Characteristics and clinical outcomes of patients with acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2)

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Abstract

Acute myeloid leukemia (AML) with inv(3)(q21q26.2)/t(3;3)(q21;q26.2) has a very poor prognosis. Determinants of clinical outcomes and optimal treatment remain uncertain. We retrospectively reviewed 108 cases of AML with inv(3)/t(3;3) and evaluated clinicopathological characteristics and clinical outcomes: 53 newly diagnosed (ND) AML and 55 relapsed/refractory (R/R) AML. Median age was 55 years. White blood cell (WBC) count ≥20x10^9/L and platelet count ≥140x10^9/L was observed in 25% and 32% of ND patients, respectively. Anomalies involving chromosome 7 were identified in 56% of patients. The most frequently mutated genes were *SF3B1, PTPN11, NRAS, KRAS* and *ASXL1*. In ND patients, the composite complete remission (CRc) rate was 46% overall; 46% with high-intensity treatments and 47% with low-intensity treatments. The 30-day mortality was 14% and 0%, with high- and low-intensity treatment, respectively. In R/R patients, the CRc rate was 14%. Venetoclax based-regimens were associated with a CRc rate of 33%. The 3-year overall survival (OS) was 8.8% and 7.1% in ND and R/R patients, respectively. The 3-year cumulative incidence of relapse was 81.7% overall. Older age, high WBC, high peripheral blast count, secondary AML and *KRAS, ASXL1, DNMT3A* mutations were associated with worse OS in univariable analyses. The 5-year OS rates were 44% and 6% with or without hematopoietic stem cell transplantation in CR1, respectively. AML with inv(3)/t(3;3) is associated with low CR rates, very high risk of relapse and dismal long-term survival. Intensive chemotherapy and hypomethylating agents provide similar rates of remission and patients achieving CR benefit from hematopoietic stem cell transplantation in first CR.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous malignancy of the hematopoietic stem and progenitor cells (HPSC) for which genetic alterations define distinct diagnostic entities with specific phenotypical and clinical characteristics.[1-3] Cytogenetic abnormalities are associated with clinical outcomes and inform treatment decisions, including the indication for allogeneic hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1).[4,5]

AML with inv(3)(q21q26.2)/t(3;3)(q21;q26.2) is a rare subtype identified in about 1% of patients with newly diagnosed AML. These chromosomal rearrangements cause the repositioning of a *GATA2*-distal hematopoietic enhancer (G2DHE) located on chromosome 3q21 to activate the expression of *EVI1* located on chromosome 3q26.2 in the *MDS1-EVI1* complex locus (*MECOM*).[6,7] *EVI1* is a transcriptional regulator involved in self-renewal, proliferation, cell differentiation and maintenance of long-term hematopoietic stem cells.[8,9] The overexpression of *EVI1* suppresses erythropoiesis and lymphopoiesis and expands myeloid cells and HPSC leading to AML.[10] The repositioning of G2DHE also causes haploinsufficiency of *GATA2*, a transcription factor regulating many genes involved in self-renewal and maintenance of HPSC, hence cooperating in the leukemogenesis and aggressiveness of AML with inv(3)/t(3;3).[11]

Patients with AML with inv(3)/t(3;3) typically have normal or elevated platelets, increased small hypolobated megakaryocytes, and multilineage dysplasia.[12] Additional chromosomal abnormalities (ACA) are often identified with inv(3)/t(3;3), most commonly monosomy 7.[13,14] In patients with myelodysplastic syndromes (MDS) or AML with inv(3)/t(3;3), frequent mutations in the RAS/MAPK signaling pathways (*NRAS, KRAS, PTPN11, NF1*) have been identified.[15,16] Our knowledge of the prognostic and therapeutic relevance of clinicopathological characteristics of AML with inv(3)/t(3;3) remains limited. Furthermore, the benefit of HSCT in this subgroup of patients is questionable given the dismal prognosis observed with current treatments. We report herein on the baseline clinicopathological characteristics, including mutation analyses, and its association with clinical outcomes in a large cohort of patients with AML with inv(3)/t(3;3).

Methods

Patients and treatments

We retrospectively reviewed all cases of AML diagnosed at or referred to the MD Anderson Cancer Center between January 1, 2000 and September 4, 2020 to identify patients with inv(3)(q21q26.2) or t(3;3)(q21;q26.2). All investigations were conducted under approval of the Institutional Review Committee and in accordance with the Declaration of Helsinki. Patients with chromosome 3q26.2 rearrangements other than *MECOM::GATA2* were excluded. Patients had either newly diagnosed (ND) untreated AML or relapsed or refractory (R/R) AML following prior therapy and patients were included in only one of these two cohorts based on their initial status at our institution. The outcomes of patients with ND or R/R AML were analyzed separately. Baseline patient characteristics were collected at the time of diagnosis in patients with ND AML or at the time of their first visit at our institution in patients with R/R AML. The type of treatment administered to patients was classified into low- or high-intensity treatment, with the latter defined as regimens including anthracyclines and/or high-dose cytarabine (≥1 g/m^2). While patients with targetable mutations could have received available small molecular inhibitors as part of their therapy, few patients fell into this category: one patient with *FLT3*-internal tandem duplication each received midostaurin or sorafenib in the frontline and one patient in the R/R cohort received midostaurin. No patients received an IDH inhibitor.

Cytogenetic and molecular analysis

The presence of inv(3)(q21q26.2) or t(3;3)(q21;q26.2) was detected by conventional chromosomal analysis of G-banding metaphase cells. *MECOM* rearrangement was confirmed by fluorescence *in situ* hybridization (FISH) using *MECOM* dual-color break-apart FISH probes. ACA were considered relevant when identified in ≥2 metaphases. Complex karyotype (CK) was defined as the presence of ≥3 unrelated clonal chromosomal abnormalities (i.e., ≥2 ACA accompanying inv(3)/t(3;3)). Monosomal karyotype (MK) was defined as the presence of ≥2 autosomal monosomies or ≥1 autosomal monosomy in combination with at least one structural chromosomal abnormality (i.e., ≥1 monosomy accompanying inv(3)/t(3;3)).[17] Somatic gene mutation data was obtained from amplicon-based targeted next-generation sequencing (NGS) from 2013 onwards and single-gene assays targeting nine genes prior to 2013. Testing was performed on the initial patients' bone marrow aspirate specimens in our CLIA-certified molecular diagnostics laboratory (additional details in the *Online Supplementary Appendix*).

