High early death rates, treatment resistance, and short survival of Black adolescents and young adults with AML

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The outcome disparity might be in part attributed to differences in cytogenetic and molecular features between Black and White AYA patients.

Key Points

• Outcome of Black AYA patients, mainly those aged 18-29 years, was worse than outcome of White patients receiving similar intensive therapy.

• The outcome disparity might be in part attributed to differences in cytogenetic and molecular features between Black and White AYA patients.

Survival of patients with acute myeloid leukemia (AML) is inversely associated with age, but the impact of race on outcomes of adolescent and young adult (AYA; range, 18-39 years) patients is unknown. We compared survival of 89 non-Hispanic Black and 566 non-Hispanic White AYA patients with AML treated on frontline Cancer and Leukemia Group B/Alliance for Clinical Trials in Oncology protocols. Samples of 327 patients (50 Black and 277 White) were analyzed via targeted sequencing. Integrated genomic profiling was performed on select longitudinal samples. Black patients had worse outcomes, especially those aged 18 to 29 years, who had a higher early death rate (16% vs 3%; P<.001), lower complete remission rate (66% vs 83%; P=.01), and decreased overall survival (OS; 5-year rates: 22% vs 51%; P<.001) compared with White patients. Survival disparities persisted across cytogenetic groups: Black patients aged 18 to 29 years with non–core-binding factor (CBF)-AML had worse OS than White patients (5-year rates: 12% vs 44%; P<.001), including patients with cytogenetically normal AML (13% vs 50%; P<.003). Genetic features differed, including lower frequencies of normal karyotypes and NPM1 and biallelic CEBPA mutations, and higher frequencies of CBF rearrangements and ASXL1, BCOR, and KRAS mutations in Black patients. Integrated genomic analysis identified both known and novel somatic variants, and relative clonal stability at relapse. Reduced response rates to induction chemotherapy and leukemic clone persistence suggest a need for different treatment intensities and/or modalities in Black AYA patients with AML. Higher early death rates suggest a delay in diagnosis and treatment, calling for systematic changes to patient care.
Introduction

Outcomes of younger patients with cancer are generally better than those of older patients, which is also true for adolescent and young adult (AYA; aged 18-39) patients with acute myeloid leukemia (AML) compared with older AML populations. Moreover, some cancer types have demonstrated a unique biology in AYA patients that can influence response to treatment, but, to our knowledge, this has not been adequately studied in AML. Differences in outcome exist between racial populations in AML as well, with Black patients having shorter disease-free (DFS) and overall survival (OS) than White patients. It remains unclear whether these survival disparities exist specifically in AYA patients, and whether there are associations with genetic characteristics of AML. In this study, we compared outcomes between Black and White AYA patients with AML receiving similar treatment on Cancer and Leukemia Group B (CALGB)/Alliance for Clinical Trials in Oncology (Alliance) protocols, and to delineate the molecular landscapes of Black and White AYA patients with AML and their potential associations with treatment outcomes.

Methods

Patients and treatment

We identified 816 AYA patients with de novo AML (excluding acute promyelocytic leukemia) with approved cytogenetic results who were enrolled on CALGB/Alliance treatment protocols between 1983 and 2016, including 714 self-reported White and 102 Black patients. Importantly, we were able to almost double the number of AYA patients analyzed compared with our previous study, including patients that underwent allogeneic hematopoietic stem-cell transplantation (HSCT) in first complete remission (CR). Thirteen percent of Black and 21% of White patients were excluded from the analyses because of inadequate treatment, off-protocol treatment, or unknown follow-up, resulting in 566 White and 89 Black AYA patients with AML eligible for analysis in our study (Figure 1A).

All patients received intensive induction treatment, followed by intensive consolidation chemotherapy or autologous HSCT. Details regarding treatment trials are provided in the supplemental Methods. For determination of DFS and OS, patients who received off-protocol allogeneic HSCT in first CR were considered as a separate group. All patients provided study-specific written informed consent to participate in treatment studies, which were approved by the institutional review board of each participating institution. The institutional review board of the Cancer Therapy Evaluation Program approved this study.

Mutational profiling

Viable cryopreserved bone marrow (BM) or blood cells were stored for future analyses prior to starting treatment. Mutational profiling was performed centrally at The Ohio State University (supplemental methods for experimental details).

