Decitabine plus all-*trans* retinoic acid *versus* decitabine monotherapy for myelodysplastic syndromes with excess blasts: a multicenter, randomized controlled trial

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Abstract

Despite standard treatment with hypomethylating agents, the prognosis of patients with higher-risk myelodysplastic syndrome (MDS) remains poor. All-*trans* retinoic acid (ATRA) has demonstrated promising efficacy in unfit patients with acute myeloid leukemia. This multicenter controlled trial randomized (1:1) untreated patients with MDS with excess blasts (MDS-EB) to ATRA plus decitabine (ATRA at 25 mg/m^2/day in 2 divided daily doses throughout the 28-day cycle plus decitabine at 20 mg/m^2 on days 1-5) or decitabine alone (20 mg/m^2 on days 1-5). The primary endpoint was the overall response rate within four treatment cycles. A total of 227 patients were randomized. Four patients who did not commence therapy were excluded from the modified intention-to-treat (mITT) analysis. The median patient age was 62 years (range, 19-81). The overall response rate was 78% (86/110) in the ATRA group *versus* 51% (58/113) in the decitabine group (odds ratio =3.40; 95% confidence interval [CI]: 1.90-6.09; *P*<0.001). The ATRA group also had a higher complete remission rate (23% *vs*. 12%; odds ratio =2.05; 95% CI: 1.02-4.25; *P*=0.042). With a median follow-up of 30.1 months, progression-free survival (PFS) was 14.9 months in the ATRA group *versus* 10.5 months in the decitabine group (hazard ratio [HR]=0.70; 95% CI: 0.51-0.97; *P*=0.03). The overall survival was 23.0 months and 19.3 months, respectively (HR=0.77; 95% CI: 0.54-1.09; *P*=0.137). The two groups did not differ in grade 3 or higher hematological adverse events. In conclusion, adding ATRA to decitabine increased the overall response rate and prolonged PFS in adult patients with MDS-EB without increasing hematological toxicity. This study was registered at Chinese Clinical Trial Registry (*www.chictr.org.cn, identifier: ChiCTR1800018307)*.

Introduction

Myelodysplastic syndrome (MDS) is a clonal malignant disease of hematopoietic stem cells. Patients with higher-risk MDS, as classified by the International Prognostic Scoring System (IPSS) or Revised International Prognostic Scoring System (IPSS-R),[1] are at high risk of progression to acute myeloid leukemia (AML). Hypomethylating agents

(HMA), including decitabine and azacytidine, are standard treatments for higher-risk MDS. However, patient outcomes remain poor despite HMA treatment. The rates of complete remission (CR) and overall response (OR) range from 7% to 17% and from 30% to 52%, respectively.[2-4] The median overall survival (OS) is 10.1-24.5 months.[2-11] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative treatment,[12] but many elderly patients are not appropriate candidates for allo-HSCT.

A variety of novel treatment strategies have been attempted for higher-risk MDS. The molecular targets of these treatments include somatic genetic mutations, cell-surface antigens, and anti-apoptotic pathways. Despite encouraging results in the early development phases, subsequent trials with larger sample sizes have generally been disappointing.[13-17] In a phase III trial of the anti-TP53 agent eprenetapopt plus azacitidine in patients with *TP53*-mutated MDS, the CR rate did not differ from that of azacitidine monotherapy.[15] The PANTHER trial compared azacitidine alone *versus* azacitidine in combination with the NEDD8 inhibitor pevonedistat and failed to show improvement in event-free survival (EFS). The ENHANCE trial compared azacitidine alone *versus* azacitidine in combination with the CD47 antibody magrolimab but failed to improve CR and OS.[18] The STIMULUS trial compared HMA alone with those combined with the TIM-3 inhibitor sabatolimab but also failed to improve CR and progression-free survival (PFS).[19]

All-*trans* retinoic acid (ATRA) induces blast differentiation in acute promyelocytic leukemia (APL) and is recommended for APL treatment. ATRA may be effective in AML without the PML-RARA fusion protein. Preclinical studies have indicated that HMA increase the sensitivity of AML cells to ATRA.[20,21] Reciprocally, ATRA can potentiate the cytotoxic effects of decitabine.[22,23] Lübbert and colleagues demonstrated the cooperative antileukemic effects of decitabine and ATRA on the AML cell lines U937 and MOLM-13. In addition to the derepression of tumor suppressor genes such as *HIC1*, the induction of transposable elements was observed with both drugs, triggering a "viral mimicry" response.[23] Our preclinical data revealed that decitabine induced Nrf2 activation and downstream anti-oxidative responses and inhibited reactive oxygen species (ROS) generation, thus leading to decitabine resistance. The addition of ATRA blocked Nrf2 activation by activating the RARα-Nrf2 complex, leading to ROS accumulation and ROS-dependent cytotoxicity.[22]

Two single-arm trials in the 2000s reported the promising efficacy of a therapeutic regimen that included HMA, ATRA, and valproate in mixed groups of AML and MDS patients.[24,25] The more recent DECIDER trial compared decitabine alone *versus* decitabine in combination with valproate, ATRA, or valproate plus ATRA in AML patients and demonstrated a higher objective response rate in patients treated with regimens that included ATRA but not valproate.[26] Notably, 56 of the 200 patients in the DECIDER trial fulfilled the criteria for oligoblastic AML (20-30% blasts) according to the current classification system but were diagnosed with refractory anemia with excess blasts in transformation (RAEB-T) according to the French-American-British classification at the time. A *post hoc* analysis of this subgroup revealed that the combination of ATRA and decitabine increased ORR and OS rates.[27] Based on these findings, we hypothesized that adding ATRA to HMA could improve treatment response in patients with MDS with excess blasts (MDS-EB) and conducted a prospective trial to compare decitabine in combination with ATRA *versus* decitabine alone in patients with newly diagnosed MDS-EB.

Methods

Participants and eligibility

This multicenter, randomized controlled trial was conducted in eight centers in China. Adult patients (≥18 years of age) with morphologically confirmed MDS-EB-1 or MDS-EB-2, as defined by the World Health Organization classification (WHO 2016), were eligible. The trial was conducted following the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonization. The Institutional Review Boards approved the trial protocol (master protocol ID: 2018850). Written informed consent was obtained from all patients before enrollment. This trial is registered at the Chinese Clinical Trial Registry (Identifier: *ChiCTR1800018307*).

Study design and procedures

Patients were randomized at a 1:1 ratio to receive ATRA plus decitabine or decitabine alone. The randomization was stratified based on centers.

Each cycle lasted 28 days, and the study treatment was planned for at least four cycles. For each cycle, all patients received 20 mg/m^2 intravenous decitabine infusion over 60 minutes during the first 5 days. For the first four cycles, patients in the ATRA group also received oral ATRA at 25 mg/m^2/day in two divided daily doses throughout the 28-day cycle (see page 16 of the *Online Supplementary Appendix*). Starting from the fifth cycle, ATRA was given at 25 mg/m^2/day only for the first 14 days of the 28-day cycle. The daily ATRA dosage was based on its recommendation in the Chinese clinical practice guidelines for APL.[28] Treatment continued until disease progression, unacceptable toxicity, or patient decision to withdraw from the trial (see pages 49-50 of the *Online Supplementary Appendix*).

