ARTICLE

Impact of cytogenetic abnormalities on outcomes of adult Philadelphia-negative acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation: a study by the Acute Leukemia Working Committee of the Center for International Blood and Marrow Transplant Research

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ABSTRACT

Cytogenetic risk stratification at diagnosis has long been one of the most useful tools to assess prognosis in acute lymphoblastic leukemia (ALL). To examine the prognostic impact of cytogenetic abnormalities on outcomes after allogeneic hematopoietic cell transplantation, we studied 1731 adults with Philadelphia-negative ALL in complete remission who underwent myeloablative or reduced intensity/non-myeloablative conditioning transplant from unrelated or matched sibling donors reported to the Center for International Blood and Marrow Transplant Research. A total of 632 patients had abnormal conventional metaphase cytogenetics. The leukemia-free survival and overall survival rates at 5 years after transplantation in patients with abnormal cytogenetics were 40% and 42%, respectively, which were similar to those in patients with a normal karyotype. Of the previously established cytogenetic risk classifications, modified Medical Research Council-Eastern Cooperative Oncology Group score was the only independent prognosticator of leukemia-free survival (P=0.03). In the multivariable analysis, monosomy 7 predicted post-transplant relapse [hazard ratio (HR)=2.11; 95% confidence interval (95% CI): 1.04-4.27] and treatment failure (HR=1.97; 95% CI: 1.20-3.24). Complex karyotype was prognostic for relapse (HR=1.69; 95% CI: 1.06-2.69), whereas t(8;14) predicted treatment failure (HR=2.85; 95% CI: 1.35-6.02) and overall mortality (HR=3.03; 95% CI: 1.44-6.41). This large study suggested a novel transplant-specific cytogenetic scheme with adverse [monosomy 7, complex karyotype, del(7q), t(8;14), t(11;19), del(11q), tetraploidy/near triploidy], intermediate (normal karyotype and all other abnormalities), and favorable (high hyperdiploidy) risks to prognosticate leukemia-free survival (P=0.02). Although some previously established high-risk Philadelphia-negative cytogenetic abnormalities in ALL can be overcome by transplantation, monosomy 7, complex karyotype, and t(8;14) continue to pose significant risks and yield inferior outcomes.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for patients with acute lymphoblastic leukemia (ALL). Risk stratification of ALL varies across studies and generally includes a spectrum of demographic (e.g., age), clinical (e.g., white blood cell count, minimal residual disease, steroid sensitivity), phenotypic (B- *versus* T-cell origin), and cytogenetic characteristics. Several cytogenetic risk stratification schemes have been developed and are used as prognostic tools at diagnosis of ALL to guide treatment decisions. However, most prior studies focusing on the prognostic significance of cytogenetics in ALL were influenced by inclusion of patients with Philadelphia chromosome-positive (Ph^+) B-ALL and defined for patients who received conventional chemotherapies.

Pivotal Medical Research Council–Eastern Cooperative Oncology Group (MRC-ECOG) and Southwest Oncology Group (SWOG) clinical trials identified commonly recognized Ph-negative (Ph^-) cytogenetic risks, including *KMT2A* (*MLL*) translocations at 11q23 associated with

t(4;11)(q21;q23), complex karyotype, t(8;14)(q24;q32), low hypodiploidy, or near triploidy, among others.[1] However, only a subset of Ph⁻ patients underwent allogeneic HCT in those trials. Thus, the applicability of existing cytogenetic risk classifications for allogeneic transplant recipients with ALL remains uncertain due to the relatively low frequency of specific Ph⁻ cytogenetic abnormalities and the modest size of prior studies. In a single-center retrospective cohort study of 333 allograft recipients with ALL, cytogenetic risk did not predict survival after allogeneic HCT.[2] Notably, in that study Ph⁺ patients accounted for the majority of patients in the poor-risk cytogenetic group, and the cytogenetic risk scheme used was chosen arbitrarily. Another study on allogeneic HCT in Ph⁻ ALL (n=373), conducted in Japan, found no difference in overall survival between patients with high-risk [t(4;11), t(8;14), low hypodiploidy, and complex karyotype] and standard-risk cytogenetics.[3] A more recent analysis of Ph⁻ B-ALL patients from GRAALL clinical trials identified t(4;11)/*KMT2A-AFF1* and t(v;14q32)/*IGH* as markers of poor clinical outcome; however, only a third of the trial patients underwent allogeneic HCT in first complete remission.[4]

In view of the conflicting prior data, we analyzed Center for International Blood and Marrow Transplant Research (CIBMTR) registry data to determine the prognostic impact of individual conventional (G-banding) cytogenetic abnormalities and major previously established Ph⁻ cytogenetic risk classifications (Table 1) on outcomes of allogeneic HCT. We also developed an allogeneic HCT–specific cytogenetic classification of Ph⁻ ALL for prediction of post-transplant relapse and survival.

Methods

Data source

Study data were obtained from the CIBMTR registry which is a voluntary network of over 450 blood and marrow transplant centers in the USA and around the world. Participating centers contributed detailed transplant-related information longitudinally to the centralized data management and statistical centers at the Medical College of Wisconsin (Milwaukee, WI, USA) and the National Marrow Donor Program (NMDP) (Minneapolis, MN, USA). Like all observational research conducted by the CIBMTR, this study adhered to strict federal regulations for the protection of human research subjects. Protected health information used in this study was collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability Accountability (HIPAA) Privacy Rule.

Table 1. Major established cytogenetic risk classifications of Philadelphia chromosome-negative acute lymphoblastic leukemia.

