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ORIGINAL ARTICLE

# Allogeneic hematopoietic cell transplantation for acute myeloid leukemia in first complete remission after 5-azacitidine and venetoclax: a multicenter retrospective study

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## Abstract

The combination of hypomethylating agents and venetoclax has revolutionized the therapeutic landscape of acute myeloid leukemia (AML), especially for patients previously deemed unfit for curative–intent treatment. Some of these patients undergo allogeneic hematopoietic cell transplant (alloHCT); yet, there are scarce data regarding transplantation outcomes. We conducted a multicenter nationwide retrospective cohort study, including patients with AML who underwent alloHCT in CR1 after frontline treatment with azacitidine plus venetoclax only (aza-ven group). We collected a historical control group of patients who achieved CR1 after first-line intensive chemotherapy only, followed by alloHCT (intensive group). Patients in the aza-ven group ($n=24$) were transplanted between 2019 and 2021. Compared to the intensive group, patients in the aza-ven group were older (median age 71.7 vs. 58.4 years), had higher incidence of therapy-related AML and AML with antecedent hematologic disorder and had more often adverse cytogenetics. They had a higher percentage of allografts from matched-unrelated donors, and reduced intensity conditioning was more commonly used. The estimated 12 months non relapse mortality was 19.1% in the aza-ven group and 11.8% in the intensive group. The estimated 12 months relapse-free survival and overall survival were 58% and 63% in the aza-ven group and 54% and 70% in the intensive group, respectively. The cumulative incidence of acute GVHD at 6 months and of chronic GVHD at 12 months were 58% and 40% in the aza-ven group and 62% and 42% in the intensive group, respectively. Analysis of the aza-ven group revealed that HCT-CI score and ELN risk category were predictive of RFS in both univariate analysis as well as multivariate analysis. Our data suggests that alloHCT for AML patients achieving first CR with aza-ven appears feasible, with short-term post-transplant outcomes similar to those expected after traditional intensive chemotherapy.

**Keywords** Azacitidine · Venetoclax · Acute myeloid leukemia · Allogeneic hematopoietic cell transplant

## Introduction

Until recently, upfront treatment paradigm for newly diagnosed acute myeloid (AML) consisted of intensive induction chemotherapy for patients deemed "fit," and low-intensity

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or palliative therapy for elderly patients or those deemed too frail to withstand such intensive regimens. Traditional induction chemotherapy yields complete remission rates of approximately 60–80% in younger patients and 40–60% in those older than 60 years [1]. Allogeneic hematopoietic cell transplant (alloHCT) at first complete remission (CR1) is offered when risk of leukemia relapse outweighs transplant-related morbidity and mortality, most often utilized in patients with intermediate- or poor-risk AML [2]. Advanced age and comorbidities have traditionally been the limiting factors for offering alloHCT [3]; yet, innovations in leukemia therapeutics, transplant protocols, and alternative donors have continued to fuel the debate on the role of alloHSCT in CR1 [4].

Regimens based on hypomethylating agents (HMA) plus venetoclax, without conventional chemotherapy, have been recently incorporated into the armamentarium available for patients with AML, expanding the population receiving curative–intent treatment. A large prospective randomized trial of first-line 5-azacitidine plus venetoclax yielded a 66.4% rate of CR or CR with incomplete hematologic recovery (CRi) in patients unfit for intensive chemotherapy [5]. Some of these patients undergo alloHCT; yet, there are scarce data in the literature regarding their post-transplant outcomes. Here, we report the post-transplant outcomes of 24 AML patients transplanted in CR1 after receiving 5-azacitidine plus venetoclax.

## Materials and methods

### Study population

We conducted a multicenter nationwide retrospective cohort study in four academic centers in Israel (Rabin medical Center, Sorasky Medical Center, Chaim-Sheba Medical Center, and Hadassah medical Center). The use of 5-azacitidine plus venetoclax before alloHCT was identified by searching the computerized systems of all participating centers and crossing these data with the departments' AML database. We included all consecutive patients with AML who had documented CR1 following first-line treatment with 5-azacitidine plus venetoclax only, and proceeded to alloHCT between January 2019 and March 2021 (aza-ven group). In addition, we collected a historical control group of consecutive patients who achieved CR1 after first-line intensive chemotherapy only followed by alloHCT between 2016 and 2019 at Rabin Medical Center (intensive group). Patient, disease, and transplant characteristics were collected using the electronic medical record system. Data regarding comorbidities included ischemic heart disease (IHD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), and chronic kidney disease (CKD). Hematopoietic cell transplantation–comorbidity index (HCT-CI) scores were calculated [6]. Conditioning intensity (MAC vs. RIC) was defined as previously described [7]. The study was approved by the Institutional Review Board of each center.

### Outcomes

Efficacy outcomes included relapse-free survival (RFS), defined as the time from transplant to the date of either disease progression, last follow-up or death, and overall survival (OS), calculated as the time from transplant to the date of last follow-up or death. Safety data included hematological and non-hematological adverse events (AE), classified according to the CTCAE criteria version 5.0 [8]. Acute GVHD was classified according to the MAGIC criteria [9], and chronic GVHD according to the NIH criteria [10].