Statistical analysis

Baseline characteristics were compared between ND and R/R patients with Wilcoxon rank sum test for continuous variables and with Fisher's exact test for categorical variables. Composite complete remission rates (CRc) included complete remission (CR) and CR with incomplete hematological recovery (CRi). Overall remission rate (ORR) included CR, CRi and morphologic leukemia-free state (MLFS).[1] Predictors of ORR were evaluated with univariate logistic regression models. Survival estimates were calculated using the Kaplan-Meier method and differences between groups were evaluated with the log-rank test. Univariable Cox proportional hazards (CPH) models were used to estimate hazard ratios (HR) for associations between predictors and overall survival (OS) or relapse-free survival (RFS). OS was defined as the time from diagnosis (ND AML) or first visit at the MD Anderson Cancer Center (R/R AML) until death or last follow-up. RFS was defined as the time from remission to relapse, death, or last follow-up. Cumulative incidence of relapse (CIR) was defined as the time from remission to relapse, considering death in remission as a competing event with the Fine and Gray method. In order to evaluate the impact of HSCT in CR1, we performed a 4-month landmark analysis for HSCT among patients who achieved clinical remission (ORR) and performed another analysis using HSCT in CR1 as a time-dependent variable in an extension of the CPH model.[18]

Results

Study population

Between January 1, 2000 and September 4, 2020, we identified 108 patients with AML with inv(3)/t(3;3); 53 with ND AML (53/4248, 1.2%) and 55 with R/R AML (55/2968, 1.9%). The baseline patient characteristics are presented

in Table 1. The median age among patients with ND AML was 63 years *versus* 48 years in patients with R/R AML (*P*<0.01). There was a trend for higher median white blood cell count (WBC) among patients with ND *versus* R/R AML (median WBC 4.1 *vs.* 3.4x10^9/L; *P*= 0.06), but no significant difference in the frequency of WBC ≥20x10^9/L. The median platelet count was 80x10^9/L *versus* 50x10^9/L in patients with ND and R/R AML, respectively, with a higher proportion of patients with platelets within or above the normal range in the ND group (32% *vs*. 15%; *P*=0.05). Thrombocytosis (>400x10^9/L) was observed in four (8%) patients with ND AML. The bone marrow blast percentage was higher in patients with R/R AML (54% *vs*. 35%; *P*=0.02). The frequency of t-AML was 32% in patients with ND AML and 5% in R/R AML (*P*<0.01). Altogether, 27% of patients had secondary AML, primarily with a preceding diagnosis of MDS. Among patients with R/R AML, the median number of prior lines of treatment was 2 (range, 1–6) and 12 of 55 (22%) patients had previously undergone HSCT.

Genetic characteristics of acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2)

Most patients (87/108, 81%) had inv(3)(q21q26.2). Intriguingly, WBC ≥20x10^9/L was only observed in patients with inv(3)(q26.2;q21) (25% *vs*. 0%; *P*=0.02). There was no other difference in clinicopathologic characteristics between the two *MECOM::GATA2* rearrangements. ACA were identified in 38 of 53 (72%) patients with ND AML and 45 of 55 (82%) patients with R/R AML (*P*=0.31, Table 1). Monosomy 7 was the most frequent ACA identified in 44% of patients, followed by del(5q) and del(7q) in 16% and 11% of patients, respectively, without differences between groups. CK was observed in 25% and 35% of ND and R/R patients, respectively (*P*=0.35) and MK was observed in 47% and 51% of ND and R/R patients, respectively (*P*=0.84) (Table 1).

The frequency of somatic gene mutations identified in ≥1% of patients with inv(3)/t(3;3) AML is represented in Figure 1 (also *Online Supplementary Table S1*). The most frequent gene mutation was in *SF3B1*, identified in 14 of 28 (50%) tested patients. Mutations in at least one of the genes in signaling pathways (*PTPN11, NRAS, KRAS, FLT3, KIT, CBL, NF1, JAK2*), were identified in 38 of 51 (75%) patients, most commonly in genes of the RAS-MAPK signaling pathway (36/51, 71%). In total, 14 of 51 (27%) patients had *PTPN11* mutation, 23 of 94 (24%) had *NRAS* mutation, 13 of 94 (14%) had *KRAS* mutation, three of 94 (3%) had both *NRAS* and *KRAS* mutations, two of 51 (4%) had *NF1* mutation and one of 51 (2%) had *CBL* mutation. Splicing factors genes

Table 1. Patient characteristics at baseline.

Characteristic	Total (N=108)	Untreated patients (N=53)	Previously treated patients (N=55)	*P*
Age in yrs, median (range) Age ≥60, N (%)	55 (16-84) 43 (41)	63 (16-84) 29 (53)	48 (18-83) 16 (30)	<0.01 0.01
Sex (male), N (%)	68 (63)	31 (58)	37 (67)	0.46
WBC (x10^9/L), median (range) WBC ≥20x10^9/L, N (%)	3.9 (0.3-143.2) 22 (20)	4.1 (0.6-143.2) 13 (25)	3.4 (0.3-101.0) 9 (16)	0.06 0.42
Hb (g/dL), median (range)	8.8 (5.7-17.1)	8.6 (5.7-17.1)	8.9 (7.0-13.8)	0.81
Plt (x10^9/L), median (range) Plt ≥140x10^9/L, N (%) Plt >400x10^9/L, N (%)	67 (7-787) 25 (23) 4 (4)	80 (15-787) 17 (32) 4 (8)	50 (7-372) 8 (15) 0 (0)	0.02 0.05 0.12
PB blasts, %, median (range)	20 (0-96)	18 (0-96)	21 (0-93)	0.34
BM blasts. %, median (range)	48 (16-94)	35 (16-94)	54 (19-92)	0.02
Secondary AML, N (%)	29 (27)	11 (21)	18 (33)	0.24
t-AML, N (%)	20 (18)	17 (32)	3 (5)	<0.01
inv(3)(q21q26.2), N (%)	87 (81)	45 (85)	42 (76)	0.38
ACA, N (%) -7 / del(7q) del(5q) CK* MK†	83 (77) 60 (56) 17 (16) 32 (30) 53 (49)	38 (72) 28 (53) 9 (17) 13 (25) 25 (47)	45 (82) 32 (58) 8 (15) 19 (35) 28 (51)	0.31 0.71 0.93 0.35 0.84

yrs: years; WBC: white blood cell; Hb: hemoglobin; Plt: platelets; PB: peripheral blood; BM: bone marrow; AML: acute myeloid leukemia; t-AML: therapy-related AML; ACA: additional chromosomal abnormalities; CK: complex karyotype; MK: monosomal karyotype. *CK was defined as the presence of ≥3 unrelated clonal chromosomal abnormalities (i.e., ≥2 ACA accompanying the inv(3)/t(3;3)). †MK was defined as the presence of ≥ 2 monosomies or ≥ 1 monosomy in the presence of a structural chromosomal abnormality (i.e., ≥1 monosomy accompanying inv(3)/t(3;3))