Study	Design highlights	Risk group	Cytogenetic abnormalities
MRC-ECOG (Moorman *et al.* Blood 2007)	• Randomized phase III • 796 pts with abnormal cytogenetics • 310 alloHCT	Poor	t(4;11), t(8;14)*, complex* (≥5 abnormalities without translocations), low hypodiploidy (30-39 chr)/near triploidy (60-78 chr)*
		Other	All other karyotypes
		Good	High hyperdiploidy (>50), del(9p)
Modified MRC-ECOG (Pullarkat *et al.* Blood 2008)	• Randomized phase III • 140 pts with evaluable cytogenetics • Re-classified by MRC-ECOG • 19 alloHCT	Very high	t(4;11), t(8;14), complex (≥5 abnormalities without translocations), low hypodiploidy (30-39 chr)/near triploidy (60-78 chr)
		High	Other 11q23/*MLL*, monosomy 7[§], del(7p), +8[§], t(1;19) or t(17;19), t(5;14)
		Intermediate	Normal diploid, low hyperdiploidy (47-50 chr), abnormal 11q (not *MLL*), del(6q), del(17p), del(9p), del(12p), del(13q), t14q32, t(10;14), tetraploidy (>80 chr), or any karyotype abnormalities not identified with a different risk group
		Standard	High hyperdiploidy (>50 chr)
SWOG (Pullarkat *et al.* Blood 2008)	• Randomized phase III trial • 140 pts with evaluable cytogenetics • 19 alloHCT	Unfavorable	Monosomy 7, +8, and 11q23/*MLL* gene rearrangements
		Miscellaneous	Any other abnormal karyotype
		Normal	Normal karyotype
NILG-ALL (Bassan *et al.* Blood 2009)	• Phase II • 276 with evaluable cytogenetics	Adverse	t(4;11) and/or MLL-AF4, +8, near triploidy, low hypodiploidy, complex (≥3 abnormalities), del(6q), t(8;14)
		Non-adverse	t(1;19) and/or *E2A-PBX1*, hyperdiploid, other karyotype abnormalities not identified with a different risk group
		Normal	Normal karyotype
North UK (Moorman *et al.* Blood 2010)	• Observational • 292 pts with evaluable cytogenetics	Poor	t(4;11), t(8;14), t(14;18), complex (≥5 abnormalities without translocations), low hypodiploidy (30-39 chr)/near triploidy (60-78 chr)
		Standard	All other karyotypes
GIMEMA 0496 (Mancini *et al.* Blood 2005)	• Phase II • 282 pts with evaluable cytogenetics	High	t(4;11), t(1;19)
		Intermediate	del(6q) and other karyotypes
		Standard	normal karyotype, del(9p)

MRC-ECOG: Medical Research Council-Eastern Cooperative Oncology Group; SWOG: Southwest Oncology Group; NILG: Northern Italy Leukemia Group; GIMEMA: Gruppo Italiano Malattie EMatologiche dell'Adulto; alloHCT: allogeneic hematopoietic cell transplantation; pts: patients; chr: chromosomes; *MLL*: mixed lineage leukemia *Independent predictors. [§]Unfavorable by Cancer and Leukemia Group B classification.

Selection of patients

The initial study population included 3,275 adults (age ≥16 years) with Ph⁻ ALL in first or second complete remission (CR1 or CR2, corresponding to morphological remission with <5% bone marrow blasts) who underwent allogeneic HCT between 1995-2011 and whose data were reported to the CIBMTR. Further restriction of the study population to the recipients of HLA-matched sibling and unrelated donor peripheral blood or bone marrow allografts (with consent to submit at least 100 days of post-transplant research reports) resulted in 2,903 eligible study participants. The CIBMTR data center requested original cytogenetic reports for cases with reportedly abnormal or unknown cytogenetics at either the time of diagnosis or prior to allogeneic HCT. Cytogenetic reports were received from participating centers for 1,013 cases, all of which were reviewed and validated by the study's principal investigators (AL, MD). Data on cytogenetics from the existing CIBMTR records were used for 743 cases for which no original cytogenetic reports were received from the queried centers. For 342 cases (12%) with prior CIBMTR cytogenetics status reported as "unknown" or "not tested" the original cytogenetic reports were requested, but not received from the transplant centers. Normal conventional cytogenetic results were confirmed with over 95% accuracy upon review of all original reports received and the remaining 805 cases with normal cytogenetics were included in the final study sample of 1,099 patients with normal cytogenetics reported. Patients with abnormal conventional cytogenetics (n=632) were included in the study population after review of all available original cytogenetic reports. Thus, a total study population of 1,731 patients from 256 reporting centers and 38 countries was analyzed.

Cytogenetics

Blood and marrow samples at the time of ALL diagnosis and prior to transplantation were cultured and evaluated for cytogenetic abnormalities by G-banding according to the standard practices of the participating centers. Original cytogenetic data reported to the CIBMTR conformed to the International System of Cytogenetic Nomenclature (ISCN).[5] According to the ISCN, a clonal abnormality was defined as the presence of a gain of the same chromosome or the presence of the same structural abnormality in ≥2 cells or the loss of the same chromosome in ≥3 cells. A normal conventional cytogenetic result was defined as the absence of clonal abnormalities in at least 20 metaphase cells. Abnormal cytogenetics were classified according to previously established cytogenetic risk classifications for Ph⁻ ALL (Table 1). Standard definitions for hypodiploid, hyperdiploid, complex, and monosomal karyotypes were based on the following modal chromosome numbers: (i) low hypodiploidy (30-39 chromosomes), (ii) high hypodiploidy (40-43), (iii) low hyperdiploidy (47-50), (iv) high hyperdiploidy (>50), (v) near triploidy (60-78), (vi) tetraploidy (>80), (vii) complex with ≥5 abnormalities[6-8] (adopted here) in the absence of established translocations or ploidy abnormalities; or ≥3 abnormalities used exclusively by the Northern Italy Leukemia Group (NILG)[9] (Table 1), and (viii) monosomal (≥2 autosomal monosomies or a single autosomal monosomy combined with a single structural abnormality). Fluorescence *in situ* hybridization (FISH) findings and/or other molecular data were available for the minority of patients and were, therefore, only used to validate cytogenetic reports when available.