Integrated genomic profiling

Four Black AYA patients with AML, for whom diagnosis and relapse samples were available, underwent integrated mutational and transcriptional profiling. This included whole-exome hybrid capture and next-generation sequencing with chromosomal tiling probes (250-fold coverage) of leukemic and matched germline tissue for detection of single nucleotide variants and small insertions and deletions, including both AML-associated and novel somatic mutations. Clonality analysis enabled evaluation of clonal hierarchies in individual patients, and copy number alterations were also assessed. Ribodepleted, paired-end 151-bp RNA sequencing (60-80 million reads per sample) was performed on diagnosis and relapse materials, followed by identification of fusion genes (known and novel), and gene-expression profiling via outlier analyses.

Definition of clinical endpoints

Early death was defined as patient’s death within 30 days of starting therapy, irrespective of cause. CR required an absolute neutrophil count ≥1.5 × 10⁹/L, a platelet count >100 × 10⁹/L, no leukemic blasts in the blood or BM, cellularity >20% with maturation of all cell lines, no Auer rods, <5% BM blast cells, and no evidence of extramedullary leukemia, all of which had persisted for at least 1 month. Relapse was defined by ≥5% BM blasts, circulating leukemic blasts, or the development of extramedullary leukemia. DFS was measured from the date of CR until the date of relapse or death; patients alive and relapse-free at last follow-up were censored. OS was measured from the date on study until the date of death, and patients alive at last follow-up were censored.

Statistical analysis

Demographic and clinical features of Black and White patients were compared using the Fisher’s exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Continuous variables were summarized using the median and range. Estimated probabilities of DFS and OS were calculated using the Kaplan-Meier method, and the log-rank test evaluated differences between survival distributions. A limited backward selection technique was used to build the final multivariable models for achievement of CR, DFS, and OS. We used logistic regression for modeling CR, and Cox proportional hazards regression for modeling DFS and OS for unfavorable and multivariable outcome analyses and then adjusted P values to control for per-family error rate. Analyses were performed by the Alliance Statistics and Data Center on a database locked on February 11, 2021, using SAS 9.4 and TIBCO Spotfire S+ 8.2.

Results

Clinical and cytogenetic characteristics of Black and White AYA patients with AML

A comparison of clinical characteristics of AYA patients with AML by race revealed almost identical age and sex distribution, and no significant differences between clinical features at diagnosis (supplemental Table 1).

Forty percent of White patients were cytogenetically normal at diagnosis, whereas only 19% of Black patients were (P < .001; Figure 1B; supplemental Table 2). The abnormal karyotypes contained chromosome rearrangements associated with core-binding factor (CBF) AML in 37% of Black and only 22% of White patients (P = .005). Specifically, Black patients harbored t(8;21)(q22;q22)/RUNX1::RUNX1T1 more commonly than White patients (22% vs 10%; P = .002), whereas the incidence of inv(16)(p13.1q22)/CBFB::MYH11 or t(16;16)(p13.1;q22)/CBFB::MYH11 was similar (15% vs 12%, P = .49). The frequencies...
Black and white AYA patients aged 18–39 years with de novo AML (excluding APL) receiving intensive, cytarabine and daunorubicin-based induction therapy followed by consolidation treatment who were enrolled on a companion study CALGB 8461 and had approved cytogenetic results (n=816)

Patients included in our study (n=89)

Patients without tissue available (n=35)

Patients included in molecular data analyses (n=50)

Patients excluded (n=13):
• Non-protocol treatment (n=11)
• Unknown follow-up (n=2)

Patients included in DFS and OS analyses (n=85)

Black patients with AML (n=102)

White patients with AML (n=714)

Patients included in DFS and OS analyses (n=481)

Patients without tissue available (n=204)

Patients received an allogeneic HSCT outside of protocol in 1st CR (n=4)

Patients received an allogeneic HSCT outside of protocol in 1st CR (n=85)

Patients included in molecular data analyses (n=277)

Patients excluded (n=148):
• Non-protocol treatment (n=68)
• Unknown follow-up (n=78)
• Ineligible for study (n=2)

Black patients 18–39 years

9% 11q23/KMT2A
3% sole +8
4% t(6;9)
3% complex karyotype
41% inv(16)
59% t(8;21)
37% CBF-AML
19% CN-AML
25% other abnormalities

White patients 18–39 years

8% 11q23/KMT2A
3% sole +8
1% t(8;9)
7% complex karyotype
46% t(8;21)
54% inv(16)
40% CN-AML
22% CBF-AML
19% other abnormalities

Figure 1.

