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Stratification of de novo Adult Acute Myelogenous Leukemia with Adverse-Risk Karyotype: Can We Overcome the Worse Prognosis of Adverse-Risk Group Acute Myelogenous Leukemia with Hematopoietic Stem Cell Transplantation?

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A B S T R A C T

Karyotype is a powerful prognostic factor for complete remission (CR) and overall survival (OS) in acute myelogenous leukemia (AML). Adverse-risk karyotype AML is now treated with intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) to overcome relapse. We attempted to stratify patients with this disease using a combination of known factors. We evaluated clinical correlates in 211 adults with AML and adverse-risk karyotypes. We divided the patients into several subgroups based on the number of chromosomal aberrations (NCAs), normal karyotype (NK) mosaicism, and monosomal karyotype (MK) status. CR rates and survival outcomes were compared among the subgroups, and the relapse rate was calculated in the allo-HSCT subgroup. The cutoff of NCA $\geq$5 showed the worst OS ($P < .001$) compared with NCA $\geq$3 or NCA $\geq$4 even after allo-HSCT. NK mosaicism significantly improved OS in both the NCA <5 ($P = .024$) and NCA $\geq$5 ($P = .030$) subgroups, but after allo-HSCT, it showed a favorable effect only in the NCA <5 subgroup. MK showed worse OS ($P = .041$), but there was no significantly worse effect after allo-HSCT compared with non-MK. Finally, we stratified patients into 4 subgroups, NCA $\geq$5 and NCA <5 with and without NK mosaicism. The most favorable OS and lower relapse rate after allo-HSCT were achieved by the NCA <5 with NK mosaicism subgroup, and the NCA $\geq$5 without NK mosaicism subgroup showed the worst prognosis in both entire group and allo-HSCT subgroup analysis. This study reveals that the combination of NCA and NK mosaicism may predict survival outcomes accurately, and suggests that novel treatment strategies for highly adverse-risk group AML should be tailored in the future.

INTRODUCTION

Numerous trials have stratified patients by karyotype into several risk groups that more accurately predict the prognosis of adult acute myelogenous leukemia (AML) and have developed risk-adapted treatment strategies [1-6]. In addition, in the case of adverse-risk karyotype groups, several reports have stratified combinatorial analysis using several different risk factors. Although many different cytogenetic classifications for adult AML are used at present, assignment to the adverse-risk group is largely concordant and generally includes abnormalities of 3q [ie, inv(3q), t(3;3) [7], 5q/-5, 7q/-7, abn(17p), t(6;9), and 11q23, except t(9;11)] and complex karyotype (CK) status [1-6]. Although these single adverse genetic abnormalities are well characterized, more than one-half of the cases are accompanied by multiple chromosomal abnormalities and are termed CK when 3 or more aberrations are included. However, the significant number of chromosomal aberrations (NCAs; ie, $\geq$3 [1-3], $\geq$4 [4], or $\geq$5 [8]) for defining the poor prognosis of CK remains to be definitively determined.

The concepts of monosomal karyotype (MK) and normal karyotype (NK) mosaicism, termed residual normal metaphases in clonal abnormality, have been considered in adult AML cytogenetics at diagnosis. MK was first introduced by Breems et al. [9] and identified as associated with extremely poor survival outcome (4% 4-yr overall survival [OS]), with other studies reporting similar results [9-12]. In the case of NK mosaicism, previous studies have shown that patients with adverse-risk karyotype AML (ie, monosomy 5 and 7 or MK) and residual normal metaphases at diagnosis had better outcomes than those without normal metaphases [13,14]. In a recent study, our group analyzed adult patients with AML and adverse-risk karyotype treated by allogeneic hematopoietic stem cell transplantation (allo-HSCT) according to the presence of NK mosaicism at diagnosis [15]. Our data indicate that NK mosaicism is a favorable factor for superior OS and lower incidence of relapse after allo-HSCT in adult AML with adverse-risk karyotype [15].

We sought to evaluate the prognostic impact of a combination of the aforementioned components to identify a new, more accurate definition for the highest-risk adult AML karyotypes, which may help identify patients with these karyotypes who might benefit from allo-HSCT. We used NCA and the combination of MK and NK mosaicism status for

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stratification in this group of patients with AML and adverse-risk karyotype.