Statistical analysis

Individual Ph⁻ cytogenetic abnormalities were included in the analysis if they were detected in ≥20 patients or in <20 patients but with previously established prognostic significance in ALL. Cytogenetic abnormalities included high hyperdiploidy (n=29), tetraploidy (n=9), near triploidy (n=6), low hypodiploidy (n=11), complex karyotype (n=51), monosomal karyotype (n=84), monosomy 17 (n=21), i(17q) (n=5), del(17p) (n=6), t(1;19) (n=33), t(4;11) (n=95), t(8;14) (n=10), t(10;11) (n=8), t(11;19) (n=10), add(5q) (n=7), del(5q) (n=20), add(7p) (n=8), i(7q) (n=10), add(12p) (n=10), del(12p) (n=18), t(14;18) (n=6), del(6q) (n=48), del(7q) (n=7), monosomy 7 (n=33), add(9p) (n=11), del(9p) (n=52), i(9q) (n=17), add(12p) (n=10), del(12p) (n=18), del(11q) (n=18), del(13q) (n=12), and trisomy 8 (n=35). Each cytogenetic abnormality was tested individually for its association with post-HCT relapse while adjusted for potential confounders. Statistically significant (P<0.05) clinical factors other than cytogenetics [conditioning regimen, remission status, donor type, and graft-*versus*-host disease (GvHD) prophylaxis among other potential confounders] were retained in the multivariable Cox proportional hazards model. Abnormalities with a hazard ratio (HR) ≥1.4 for relapse were subsequently grouped as adverse risk; abnormalities with a HR ≤0.6 for relapse were grouped as favorable, whereas all other abnormalities, and normal cytogenetics, were grouped as intermediate risk. Relapse was used as the primary endpoint for evaluation of individual cytogenetic abnormalities and it was calculated as the cumulative incidence of ALL recurrence with treatment-related mortality as the competing risk. Leukemia-free survival was used as the primary endpoint for evaluation of previously established and study-derived cytogenetic risk classifications and was defined as the time to death or relapse with survivors in continuing complete remission censored at last follow-up. Adjusted probabilities of leukemia-free survival and relapse were calculated using multivariable models, stratified by cytogenetic risk scheme and weighted by the pooled sample proportion value for each prognostic factor.[10,11] Overall survival was a secondary study endpoint and was defined as the time to death from any cause with surviving patients censored at last follow-up. Treatment failure (1 – leukemia-free survival) and overall mortality (1 – overall survival) were used to model all Cox regression HR estimates. SAS version 9.4 (SAS Institute, Cary, NC, USA) and GraphPad Prism version 7.04 were used for all data analysis and graphics.

Results

Study population and transplant characteristics

A description of the entire study population and the distribution of the main study variables among patients with abnormal and normal cytogenetics are summarized in Table 2. The study cohort consisted predominantly of young (82% <45 years) male (63%) patients with B-precursor ALL (69%). Patients with hyperleukocytosis (white blood cell count >30×10⁹/L for B-ALL and >100×10⁹/L for T-ALL) at the time of initial diagnosis accounted for 22% of the entire cohort and 57% of patients underwent allogeneic HCT in CR1 with a median time to achieve CR1 of 6 weeks (range, 1-123).

Post-transplant outcomes classified by established cytogenetic schemes

Patients with abnormal cytogenetics had 5-year leukemia-free and overall survival rates of 40% and 42%, respectively, which were similar to those of patients with a normal karyotype (both P>0.6). The cytogenetic risk categories defined by the MRC-ECOG, SWOG, NILG-ALL, North UK, and GIMEMA 0496 (Table 1) had no prognostic significance for leukemia-free survival, relapse, or overall survival (all P-values >0.15). However, the cytogenetic risk

Table 2. Patient and transplant characteristics.