B

Black patients 18–39 years

KRAS
FLT3-ITD
NRAS
ASXL1
DNMT3A
BCOR
CALR
FLT3-TKD
RUNX1
TET2
WT1
IDH2
KIT
ZRSR2
IDH1
NPM1
PHF6
SF3B1
STAG2
CEBPA
NF1
GATA2

C

% Mutated patients

Figure 1.
of other recurrent cytogenetic abnormalities, such as rearrangements of 11q23/KMT2A, t(6;9)(p23;q34), complex karyotype, or sole trisomy 8, did not differ significantly between Black and White patients (Figure 1B; supplemental Table 2).

**Molecular characteristics**

With respect to known pathogenic AML-associated gene variants, we detected notable differences in the patterns of altered genes. Black patients had a higher incidence of ASXL1 (12% vs 1%; P < .001), KRAS (16% vs 5%; P = .01), ZRSR2 (6% vs 0.4%; P = .01), BCO2 (8% vs 2%; P = .05), and CALR (8% vs 2%; P = .05) variants, whereas White patients carried NPM1 (29% vs 4%; P < .001) and biallelic CEBPA (17% vs 3%; P = .02) variants more frequently (Figure 1C; supplemental Table 3). Analysis of families of variants by gene function revealed that the Black AYA patients had higher numbers of variants affecting genes involved in chromatin remodeling (20% vs 5%; P < .001; supplemental Table 3).

To gain insights into the genetic features of Black AYA patients with AML, and to explore whether race-specific molecular features at diagnosis or relapse might help explain the observed survival disparities, we performed integrated genomic profiling of 4 Black AYA patients. We identified 84 variants with a variant allele fraction ≥2% in 79 genes at diagnosis or relapse (supplemental Table 4). Although the only genes found mutated in 2 or more patients were the known AML-associated genes, FLT3, NPM1, and NRAS, almost one-third of the genes mutated in single patients (n = 27 genes, 34%) have not been described thus far in the combined hallmark AML sequencing studies.17-19

All 4 patients exhibited relatively high clonal stability at relapse, with the original dominant leukemia clone persisting at relapse in every patient, albeit with either expansion of preexisting smaller clones or emergence of additional novel subclones at relapse (Figure 2A-B; supplemental Figure 1). Similarly, the expression profiles of patients also showed relatively high stability, with consistent individual outlier gene expression identified in each pretreatment and relapse patient sample (supplemental Figure 2). Notably, measurable residual disease was detectable in both NPM1-mutated patients at the time of morphologic CR, after consolidation treatment in 1 patient, and after completion of induction but prior to consolidation in the second.

Copy number analyses revealed additional involvement of AML-associated genes, including subclonal loss of heterozygosity of chromosome 1 containing the NRAS locus (1p13.2) in patient 1, resulting in a clonal population with a homozygous NRAS mutation (Figure 2B). Patients 2 and 4, both of whom had cytogenetically normal AML (CN-AML), harbored a uniparental disomy of chromosome 13,20 which contains the FLT3 locus (13q12.2). Patient 4 harbored a FLT3-ITD at diagnosis and gained the chromosome 13 UPD at relapse, which is consistent with a biologic mechanism of increasing the mutant copies of FLT3 (ie, high FLT3-ITD allelic ratio).

**Outcomes of Black and White AYA patients with AML treated on CALGB/Alliance protocols**

Within the entire patient cohort, Black patients had worse outcomes than White patients (Table 1), including a higher early death rate (defined as death within 30 days of protocol enrollment; 11% vs 2%; P < .001), a trend toward lower CR rate (73% vs 82%; P = .06), and shorter OS (5-year rates, 32% vs 46%; P = .002), but not DFS (5-year rates, 32% vs 40%; P = .25; Figure 3A-B). There were no significant differences in pretreatment clinical, demographic, or molecular characteristics between Black and White AYA patients who died early (supplemental Table 5).