METHODS

Patients and Cytogenetic Analysis

This study was approved by the Catholic Medical Center's Institutional Review Board. A total of 1659 patients (age range, 18 to 92 yr) from the Catholic Medical Center's Department of Hematology database between April 2001 and March 2012 were evaluated to identify patients with adult AML karyotypes. Forty-nine patients with secondary AML and 22 patients with therapy-related AML were identified, 18 of whom had an adverse-risk karyotype. We excluded these 71 patients and focused on the 1588 patients with de novo AML. All cytogenetic samples were bone marrow (BM) cells, and analysis was performed on at least 20 metaphases by the GTG banding method after 24/48 h of unsynchronized culture. The International System for Cytogenetic Nomenclature [16] and National Comprehensive Cancer Network [5] 2012 guidelines were used for classification purposes.

We could not assess the karyotype results for 46 of the 1588 patients with de novo AML (2.9%) owing to a lack of properly evaluable metaphases. The 1542 that could be evaluated included 620 (39.0%) with a normal karyotype, 213 (13.4%) with an unclassified abnormal karyotype, 184 (11.6%) with t(8;21), 163 (10.3%) with t(15;17), 65 (4.1%) with inv(16) or t(16;16), 58 (3.6%) with trisomy 8, 12 (0.8%) with t(9;11), and 16 (1.0%) with t(9;22)—Philadelphia (Ph)-positive chromosome. We excluded all of these patients, and enrolled 211 patients (13.3%) with a median age of 50 yr (range, 18 to 85 yr) for adverse-risk karyotype analysis. The median follow-up duration for survivors was 45.6 mo (range, 6.4 to 123.6 mo). We excluded 16 patients with t(9;22), even those these patients are classified as an adverse-risk group according to the National Comprehensive Cancer Network guidelines, because of the risk of misdiagnosis with myeloid blastic phase of chronic myelogenous leukemia owing to ambiguous distinctions. Some previously published guidelines did not include t(9;22) in classification of AML karyotypes [17].

An abnormality was considered clonal and mentioned in the karyotype when at least 2 metaphases had the same aberration in cases of a structural abnormality or an extra chromosome. The following abnormalities were scored for each chromosome: loss of a chromosome (monosomy), extra copy of a chromosome (trisomy or tetrasomy), structural cytogenetic abnormalities (deletion of part of a chromosome, inversion within a chromosome, translocation between chromosomes, or addition of chromosomal material), marker chromosomes, and ring chromosomes. We used ≥1 copy of normal metaphase as the determinant of a NK mosaicism [15,18]. MK was defined as multiple (ie, ≥2) autosomal monosomies or 1 autosomal monosomy in combination with at least 1 structural chromosomal abnormality [9]. We used ≥3 copies of cells including monosomies as the determinant of a clone.

Stratification of Adverse-Risk Karyotype

We divided the patients into various subgroups according to NCA and whether MK or NK mosaicism was combined or not, then compared the treatment outcomes among the subgroups. First, to determine the appropriate cutoff, we evaluated NCA at the 3, 4, and 5 levels. We defined CK as ≥3 abnormal chromosomal aberrations and analyzed outcomes in 4 designated subgroups: CK^+MK^+, CK^+MK^-, CK^-MK^+, and CK^-MK^-. We also created subgroups combining MK status with NCA ≥5 or <5. Next, based on NCA with NK mosaicism, we evaluated treatment outcomes in 4 other subgroups: subgroup 1, NCA <5 with NK mosaicism; subgroup 2, NCA <5 without NK mosaicism; subgroup 3, NCA ≥5 with NK mosaicism; and subgroup 4, NCA ≥5 without NK mosaicism.

Treatment Courses

Of the 211 patients, 41 opted for conservative treatment, and 170 were treated with various induction chemotherapy regimens. Among these 170 patients, 109 (64.1%) patients were treated with 3 + 7 idarubicin (IDA) plus N^4-behenoyl-1-β-D-arabinofuranosyl cytosine (BHAC) as remission induction chemotherapy. IDA was administered daily at a dose of 12 mg/m^2 i.v. for 3 consecutive days, and BHAC was administered daily at 300 mg/m^2 for 7 consecutive days [19]. Twenty-five patients (14.7%) were treated with 3 + 7IDA plus cytosine arabinoside (ARA-C) at a dose of 100 mg/m^2. Twenty-three elderly patients (13.5%) with a Eastern Cooperative Oncology Group performance status of 2 [20] were treated with several doses of abbreviated-schedule induction chemotherapy, and 13 elderly patients (7.6%) with significant comorbidity were treated with modified low-dose ARA-C (20 mg/m^2 every 12 h) combined with oral etoposide, 100 mg for 14 consecutive days (mLDAC) [21].