Variables	All	Cytogenetics Abnormal	Cytogenetics Normal
Number of patients	1731	632 (36.5)	1099 (63.5)
Number of centers	256	178	226
Recipient age, median (range), years	29 (16-68)	28 (16-65)	29 (16-68)
Gender, female, n (%)	636 (37)	234 (37)	402 (37)
Recipient race, n (%)			
Caucasian	1429 (83)	534 (84)	895 (81)
African-American	42 (2)	12 (2)	30 (3)
Asian	154 (9)	49 (8)	105 (10)
Other	106 (7)	37 (6)	69 (6)
Karnofsky score ≥ 90%, n (%)	1245 (72)	459 (73)	786 (72)
Disease status prior to alloHCT, n (%)			
CR1	990 (57)	395 (62.5)	595 (54)
CR2	741 (43)	237 (37.5)	504 (46)
Time to CR1, median (range), weeks	6 (1-123)	5 (2-123)	6 (1-113)
Time from CR1 to alloHCT[1], median (range), months	3 (<1-16)	3 (<1-13)	4 (<1-16)
Time from CR1 to relapse[2], median (range), months	20 (<1-111)	18 (<1-103)	21 (1-111)
ALL lineage, n (%)			
B-ALL	1197 (69)	474 (75)	723 (66)
T-ALL	393 (23)	121 (19)	272 (25)
Unknown	141 (8)	37 (6)	104 (9)
Hyperleukocytosis at diagnosis, n (%)			
B-ALL (>30x10^9 WBC/L)	299 (17)	150 (24)	149 (14)
T-ALL (>100x10^9 WBC/L)	81 (5)	31 (5)	50 (4)
Extramedullary ALL at diagnosis, n (%)			
CNS	105 (6)	35 (6)	70 (6)
Non-CNS	202 (12)	70 (11)	132 (12)
Conditioning intensity, n (%)			
MAC (+TBI)	1343 (78)	522 (83)	821 (75)
MAC (-TBI)	254 (15)	72 (11)	182 (17)
NMA/RIC	98 (6)	28 (5)	70 (7)
Unknown	36 (2)	10 (2)	26 (2)
GvHD prophylaxis, n (%)			
Tacrolimus-based	576 (33)	217 (34)	359 (33)
Cyclosporine A-based	1000 (58)	350 (55)	650 (59)
T-cell depletion (*ex-vivo*)	123 (7)	55 (9)	68 (6)
In-vivo T-cell depletion, n (%)			
Alemtuzumab	46 (3)	19 (3)	27 (2)
ATG	286 (17)	99 (16)	187 (17)
Graft source, n (%)			
Bone marrow	790 (46)	281 (44)	509 (46)
Peripheral blood	941 (54)	352 (46)	590 (54)
Donor type, n (%)			
HLA-identical sibling	819 (47)	270 (43)	549 (50)
Well-matched unrelated donor	469 (27)	188 (30)	281 (26)
Partially-matched/mismatched unrelated donor	357 (21)	141 (22)	216 (20)
Other related/unrelated donor	172 (10)	70 (11)	102 (9)
Donor/recipient CMV serostatus, n (%)			
Donor+/recipient+	574 (33)	170 (27)	404 (37)
Donor+/recipient-	193 (11)	78 (12)	115 (10)
Donor-/recipient+	385 (22)	143 (23)	242 (22)
Donor-/recipient-	494 (29)	210 (33)	284 (26)
Unknown	85 (5)	31 (5)	54 (5)
Donor/recipient gender match, n (%)			
Male-male	691 (40)	256 (41)	435 (40)
Male-female	340 (20)	127 (20)	213 (19)
Female-male	401 (23)	142 (22)	259 (24)
Female-female	295 (17)	107 (17)	188 (17)
Unknown	4 (<1)	0	4 (<1)
Year of alloHCT, n (%)			
1995-2000	557 (32)	194 (31)	363 (33)
2001-2005	604 (35)	217 (34)	387 (35)
2006-2011	570 (33)	221 (35)	349 (32)
Median follow up of survivors (range), months	75 (2-224)	87 (3-224)	73 (2-218)

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alloHCT: allogeneic hematopoietic cell transplantation; CR1: first complete remission; CR2: second complete remission; ALL: acute lymphoblastic leukemia; WBC: white blood cell; CNS: central nervous system; MAC: myeloablative conditioning; TBI: total body irradiation; NMA: non-myeloablative; RIC: reduced-intensity conditioning; HLA: human leukocyte antigen; GvHD: graft-*versus*-host disease; ATG: antithymocyte globulin; CMV: cytomegalovirus. [1]Referred to patients in CR1. [2]Referred to patients in CR2.

classification defined by the modified MRC-ECOG was significantly associated with both treatment failure (overall P=0.02) and overall survival (overall P=0.03) in multivariable analyses adjusted for recipient age, disease status, conditioning intensity, Karnofsky Performance Status, donor type, and GvHD prophylaxis (Figures 1A and 2). Significant associations between the modified MRC-ECOG classification and major clinical outcomes appeared to be largely driven by the favorable outcomes of patients with standard-risk cytogenetics (n=24), all with a high hyperdiploid karyotype. There was no difference between high or very high modified MRC-ECOG cytogenetic risk groups compared to the intermediate group. In contrast, good-risk cytogenetics according to the MRC-ECOG classification included del(9p), in addition to high hyperdiploidy, and was not significantly associated with any of the clinical outcomes of interest.

Individual cytogenetic abnormalities: relapse

Monosomy 7 [HR=2.11; 95% confidence interval (CI): 1.04-4.27, P=0.04] and complex karyotype (HR=1.69; 95% CI: 1.06-2.69, P=0.03) were both associated with increased risk of relapse in multivariable analysis adjusted for conditioning intensity, ALL remission status prior to transplantation, and monosomal karyotype (Figure 3, Table 3). Patients with high hyperdiploidy had an estimated 54% lower risk of relapse, whereas those with del(7q), t(8;14), t(11;19), del(11q), or a tetraploid/near triploid karyotype had a HR of at least 40% higher for relapse, which did not reach statistical significance (Figure 3). The magnitude and strength of associations with relapse for the remaining individual cytogenetic categories, such as trisomy 8, monosomal karyotype, monosomy 17, del(17p)/i(17p), low hypodiploidy, del(6q), t(1;19), t(4;11), and normal karyotype, did not demonstrate any meaningful clinical associations (all HR between 0.6 and 1.4), and none was statistically significant (all P-values >0.1).