(*SF3B1, SRSF2, U2AF1*) were mutated in 17 of 28 (61%) patients and myeloid transcription factor genes (*GATA2, RUNX1, CEBPA*) were mutated in 14 of 51 (27%) patients. Tumor suppressors genes (*TP53, WT1*), DNA methylation genes (*DNMT3A, IDH1, IDH2, TET2*) and chromatin modifier genes (*ASXL1, NPM1*) were each mutated in eight of 51 (16%) patients (*Online Supplementary Table S1*). WBC ≥20x10^9/L was more frequent in patients with *NRAS* mutation (39% *vs*. 14%; *P*=0.02), and peripheral blood blast percentage was higher in patients with *KRAS* mutations (median, 52% *vs*. 16%; *P*<0.01). No other significant association between WBC, peripheral blood percentage and mutations was identified. *NRAS* mutations were more frequent in R/R AML (14% ND *vs*. 33% R/R; *P*=0.03) and *TP53* were more frequent in ND AML (16% ND *vs*. 0% R/R; *P*=0.04). *RUNX1* mutations were identified in four of 15 (27%) patients with ND AML *versus* two of 34 (6%) patients with R/R AML (*P*=0.06). No patient with ND AML had *GATA2* mutation *versus* seven of 34 (21%) patients with R/R AML (*P*=0.17). *ASXL1* and *NRAS* mutations were more frequent in patients with secondary AML (*ASXL1*, 33% *vs*. 6%; *P*=0.046; NRAS, 46% *vs*. 16%; *P*<0.01)

Remission rates

Twelve patients (1 ND, 11 R/R) did not receive treatment at our institution. Therefore, 96 patients were evaluable for treatment response (52 ND, 44 R/R). Intensive treatment was administered in 35 of 52 (67%) ND patients and 20 of 44 (45%) R/R patients (Table 2). CRc was achieved in 24 of 52 (46%) patients with ND AML and six of 44 (14%) patients with R/R AML (*P*<0.01). Two additional ND patients achieved MLFS for an ORR of 50% (26 of 52) in ND AML. Among patients who achieved CRc, the rate of measurable residual disease (MRD) negativity by flow cytometry was 38% (5/13 evaluable patients) for ND AML and 0% (0/6 evaluable patients) for R/R AML. In patients with ND AML, CRc was 46% and 47% with high and low-intensity treatments, respectively (*P*=1.00) and the 30-day mortality rates were 14% and 0%, respectively (*P*=0.16). Among the six patients with R/R AML who achieved remission, all had received only one or two prior lines of therapy. Among patients with R/R AML, CRc rate was 20% and 8% with high- and low-intensity treatments, respectively (*P*=0.39) and the 30-day mortality rates were 5% and 8%, respectively (*P*=1.00). In univariable logistic regression analysis for CRc in patients with ND AML (*Online Supplementary Table S2*), higher peripheral blood blasts percentage was significantly associated with lower CRc (odds ratio [OR]=0.98; 95% confidence interval [CI]: 0.96–1.00; *P*=0.02). Patients with secondary AML had a lower CRc of 9% (2/20) *versus* 38% (28/74) for *de novo* AML (*P*=0.02). Patients with ACA had a CRc rate of 27% (20/74) compared to 40% (10/22) in those with inv(3)/t(3;3) as their sole cytogenetic abnormality (*P*=0.17). CRc rates were numerically lower in patients with monosomy 7 (10/43, 23% *vs*. 20/53, 38%; *P*=0.19), CK (6/28, 21% *vs*. 24/68, 35%; *P*=0.28) and MK (11/48, 23% *vs*. 19/48, 40%; *P*=0.12), although none of these differences were statistically significant. Patients whose karyotype met both definitions for CK and MK had a remission rate of 10% (2/20) compared to 38% (15/40) in those with neither CK or MK. Patients with *NRAS* mutations had remission rates of 22% (4/18) *versus* 38% (24/64)

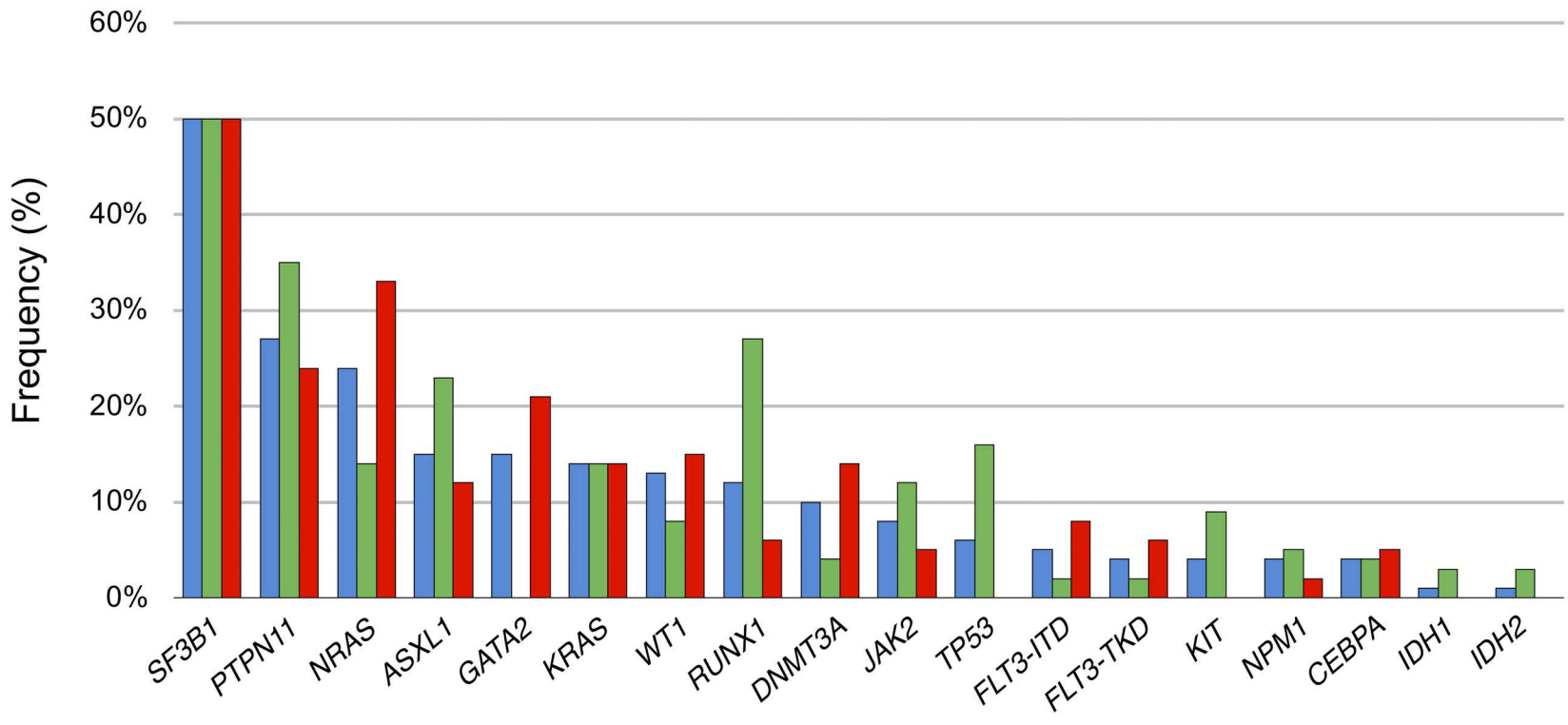

Figure 1. Frequency of gene mutation in acute myeloid leukemia with inv(3)/t(3;3). The bars represents the frequency of gene mutations in the global cohort (blue bar), the newly diagnosed cohort (green bar) and relapsed/refractory cohort (red bar). The number of patients with available mutational data differ for each gene represented on this figure. The number of patients tested and the number of patients with mutation for each gene is detailed in the *Online Supplementary Table S1*.

in patients without (*P*=0.35). No other association between ORR and mutational status was observed.