We also separately assessed outcomes of 2 age subsets separated by a decade within the AYA population, namely, patients aged 18 to 29 years and those aged 30 to 39 years (Table 1). We found that the survival difference between Black and White patients occurred mostly in the younger subset, wherein Black patients had a dramatically higher early death rate (16% vs 3%; P = .002). There was no significant difference with respect to the day of early death between Black and White patients (median day post study enrollment, day 14 vs day 11), and no enrichment of patients experiencing early death in any study protocol, time frame, or study site. Black patients aged 18 to 29 years also had a lower CR rate (66% vs 83%; P = .01), and a race-associated OS gap of almost 9 years: the median OS of Black patients was 1.3 years, whereas White patients had a median OS of 10.2 years (P < .001).

In contrast, there were no significant differences in the OS between Black and White patients who were 30 to 39 years of age, nor in DFS in either age subset (Table 1; Figure 3C-D).

Next, we performed a multivariable analysis to determine whether Black race represented an independent prognosticator for outcome in AYA patients with AML. Indeed, after adjustment for white blood cell counts and the presence of CBF-AML, Black race was a significant predictor of both shorter DFS (P = .04) and shorter OS (P < .001; Table 2; supplemental Figure 4).

**Allogeneic HSCT in first CR of AYA patients with AML**

Fifteen percent (n = 85) of White AYA and only 4.5% (n = 4) of Black AYA patients with AML received an allogeneic HSCT in first CR, for whom we next performed a dedicated outcome analysis. White patients who underwent allogeneic HSCT had longer DFS than did Black patients who did not undergo this intensive regimen (P = .01; Figure 4A). Despite notable Kaplan-Meier curve separation, there was no statistically significant difference in OS among the treatment groups (P = .21; Figure 4B). In our multivariable analysis, Black race remained significant in a model for OS that included both patients treated postremission with chemotherapy or autologous HSCT and those who received an allogeneic HSCT in first CR (P < .001; Table 1).

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**Figure 1.** Patient cohort composition and observed cytogenetic and molecular landscapes of Black and White AYA patients with AML. (A) A consort diagram of AYA patients with AML aged 18 to 39 years who were treated on the CALGB/Alliance study protocols. APL, acute promyelocytic leukemia. (B) The frequency distribution of cytogenetic findings in Black compared with that in White patients. (C) Bar graphs showing frequencies of pathogenic variants in known AML-associated genes detected in Black and White patients with AML, sorted by descending frequencies of variants found in Black patients. Depicted are only genes that were found mutated in ≥3% of patients.
Figure 2. Molecular composition and clonal evolution of select Black AYA patients with AML at the time of AML diagnosis and at relapse. (A) Fish plots depicting clonal changes in pathogenic variants of AML-associated and less well-known genes between diagnosis and relapse, as identified by whole-exome sequencing of samples from 4 Black patients with AML. (B) Copy number changes detected at diagnosis and relapse in the same 4 Black patients with AML.
Comparison of outcomes of AYA Black and White patients with CBF-AML and those with other karyotypes

As a relatively large proportion of Black patients harbored chromosome rearrangements that define CBF-AML, we analyzed the outcomes of patients in this subset \( (n = 155) \). Black patients with CBF-AML tended to have a higher rate of early death \( (12\% \text{ vs } 3\%; \ P = .06) \) and lower CR rate \( (85\% \text{ vs } 95\%; \ P = .06) \) and had a shorter OS (5-year rates, 54\% vs 70\%; \( P = .05 \)), but not DFS, compared with White patients (Figure 5A-B; supplemental Table 6). Our comparison of presenting clinical features between Black and White AYA patients with CBF-AML, including Eastern Cooperative Oncology Group performance status, revealed no obvious differences that could explain the higher rate of early deaths in the Black AYA patients (supplemental Table 7). With respect to specific subtypes of CBF-AML, DFS or OS did not differ significantly between Black and White patients with CBF-AML.

### Table 1. Treatment outcomes of Black and White AYA patients with AML

| Endpoint | Black patients \( (n = 89) \) | White patients \( (n = 566) \) | \( P^* \) | OR/HR (95% CI) |
|----------|---------------------------------|------------------------------|---------|-----------------|
| Early death, n (%)^†‡ | 10 (11) | 14 (2) | <.001 | 7.50 (1.91, 29.51)^‡ |
| CR, n (%)^† | 65 (73) | 463 (82) | .06 | 1.28 (0.83, 1.37) |
| DFS | n = 61‡ | n = 378‡ | .25 | 0.90 (0.58, 1.47) |
| Median, y | 1.2 | 1.4 | <.001 | 0.67 (0.47, 0.96) |
| Disease-free at 5 y, % (95% CI) | 32% (21-44) | 40% (35-45) | |
| OS | n = 85‡ | n = 481‡ | .002 | 0.67 (0.47, 0.96) |
| Median, y | 1.5 | 3.1 | <.001 | 0.48 (0.28, 0.81) |
| Alive at 5 y, % (95% CI) | 32% (23-42) | 46% (41-50) | |

