is not capable of eradicating the initiating stem-cell leukemic clone of high-risk AML, harbouring strong chemoresistance mechanisms [7], and only the potent graft-versus-leukemia effect arising after allo-HCT may overcome the poor prognosis of these high-risk AML subtypes [8]. Indeed, several reports have confirmed the significant advantage of allo-HCT in high-risk AML, especially when performed early in the course of the disease [9–11]. Complex karyotype (CK) has been one of the most frequent high-risk subgroups reported and is defined as three or more, four or more and five or more chromosomal abnormalities by different groups [5,7]. Nevertheless, CK refers to a very heterogeneous and loosely defined category which comprises a high diversity of cytogenetic subtypes, which is highly enriched with specific cytogenetic subtypes characterized by losses of chromosomal material at critical regions known to confer a poor prognosis *per se*, such as del(7q)/-7, del(5q)/-7 or abnormalities leading to 17p region loss [12,13]. More recently, a monosomal karyotype (MK) has been associated with a very poor outcome with an estimated 4-year survival rate of 4% [14,15], and has provided a more appropriate classification of “complexity” than the conventional CK group. Within this MK subgroup, the presence of numerical abnormalities such as trisomy or tetrasomy had no impact on survival [14]. We recently reviewed 303 AML patients with MK

undergoing allo-HCT [16]. In our study we found that CK and also hypodiploidy were both associated with worse outcomes. We recently reviewed 501 AML patients with monosomy 5 or deletion 5q after allo-HCT [17]. Outcomes were significantly worsened by the presence of MK or 17p abnormalities but not by CK. Similarly, in a cohort of 1109 AML patients harbouring monosomy 7 or deletion 7q, we found that patients with monosomy 7 or deletion 7q with or without CK have much better outcomes after allo-HCT than with the presence of MK, 17p abnormalities, or inv(3) [18]. Our observations suggest that CK by itself is definitively not sufficient to impact outcomes after allo-HCT. In this setting, *Chilton et al.* described AML characterized by only multiple numerical abnormalities known as pure hyperdiploid karyotype (pHDK) and defined by the presence of 49 or more chromosomes. In this study patients with pHDK had much better outcomes than patients harbouring HDK with other adverse features such as monosomy 5, monosomy 7, 17p abnormalities, or 3q abnormalities. They suggested that patients with pHDK may not be automatically consigned to the adverse cytogenetics group [19]. The purpose of this study is to retrospectively review outcome of AML with complex HDK after allo-HCT. Our hypothesis is that patients with pHDK have improved survival compared to patients harbouring additional cytogenetic abnormalities such as monosomy 5 or deletion 5q, monosomy 7 or deletion 7q, inversion of chromosome 3, 11q23 abnormalities, abn(17p), or MK.

Methods

Patient selection and data collection

This is a retrospective registry-based analysis on behalf of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a non-profit, scientific society representing more than 600 transplant centers mainly in Europe that are required to report all consecutive stem cell transplantations and their follow-up once a year. Data are entered, managed, and maintained in a central database with internet access; each EBMT center is represented in this database. Audits are routinely performed to determine the accuracy of the data. Patients or legal guardians provide informed consent authorizing the use of their personal information for research purposes. The study was approved by the ALWP review board.

Eligibility criteria for the study included all patients ≥ 18 years with *de novo* or secondary AML transplanted between 1 January 2000 and 31 December 2018 from an HLA-matched related (MRD) or a unrelated donor (UD). Patients undergoing second transplantation as well as patients having a haplo-identical or cord blood transplantation were excluded. We further selected patients with a full karyotype report in the database and harboring a complex HDK defined by the presence of 49 chromosomes or more. We then classified them as pure HDK (pHDK) or HDK with other cytogenetic abnormalities (HDK+), characterized by HDK and the presence of a prognostic-defining cytogenetic abnormality such as MK, del(5q)/-5, del(7q)/-7, del(17p)/-17/i(17q), inv(3q21-26)/t(3;3)(q21;q26) or 11q23 abnormalities. For numerical abnormalities, we didn't include sex chromosomes or marker chromosomes.

A total of 236 patients from 107 centers met the study inclusion criteria and were selected for further analysis. Myeloablative conditioning (MAC) was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 6 Gy, a total dose of oral busulfan (Bu) greater than 8 mg/kg, or a total dose of intravenous Bu greater than 6.4 mg/kg. All other regimens were defined as reduced intensity conditioning (RIC) [20].