Efficacy of venetoclax-based regimens

Venetoclax-based regimens have been administered to patients with AML with inv(3)/t(3;3) in our cohort; five with ND AML and seven with R/R AML. Of these patients two (40%) with ND and four (57%) with R/R AML had pretreatment *NRAS* or *KRAS* mutations. In patients with ND AML, four patients received venetoclax in combination with hypomethylating agents (HMA) and one patient in combination with intensive chemotherapy. Among these patients, two of five (40%) had a response (1 CRi, 1 MLFS); both with HMA plus venetoclax (therefore 2/4, ORR=50% with HMA plus venetoclax among patients ineligible for intensive chemotherapy) (Table 2). One relapsed after six cycles and died of progressive disease and one remains alive in remission with a follow-up of 3 months. Among patients with R/R AML after one to two prior lines of therapy, four patients received venetoclax in combination with HMA and three patients in combination with intensive chemotherapy (Table 2). Of these, three of seven (43%) patients achieved CRi: one with decitabine plus venetoclax and two with FLAG-Ida plus venetoclax.[19] One patient who had relapsed post-transplant died of transplant-related complications after achieving remission with FLAG-Ida plus venetoclax. The two other patients achieving CRi proceeded to HSCT, but both relapsed at 3 and 4 months post-transplant and eventually died of progressive disease. Altogether, venetoclax-based regimens were associated with a CRc rate of 33% (4/12) and ORR of 42% (5/12) in patients with AML with inv(3)/t(3;3) (Table 2). In comparison, the CRc rate was 31% (26/84) in patients who received regimens without venetoclax (49% in ND AML and 8% in R/R AML). Remissions with venetoclax-based regimens were short-lived (median CR duration 5.4 months) and no sustained remission beyond 6 months have been observed with these regimens in our cohort.

Survival outcomes

With a median follow-up of 83 months, the median OS was 7.9 months and 5.9 months in patients with ND and R/R AML, respectively. The 3-year OS was 8.8% (95% CI: 3.3–22.4) in ND patients and 7.1% (95% CI: 2.2–22.6) in R/R patients (Figure 2A). Among patients who achieved remission, the median RFS was 4.1 months, the 3-year RFS was 8.6% (95% CI: 2.4–31.0) and the 3-year CIR was 81.7% (95% CI: 65.7–97.6) (Figure 2B, C). Most relapses (62.5%) occurred within 6 months after achieving remission. Six patients (6%) were alive in remission at last follow-up or had RFS beyond 5 years: four after undergoing HSCT in CR1, one after undergoing HSCT with refractory disease, and one in remission with 3-month follow-up. In univariable analyses (UVA), older age (HR=1.01; 95% CI: 1.00–1.03; *P*=0.04), higher WBC at diagnosis (HR=1.02; 95% CI: 1.01–1.02; *P*<0.01), higher peripheral blood blasts percentage (HR=1.01; 95% CI: 1.00–1.02; *P*<0.01) and secondary AML (HR=1.81; 95% CI:1.31-2.91; *P*=0.01) were significantly associated with inferior OS (*Online Supplementary Table S3*). Baseline platelet count was not prognostic for OS. Pa-

Table 2. Treatment response.

Clinical outcome	Total (N=96)	Previously untreated patients			Previously treated patients		
		Total (N=52)	High intensity (N=35)	Low intensity (N=17)	Total (N=44)	High intensity (N=20)	Low intensity (N=24)
CRc, N (%) CR CRi	30 (31) 16 (17) 14 (15)	24 (46) 15 (29) 9 (17)	16 (46) 9 (26) 7 (20)	8 (47) 6 (35) 2 (12)	6 (14) 1 (2) 5 (11)	4 (20) 1 (5) 3 (15)	2 (8) 0 2 (8)
MLFS (%)	2 (2)	2 (4)	0	2 (12)	0	0	0
ORR (%)	32 (33)	26 (50)	16 (46)	10 (59)	6 (14)	4 (20)	2 (8)
Cycles to remission, N, median (range)	1 (1-4)	1 (1-4)	1 (1-2)	1.5 (1-4)	1.5 (1-3)	1.5 (1-3)	1.5 (1-2)
Median days to remission, N (range)	39.5 (19-126)	37 (19-126)	34.5 (20-85)	53 (19-126)	53.5 (27-102)	73 (31-102)	42 (27-57)
30-day mortality, N (%)	8 (8)	5 (10)	5 (14)	0 (0)	3 (7)	1 (5)	2 (8)
CRc according to treatment type, N/N (%) With venetoclax Without venetoclax With HMA Without HMA	 4/12 (33)* 26/84 (31) 8/22 (36) 2/19 (10)*	 1/5 (20)* 23/47 (49) 6/12 (50) 2/5 (40)*	 0/1 (0) 16/34 (47) NA NA	 1/4 (25)* 7/13 (54) 6/12 (50) 2/5 (40)*	 3/7 (43) 3/37 (8) 2/10 (20) 0/14 (0)	 2/3 (66) 2/17 (12) NA NA	 1/4 (24) 1/20 (5) 2/10 (20) 0/14 (0)

CRc: composite complete remission; CR: complete remission; CRi: incomplete hematological recovery; ORR: overall remission rates; N: number; HMA: hypomethylating agents; NA: not applicable. *An additional patient treated with a low-intensive venetoclax-based regimen achieved morphologic leukemia-free state (MLFS) and is not included in the CRc rates.

tients with WBC ≥20x10^9/L had a significantly worse survival than patients with lower WBC (HR=2.19; 95% CI: 1.34–3.59; *P*<0.01; Figure 3A, B). Clinical outcomes were not different depending on the type of *MECOM* rearrangement (Figure 3C, D), the presence of monosomy 7 (Figure 3E, F) or the presence of CK or MK (*Online Supplementary Figure S2*). ND patients with *NRAS* mutation had a trend towards worse OS (HR=2.39; 95% CI: 0.97–5.85; *P*=0.06) (Figure 4A, B) and patients with *KRAS* mutation had a worse OS (HR=2.37; 95% CI: 1.20–4.68; *P*=0.01), most significantly among patients with R/R disease (Figure 4C, D). Mutations in *ASXL1* and *DNMT3A* were also associated with an adverse outcome (*ASXL1*: HR=2.62; 95% CI: 1.07–6.42; *P*=0.04; *DNMT3A*: HR=3.09; 95% CI: 1.17–8.16; *P*=0.02). In multivariable analyses (MVA) including significant variables in UVA, WBC ≥20x10^9/L (HR=5.67; 95% CI: 1.70–18.86; *P*<0.01), secondary disease (HR=4.14; 95% CI:1.66 –10.28; *P*<0.01) and *ASXL1* mutation (HR=2.83; 95% CI: 1.01–7.94; *P*=0.049) were independent factors associated with inferior OS.