A significant interaction was detected between t(4;11) and pre-transplant remission status (P<0.001) with the adverse impact of t(4;11) on relapse observed only in patients undergoing allogeneic HCT in CR2 (HR=2.82; 95% CI: 1.25-6.36, P=0.01), but not in CR1 (HR=0.86,95% CI: 0.53-1.41, P=0.55).

Individual cytogenetic abnormalities: treatment failure

Monosomy 7 (HR=1.97; 95% CI: 1.20-3.24, P=0.007) and t(8;14) (HR=2.85; 95% CI: 1.35-6.02, P=0.006) were

prognostic for treatment failure after adjustments for recipient age, pre-transplant remission status, conditioning intensity, donor type, and GvHD prophylaxis in multivariable analyses (Table 4). Trends toward increased risk of treatment failure were observed for patients with del(7q) (HR=2.16; 95% CI: 0.95-4.90, *P*=0.06) and del(17p)/i(17q) (HR=1.95; 95% CI: 0.80-4.75, *P*=0.1). In contrast, patients with high hyperdiploidy (HR=0.62; 95% CI: 0.37-1.04, *P*=0.07) and monosomal karyotype (HR=0.73; 95% CI: 0.54-1.01, *P*=0.05) trended toward less risk of treatment failure. Although t(4;11) was not associated with treatment failure (HR=1.12; 95% CI: 0.85-1.48, *P*=0.41) within the entire cohort or in CR1 patients (n=83) (HR=0.98; 95% CI: 0.72-1.33, *P*=0.89), it was associated with a significantly higher risk of treatment failure in CR2 patients (n=11) (HR=2.35; 95% CI: 1.25-4.43, *P*=0.008).

Individual cytogenetic abnormalities: overall mortality

After adjustment for recipient age (HR=1.55; 95% CI: 1.17-2.06, *P*<0.01 for age >55 years *versus* <40 years), Karnofsky Performance Status <90 (HR=1.29; 95% CI: 1.12-1.48, *P*<0.001), ALL in CR2 (HR=1.56; 95% CI: 1.36-1.77, *P*<0.001), myeloablative conditioning without total body irradiation (HR=1.35; 95% CI: 1.13-1.62, *P*<0.001), mismatched unrelated donor (HR=1.49; 95% CI: 1.27-1.76, *P*<0.001), and GvHD prophylaxis (HR=1.41; 95% CI: 1.11-1.79, *P*=0.005 for non-calcineurin inhibitor- *versus* tacrolimus-based) in multivariable analysis, only t(8;14) was associated with higher mortality after allogeneic HCT (HR=3.03; 95% CI: 1.44-6.41, *P*=0.004).

Novel allogeneic hematopoietic cell transplantation-specific cytogenetic classification

Based on the relapse model adjusted for significant clinical factors and individual cytogenetic abnormalities (Figure 3), the following cytogenetic markers with HR≥1.4 were categorized as adverse risk (n=125): monosomy 7, complex karyotype, del(7q), t(8;14), t(11;19), del(11q), and tetraploid/near triploid karyotype. Conversely, high hyperdiploidy (n=29) was identified as