**Patients aged 18-29 y**

| Endpoint | Black patients \( (n = 44) \) | White patients \( (n = 252) \) | \( P^* \) | OR/HR (95% CI) |
|----------|---------------------------------|------------------------------|---------|-----------------|
| Early death, n (%)^†‡ | 7 (16) | 7 (3) | .002 | 16.23 (2.45, 107.72)^‡ |
| CR, n (%)^† | 29 (66) | 208 (83) | .01 | 3.17 (1.03, 9.80) |
| DFS | n = 27§ | n = 168§ | .16 | 0.96 (0.49, 1.89) |
| Median, y | 1.2 | 1.8 | <.001 | 0.48 (0.28, 0.81) |
| Disease-free at 5 y, % (95% CI) | 24% (10-42) | 42% (34-49) | |
| OS | n = 42§ | n = 212§ | <.001 | 0.48 (0.28, 0.81) |
| Median, y | 1.3 | 10.2 | <.001 | 0.48 (0.28, 0.81) |
| Alive at 5 y, % (95% CI) | 22% (11-36) | 51% (44-57) | |

**Patients aged 30-39 y**

| Endpoint | Black patients \( (n = 45) \) | White patients \( (n = 214) \) | \( P^* \) | OR/HR (95% CI) |
|----------|---------------------------------|------------------------------|---------|-----------------|
| Early death, n (%)^†‡ | 3 (7) | 7 (2) | .12 | 2.83 (0.28, 28.70)^‡ |
| CR, n (%)^† | 36 (80) | 255 (81) | .84 | 0.54 (0.15, 1.96) |
| DFS | n = 34§ | n = 210§ | .73 | 0.81 (0.46, 1.44) |
| Median, y | 1.2 | 1.4 | <.001 | 0.48 (0.28, 0.81) |
| Disease-free at 5 y, % (95% CI) | 8% (22-54) | 39% (32-45) | |
| OS | n = 43§ | n = 269§ | .49 | 0.87 (0.53, 1.44) |
| Median, y | 2.2 | 2.2 | <.001 | 0.48 (0.28, 0.81) |
| Alive at 5 y, % (95% CI) | 42% (27-56) | 42% (36-48) | |

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

*P values for categorical variables are from Fisher’s exact test; \( P \) values for the time to event variables are from the log-rank test.

†For early death and CR analyses, the denominator included patients who received an allogeneic HSCT in first CR.

‡Because of a wide CI, the result should be interpreted with caution.

§DFS and OS analyses exclude patients who received an allogeneic HSCT in first CR.

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Figure 3. Treatment outcome of Black and White AYA patients with AML. DFS (A) and OS (B) of Black and White AYA patients aged 18 to 39 years. DFS (C) and OS (D) of Black and White AYA patients with AML, separated into the age groups of 18 to 29 and 30 to 39 years.

Table 2. Final multivariable models for DFS and OS in Black and White AYA patients with AML who received consolidative chemotherapy, and for OS in a combined group of patients who received either consolidation with chemotherapy or allogeneic HSCT in first CR off-protocol.

| Variable                                | Categories               | $P$  | HR (95% CI)        |
|-----------------------------------------|--------------------------|------|--------------------|
| DFS (no allogeneic HSCT in first CR)    | Race                     | .04  | 0.70 (0.50, 0.98)  |
|                                        | White vs Black           |      |                    |
|                                        | White blood cell count   | <.001| 1.32 (1.19, 1.48)  |
|                                        | Continuous, 50-unit increase |  |  |
|                                        | CBF-AML                  | <.001| 0.51 (0.39, 0.67)  |
| OS (no allogeneic HSCT in first CR)     | Race                     | <.001| 0.57 (0.43, 0.76)  |
|                                        | White vs Black           |      |                    |
|                                        | White blood cell count   | <.001| 1.31 (1.20, 1.43)  |
|                                        | Continuous, 50-unit increase |  |  |
|                                        | CBF-AML                  | <.001| 0.42 (0.32, 0.56)  |
| OS (including allogeneic HSCT in first CR) | Race                  | <.001| 0.55 (0.42, 0.73)  |
|                                        | White vs Black           |      |                    |
|                                        | White blood cell count   | <.001| 1.20 (1.12, 1.29)  |
|                                        | Continuous, 50-unit increase |  |  |
|                                        | CBF-AML                  | <.001| 0.44 (0.33, 0.58)  |