Outcomes

The primary endpoint was the overall response rate (ORR), which was calculated based on the best response within four cycles and included CR, partial remission (PR), marrow CR (mCR), and hematologic improvement (HI) according to the modified International Working Group (IWG) 2006 response criteria in the MDS.[27]

The secondary endpoints included the bone marrow blast response (CR+mCR), hematological response (CR+PR+HI), progression-free survival (PFS), OS, and treatment-emergent adverse events.

Statistical analysis

The sample size requirement was estimated via PASS 11.0 software (NCSS, Kaysville, UT) based on the following assumptions: (i) an ORR of 50% in the decitabine group[11] and 70% in the ATRA group; (ii) an α of 0.05; and (iii) a power (1-β) of 80%. The calculation yielded 180 subjects (90 per group). Assuming a 20% dropout rate, we planned to enroll 226 patients. All efficacy endpoints and treatment-emergent adverse events were calculated using a modified intent-to-treat (mITT) population that included all patients who received at least one dose of the assigned treatment. Categorical variables were analyzed via the χ^2 test or Fisher's exact test, as appropriate. Continuous variables with a normal distribution were analyzed via Student's *t* test and are presented as the means ± standard deviations. Continuous variables not normally distributed were analyzed via the Mann-Whitney U test and are presented as the median and interquartile range (IQR). Survival outcomes were estimated via the Kaplan-Meier method and compared via the log-rank test. All the statistical analyses were conducted via SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Between September 11, 2018, and September 10, 2022, 243 patients were assessed for eligibility, and 227 were enrolled (113 and 114 patients in the ATRA and decitabine groups, respectively; Figure 1). The disease subtype was MDS-EB-1 in 109 patients and MDS-EB-2 in 118 patients. 28 (25%) patients in the ATRA group and 25 (22%) in the decitabine group received allo-HSCT. Twelve (11%) patients

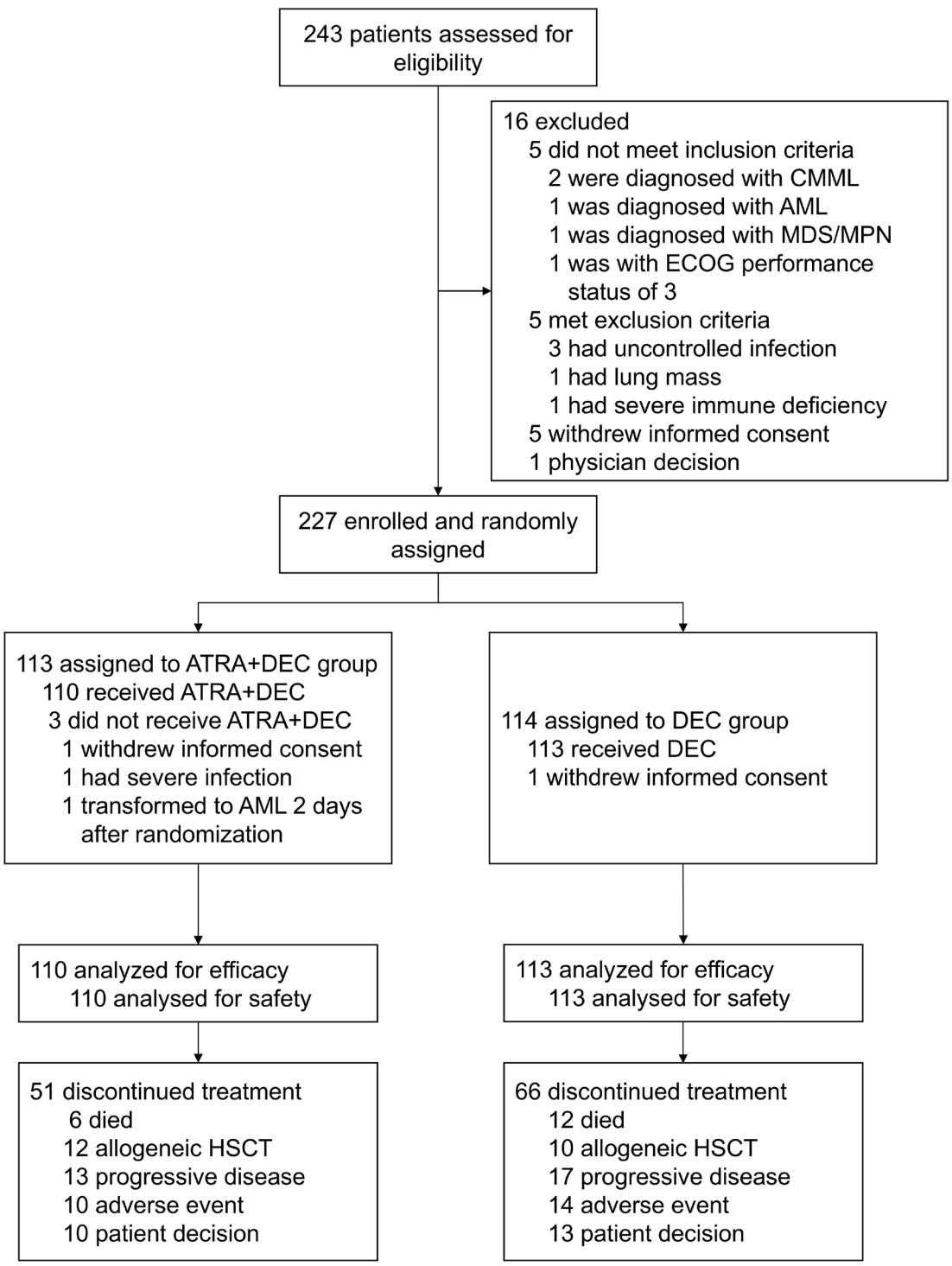

Figure 1. Patient flow through the trial. CMML: chronic myelomonocytic leukemia; AML: acute myeloid leukemia; MDS: myelodysplastic syndromes; MPN: myeloproliferative neoplasms; ECOG: Eastern Cooperative Oncology Group; ATRA: all-*trans* retinoic acid; DEC: decitabine; HSCT: hematopoietic stem cell transplantation.

in the ATRA group and ten (9%) in the decitabine group received allo-HSCT within four cycles. At the time of data cutoff (May 31, 2023), 13 patients in the ATRA group and ten in the decitabine group were still receiving the assigned treatment.

The median patient age was 62 years (IQR, 54-68; range, 19-81; Table 1). The IPSS-R category was high or very high in 181 (81%), intermediate in 33 patients (15%), and low in the remaining patient (0.4%). Mutated genes were generally balanced between the two groups (Figure 2). *Post hoc* reclassification of the patients with next-generation sequencing data based on the IPSS-M is shown on page 17 of the *Online Supplementary Appendix*.