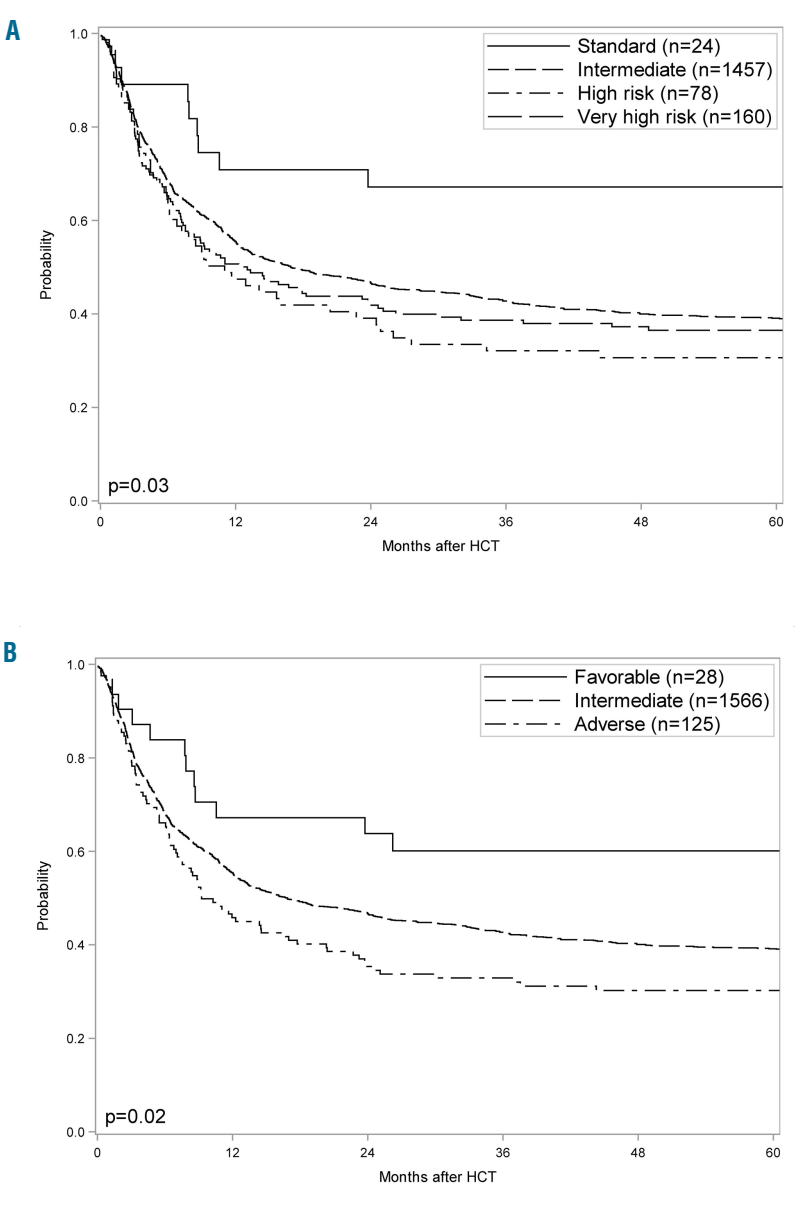

Figure 1. Adjusted leukemia-free survival by cytogenetic risk classifications. (A) Adjusted leukemia-free survival by modified Medical Research Council – Eastern Cooperative Oncology Group cytogenetic risk classification. (B) Adjusted leukemia-free survival by Center for International Blood and Marrow Transplant Research acute lymphoblastic leukemia risk classification. HCT: hematopoietic cell transplantation.

the sole cytogenetic abnormality with a HR≤0.6 for relapse, and was categorized as favorable risk. The remaining cytogenetic markers, including normal cytogenetics, were categorized as intermediate risk (n=1566). This novel allogeneic HCT-specific cytogenetic risk classification (hereafter called CIBMTR ALL risk) was found to be prognostic for both post-transplant relapse (*Online Supplementary Figure S1*) and leukemia-free survival (log-rank *P*=0.04) (Figure 1B). Furthermore, in the multivariable Cox proportional hazards model adjusted for recipient age, pre-transplant remission status, conditioning intensity, Karnofsky Performance Status, donor type, and GvHD prophylaxis, patients with CIBMTR adverse-risk cytogenetics had a higher risk of treatment failure (HR=1.26; 95% CI: 1.01-1.57, *P*=0.04), and those with favorable risk had a lower risk (HR=0.6; 95% CI: 0.35-1.02, *P*=0.06) compared to those with intermediate-risk cytogenetics (Table 5). There was a significantly greater risk of treatment failure in those with adverse *versus* favorable risk cytogenetic abnormalities (HR=2.10; 95% CI: 1.19-3.70, *P*=0.01). Similarly, there was a significantly greater risk of overall mortality in patients with adverse *versus* favorable risk cytogenetic abnormalities (HR=1.91; 95% CI: 1.08-3.38, *P*=0.03).

Discussion

This large CIBMTR analysis of allogeneic HCT recipients with Ph- ALL defined a cytogenetic classification specific to allogeneic transplantation. Of the established

Table 3. Multivariable model of prognostic factors for post-transplant relapse.

Factors	N	HR (95% CI)	*P*-value
Conditioning regimens			
MAC (+TBI)	1334	1.0	
MAC (-TBI)	253	1.54 (1.22-1.96)	<0.001
RIC/NMA	96	1.9 (1.38-2.61)	<0.001
Remission status pre-alloHCT			
CR1	986	1.0	
CR2	733	1.71 (1.44-2.04)	<0.001
Cytogenetics			
Complex karyotype*	51	1.69 (1.06-2.69)	0.03
Monosomy 7*	33	2.11 (1.04-4.27)	0.04

N: number; HR: hazard ratio; 95% CI: 95% confidence interval; MAC: myeloablative conditioning; TBI: total body irradiation; RIC: reduced-intensity conditioning; NMA: non-myeloablative; alloHCT: allogeneic hematopoietic cell transplantation; CR1: first complete remission; CR2: second complete remission. *Adjusted for monosomal karyotype.

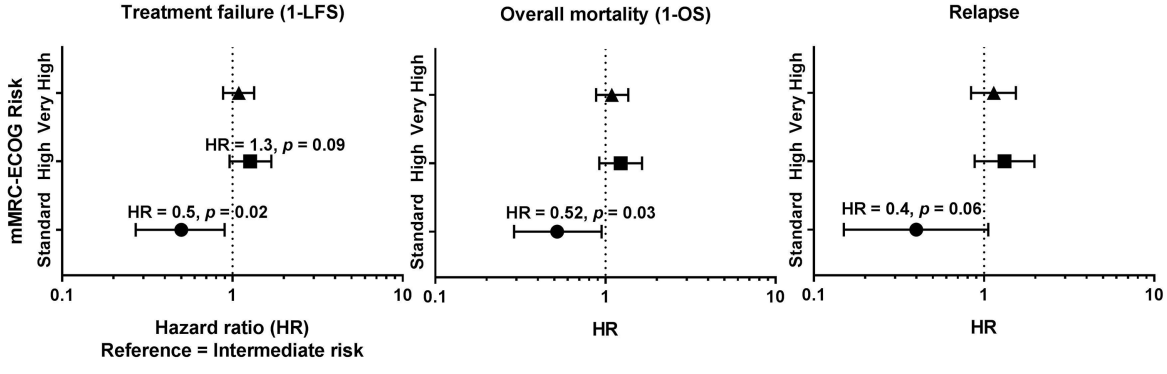

Figure 2. Cytogenetic risks by modified Medical Research Council – Eastern Cooperative Oncology Group cytogenetic risk classification and post-transplant outcomes. All multivariable models were adjusted for recipient age, disease status, conditioning intensy, Karnofsky Performance Status, donor type and graft-*versus*-host disease prophylaxis. mMRC-ECOG: modified Medical Research Council-Eastern Cooperative Oncology Group classification with its three cytogenetic risk groups on Y-axis, relative to the Intermediate risk (reference with HR=1) on X-axis; LFS: leukemia-free survival; OS: overall survival.