The following variables were selected and included in the analysis: year of transplantation, age, gender, white blood cell count (WBC) at diagnosis, *de novo* or secondary AML condition, number of induction courses to achieve CR, status at transplantation, time from diagnosis to SCT, type of conditioning regimen, use of TBI, *in vivo* T-cell depletion (TCD) (including both anti-thymocyte globulins and alemtuzumab), cytomegalovirus (CMV) status of donor and recipient, donor type, source of stem cells, Karnofsky performance status (KPS) at transplantation, engraftment, presence of acute and chronic graft-versus-host disease (GvHD), grade of acute GvHD, severity of chronic GvHD. Secondary AML has been defined as AML with previous diagnosis of myelodysplastic syndromes or myeloproliferative neoplasms or AML secondary to cytotoxic therapies. For the analysis of additional cytogenetic abnormalities, we included the presence of abnormalities of 3q26 (e.g., inv(3)(q21q26) or t(3;3)(q21;q26)), abnormalities leading to loss of chromosome 17p (abn(17p)), monosomy 5 or deletion 5q, 11q23 abnormalities, MK and HDK classified according to the cytogenetic status as per UK Medical Research Council criteria [5].

Statistical analysis and endpoints definitions

The primary endpoint was LFS. Secondary endpoints included relapse incidence (RI), non-relapse mortality (NRM), overall survival (OS), acute and chronic GvHD, and refined GvHD-free, relapse-free survival (GRFS). All outcomes were measured from the time of transplant. LFS was defined as survival without relapse; patients alive without relapse were censored at the time of last contact. OS was based on death from any cause. NRM was defined as death without previous relapse. GRFS was defined as survival without grade III-IV acute GvHD, extensive chronic GvHD, relapse or death[21]. Surviving patients were censored at the time of last contact. The probabilities of OS, LFS, and GRFS were calculated by the Kaplan-Meier method, and those of acute and chronic GvHD, NRM, and RI by the cumulative incidence function to accommodate competing risks. For NRM, relapse was the competing risk, and for relapse, the competing risk was NRM. For acute and chronic GvHD, death without the event and relapse were the competing risks. Univariate comparisons between groups were performed using the Chi-square and Fischer's exact test for categorical variables and the Mann-Whitney test for continuous variables, the Gray's statistic for cumulative incidence functions (GvHD, NRM, RI) and the log-rank test for survival outcomes (OS, LFS and GRFS). For all univariate analyses, continuous variables were categorized, and the median value was used as a cut-off point. A Cox proportional-hazards model was used for multivariate regression including factors differing in distribution between the groups or conceptually important, and pHDK/HDK + subgroups. To test for a centre effect, we introduced a random effect or frailty for each centre into the model. Proportional hazards assumptions were checked systematically using the Grambsch-Therneau residual-based test. Results were expressed as the hazard ratio (HR) with

the 95% confidence interval (CI). Statistical analyses were performed with SPSS 25.0 (SPSS Inc, Chicago, IL, USA) and R 4.0.2 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Results

Patients' characteristics

Table 1 summarizes patients characteristics stratified by cytogenetic groups. A total of 236 patients has been included in the present analysis. Median age at allo-HCT was 53 year-old (interquartile range (IQR) 42-61) and median follow-up was 43 months (IQR 35-56). There were significantly more females in the HDK+ group. Most patients were transplanted in remission and 20% had secondary AML. Regarding UD, there were 94 matched and 38 mismatched. Most patients were transplanted with a good performance status. Except for gender and type of donor, all characteristics were well balanced between both cytogenetic groups. The most frequent trisomies were +8, +13, +21 and +22. Numerical abnormalities included all autosomal chromosomes (those not reported in Table 1 had a frequency < 20%).

Transplant outcomes by univariate analysis

The 2-year RI was 35.4% [95% CI: 29.1-41.8] for the entire study population. Our cytogenetic subgroups were significantly associated with RI with a 2-year RI of 22.4% [95% CI: 14.3-31.6] for pHDK and 44.2% [95% CI: 35.5-52.6] for HDK+ (p=0.001, Figure 1A). The 2-year probability of LFS was 38.2% [95% CI: 31.8-44.7] for the whole study population. The presence of a pHDK was significantly associated with a better LFS (49.6% [95% CI: 38.7-59.6] versus 30.6% [95% CI: 22.9-38.7], p=0.003) as shown in Figure 1B.