The median number of decitabine cycles was 4 (range, 1-17) in the ATRA group and 3 (range, 1-20) in the decitabine group. The reasons for treatment discontinuation within four cycles are shown in Figure 1. ATRA was reduced in dosage in 13 patients and permanently discontinued in four patients before the completion of four cycles; decitabine was continued in all 17 patients.

Treatment response

Owing to the outbreak of COVID-19, 38 of the 110 patients in the ATRA group and 32 of the 113 patients in the decitabine group missed at least one scheduled bone marrow examination during the follow-up.

The ORR was 78% (86/110) in the ATRA group *versus* 51% (58/113) in the decitabine group (odds ratio =3.40; 95% confidence interval [CI]: 1.90-6.09; $P<0.001$; Table 2). The ATRA group also had a higher CR rate (23% *vs*. 12%; odds ratio =2.05; 95% CI: 1.02-4.25; $P=0.042$), CR+mCR rate (72% *vs*. 49%; odds ratio =2.69; 95% CI: 1.54-4.68; $P<0.001$), and CR+PR+HI rate (48% *vs*. 34%; odds ratio =1.84; 95% CI: 1.07-3.15; $P=0.027$). In patients with *TP53* mutation, ORR was 79% (11/14) and 54% (7/13) in the ATRA+decitabine and decitabine alone groups, respectively (odds ratio =3.14; 95% CI: 0.59-16.85; $P=0.181$). The CR rate was 29% (4/14) in ATRA group and 23% (3/13) in decitabine group (odds ratio =1.33; 95% CI: 0.24-7.56; $P=0.745$). The median time to initial response did not differ between the two groups (1 cycle in both groups). The rate of response type after one treatment cycle was 3.6% (4/110) CR, 12.7% (14/110) mCR+HI, 38.2% (42/110) mCR without HI, and 6.4% (7/110) HI only in the ATRA plus decitabine group *versus* 2.7% (3/113) CR, 10.6% (12/113) mCR+HI, 23.9% (27/113) mCR without HI, and 3.5% (4/113) HI in the decitabine alone group. The rate of leukemic transformation was 58% (64/110) in the ATRA group *versus* 66% (75/113) in the decitabine group (odds ratio =1.42, 95% CI: 0.82-2.44; $P=0.207$). In patients with abnormal cytogenetic data at baseline, the rate of cytogenetic response was 76% (22/29) in the ATRA group and 57% (16/28) in the decitabine group (odds ratio =2.36; 95% CI: 0.76–7.32; $P=0.134$). The main effect (higher ORR in the ATRA group) was observed across all subgroups, except for women (P for interaction =0.032; Figure 3). The cause of

Table 1. Demographic and baseline characteristics.

Characteristics	ATRA plus decitabine N=110	Decitabine N=113
Median age, years (IQR)	62 (52-68)	62 (55-68)
Sex, N (%)		
Male	70 (64)	75 (66)
Female	40 (36)	38 (34)
ECOG performance score, N (%)		
0	14 (13)	12 (11)
1	62 (56)	65 (57)
2	34 (31)	36 (32)
Disease type*, N (%)		
MDS-EB-1	52 (47)	56 (50)
MDS-EB-2	58 (53)	57 (50)
IPSS-R cytogenetic risk category, N (%)		
Very good	1 (1)	1 (1)
Good	54 (49)	59 (52)
Intermediate	29 (26)	25 (22)
Poor	6 (5)	6 (5)
Very poor	16 (15)	18 (16)
No mitosis	4 (4)	4 (4)
IPSS-R risk category, N (%)		
Very low	0	0
Low	0	1 (1)
Intermediate	16 (15)	17 (15)
High	46 (42)	33 (29)
Very high	44 (40)	58 (51)
Not evaluable	4 (4)	4 (4)
Neutrophil count, $\times10^9$/L, N (%)		
<0.8	58 (53)	62 (55)
≥0.8	52 (47)	51 (45)
Hemoglobin concentration, g/L, N (%)		
<80	67 (61)	74 (65)
80-99	23 (21)	21 (19)
≥100	20 (18)	18 (16)
Platelet count, $\times10^9$/L, N (%)		
<50	46 (42)	59 (52)
50-99	36 (33)	30 (27)
≥100	28 (25)	24 (21)
Mutations‡, N/N (%)		
ASXL1	29/81 (36)	20/77 (26)
U2AF1	16/81 (20)	13/77 (17)
TET2	16/81 (20)	9/77 (12)
RUNX1	15/81 (19)	18/77 (23)
TP53	14/81 (17)	13/77 (17)
DNMT3A	11/81 (14)	12/77 (16)

ATRA: all-*trans* retinoic acid; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; IPSS-R: revised International Prognostic Scoring System; MDS; myelodysplastic syndromes; MDS-EB-1: myelodysplastic syndromes with excess blasts 1; MDS-EB-2: myelodysplastic syndromes with excess blasts 2. *Classified according to the World Health Organization (2016). ‡Baseline mutations were determined using a targeted-gene next-generation sequencing panel on genomic DNA from bone marrow mononuclear cells.