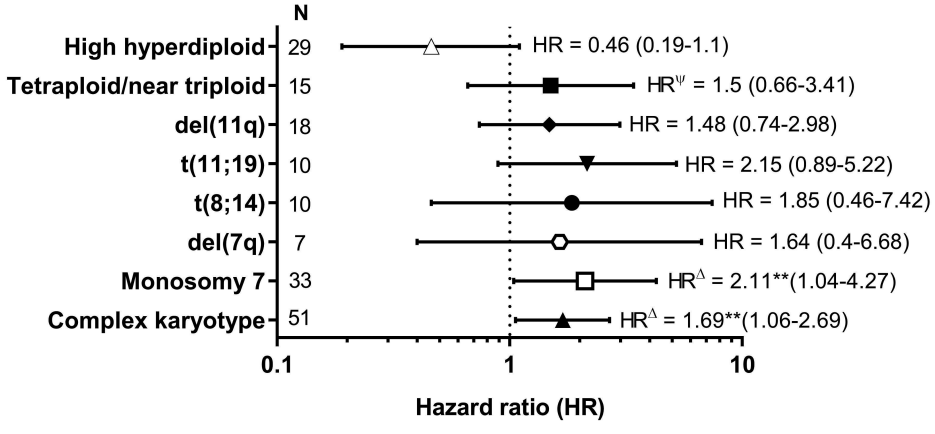

Figure 3. Forest plots of cytogenetic markers associated with post-transplant relapse. All hazard ratios (HR) and corresponding 95% confidence intervals (CI) are adjusted for conditiong intensity and remisssion status; CK: complex karyotype; N: sample size of carriers of each cytogenetic marker. * Defined as 40% risk increase or decrement; **Markers with *P*<0.05; ΨAdjusted also for complex karyotype. ΔAdjusted also for monosomal karyotype.

major ALL cytogenetic risk schemes, only the modified MRC-ECOG classification could be validated in our dataset for its association with post-transplant outcomes. The association of the modified MRC-ECOG classification was largely explained by favorable outcomes for patients with high hyperdiploidy, a factor known to be associated with better outcomes.[12,13] While a few individual high-risk cytogenetic abnormalities maintained their prognostic relevance for recipients of allogeneic HCT, many others had no significant prognostic influence on the transplant outcomes. Thus, the aggregate effects of previously established high or very high risk cytogenetic groups defined by MRC-ECOG, SWOG, NILG-ALL, North UK, and GIMEMA 0496 were overcome by allogeneic HCT and did not predict the outcomes of the transplant recipients. High-risk cytogenetic abnormalities including trisomy 8, low hypodiploidy, t(1;19), del(6q) could be overcome, in part, by the graft-*versus*-leukemia effect of allogeneic HCT, and thus, were not unfavorable in this analysis. In contrast to findings in acute myeloid leukemia[14,15] and recently reported cases of ALL,[4,16] in our dataset and elsewhere,[17] monosomal karyotype did not predict poor post-transplant outcomes for Ph$^-$ ALL. Similarly, our analysis did not confirm the adverse effect of t(4;11) on relapse or leukemia-free survival among all carriers of this well-known cytogenetic risk, but uncovered a differential effect of t(4;11) on transplant outcomes which was modified by pre-transplant disease status. Nevertheless, given the relatively small subset of patients with t(4;11) in CR2, the results of our post-hoc analysis should be interpreted with caution. Moreover, the infrequency of CR2 allografts in patients with t(4;11) may reflect intrinsic difficulty for those patients to effectively maintain maintain subsequent remissions. A recent comparison of allograft recipients with t(4;11) and normal karyotype in CR1 demonstrated relatively favorable survival of patients with t(4;11) and especially those with undetectable pretransplant minimal residual disease.[18] Allogeneic HCT in CR1 for adult ALL patients with t(4;11) remains valuable.[19]

High-risk cytogenetic abnormalities found in this study included t(8;14), complex karyotype, and monosomy 7, previously known poor-risk categories in major classification schemes, excluding GIMEMA 0496 (Table 1). Patients with these high-risk cytogenetic abnormalities were predominantly young adults, most of whom received myeloablative conditioning and still had poor outcomes, thus confirming the high-risk nature of cytogenetic abnormalities.

The t(8;14) is a rare recurrent abnormality among patients with ALL[20-23] and has been associated with a poor outcome.[7] It was observed in ten allogeneic HCT recipients (median age, 21) who had a nearly 3-fold significantly lower leukemia-free survival in our cohort. In addition to the *IGH-MYC* fusion resulting from the t(8;14), other *IGH* translocations involving *BCL2* (when present together

Table 4. Multivariable model of prognostic factors for post-transplant treatment failure.