The 2-year cumulative incidence of NRM was 26.3% [95% CI: 20.7-32.3] for the entire study population. The cytogenetic subgroups were not associated with NRM as illustrated in Figure 1C (28.1% [95% CI: 19.1-37.8] for pHDK and 25.1% [95% CI: 18.1-32.8] for HDK+, p=0.51). The 2-year probability of OS was 44.6% [95% CI: 37.8-51.1] for all patients. Patients with pHDK showed a much better OS (57.3% [95% CI: 46.2-66.9]) compared to patients with HDK+ (36.2% [95% CI: 27.9-44.5], p=0.007) as shown in Figure 1D.

The overall cumulative incidence of grade III-IV acute GvHD was 14% [95% CI: 9.8-18.9]. The presence of pHDK or HKD+ were not associated with the occurrence of acute GvHD (p=0.11). The 2-year cumulative incidence of chronic GvHD was 32.6% [95% CI: 26.3-39] in the overall study population. Cytogenetic subgroup was not associated with chronic GvHD (p=0.46). The overall 2-year probability of GRFS was 27.2% [95% CI: 21.5-33.3] in our analysis. Patients harboring pHDK showed a better GRFS (36.4% [95% CI: 26.6-46.4]) than patients with HDK+ (20.8% [95% CI: 14.1-28.4], p=0.011).

Multivariate analysis

The multivariate analysis confirmed that patients harboring pHDK were associated with lower RI and better LFS and OS compared to patients with additional adverse cytogenetic features as shown in Table 2. Patients transplanted in the more recent period showed decrease RI (HR=0.96; 95% CI: 0.92-1. P=0.036)

and NRM (HR=0.94; 95% CI: 0.90-1. P=0.034) as well as improved LFS (HR=0.95; 95% CI: 0.92-0.98. P=0.004) and OS (HR=0.96; 95% CI: 0.96-0.99. P=0.018). Increasing age (per 10 years) was associated with worse OS (HR=1.17; 95% CI: 1-1.37. P=0.047). Being transplanted in CR was associated with lower RI (HR=0.52; 95% CI: 0.31-0.89; P=0.017) and NRM (HR=0.37; 95% CI: 0.19-0.71. P=0.003) and better LFS (HR=0.47; 95% CI: 0.31-0.70. P=0.0002) and OS (HR=0.43; 95% CI: 0.29-0.65. P<0.0001). Regarding GRFS (data not showed), the presence of additional adverse cytogenetic features translated into worse GRFS (HR=1.65; 95%CI: 1.19-2.29; p=0.003). Allo-HCT performed recently was associated with improved GRFS (HR=0.96; 95%CI: 0.93-0.99; p=0.005) as well as transplantation in CR (HR=0.39; 95%CI: 0.26-0.57; p<0.0001). The incidence of grade II-IV acute GvHD and chronic GvHD (data not showed) were lower in patients transplanted in CR (HR=0.44; 95%CI: 0.23-0.86; p=0.016 and HR=0.41; 95%CI: 0.18-0.89; p=0.024, respectively). The combination of a female donor to a male recipient retained its significance with higher incidence of chronic GvHD (HR=2.19; 95%CI: 1.21-3.97; p=0.01).

Discussion

AML with CK is consistently associated with a bad prognosis according to the most recent classification and remains a standard indication for allo-HCT [1,5,22]. However, CK is a very heterogenous and poorly defined subgroup including a high diversity of cytogenetic abnormalities. The definition of CK has been a matter of debate for years and is described by different groups as three or more, four or more and five or more chromosomal abnormalities [5,7]. *Schoch et al.* tried to give a better description of a classical CK as the presence of loss of 5q, 7q or 17p and the deletion of at least one additional region within 18q21q22, 12p13, 16q22q24 or gain of regions including 11q23q25, 1p33p36, 8q22q24 or 21q11q22 [7]. In this definition, gain of a whole chromosome was not included. MK has been recently proposed as a better definition of complexity than conventional CK, in which numerical abnormalities have no impact on survival [14]. We recently reviewed a large cohort of AML with either 7q or 5q abnormalities after allo-HCT and showed that outcomes were significantly and adversely impacted by specific bad cytogenetic features such as MK, 5q abnormalities, 7q abnormalities, abn(17p) and 3q26 abnormalities [17,18]. In this study, CK after excluding these adverse cytogenetic features was no longer associated with outcomes after allo-HCT, suggesting that CK may not always be associated with very poor outcomes. Hyperdiploid CK defined by the presence of 49 or more chromosomes is a rare event in AML [19,23]. Hyperdiploid AML remains a heterogenous entity which can be further classified as pHDK and those harbouring other cytogenetic abnormalities. pHDK has been associated with a better outcome after standard therapy [19,24] and the new 2022 European Leukemia Net (ELN) classification considers pHDK as no longer being part of CK and of the adverse-risk group [22]. As HDK AML has for many years been classified as high-risk disease, it has been a frequent indication for allo-HCT. Here, we described a large population of HDK AML after allo-HCT and showed that overall, HDK AML translated into a 2-year probability of LFS of 38% which is close to what is observed for CK AML as a group [10]. However, patients with pHDK AML showed a significantly better outcome after allo-HCT with a 2-year probability of LFS of 49% compared to only 30%