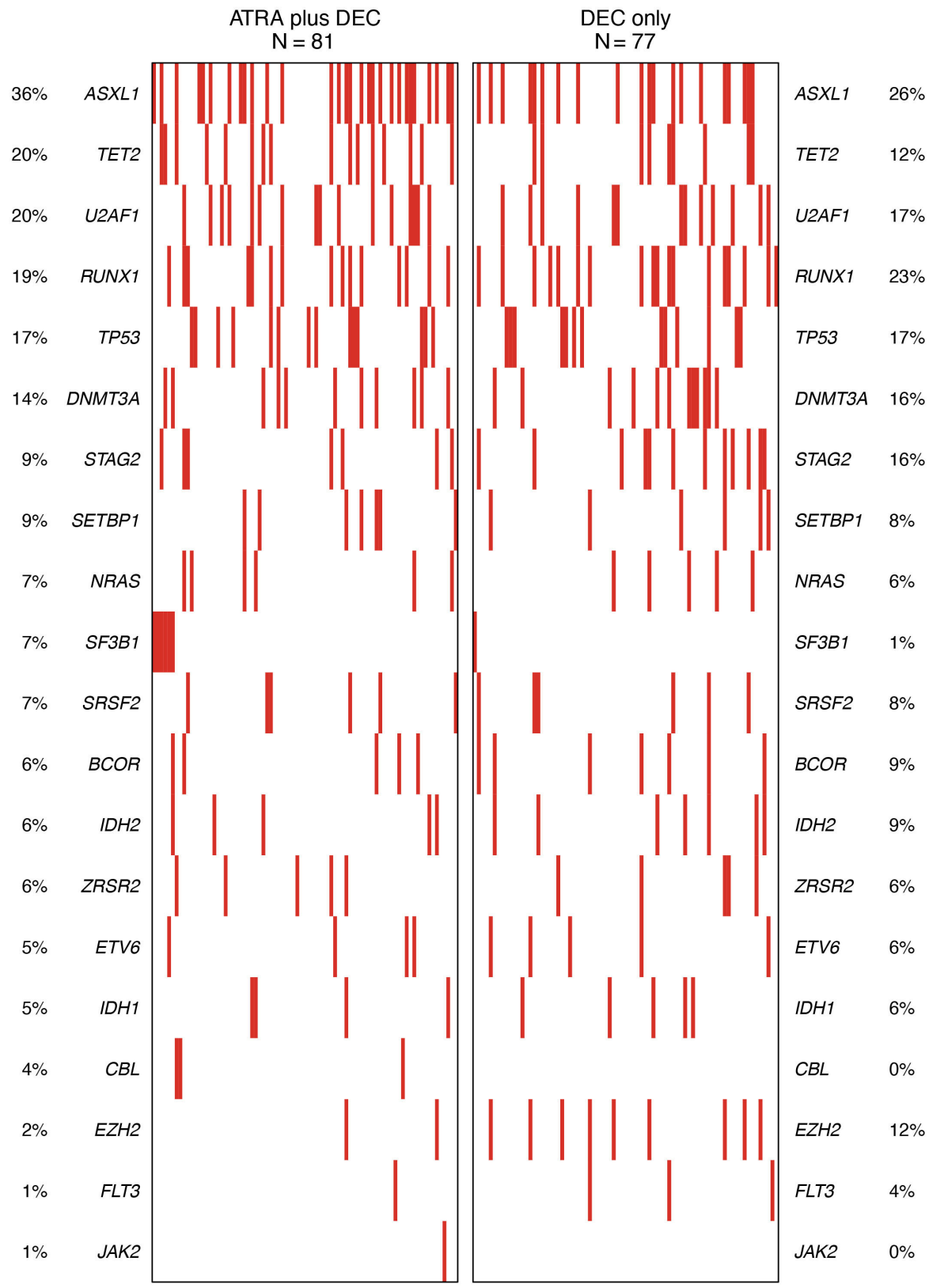

Figure 2. Distribution of genes associated with poor prognosis and frequently mutated genes in patients by treatment group. Mutational analysis was conducted on 158 bone marrow aspirate samples collected at screening (N=81 in the all-*trans* retinoic acid [ATRA] group and N=77 in the decitabine [DEC] group).

the difference in efficacy between men and women needs further exploration. Subgroup analysis of overall response (CR+PR+mCR+HI) in patients with mutations is shown on page 9 of the *Online Supplementary Appendix*.

Survival outcomes

Within a median follow-up of 30.1 months (interquartile range [IQR], 17.7-44.8), a total of 129 (58%) patients died. The number of patients with disease progression and relapse was 68 (62%) in the ATRA group and 82 (73%) in the decitabine group. The median PFS was 14.9 months (95% CI: 9.5-20.3) in the ATRA group and 10.5 months (95% CI: 7.2-13.7) in the decitabine group (hazard ratio [HR]=0.70; 95% CI: 0.51-0.97; *P*=0.032; Figure 4). The two groups did not differ in median time to AML transformation (18.9 *vs*. 15.8 months; HR=0.81; 95% CI: 0.58-1.14; *P*=0.221) or OS (23.0 *vs*. 19.3 months; HR=0.77, 95% CI: 0.54-1.09; *P*=0.137). PFS censored for HSCT also supported the favorable results of the ATRA group (shown on page 33 of the *Online Supplementary Appendix*). For patients with *TP53* mutation, median PFS was 8.3 months (95% CI: 1.88-14.71) in the ATRA group and 9.4 months (95% CI: 2.47-16.33) in the decitabine

group (HR=0.80; 95% CI: 0.34-1.86; *P*=0.605 and OS was 10.7 months (95% CI: 3.7-17.7) in the ATRA group and 10.5 months (95% CI: 3.0-18.0) in decitabine group (HR=0.68; 95% CI: 0.27-1.69; *P*=0.401) was numerically shorter than in the overall patient. Subgroup analyses of PFS, OS, and time to AML transformation are shown on pages 18-20 of the *Online Supplementary Appendix*. *Post hoc* subgroup analyses to assess survival outcomes according to IPSS-R and IPSS-M scores are shown on pages 21-32 of the *Online Supplementary Appendix*.

Adverse events

An overview of treatment-emergent adverse events is shown in Table 3. The most common treatment-emergent adverse events of any grade were thrombocytopenia (75% in the ATRA group *vs*. 70% in the decitabine group), followed by leukopenia (71% *vs*. 71%), neutropenia (59% *vs*. 55%), anemia (37% *vs*. 31%), dry skin (35% *vs*. 5%), febrile neutropenia (28% *vs*. 27%), fatigue (25% *vs*. 27%), headache (19% *vs*. 6%), hypertriglyceridemia (17% *vs*. 5%), and pneumonia (14% *vs*. 17%) (Table 3). The most common treatment-emergent adverse events of grade 3 or higher were thrombocytopenia (66% in the ATRA group *vs*. 63% in the decitabine group) and leukopenia (66% *vs*. 63%), followed by neutropenia (55% *vs*. 54%), febrile neutropenia (28% *vs*. 27%), and anemia (26% *vs*. 24%). The majority of the non-hematologic treatment-emergent adverse events were grade 1-2. The ATRA group had higher rates of dry skin (35% *vs*. 5%; *P*<0.001), headache (19% *vs*. 6%; *P*=0.020), and hypertriglyceridemia (17% *vs*. 5%; *P*=0.019) (Table 3). No differentiation syndrome was observed.

The rate of serious hematological treatment-emergent adverse events was 86% (94/110) in the ATRA group and 80% (90/113) in the decitabine group (*P*=0.254). The rate of non-hematological treatment-emergent serious adverse events was 35% (38/110) in the ATRA group and 23% (26/113) in the decitabine group (*P*=0.057). Details of serious treatment-emergent adverse events with a ≥3% frequency in either group are listed on page 8 of the *Online Supplementary Appendix*.

The rates of death due to serious treatment-emergent adverse events were 1% (1/110) in the ATRA group and 3% (3/113) in the decitabine group (*P*=0.622). The death in the ATRA group was attributed to intracranial bleeding. The cause of death for the three patients in the decitabine-only group was infection.

Table 2. Hematological responses.

Response	ATRA plus decitabine N=110	Decitabine N=113	*P**
ORR, N (%)	86 (78)	58 (51)	<0.001
Best overall response, N (%)†			
CR	25 (23)	14 (12)	0.042
PR	0	0	
mCR+HI	21 (19)	21 (19)	
mCR without HI	33 (30)	20 (18)	
HI only	7 (6)	3 (3)	0.181
SD	7 (6)	21 (19)	0.006
PD	17 (16)	34 (30)	0.009
Hematologic response, N (%)	53 (48)	38 (34)	0.027
Neutrophil response, N (%)			
Yes	21 (19)	12 (11)	0.011
No	40 (36)	63 (56)	
Not applicable	49 (45)	38 (33)	
Erythroid response, N (%)			
Yes	34 (31)	23 (20)	0.061
No	60 (55)	79 (70)	
Not applicable	16 (14)	11 (10)	
Platelet response, N (%)			
Yes	37 (34)	30 (27)	0.286
No	45 (41)	58 (51)	
Not applicable	28 (25)	25 (22)	
Cytogenetic response, N/N (%)	22/29 (76)	16/28 (57)	0.134
Partial	8/29 (28)	6/28 (21)	
Complete	14/29 (48)	10/28 (36)	

ATRA: all-*trans* retinoic acid; CR: complete remission; HI: hematologic improvement; IWG: International Working Group 2006 criteria; mCR: marrow complete remission; ORR: overall response rate; PD: progressive disease; PR: partial remission; SD: stable disease. *Assessed by Cochran-Mantel Haenszel general association χ^2 test. †Assessed per International Working Group 2006 Criteria.