*P values are from Cox proportional hazard models. An HR >1 (<1) indicates higher (lower) risk for the categorical variable listed first or higher values of a continuous variable.
disparity occurred exclusively among the younger AYA patients to the Alliance/CALGB treatment protocols. Strikingly, this survival of Black AYA patients was inferior to the outcome of Black AYA patients with non–CBF-AML and those with CN-AML. The outcome of younger Black AYA patients with non–CBF-AML was dramatically poor and worse than that of White patients with CBF-AML (DFS, 5-year rates: 14% vs 34%, \(P < .001\); OS, 5-year rates: 12% vs 44%, \(P < .001\); Figure 5E-F). Although Black AYA patients aged 18 to 29 years with CBF-AML had better survival than Black patients with non–CBF-AML, the survival of Black patients with CBF-AML was similar to that of White patients with non–CBF-AML. Similarly, Black patients with CN-AML had very poor outcomes. Not a single 18- to 29-year-old Black patient with CN-AML was disease-free 5 years after diagnosis (5-year rates: 0% vs 43%), and only 1 of 9 patients was alive (5-year rates: 13% vs 50%, \(P = .003\); supplemental Figure 3C-D; supplemental Table 9).

Discussion
We show that the outcome of Black AYA patients was inferior to that of White patients in a large cohort of 665 AYA patients with AML, all of whom received similar intensive therapy on frontline Alliance/CALGB treatment protocols. Strikingly, this survival disparity occurred exclusively among the younger AYA patients (aged 18-29 years), whereas Black and White patients aged 30 to 39 years had similar outcomes. Specifically, 18- to 29-year-old Black patients with AML had alarmingly high early death rates within the first 30 days of study enrollment, indicating possible delays in diagnosis and care, and a low CR rate of only 66% that suggests inherently different responses to induction therapy. These features contributed to these very young adult Black patients having a median survival nearly 9 years shorter than White patients in the same age group. The race-associated survival disparity was present across different cytogenetic subgroups, including patients with CBF-AML. However, despite inferior survival of Black patients with CBF-AML compared with Whites, the prognosis of Black patients with CBF-AML was still relatively favorable, because the 5-year OS rate of 18- to 29-year-old Black patients with non–CBF-AML was only 12% vs 54% in Black patients with CBF-AML. In fact, the high proportion of CBF-AML among Black vs White AYA patients likely resulted in the longer OS of all young Black patients with AML when analyzed together and compared with that of all young White patients.

We show that ~40% of Black AYA patients harbor a CBF-AML–defining chromosomal abnormality, indicative of a distinct disease biology in this population that requires further attention and exploration. Notably, a high incidence of CBF-AML–defining rearrangements, and specifically of t(8;21), was previously reported in adult Black patients with AML.21 Our data suggest that this might be mostly driven by AYA patients. Interestingly, a high frequency of t(8;21) in Black patients with AML has also recently been reported in pediatric AML, with 21.3% of Black vs 10.9% of non-Hispanic White patients harboring the t(8;21) translocation.22

We observed differences in the frequencies of AML-associated mutations, with Black AYA patients harboring more often mutations in the ASXL123-25 and BCO226-29 genes, which have been reported to confer worse outcomes, and carrying less frequently prognostically favorable NPM1 mutations23 and biallelic mutations in the CEBPA gene.26,30,31 Although the lower frequency of those 2 favorable risk markers we report herein may be considered

Figure 4. Outcomes of Black and White AYA patients with AML who received different consolidation treatment. DFS (A) and OS (B) of Black and White AYA patients with AML who received consolidation with chemotherapy or autologous HSCT compared with patients who underwent allogeneic HSCT in first CR off-protocol. Only 4 Black patients received an allogeneic HSCT in first CR and are not depicted in the diagram.