Utility of hematopoietic stem cell transplantation

Among patients who achieved CRc or MLFS, ten of 32 (31%) have undergone HSCT in CR1: five with ND AML and five with R/R AML. Transplant-related characteristics and outcomes are summarized in Table 3. The median time from CRc/MLFS to HSCT was 56 days and 39 days in patients with ND and R/R AML, respectively. The median duration of follow-up for patients who received an allogeneic HSCT in CR1 was 36.6 months (range, 11.1–94.8). Among the ten patients proceeding to HSCT in CR1, four remain alive in remission, one remains alive with relapse post-HSCT and five patients have died from AML (n=4) or post-transplant complications (n=1). The median time from CRc/MLFS to HSCT was 24.5 days in patients with long-term remission *versus* 60.5 days in patients with subsequent relapse or death. With a 4-month landmark analysis, HSCT in CR1 was significantly associated with improved OS (HR=0.33; 95% CI: 0.12–0.91; *P*=0.03) (Figure 5A). The 5-year OS among patients who have undergone

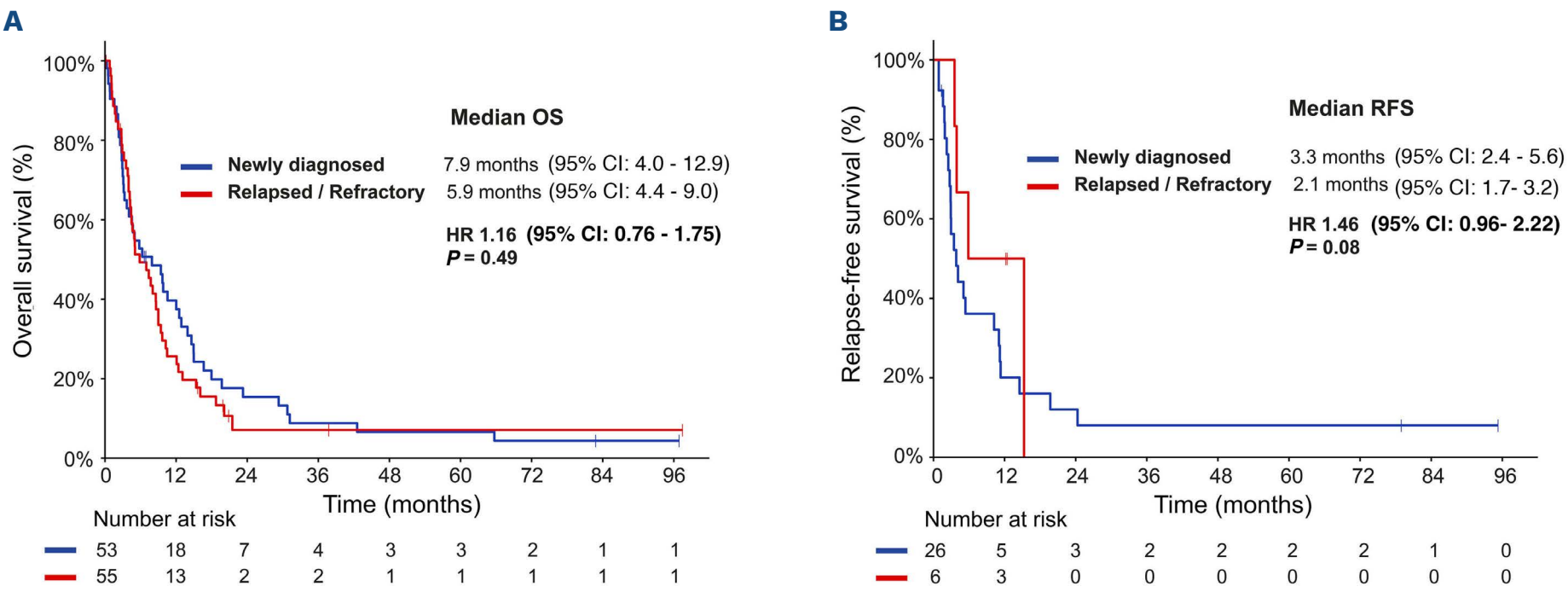

Figure 2. Clinical outcomes in patients with acute myeloid leukemia with inv(3)/t(3;3). (A) Overall survival (OS), (B) relapse-free survival (RFS) and (C) cumulative incidence of relapse in patients with acute myeloid leukemia with inv(3)/t(3;3). HR: hazard ratio; CI: confidence interval.