Discussion

In this multicenter, randomized controlled trial, we demonstrated a higher ORR (78% in the ATRA group *vs*. 51% in the decitabine group), a higher rate of hematological response (CR+PR+HI rate 48% *vs*. 34%, response not including mCR) a higher rate of CR (23% *vs*. 12%), and improved PFS (14.9 months *vs*. 10.5 months) in the ATRA group. Hematological treatment-emergent adverse events did not differ between the two groups.

The ORR in the decitabine group in this trial was 51%. This rate was generally consistent with the ORR as a composite of CR, PR, HI, and mCR without HI in MDS-RAEB patients receiving monotherapy with decitabine reported in previous studies.[11] The modified ORR, which included CR, PR, and HI, was exclusive of mCR without HI in this trial (34%) and was also similar to that reported for decitabine monotherapy in MDS patients (30%).[4] The CR rate in this trial (12%) was also consistent with that reported in a previous study (9%).[4] The median time to progression to AML or death in this trial (15.8 months) was also similar to that reported in a previous study (12.1 months).[4] These results demonstrated that the patient sample in this trial was representative, which highlights the potential for applicability to a general population of patients with MDS-EB-1 or MDS-EB-2.

Since mCR (a reduction in BM blast count to ≤5% without HI) has not been shown to be associated with prolonged OS, including mCR without HI in the ORR could result in

Subgroup	ATRA plus decitabine (response/patients)	Decitabine (response/patients)	OR (95% CI)	*P* for interaction
Sex				
Male	55/70	32/75	5.38 (2.56−11.30)	0.03
Female	30/40	26/38	1.39 (0.52−3.73)	
Age				
≥60	45/61	32/65	2.90 (1.37−6.14)	0.51
<60	41/49	26/48	4.34 (1.68−11.18)	
ECOG performance status				
0	13/14	8/12	6.50 (0.61−68.96)	
1	47/62	31/65	3.44 (1.61−7.33)	0.63
2	26/34	19/36	2.91 (1.04−8.13)	
Disease type				
EB-1	41/52	29/56	3.47 (1.49−8.10)	0.95
EB-2	45/58	29/57	3.34 (1.49−7.49)	
IPSS-R risk score				
>4.5	73/94	45/94	3.79 (2.01−7.12)	0.46
≤4.5	13/16	13/19	2.00 (0.41−9.76)	
Karyotype				
Normal	46/56	34/61	3.25 (1.42−7.45)	0.88
Abnormal	40/54	24/52	3.68 (1.61−8.43)	
Complex	18/23	11/23	5.18 (1.34−20.06)	0.77
Non complex	22/31	13/29	3.01 (1.04−8.74)	
Neutrophils × 10^9/L				
≥0.8	40/52	27/51	2.96 (1.27−6.92)	0.67
<0.8	46/58	31/62	3.83 (1.71−8.59)	
Hemoglobin g/L				
≥80	37/43	23/39	4.29 (1.47−12.54)	0.60
<80	49/67	35/74	3.10 (1.53−6.27)	
Platelets × 10^9/L				
≥50	47/63	30/54	2.35 (1.08−5.13)	0.18
<50	39/47	28/59	5.40 (2.16−13.50)	
Molecular marker				
ASXL1	22/29	9/20	3.84 (1.13−13.07)	0.89
RUNX1	12/15	7/18	6.27 (1.29−30.54)	0.48
U2AF1	12/16	6/13	3.50 (0.73−16.85)	0.87
TET2	13/16	2/9	15.17 (2.03−113.35)	0.17
TP53	11/14	7/13	3.14 (0.59−16.85)	0.79
DNMT3A	8/11	4/12	5.33 (0.89−31.92)	0.71
All patients	86/110	58/113	3.40 (1.90−6.09)	

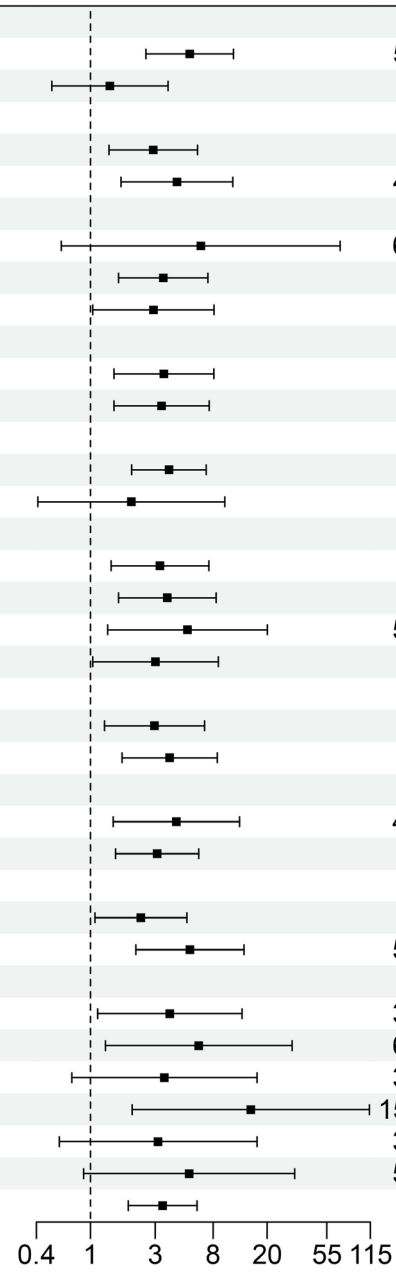

Figure 3. Forest plot of the subgroup analysis. Effect of treatment on the overall response rate in subgroups with different demographic and disease characteristics. *P* values are for interactions. ATRA: all-*trans* retinoic acid; OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EB: excess blasts; IPSS-R: revised International Prognostic Scoring System.

overestimation of treatment response and bias in the group comparison. We therefore analyzed treatment response by excluding mCR (i.e., CR+PR+HI), and the results continued to show a higher response rate in the ATRA group *versus* the decitabine alone group (48% *vs*. 34%; *P*=0.027). Furthermore, since reduction in marrow blasts may be beneficial in patients who would be bridged to allo-HSCT, higher rate of marrow response (i.e., CR+mCR) in the ATRA group also supported its potential benefits in bridging patients to allo-HSCT.[29-31] However, very-high risk MDS patients exhibited reduced responsiveness to decitabine-ATRA. Therefore, future therapeutic strategies should focus on more intensified or rationally designed treatment regimens. Promising strategies may include: triplet combinations incorporating venetoclax, immunomodulatory agents (such as anti-CD47 or anti-TIM-3 antibodies), or targeted inhibitors (e.g., IDH1/2 inhibitors); optimization of ATRA and/or HMA dosing based on bone marrow niche targeting; and biomarker-guided patient selection for ATRA-based combination therapies.