for patients harbouring adverse cytogenetic features in addition to HDK, which was confirmed by multivariate analysis.

The prognostic impact of trisomies has long been a matter of debate and AML with trisomy has been classified as intermediate-risk [25] or adverse-risk [26]. Trisomy 8 is the most frequent cytogenetic abnormality in AML [27] and is also the most prevalent one in our study population, present in more than 70% of the patients. Currently, trisomy as a sole abnormality is associated with an intermediate-risk according to the ELN 2022 [22] and the presence of an additional trisomy does not impact further outcomes of the underlying favourable or adverse cytogenetic feature [14,28]. The mechanism by which trisomies contribute to leukemogenesis remains to date elusive and most trisomies are more a secondary event, not sufficient alone to induce leukemia. However, a gene-dosage effect has been postulated with subsequent overexpression of key genes on the triplicated chromosome, such as *MYC* localized on chromosome 8 [29] but the overall genes expression profile associated with hyperdiploidy remain heterogeneous, suggesting that this gene-dosage effect is not a determinant for prognosis [30]. If trisomy is not the main event for leukemogenesis, the driver of disease should rely on specific gene mutations. With the acquisition of next-generation sequencing as a routine diagnostic tool, gene mutations have nowadays been included in the most recent AML classification and associated with specific outcomes [22,31]. ASXL1 and RUNX1 mutations have been found in AML patients with trisomy 8 [32–35], RUNX1 and SRSF2 mutations with trisomy 13 [36–38] and more generally methylation-related genes as well as spliceosome-encoding genes were more frequently observed with the presence of trisomies [33]. Unfortunately, we currently do not have molecular data within the EBMT registry to further investigate the impact of such mutations in our study population. As trisomy does not seem to impact prognosis by itself, we may hypothesize that our pHDK population might be further characterized in the future with the addition of molecular data. Other limitations of such registry-based study are the risk of patients' selection as well as the lack of data on minimal residual disease before allo-HCT.

If the results observed with pHDK AML are good, we may wonder if those patients, not classified as high-risk in the new ELN 2022 classification, do still need a consolidation with allo-HCT in first remission (CR1) [22]. Unfortunately, we do not have such a transplant versus no-transplant comparison in a registry-based study but historical data can help us to approach this question. *Chilton et al.* described 75 patients with pHDK AML after different consolidation therapies and described a 5-year relapse-free survival of only 33%, which is much lower than what we observed in our study population [19]. Moreover, if we look at the results of favourable-risk AML such as CBF-AML or isolated NPM1 mutated AML in CR1 after allo-HCT, we observe a LFS higher than 65%, which is better than the outcome reported in our study [39,40]. Therefore, pHDK AML should be managed as intermediate-risk AML, and the decision to bring such patients to allo-HCT should be integrated with co-morbidities and donor availability [41,42]. It has been confirmed in our study population that increasing age was associated with worse survival [43] and older and frail patients with pHDK AML may therefore not have the benefit of allo-HCT. Conditioning intensity in this population

was associated with better LFS and OS in univariate analysis (data not shown) but not in multivariate analysis and we may therefore not advise a MAC regimen for such patients.

In conclusion, pHDK AML is a distinct cytogenetic subtype of AML with a much better outcome after allo-HCT than other CK AML harbouring adverse features. Patients with pHDK AML should be managed as intermediate-risk AML and allo-HCT should be offered where appropriate. As additional chromosomes are not the driver of disease, the enrichment with molecular data in the near future will help us to further characterize this subgroup of AML. However, pHDK CK AML seems to have a better sensitivity to the graft-versus-leukemia effect leading to better survival after allo-HCT.