![Graph showing outcomes of Black and White AYA patients with AML](image-url)
as possible contributors to the inferior treatment outcome of Black AYA patients as compared with the outcome of White AYA patients, the previous notion of poor survival specifically of NPM1-mutated/FLT3-ITD low/no younger Black patients with AML may instead raise the possibility of differences in the disease biology of favorable risk AML between Black and White patients with AML.

Our pilot exome-sequencing data indicate that common AML mutations are also found in Black patients. However, almost one-third of the detected variants were found in genes thus far not associated with AML, indicating the need for larger studies in this population to assess frequencies of these gene mutations and their associations with disease. Importantly, the integrated genomic

Figure 5. Treatment outcomes of Black and White AYA patients with respect to cytogenetic findings. DFS (A) and OS (B) of all Black and White AYA patients diagnosed with CBF-AML. DFS (C) and OS (D) of Black and White patients with AML aged 18 to 29 years and those aged 30 to 39 years who harbored inv(16)/t(16;16). Two Black patients with inv(16) aged 30 to 39 years are not included in the DFS plot. DFS (E) and OS (F) of patients aged 18 to 29 years with CBF-AML and of those with non-CBF-AML.
profiling of pretreatment and relapse samples demonstrated relatively high clonal stability and persistence of the driver clone, suggesting the need for more intense treatment or an alternate approach for successful eradication of the leukemic clone. Although the interpretation of these findings is limited by the small number of studied patients, it highlights the need for large-scale sequencing studies to appreciate possible ancestry-associated differences in genetic findings and associated genomic response.

Our study is limited by relatively small sample sizes of the particular molecular subgroups. Furthermore, in view of the observed differences in the early death rates, the incompleteness of records with causes of patients’ early death and sociodemographic features precluded more in-depth analyses that could potentially help explain this alarming disparity, thus making further large studies necessary. On the other hand, the strength of our study lies in the fact that proportions of Black and White patients we analyzed mirror closely the ancestry composition of the general US population.32

Reasons for the racial disparities in outcomes are undoubtedly multifaceted, as previously demonstrated.1,23-35 The high early death rates might suggest treatment delays or inferior care as well as comorbidities that could reflect cultural biases and structural racism but could also be indicative of a more aggressive disease biology. Likewise, lower CR rates may indicate chemoresistant disease or could point to a pharmacogenomic etiology based on alternate drug metabolism resulting in lower target exposure and may warrant dedicated follow-up studies. For the youngest Black patients, the median DFS of 1.2 years is essentially equal to the median OS of 1.3 years in this group, suggesting that the initial treatment outcome was paramount to OS. This result encompasses not only early deaths and primary refractory disease but also lack of successful salvage upon relapse. Based on our data, even Black AYA patients aged 18 to 29 years with favorable risk genetics have a considerable risk of relapse with current standard of care treatment, and consolidation type and/or intensity may need to be reconsidered for this patient population, especially on the backgrounds that there was no difference in the numbers of consolidation cycles received between Black and White patients. The detection of MRD in the 2 NPM1-mutated cases at the time of morphologic CR further supports the routine use of MRD assessment, in line with current guidelines.36-41

We believe that these and other data10,42,43 justify further prospective studies of Black AYA patients with AML, including evaluation of alternate frontline and/or consolidation treatments, collection of the Social Determinants of Health to try to assess nonclinical reasons for poor outcomes, as well as careful consideration and enhanced monitoring for the individual Black AYA patients with AML being treated in the clinic today.

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Celebrating the life and accomplishments of Clara D. Bloomfield (1942-2020), who died unexpectedly on March 1, 2020.

Authorship

Contribution: A.-K.E., K.T.L., J.C.B., and E.R.M. contributed to the study design; K.T.L., D.N., K.M., E.R.M., E.D.P., J.C.B., and A.-K.E. contributed to the data interpretation; K.T.L., K.M., and A.-K.E. wrote the manuscript; A.-K.E., K.E.M., A.S.M., I.B., J.S.B., C.C.O., A.H., H.D., and S.O. performed laboratory-based research; B.J.K., K.E.M., C.J.W., S.L., S.W., G.W., and J.K. performed genomics data analysis; D.N. and J.K. performed statistical analysis; A.J.C., K.M., W.B., B.L.P., J.E.K., J.O.M., R.J.M., R.A.L., R.M.S., and J.C.B. were involved directly or indirectly in the care of patients and/or sample procurement; and all authors read and agreed on the final version of the manuscript.

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