The median PFS was 14.9 months in the ATRA group *versus* 10.5 months in the decitabine group (*P*=0.032) in this trial. OS did not differ between the two groups. This discrepancy between PFS and OS outcomes may be partly explained by the variety of subsequent treatments administered to patients in both the combination therapy and control groups after disease progression. These treatments included HSCT, other hypomethylating agents, and conventional chemotherapy. Such factors are likely to act as significant confounders, thereby interfering with an accurate assessment of the independent survival benefit attributable to the decitabine-ATRA combination regimen itself. Additionally, the relatively small sample size may have contributed to limited statistical power. Even if the combination therapy holds potential clinical value, this limited power could have

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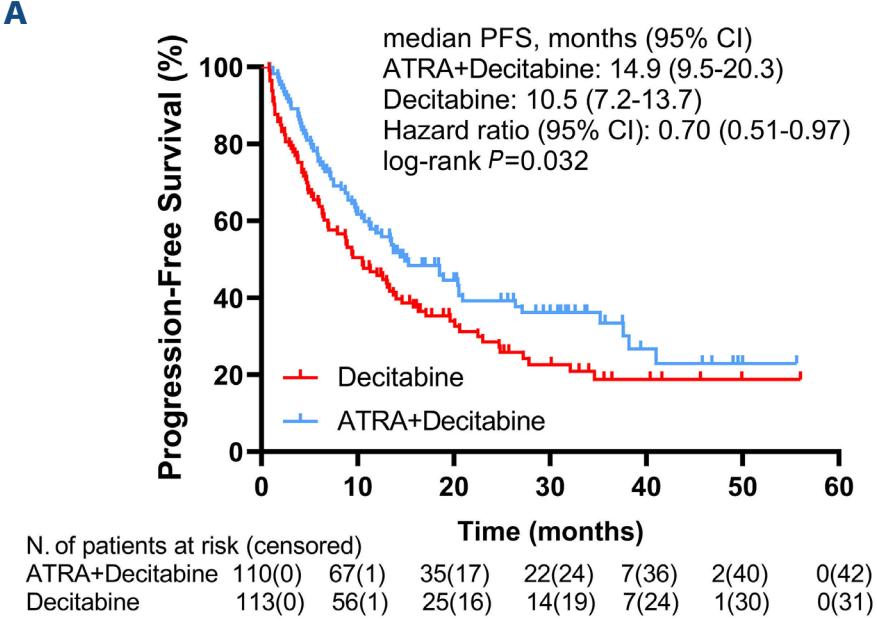

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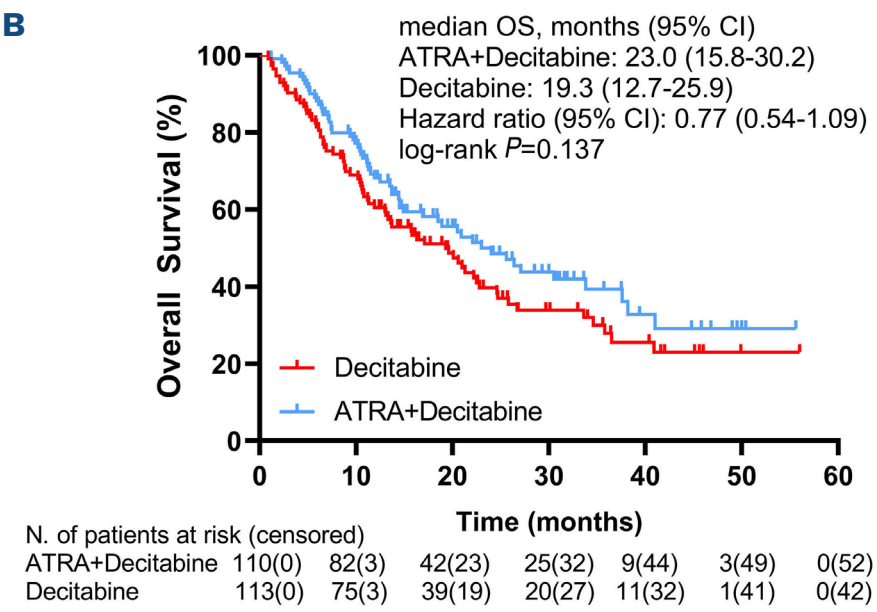

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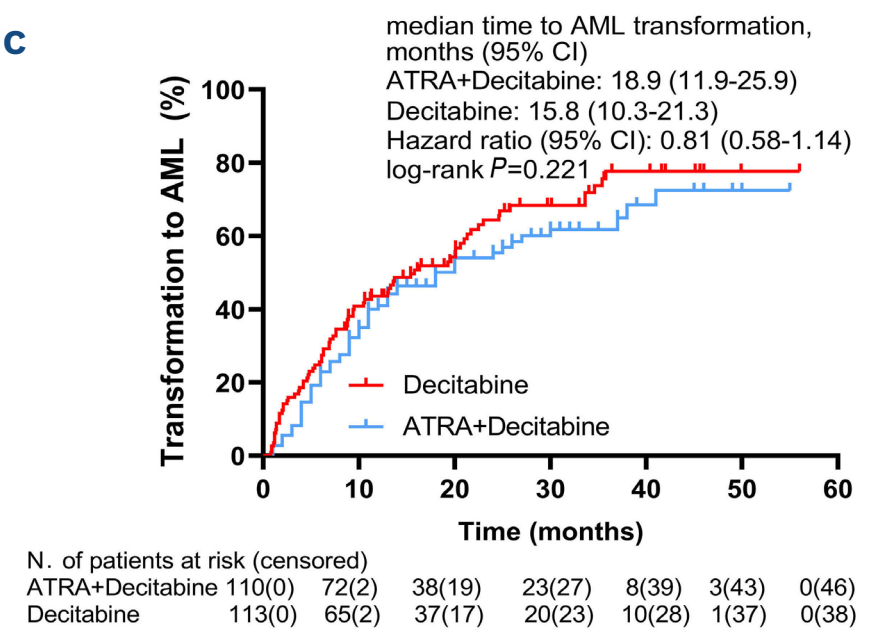

Figure 4. Kaplan-Meier curves for survival outcomes. (A) Progression-free survival (PFS), (B) overall survival (OS) and (C) transformation to acute myeloid leukemia (AML) in the modified intention-to-treat population at the final analyses. ATRA: all-*trans* retinoic acid; HR: hazard ratio; CI: confidence interval.

Table 3. Treatment-emergent adverse events.