Declarations

Author Contributions

XP, AN, JE and MM wrote the manuscript; XP, ML, AN, JE and MM designed the study; XP, ML, AN, JE and MM analysed the data; EP, AG, GS, TGD, EF, JF, YC, CEB, IYA, MA, NK and IWB provide the data and reviewed the manuscript.

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Tables

Table 1 Patients' characteristics (N=236)

	pHDK (N=95)	HDK+ (N=141)	p-values
Median Follow-up (IQR)	51 months (35-68)	38 months (27-53)	0.14
Median age (range)	53 (19-74)	52 (18-71)	0.25
Median year of allo-HCT (range)	2012 (2000-2018)	2015 (2001-2018)	0.04
Patient Gender Male/female	60 (63%) / 35 (37%)	62 (44%) / 79 (56%)	0.004
Disease Status (%)			0.31
CR1	77 (81%)	103 (73%)	
CR2/CR3	4 (4%)	6 (4%)	
Active disease	14 (15%)	32 (23%)	
Secondary AML (%)	16 (17%)	32 (23%)	0.27
MRD/UD (%)	43/52 (45%/55%)	42/99 (30%/70%)	0.015
KPS ≥ 90 (%)	67 (71%)	98 (70%)	0.87
MAC/RIC (%)	45/50 (47%/53%)	64/77 (45%/55%)	0.76
BM/PB (%)	14/81 (15%/85%)	13/128 (9%/91%)	0.19
In vivo TCD (%)	58 (62%)	96 (69%)	0.24
Trisomies			
+6	26 (27%)	40 (28%)	0.87
+8	71 (75%)	102 (72%)	0.68
+9	23 (24%)	39 (28%)	0.55
+10	26 (27%)	27 (19%)	0.14
+11	25 (26%)	37 (26%)	0.99
+13	40 (42%)	52 (37%)	0.42
+14	21 (22%)	42 (30%)	0.19
+19	25 (26%)	47 (33%)	0.25
+21	45 (47%)	58 (41%)	0.34
+22	27 (28%)	46 (33%)	0.49

Abbreviations: pHDK: pure hyperdiploid karyotype; HDK+ : non-pure hyperdiploid karyotype ; allo-HCT : allogeneic hematopoietic cell transplantation ; CR : complete remission ; AML : acute myeloid leukemia ; MRD : matched related donor ; UD : unrelated donor ; KPS : Karnofsky's performance status ; MAC : myeloablative conditioning regimen ; RIC : reduced-intensity conditioning regimen; BM : bone marrow; PB : peripheral blood ; TCD : T-cell depletion

Table 2 Multivariate analysis using a Cox proportional hazard model in the entire cohort for RI, NRM, OS and LFS.

	p-value	HR	95% CI		p-value	HR	95% CI
RI				**LFS**			
HDK+ versus pHDK	0.0002	2.54	1.57-4.13	HDK+ versus pHDK	0.002	1.76	1.23-2.5
Year of allo-HCT	0.037	0.96	0.92-1	Year of allo-HCT	0.004	0.95	0.92-0.98
Age (per 10 year)	0.2	1.13	0.94-1.37	Age (per 10 year)	0.25	1.09	0.94-1.26
Secondary AML	0.94	1.02	0.6-1.75	Secondary AML	0.51	1.15	0.76-1.73
UD vs MRD	0.87	0.96	0.61-1.51	UD vs MRD	0.59	1.1	0.77-1.57
CR vs not CR	0.017	0.52	0.31-0.89	CR vs not CR	0.0002	0.47	0.31-0.7
Female donor to male	0.81	0.93	0.51-1.68	Female donor to male	0.69	1.09	0.71-1.69
KPS ≥ 90%	0.14	0.71	0.45-1.12	KPS ≥ 90%	0.17	0.78	0.55-1.11
RIC vs MAC	0.63	1.13	0.69-1.87	RIC vs MAC	0.58	1.12	0.76-1.64
Centre (frailty)	0.93			Centre (frailty)	0.24		
NRM				**OS**			
HDK+ versus pHDK	0.76	1.09	0.62-1.92	HDK+ versus pHDK	0.004	1.72	1.18-2.5
Year of allo-HCT	0.034	0.94	0.9-1	Year of allo-HCT	0.018	0.96	0.93-0.99
Age (per 10 year)	0.68	1.05	0.83-1.33	Age (per 10 year)	0.047	1.17	1-1.37
Secondary AML	0.43	1.3	0.67-2.52	Secondary AML	0.54	1.14	0.74-1.76
UD vs MRD	0.33	1.34	0.74-2.42	UD vs MRD	0.65	1.09	0.75-1.58
CR vs not CR	0.003	0.37	0.19-0.71	CR vs not CR	<0.0001	0.43	0.29-0.65
Female donor to male	0.41	1.33	0.68-2.64	Female donor to male	0.99	1	0.63-1.57
KPS ≥ 90%	0.82	0.93	0.51-1.7	KPS ≥ 90%	0.75	0.94	0.65-1.37
RIC vs MAC	0.77	1.1	0.59-2.07	RIC vs MAC	0.86	1.04	0.7-1.53
Centre (frailty)	0.23			Centre (frailty)	0.24		