Factors	N	HR (95% CI)	*P*-value
Age, years			
16-39	1270	1.0	
40-55	363	1.21 (1.04-1.41)	0.02
55+	86	1.42 (1.07-1.88)	0.01
Remission status pre-alloHCT			
CR1	986	1.0	
CR2	733	1.53 (1.34-1.74)	<0.001
Conditioning regimens			
MAC (+TBI)	1334	1.0	
MAC (-TBI)	253	1.4 (1.18-1.66)	<0.001
MAC (+TBI)	1334	1.0	
RIC/NMA	96	1.26 (0.97-1.64)	0.09
Performance status			
KPS≥90	1234	1.0	
KPS<90	423	1.32 (1.15-1.52)	<0.001
Donor type			
MSD	818	1.0	
Matched URD	464	1.06 (0.9-1.24)	0.49
Mismatched URD	351	1.43 (1.21-1.68)	<0.001
Other RD/URD	86	1.36 (1.02-1.81)	0.03
GvHD prophylaxis			
Tac-based	569	1.0	
CsA-based	996	1.11 (0.96-1.28)	0.15
Other	134	1.39 (1.1-1.75)	0.006
Cytogenetics			
t(8;14)	10	2.85 (1.35-6.02)	0.006
Monosomy 7*	33	1.97 (1.2-3.24)	0.007

N: number; HR: hazard ratio; 95% CI: 95% confidence interval; alloHCT: allogeneic hematopoietic cell transplantation; CR1: first complete remission; CR2: second complete remission; MAC: myeloablative conditioning; TBI: total body irradiation; RIC: reduced-intensity conditioning; NMA: non-myeloablative; KPS: Karnofsky Performance Status; MSD: matched sibling donor; RD: related donor; URD: unrelated donor; GvHD: graft-*versus*-host disease; CSA: cyclosporine. *Adjusted for monosomal karyotype.

Table 5. Novel Center for International Blood and Marrow Transplant Research risk scheme for post-transplant Philadelphia-negative acute lymphoblastic leukemia outcomes

Cytogenetic risk groups	N	HR (95% CI)*		
		Treatment failure(1-LFS)	Relapse	Overall mortality (1-OS)
Favorable (high hyperdiploidy)	28	0.6 (0.35-1.02)	0.39 (0.15-1.05)	0.64 (0.37-1.08)
Intermediate (normal karyotype and all other abnormalities[§])	1578	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Adverse (monosomy 7, complex karyotype, del(7q), t(8;14), t(11;19), del(11q), tetraploidy/near triploidy)	125	1.26 (1.01-1.57)	1.48 (1.09-2.0)	1.22 (0.97-1.53)
Adverse vs. favorable	-	2.1 (1.19-3.7)	3.78 (1.36-1.76)	1.91 (1.08-3.38)

HR: hazard ratio; 95% CI: 95% confidence interval; LFS: leukemia-free survival; OS: overall survival. *Adjusted for conditioning intensity, disease status prior to transplantation, recipient age, Karnofsky Performance Status, donor type, graft-versus-host disease prophylaxis, as applicable based on the individual models. §Except for those included in the adverse and favorable groups

with *IGH-MYC*) and *CRLF2* have also been reported to yield poor outcomes.[24-26]

Our study confirmed the previously established unfavorable risk associated with a complex karyotype[6,27] after allogeneic HCT. Notably, we observed substantial overlap between complex karyotype, monosomal karyotype, and other common abnormalities, mandating careful data analysis and interpretation of complex cytogenetics in future studies.

Monosomy 7 was consistently associated with worse post-transplant outcomes in this and prior studies.[8] Multiple mechanisms have been proposed to explain the effects of monosomy 7 on leukemogenesis including, but not limited to, loss of tumor suppressor genes, haploinsufficiency, or monoallelic loss of *IKZF1*, an important adverse prognostic marker in B-cell ALL which is localized to chromosome 7p.[28,29] Haploinsufficient deletions of *IKZF1* are enriched among Ph- ALL cases and associated with inferior survival.[30]

Our observed higher risk of relapse among allogeneic HCT recipients with t(11;19) was also consistent with the previously reported poor survival of ALL patients with t(11;19)(q23;p13.3).[31]

We propose an allogeneic HCT-specific cytogenetic risk classification for Ph- ALL separating patients into three prognostic risk categories based on the presence of monosomy 7, del(7q), t(8;14), t(11;19), del(11q), complex, tetraploid/near triploid, and high hyperdiploid karyotypes (Table 5). This novel CIBMTR ALL risk classification of Ph- patients treated with allogeneic HCT is directly relevant to pre-HCT decision-making and might help in stratifying clinical trial candidates undergoing allogeneic HCT for Ph- ALL.

Unfortunately we could not account in our analysis for pre-transplant minimal residual disease (MRD), defined by flow cytometry or FISH/molecular testing. Pre-transplant MRD has been important in predicting ALL relapse and future research should combine cytogenetic classifications with pre-transplant MRD status. Pretreatment complex karyotype and low hypodiploidy/near-triploidy portended poor survival after adjustment for MRD in a recent single-institution study.[27] Our analysis validated other established patient- and transplant-related prognostic factors and thereby confirmed the additional importance of the cytogenetic groupings. As most patients in this cohort received allografts with myeloablative conditioning, future validation of the CIBMTR ALL risk scheme among recipients treated with reduced intensity conditioning will test this prognostic tool in older and/or less fit ALL patients.

Our study focused on the transplant period preceding Food and Drug Administration approvals and broader use of liposomal vincristine, blinatumomab, inotuzumab ozogamycin, or tisagenlecleucel, and it thereby focused on a more homogeneous patient population with no differential effect on treatment outcomes found according to quinquennial transplant periods from 1995 to 2011.

While many patients with previously established high-risk Ph- cytogenetic abnormalities can benefit from allogeneic HCT, those with monosomy 7, complex karyotype, and t(8;14) remain at high risk for treatment failure after transplantation. Selective targeting of these and other clinically-defined high-risk cohorts will be necessary to improve post-transplant survival of patients with Ph- ALL.

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