TEAE	ATRA plus decitabine N=110	Decitabine N=113	*P*
Hematological events, N (%)			
Thrombocytopenia Grade 3 or above	82 (75) 72 (66)	79 (70) 71 (63)	0.440 0.683
Leukopenia Grade 3 or above	78 (71) 72 (66)	80 (71) 71 (63)	0.985 0.683
Neutropenia Grade 3 or above	65 (59) 60 (55)	62 (55) 61 (54)	0.524 0.933
Anemia Grade 3 or above	39 (37) 29 (26)	35 (31) 27 (24)	0.477 0.671
Febrile neutropenia Grade 3 or above	31 (28) 31 (28)	30 (27) 30 (27)	0.784 0.784
Non-hematological events, N (%)			
Dry skin Grade 3 or above	38 (35) 2 (2)	6 (5) 0	<0.001 0.242
Fatigue Grade 3 or above	27 (25) 3 (3)	31 (27) 4 (4)	0.830 1.000
Headache Grade 3 or above	21 (19) 2 (2)	7 (6) 0	0.020 0.242
Vomiting Grade 3 or above	17 (16) 0	16 (14) 1 (1)	0.631 1.000
Pneumonia Grade 3 or above	15 (14) 15 (14)	19 (17) 19 (17)	0.509 0.509
Hemorrhage Grade 3 or above	21 (20) 3 (3)	25 (22) 1 (1)	0.576 0.595
Nasal hemorrhage Grade 3 or above	4 (4) 0	6 (5) 0	0.880 -
Intracranial hemorrhage Grade 3 or above	3 (3) 3 (3)	2 (2) 1 (1)	0.491 0.595
Other hemorrhage Grade 3 or above	14 (13) 0	17 (15) 0	0.503 -
Hypertriglyceridemia Grade 3 or above	19 (17) 2 (2)	6 (5) 0	0.019 0.242
Hypercholesterolemia Grade 3 or above	2 (2) 0	0 0	0.242 -
Increased alanine aminotransferase Grade 3 or above	12 (10) 1 (1)	6 (5) 1 (1)	0.456 1.000
Increased total bilirubin Grade 3 or above	10 (9) 0	11 (10) 1 (1)	0.967 1.000
Increased aspartate aminotransferase Grade 3 or above	8 (7) 0	4 (4) 0	0.478 -
Increased urea nitrogen Grade 3 or above	4 (4) 0	6 (5) 0	0.583 -
Increased creatinine Grade 3 or above	3 (3) 0	5 (4) 0	1.000 -

Continued on following page.

TEAE	ATRA plus decitabine N=110	Decitabine N=113	*P*
Non-hematological events, N (%)			
Upper respiratory tract infection Grade 3 or above	11 (10) 2 (2)	7 (6) 2 (2)	0.476 1.000
Skin infection Grade 3 or above	6 (5) 1 (1)	3 (3) 0	0.661 0.493
Soft tissue infection Grade 3 or above	5 (5) 3 (3)	6 (5) 3 (3)	1.000 1.000
Urinary tract infection Grade 3 or above	3 (3) 0	5 (4) 1 (1)	1.000 1.000
Other infections Grade 3 or above	12 (11) 3 (3)	15 (13) 2 (2)	0.368 0.976
Oral mucositis Grade 3 or above	12 (11) 2 (2)	7 (6) 1 (1)	0.621 0.981
Cheilitis Grade 3 or above	11 (10) 0	5 (5) 0	0.208 -
Bone pain Grade 3 or above	8 (7) 0	4 (4) 0	0.419 -
Abdominal pain Grade 3 or above	7 (6) 0	4 (4) 0	0.574 -
Maculopapule Grade 3 or above	9 (8) 0	5 (5) 0	0.525 -
Constipation Grade 3 or above	8 (7) 0	9 (8) 0	1.000 -
Diarrhea Grade 3 or above	7 (6) 1 (1)	10 (9) 0	0.362 0.493
COVID-19 Grade 3 or above	4 (4) 0	1 (1) 0	0.165 -

TEAE: treatment-emergent adverse events; ATRA: all-*trans* retinoic acid; COVID-19: coronavirus disease 2019.

resulted in the failure to detect a statistically significant difference in OS between the two groups.

Hematologic treatment-emergent adverse events did not differ between the two groups in this trial, supporting the hematologic safety of ATRA. However, the ATRA group had a higher rate of several non-hematologic treatment-emergent adverse events, including dry skin, headache, and hypertriglyceridemia. This profile is generally consistent with previous trials of ATRA in humans.[26,32-36] In addition, consistent with results previously reported in AML patients,[26] most of the non-hematologic treatment-emergent adverse events reported in this trial were of low grade and reversible upon dose reduction or delay.

Interestingly, while the phase III SELECT-MDS-1 trial recently failed to demonstrate a significant improvement in CR rates with azacitidine plus tamibarotene, a selective *RARA* agonist, compared to azacitidine plus placebo in higher-risk MDS patients overexpressing *RARA*,[37] our study showed that ATRA, also an *RARA* agonist, significantly improved response rates and PFS when combined with decitabine. This discrepancy suggests that ATRA may exert anti-tumor effects through mechanisms beyond *RARA* agonism. Notably, emerging evidence indicates that ATRA can degrade β-catenin in the bone marrow niche independently of genetic mutations, thereby disrupting the β-catenin-Jag1 axis and potentially contributing to therapeutic efficacy in non-APL myeloid malignancies.[38] This mechanism, which is not shared by all RARα agonists, may help explain the enhanced activity observed in our trial and highlights the multifaceted nature of ATRA's mode of action. In addition, the two different drugs and schedules (in combination with azacitidine instead of decitabine) used in the two studies made it quite difficult to compare.

This trial has several limitations. First, the primary endpoint was the ORR rather than survival outcomes. Future trials with either PFS or OS as the primary endpoint are needed to verify the potential survival advantage of ATRA plus decitabine. Second, bone marrow follow-up has deviated substantially from the plan due to the disruption caused by the COVID-19 pandemic. Accordingly, PFS and time to leukemia transformation might have been overestimated. Third, quality of life was not examined as planned. Fourth, genetic testing for mutation panels varied significantly across trial centers.

In conclusion, treatment with decitabine plus ATRA resulted in a higher ORR and prolonged PFS than decitabine monotherapy in patients with MDS-EB without increasing hematologic treatment-emergent adverse events. No new non-hematologic treatment-emergent adverse events were reported. These findings encourage phase III trials using survival outcomes as the primary endpoint.

Disclosures

No conflicts of interest to disclose.

Contributions

HT and XZ were involved in the study design, data acquisition and interpretation, manuscript writing and critical review, and accessed and verified the data. HT, XZ, YL, YG, ZG, LH, JZ, HC, GO, YT, YK, FZ, LS, WJ, GX, LM, LY, CM, JJ and FM enrolled and treated patients and gathered data. JL conducted the statistical analysis. XZ drafted the manuscript. All the authors reviewed the final manuscript and took responsibility for the data. All the authors approved the article for publication.

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Data-sharing statement

Original data are available from the corresponding author upon request.