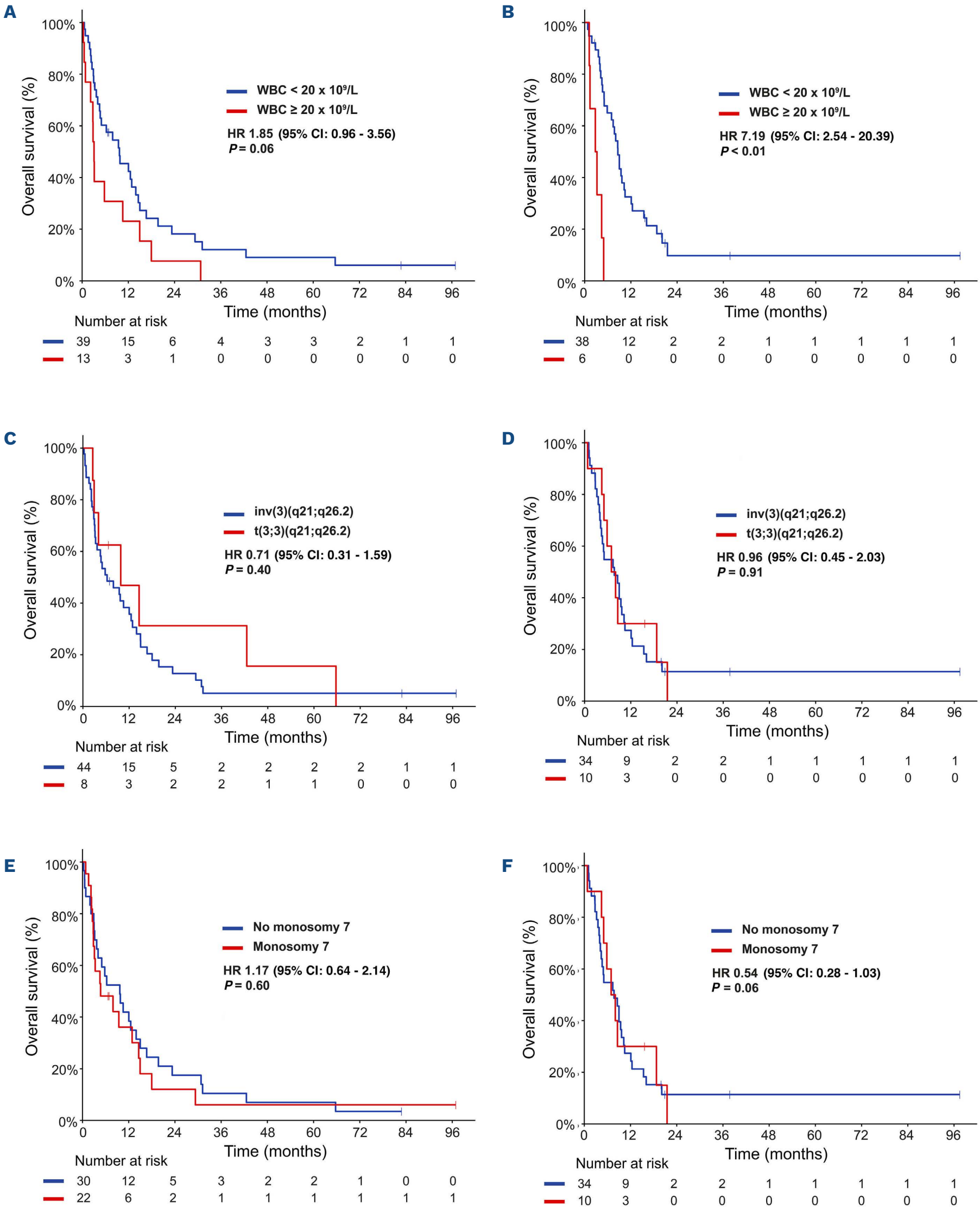

Figure 3. Overall survival according to baseline characteristics. Overall survival (OS) according to white blood cell (WBC) count in (A) newly diagnosed (ND) patients and (B) relapsed/refractory (R/R) patients. OS according to type of chromosomal rearrangement in (C) ND patients and D) R/R patients. OS according to presence of monosomy 7 in (E) ND patients and (F) R/R patients. HR: hazard ratio; CI: confidence interval.

HSCT in CR1 was 44% (95% CI: 20 –96) *versus* 6% (95% CI: 1–38) among patients who have not and the 2-year CIR was 57% (95% CI: 16–97) and 86% (95% CI: 68–100), respectively (*P*=0.03) (Figure 5B). Importantly, four of six patients alive in remission at last follow-up have undergone HSCT in CR1. When using HSCT in CR1 as a time-dependent variable, HSCT in CR1 was significantly associated with improved RFS (HR=0.39; 95% CI: 0.15–0.98; *P*=0.046) and trended to be associated with improved OS (HR=0.41; 95% CI: 0.15–1.12; *P*=0.08). Four patients have undergone HSCT in second remission of whom none maintained long-term remission. Five patients have undergone HSCT with active disease on their previous bone marrow aspiration of whom one achieved sustained remission of more than 7 years and one was alive with R/R AML at last follow-up. Others died from relapsed disease (n=2) or transplant-related complications (n=1).

Discussion

AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) is a rare subtype of AML with dismal clinical outcomes. The optimal treatment for this aggressive leukemia remains unknown and the prognostic implications of its genetic and clinical features had previously not been fully characterized.

In this study, we confirmed the markedly adverse prognosis associated with AML with inv(3)/t(3;3). CRc rates were 46% in ND AML and 14% in R/R AML, attesting to the chemo-resistant nature of this aggressive leukemia. The

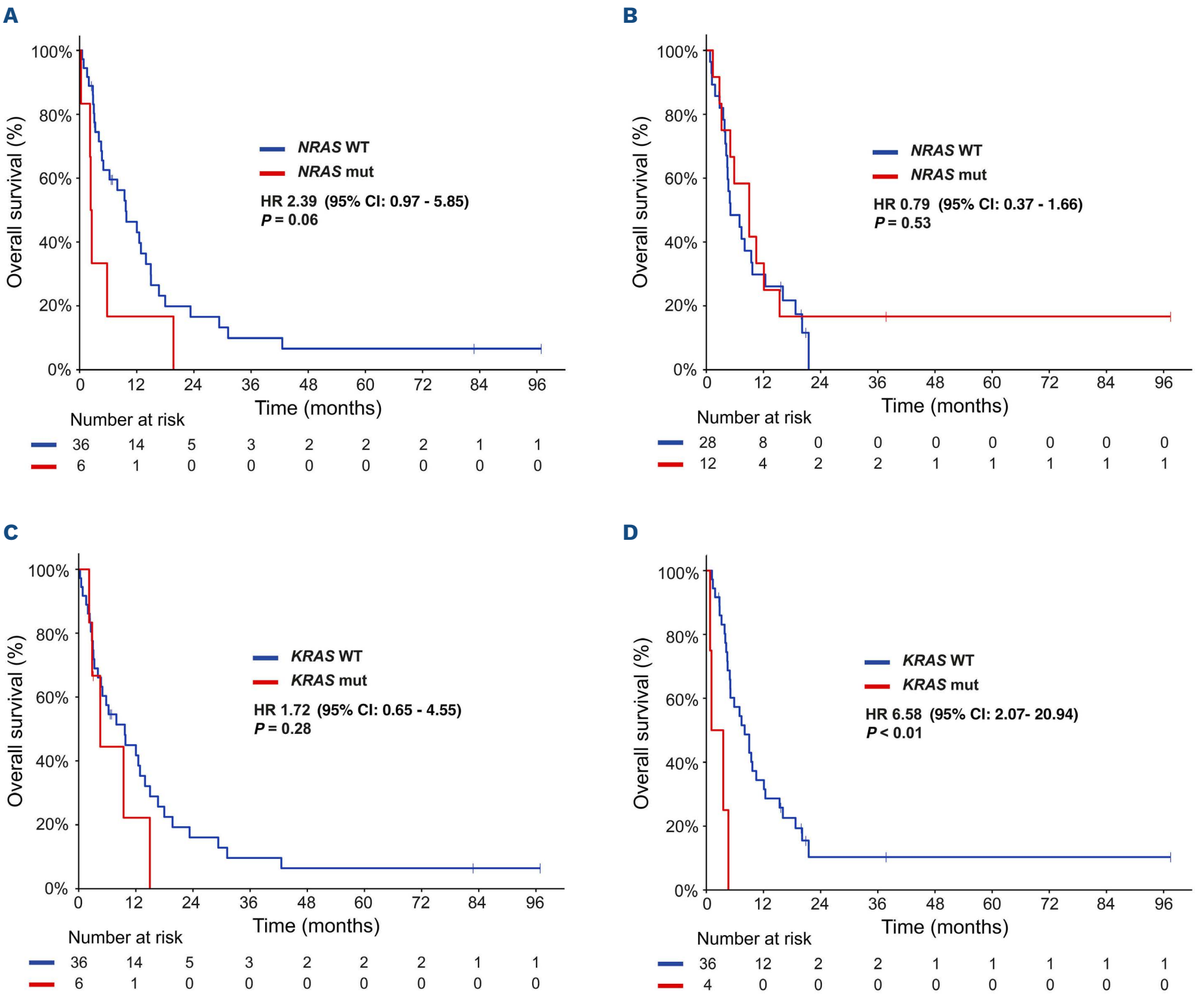

Figure 4. Overall survival according to *NRAS* or *KRAS* mutation. Overall survival (OS) according to *NRAS* mutation in (A) newly diagnosed (ND) patients and (B) relapsed/refractory (R/R) patients. OS according *KRAS* mutation in (C) ND patients and (D) R/R patients. HR: hazard ratio; CI: confidence interval; mut: mutated; WT: wild-type.