Patients who achieved complete remission (CR) received more than course of 1 consolidation chemotherapy until suitable matched related or unrelated donor was available for allogeneic (allo)-HSCT. Our standard consolidation chemotherapy consisted of "3 + 5" mitoxantrone (12 mg/m^2 i.v.) plus intermediate-dose ARA-C (1.0 g/m^2 i.v.) or IDA (12 mg/m^2) plus intermediate-dose ARA-C, applied alternatively. Fifty patients relapsed or died during chemotherapy, and 120 patients received final treatment (ie, allo-HSCT, autologous [auto]-HSCT, or at least 2 cycles of consolidation chemotherapy after induction chemotherapy). Among these 120 patients, 72 (63 in CR, 9 not in CR) had variable allo-HSCT courses. Thirty-six patients with an available HLA-matched sibling donor and 29 patients with a suitably matched (<2 allele-mismatched) unrelated donor underwent allo-HSCT. After 2009, 7 patients received a haploidentical familial mismatched transplant (FMT).

As a reduced-intensity conditioning regimen, we administered busulfex 6.4 mg/kg and fludarabine 150 mg/m^2 with 400 cGy total body irradiation (TBI). Our myeloablative conditioning (MAC) regimen included

Table 1
CR Rate and Treatment Outcomes of Patients with AML and an Adverse-Risk Karyotype According to the Combination of NCA, MK Status, and NK Mosaicism at Diagnosis

	NK Mosaicism (+)			NK Mosaicism (−)			*P* Value	
	n	CR, n (%)	3-yr OS, %	n	CR, n (%)	3-yr OS, %	CR Rate	OS
Total cohort (n = 211)	119	72 (60.5)	26	92	39 (42.4)	12	.009*	.004*
Age (median, 50 yr; range, 18-85 yr)								
<50 yr (n = 105)	61	50 (81.9)	36	44	29 (65.9)	21	.060	.058
≥50 yr (n = 106)	58	22 (37.9)	16	48	10 (20.8)	0	.056	.026*
Sex								
Male (n = 128)	67	38 (56.7)	20	51	21 (41.2)	12	.094	.158
Female (n = 93)	52	34 (65.4)	33	41	18 (43.9)	10	.038*	.010*
Karyotype subgroup								
NCA ≥5 (n = 73)	42	21 (50.0)	17	31	7 (22.6)	0	.017*	.024*
NCA <5 (n = 138)	77	51 (66.2)	31	61	32 (52.5)	19	.101	.030*
NCA 3/4 (n = 46)	28	20 (71.5)	36	18	6 (33.3)	24	.011*	.120
NCA ≥3 (n = 119)	70	41 (58.6)	25	49	13 (26.5)	8	.001*	.004*
CK^+MK^+ (n = 53)	32	18 (58.2)	25	21	3 (14.3)	0	.002*	.002*
CK^+MK^- (n = 66)	38	23 (60.5)	25	28	10 (35.7)	14	.046*	.195
NCA <3 (n = 92)	49	31 (63.3)	28	43	26 (60.5)	17	.783	.104
Inv(3), t(3;3) (n = 16)	7	2 (28.6)	0	9	2 (22.2)	0	.608	.356
Abnormal 5q/−5 (n = 10)	6	5 (83.3)	42	4	—	—	—	—
Abnormal 7q/−7 (n = 23)	16	7 (43.8)	22	7	3 (42.9)	0	.663	.532
11q23 (n = 27)	11	9 (81.8)	46	16	13 (81.3)	34	.684	.366
t(6;9) (n = 15)	9	6 (66.7)	22	6	3 (50)	0	.519	.384
CK^- MK^+ (n = 6)	5	2 (40.0)	0	1	—	—	—	—
CK^- MK^- (n = 86)	44	29 (65.9)	31	42	25 (59.6)	17	.540	.126
MK^+ (total, n = 59)	37	20 (54.1)	22	22	4 (18.2)	0	.007*	.001*

CR includes incomplete CR (BM CR without complete blood count recovery, including neutrophils >1000 × 10^6/L and platelets >100,000 × 10^6/L).
* $P < .05$.