Abbreviations; HR: hazard ratio; CI: confidence interval; HDK+: non-pure hyperdiploid karyotype; pHDK: pure hyperdiploid karyotype; allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; UD: unrelated donor; MRD: matched related donor; CR: complete remission; KPS: Karnofsky's performance status; RIC: reduced-intensity conditioning; MAC: myeloablative conditioning

Figures

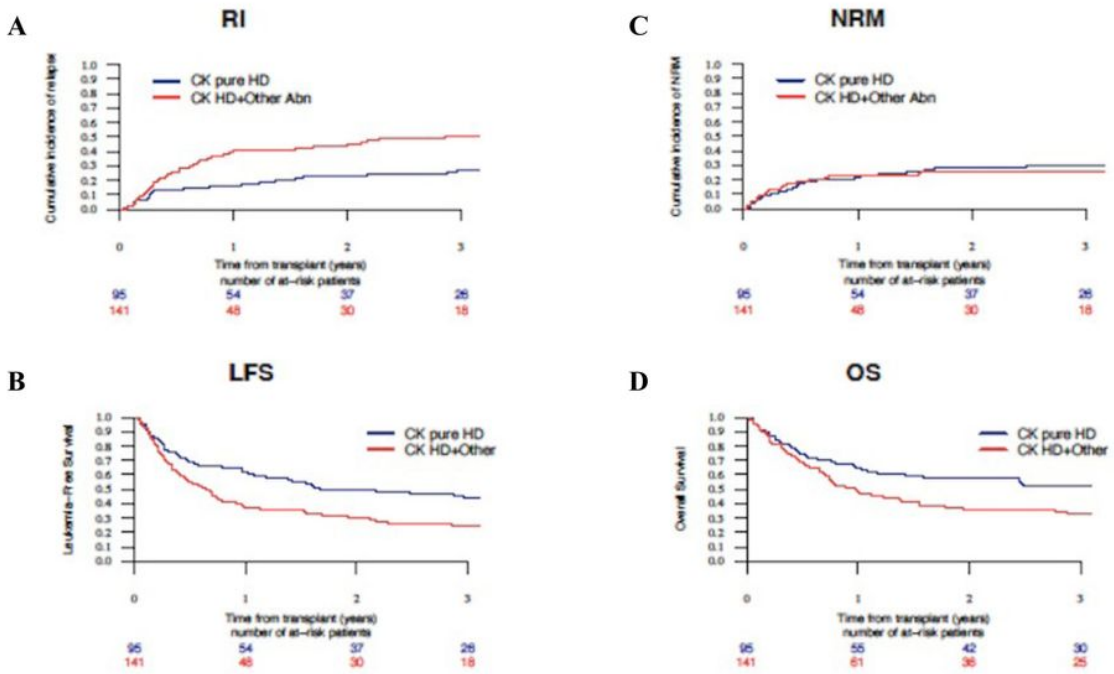

Figure 1

Relapse Incidence (RI), Leukemia-free survival (LFS), non-relapse mortality (NRM) and overall survival (OS) by cytogenetic groups.

The 2-year cumulative incidence of relapse of 22.4% [95% CI: 14.3-31.6] for pHDK and 44.2% [95% CI: 35.5-52.6] for HDK+ (p=0.001) (A). The 2-year probability of LFS 49.6% [95% CI: 38.7-59.6] for pHDK versus 30.6% [95% CI: 22.9-38.7], p=0.003) for HDK+ (p=0.003) (B). The 2-year cumulative incidence of NRM was 28.1% [95% CI: 19.1-37.8] for pHDK and 25.1% [95% CI: 18.1-32.8] for HDK+ (p=0.51) (C). The 2-year probability of OS was 57.3% [95% CI: 46.2-66.9]) for patients with pHDK compared to 36.2% [95% CI: 27.9-44.5] for patients with HDK+ (p=0.007) (D).