3-year OS was 8.8% and 7.1% in ND patients and R/R patients, respectively. Previous reports of AML with inv(3)/t(3;3) have reported CR rates of 31-36% and long-term OS rate below 5%.[4,13] Interestingly, among ND patients, the CRc rates were similar between high- and low-intensity treatments (46% *vs*. 47%), but a higher rate of early mortality was observed with higher-intensity treatment (14% *vs*. 0%). Patients with early death after intensive chemotherapy had secondary or t-AML, or were older, which may explain the higher induction mortality in these patients.[20] Among low-intensity treatments, HMA-based regimens specifically were associated with CRc of 50% in ND AML. Since *MECOM* overexpression is associated with an aberrant hypermethylation signature via interactions with DNA methyltransferases (DNMT), there may be a biological rationale for using HMA (DNMT inhibitors) in AML with inv(3)/t(3;3).[21] Similar to our data, other studies evaluating the outcomes of patients with MDS/AML with inv(3)/t(3;3) treated with azacitidine reported an ORR of 42-50% and a CR rate of 24-29%, which compares favorably to unselected cohorts of patients treated with HMA.[22-26] In contrast, patients with AML with inv(3)/t(3;3) treated with intensive chemotherapy definitively have worse prognosis compared to other cytogenetics subgroups.[4,13,27] Although the addition of venetoclax to HMA or low-dose cytarabine (LDAC) have been shown to improve remission rates and survival in patients with AML ineligible for intensive chemotherapy, data specifically in patients with AML with inv(3)/t(3;3) has been lacking.[28,29] In patients treated with venetoclax-based regimens in our cohort, one of five (20%) patients with ND AML and three of seven (43%) patients with R/R AML achieved CRc. Although limited by small numbers of patients, these rates are lower than general response rates observed with venetoclax plus HMA, LDAC, or intensive chemotherapy in ND or R/R AML.[19,28-30] Altogether, our study suggests that HMA-based regimens for patients with ND AML with inv(3)/t(3;3) offer similar remission rates remission compared to intensive therapy and lower rates of treatment-related mortality. Based on our data, there is no clear signal of benefit to the addition of venetoclax to chemotherapy in ND AML with inv(3)/t(3;3), but further data in this subset is needed.

We described the largest cohort of AML with inv(3)/t(3;3) with clinicopathologic characteristics and mutational data in relation to clinical outcomes. AML with inv(3)/t(3;3) was frequently associated with normal platelet counts or thrombocytosis as previously reported.[12] Nearly half of the patients had a secondary or therapy-related AML which is more frequent than in unselected cohorts of patients with AML.[31,32] Current diagnostic classifications of myeloid neo-

Table 3. Transplant-related characteristics and outcomes in patients undergoing hematopoietic stem cell transplantation in complete remission.

Age in yrs/Sex	Disease status	Response prior to HSCT	Time from CR to HSCT (days)	HCT-CI	Conditioning	Intensity	Donor	Acute GvHD	Outcome
28/F	ND	CR, MRD-	56	6	Flu/Mel/TT^	RIC^	MUD	Yes (grade 2)	Alive in remission
48/M	ND	CR†, MRD+	47	4	Flu/Bu/ATG	MAC	MUD	Yes (grade 2)	Death (AML)
61/F	ND	CR†, MRD-	1	9	Flu/Bu (AUC 5,000)	MAC	MUD	Yes (grade 0)	Alive in remission
29/F	ND	CR†, MRD+	86	4	Flu/Bu/ATG (AUC 6,000)	MAC	MUD	No	Death (AML)
47/F	ND	CR, MRD+	138	4	Flu/Mel^	RIC^	MUD	No	Death (AML)
32/M	R/R	CR†, MRD+	10	0	Flu/Clofa/Bu/TBI 200 (AUC 5,000)^	MAC^	Haplo	No	Alive in remission
45/F	R/R	CR†, MRD+	39	1	Flu/Mel/ATG	RIC	MUD	Yes (grade 2)	Alive in remission
48/M	R/R	CR†, MRD+	13	1	Flu/Mel/ATG	RIC	MUD	Yes (grade 2)	Alive with R/R AML
46/F	R/R	CR, MRD-	65	8	Flu/Mel/ TBI 200^	RIC^	Haplo	No	Death (NRM)
18/M	R/R	CR†, MRD+	56	0	Flu/Bu (AUC 6,000)	MAC	MSD	No	Death (AML)

†Persistent cytogenetic aberrations. ^Received post-transplant cyclophosphamide; HSCT: hematopoietic stem cell transplant; yrs: years; F: female, M: male; CR: complete remission; HCT-CI: hematopoietic stem cell comorbidity index; GvHD: graft-*versus*-host disease; ND: newly diagnosed; R/R: relapsed or refractory; MRD: measurable residual disease by flow cytometry; Flu: fludarabine; Mel: melphalan; TT: thiotepa; Bu: busulfan; ATG: anti-thymocyte globulin; Clofa: clofarabine; TBI: total body irradiation; RIC: reduced-intensity conditioning; MAC: myeloablative conditioning; MUD: matched unrelated donor; AUC: area-under-the-curve; MSD: matched sibling donor; AML: acute myeloid leukemia; NRM: non-relapse mortality.

plasms now include inv(3)/t(3;3) as a genetic lesion defining a single entity (AML or MDS/AML) because of similar disease characteristics and dismal outcome irrespective of blast percentage.[2,3,14,33,34] In our cohort, bone marrow blast count percentage was not associated with survival, indirectly supporting these new classifications, although patients with <20% blasts were not included. However, high WBC count and peripheral blast percentage, typically associated with AML, were associated with *NRAS* or *KRAS* mutations and worse outcomes in our cohort. Mutations in the RAS-MAPK pathway might be associated with a more proliferative and aggressive disease, historically classified as AML with ≥20% blasts, but further studies with larger number of patients are required to compare the frequencies of gene mutations in patients with inv(3)/t(3;3) according to WBC count and peripheral blast percentage.[16]

Age, high WBC count and secondary disease were clinical predictors of survival in UVA in our cohort consistent with previous reports,[35] however age was not significant in MVA. This could be explained by the greater proportion of older patients receiving HMA-based treatment which has comparable efficacy to intensive chemotherapy for AML with inv(3)/t(3;3). ACA were observed in about 75% of patients, most commonly involving chromosome 7, yet these abnormalities were not associated with OS in contrast to some published series, but consistent with others.[4,13,14,27] In our cohort, CK and MK were observed in 30% and 49% of patients, respectively and were also not associated with outcomes adding to conflicting data in the literature.[14,27] We showed that *NRAS, KRAS, ASXL1* and *DNMT3A* mutations were associated with inferior survival in UVA. Interestingly, *ASXL1* mutations was the only independent genetic factor associated with poor OS in MVA despite its strong association with secondary AML.