References

1. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-2465.
2. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20(10):2429-2440.
3. Garcia JS, Swords RT, Roboz GJ, et al. A systematic review of higher-risk myelodysplastic syndromes clinical trials to determine the benchmark of azacitidine and explore alternative endpoints for overall survival. Leuk Res. 2021;104:106555.
4. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006;106(8):1794-1803.
5. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223-232.
6. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol. 2006;24(24):3895-3903.
7. Lübbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol. 2011;29(15):1987-1996.
8. Hasegawa K, Wei AH, Garcia-Manero G, et al. Azacitidine monotherapy in patients with treatment-naïve higher-risk myelodysplastic syndrome: a systematic literature review and meta-analysis. Clin Lymphoma Myeloma Leuk. 2023;23(2):127-137.
9. Rajakumaraswamy N, Gandhi M, Wei AH, et al. Real-world effectiveness of azacitidine in treatment-naive patients with higher-risk myelodysplastic syndromes. Clin Lymphoma Myeloma Leuk. 2024;24(4):260-268.e2.
10. Sallman DA, Al Malki MM, Asch AS, et al. Magrolimab in combination with azacitidine in patients with higher-risk myelodysplastic syndromes: final results of a phase Ib study. J Clin Oncol. 2023;41(15):2815-2826.
11. Lee YG, Kim I, Yoon SS, et al. Comparative analysis between azacitidine and decitabine for the treatment of myelodysplastic syndromes. Br J Haematol. 2013;161(3):339-347.
12. Michelis FV, Atenafu EG, Gupta V, et al. Comparable outcomes post allogeneic hematopoietic cell transplant for patients with de novo or secondary acute myeloid leukemia in first remission. Bone Marrow Transplant. 2015;50(7):907-913.
13. Sekeres MA, Watts J, Radinoff A, et al. Randomized phase 2 trial of pevonedistat plus azacitidine versus azacitidine for higher-risk MDS/CMML or low-blast AML. Leukemia. 2021;35(7):2119-2124.
14. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-629.
15. Sallman DA. To target the untargetable: elucidation of synergy of APR-246 and azacitidine in TP53 mutant myelodysplastic syndromes and acute myeloid leukemia. Haematologica. 2020;105(6):1470-1472.
16. Curigliano G, Gelderblom H, Mach N, et al. Phase I/Ib clinical trial of sabatolimab, an anti-TIM-3 antibody, alone and in combination with spartalizumab, an anti-PD-1 antibody, in advanced solid tumors. Clin Cancer Res. 2021;27(13):3620-3629.
17. Majeti R, Chao MP, Alizadeh AA, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell. 2009;138(2):286-299.
18. DeZern AE, Thepot S, de Botton S, et al. Pivotal results of SELECT-MDS-1 phase 3 study of tamibarotene with azacitidine in newly diagnosed higher-risk MDS. Blood Adv. 2025;9(16):4090-4099.
19. Zeidan AM, Ando K, Rauzy O, et al. Sabatolimab plus hypomethylating agents in previously untreated patients with higher-risk myelodysplastic syndromes (STIMULUS-MDS1): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Haematol. 2024;11(1):e38-e50.
20. Momparler RL, Doré BT, Momparler LF. Effect of 5-aza-2'-deoxycytidine and retinoic acid on differentiation and c-myc expression in HL-60 myeloid leukemic cells. Cancer Lett. 1990;54(1-2):21-28.
21. Blagitko-Dorfs N, Jiang Y, Duque-Afonso, et al. Epigenetic priming of AML blasts for all-trans retinoic acid-induced differentiation by the HDAC class-I selective inhibitor entinostat. PLoS One. 2013;8(10):e75258.
22. Wang L, Zhang Q, Ye L, et al. All-trans retinoic acid enhances the cytotoxic effect of decitabine on myelodysplastic syndromes and acute myeloid leukaemia by activating the RARα-Nrf2 complex. Br J Cancer. 2023;128(4):691-701.
23. Meier R, Greve G, Zimmer D, et al. The antileukemic activity of decitabine upon PML/RARA-negative AML blasts is supported by all-trans retinoic acid: in vitro and in vivo evidence for cooperation. Blood Cancer J. 2022;12(8):122.
24. Raffoux E, Cras A, Recher C, et al. Phase 2 clinical trial of 5-azacitidine, valproic acid, and all-trans retinoic acid in patients with high-risk acute myeloid leukemia or myelodysplastic syndrome. Oncotarget. 2010;1(1):34-42.
25. Soriano AO, Yang H, Faderl S, et al. Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome. Blood. 2007;110(7):2302-2308.
26. Lübbert M, Grishina O, Schmoor C, et al. Valproate and retinoic acid in combination with decitabine in elderly nonfit patients with acute myeloid leukemia: results of a multicenter, randomized, 2 × 2, phase II trial. J Clin Oncol. 2020;38(3):257-270.
27. Rummelt C, Grishina O, Schmoor C, et al. Activity of decitabine combined with all-trans retinoic acid in oligoblastic acute

myeloid leukemia: results from a randomized 2x2 phase II trial (DECIDER). Haematologica. 2023;108(8):2244-2248.
28. Chinese Society of Hematology, Chinese Medical Doctor Association; Chinese Medical Association, Chinese Medical Doctor Association. Chinese guidelines for diagnosis and treatment of acute promyelocytic leukemia. Zhonghua Xue Ye Xue Za Zhi. 2018; 39(3):179-183.
29. Scott BL. Existing agents, novel agents, or transplantation for high-risk MDS. Hematology Am Soc Hematol Educ Program. 2020(1):411-417.
30. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Société Française de Greffe de Moelle et de Thérapie-cellulaire and the Groupe-Francophone des Myélodysplasies. J Clin Oncol. 2012;30(36):4533-4540.
31. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med. 2017;376(6):536-547.
32. Tobin RP, Cogswell DT, Cates VM, et al. Targeting MDSC differentiation using ATRA: a phase I/II clinical trial combining pembrolizumab and all-trans retinoic acid for metastatic melanoma. Clin Cancer Res. 2023;29(7):1209-1219.
33. Querfeld C, Rosen ST, Guitart J, et al. Comparison of selective retinoic acid receptor- and retinoic X receptor-mediated efficacy, tolerance, and survival in cutaneous t-cell lymphoma. J Am Acad Dermatol. 2004;51(1):25-32.
34. Schlenk RF, Fröhling S, Hartmann F, et al. Phase III study of all-trans retinoic acid in previously untreated patients 61 years or older with acute myeloid leukemia. Leukemia. 2004;18(11):1798-1803.
35. Schlenk RF, Lübbert M, Benner A, et al. All-trans retinoic acid as adjunct to intensive treatment in younger adult patients with acute myeloid leukemia: results of the randomized AMLSG 07-04 study. Ann Hematol. 2016;95(12):1931-1942.
36. Greenberg PL, Stone RM, Abaza Y, et al. NCCN Guidelines® Insights: Myelodysplastic Syndromes, Version 2.2025. J Natl Compr Canc Netw. 2025;23(3):66-75.
37. DeZern AE, Thepot S, de Botton S, et al. Pivotal results of SELECT-MDS-1 phase 3 study of tamibarotene with azacitidine in newly diagnosed higher-risk MDS. Blood Adv. 2025;9(16):4090-4099.
38. Mosialou I, Ali AM, Labella R, et al. A niche driven mechanism determines response and a mutation-independent therapeutic approach for myeloid malignancies. Cancer Cell. 2025;43(6):1007-24.e13.