The benefit of HSCT in CR1 has been questioned in very high-risk genetic subgroups of AML, such as in patients with AML with anomaly of chromosome 17p and remains uncertain in patients with inv(3)/t(3;3) given conflicting data in previous series.[14,22,27,36] While the numbers are small, our data suggest that HSCT in CR1 is beneficial in patients with AML with inv(3)/t(3;3) and is seemingly the only hope for a cure, albeit low, with our currently available treatment options. Donor search should start as soon as possible in potentially eligible patients diagnosed with AML with inv(3)/t(3;3). These patients should proceed to HSCT as soon as possible after achieving remission to seize the narrow window of opportunity before an almost certain relapse. Achieving a second CR is rarely possible with AML with inv(3)/t(3;3) and HSCT in CR2 is likely futile based on our data. Our study indirectly supports the use of transplantation in patients with myeloid neoplasms with inv(3)/t(3;3) at an earlier stage of disease when WBC are low and blasts are below 20%. Only one patient with secondary AML proceeded to HSCT in CR1. Once patients have progressive disease with blasts ≥20%, they are less likely to achieve remission and subsequently be amenable to HSCT. Although HSCT is the only curative option for patients with AML with inv(3)/t(3;3), only 10% of patients in our study were able to proceed to HSCT because of a high rate of refractory disease and rapid relapse in those achieving remission. Our study underscores the urgent unmet need for more effective therapeutic approaches to treat AML with inv(3)/t(3;3). Potential therapeutic approaches including bromodomain and extra-terminal motif (BET) inhibitors, PARP inhibitors, MEK or ERK inhibitors in presence of RAS-

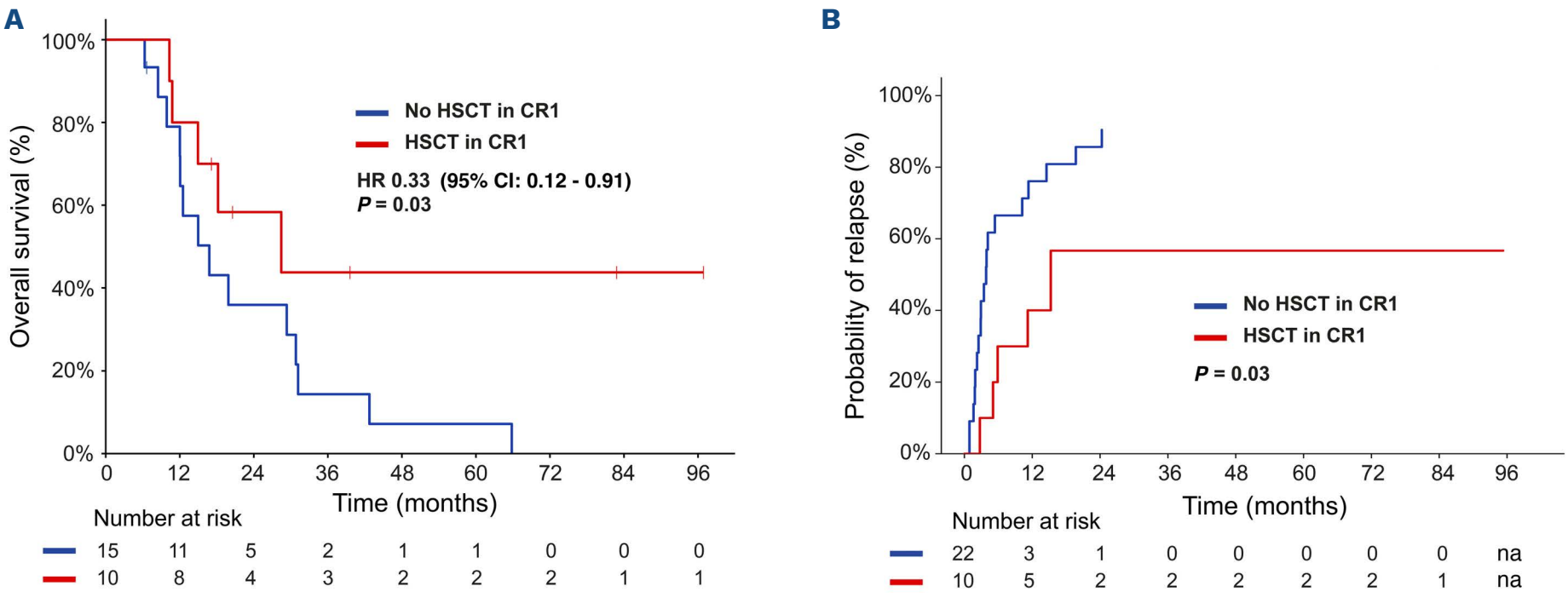

Figure 5. Impact of hematopoietic stem cell transplantation in first complete remission. Four-month landmark analysis for hemtopoietic stem cell transplantation (HSCT) in first complete remisssion (CR1) among patients who achieved remission. (A) Overall survival and (B) cumulative incidence of relapse (CIR). HR: hazard ratio; CI: confidence interval.

MAPK pathway gene mutations or targeting LSC with monoclonal antibodies have shown promising results as reviewed by Birdwell and colleagues.[37] Otherwise, our data suggests that the addition of venetoclax might not be particularly beneficial. Targeting other BCL2 family members might be a more effective strategy since *EVI1* induces BCL-xl expression.[37,38] Given their good tolerability, HMA likely represent the preferred backbone to combine drugs to improve upon its efficacy.

In conclusion, we confirm that AML with inv(3)/t(3;3) is associated with dismal outcomes, especially in patients with prior hematological malignancy, high WBC count and mutations in *ASXL1*. The best approach with currently available treatment option appears to be HMA-based regimens to achieve remission followed by HSCT in CR1 to prevent relapse. Development of novel effective therapies are urgently needed for this aggressive subtype of AML.

Disclosures

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Contributions

GRC collected and analyzed the data. GRC and TMK wrote the manuscript. CRR, KS, DH, KM collected data and reviewed the manuscript. KT and RKS provided genomic data and reviewed the manuscript. GT provided and reviewed cytogenetic data and reviewed the manuscript. EJS and AA provided transplant data and reviewed the manuscript. KB, CDD, GB, NP, NGD, GGM, MYK, FR, HMK, and TMK have treated patients included in this study, generated clinical data and reviewed the manuscript.

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Data-sharing statement

Qualified researchers may request access to individual patient-level data reported in this article after print publication of the current article. No identifying data will be provided. All requests for data must include a description of the research proposal and be submitted to the corresponding author.

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