### Statistics

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean and standard deviation for normally distributed variables and as median and range for non-normally distributed variables. Differences in continuous variables were estimated by *t*-test or Mann–Whitney test, as applicable. Differences in categorical variables were estimated by the Fischer exact test. The probability of OS and RFS were estimated by the Kaplan–Meier method. GVHD incidence analyses were performed through competing risk analysis with death and relapse as competing risks (Fine and Gray model).

In the aza-ven group, Cox proportional hazards regression models were fitted to predict effect of covariates on OS and RFS in univariable models. GVHD as a predictor was also tested in the model and treated as time dependent variable. Covariates with a $P$ value $\leq 0.05$ were retained in the cox regression multivariable model for OS and RFS. All statistics were performed with IBM SPSS, version 27.0 (SPSS, Chicago, IL) and SAS software version 9.4 (SAS Institute, North Carolina, USA).

## Results

### Patient characteristics

Twenty four AML patients were included in the aza-ven group and 24 patients in the intensive group. Patient, disease, and transplant characteristics are shown in Table 1.

Patients in the aza-ven group were older (median age 71.7 vs. 58.4 years), had more often therapy-related AML (t-AML) and AML with antecedent hematologic disorder (AHD) (21% and 42% vs. 13% and 0%) and adverse

**Table 1** Baseline patient, disease, and treatment characteristics

| | N, (%) | | | |
|---|---|---|---|---|
| **Patient characteristics** | All ($n=48$) | Aza-ven ($n=24$) | Intensive ($n=24$) | $P$ value |
| Gender (male) | 27 (56) | 14 (58) | 13 (54) | |
| Age (median, range) | 67 (34 – 76) | 71.7 (43 – 76) | 58.4 (34 – 74) | * |
| HCT-CI (median, range) | 1 (0 – 5) | 1 (0 – 5) | 0 (0 – 4) | |
| HCT-CI score | | | | |
| 0 | 21 (45) | 8 (35) | 13 (54) | |
| 1 | 9 (19) | 4 (17) | 5 (21) | |
| 2 | 4 (9) | 2 (9) | 2 (8) | |
| 3 | 8 (17) | 5 (21) | 3 (13) | |
| 4 | 3 (6) | 2 (9) | 1(4) | |
| 5 | 2 (4) | 2 (9) | 0 (0) | |
| Missing | 1 | 1 | 0 | |
| Comorbidity | | | | |
| IHD | 6 (13) | 5 (21) | 1 (4) | |
| CHF | 6 (13) | 5 (21) | 1 (4) | |
| COPD | 6 (13) | 5 (21) | 1 (4) | |
| DM | 10 (21) | 7 (29) | 3 (13) | |
| CKD | 2 (4) | 2 (8) | 0 (0) | |
| Other malignancy | 11 (23) | 7 (29) | 4 (17) | |
| **Disease characteristics** | | | | |
| AML classification | | | | * |
| De novo AML | 30 (63) | 9 (38) | 21 (88) | |
| AML with AHD | 10 (21) | 10 (42) | 0 (0) | |
| Therapy related AML | 8 (17) | 5 (21) | 3 (13) | |
| ELN cytogenetic risk criteria | | | | |
| Favorable | 5 (10) | 1 (4) | 4 (17) | |
| Intermediate | 32 (67) | 15 (63) | 17 (71) | |
| Adverse | 11 (23) | 8 (33) | 3 (13) | |
| NPM1 mutated | 12 (25) | 2 (8) | 10 (42) | * |
| FLT3-ITD mutated | 12 (25) | 2 (8) | 10 (42) | * |
| Karyotype status | | | | * |
| Normal | 21 (44) | 8 (33) | 13 (54) | |
| Complex karyotype | 7 (15) | 7 (29) | 0 (0) | |
| Monosomal karyotype | 1 (2) | 1 (4) | 0 (0) | |
| Other | 8 (17) | 3 (13) | 5 (21) | |
| Missing | 11 (22) | 5 (21) | 6 (25) | |
| **Pretransplant treatment** | | | | |
| Azacitidine + venetoclax cycles | | | | |
| 1 | | 3 (13) | | |
| 2 | | 8 (33) | | |
| 3 | | 3 (13) | | |
| 4 | | 9 (38) | | |
| Intensive chemotherapy | | | | |
| "7 + 3" with daunorubicin 60 mg/m$^2$ | | | 16 (67) | |
| "7 + 3" with daunorubicin 90 mg/m$^2$ | | | 8 (33) | |
| Added Tx during induction | | | | |
| Midostaurin | | | 11 (46) | |
| GO | | | 2 (8) | |
| Consolidation treatment | | | | |

**Table 1** (continued)

| Patient characteristics | N, (%) All ($n=48$) | Aza-ven ($n=24$) | Intensive ($n=24$) | $P$ value |
|---|---|---|---|---|
| HDAC | | | 7 (29) | |
| IDAC | | | 8 (33) | |
| Consolidation cycles | | | | |
| 0 | | | 9 (38) | |
| 1 | | | 13 (54) | |
| 2 | | | 2 (8) | |
| **Transplant parameters** | | | | |
| Graft source | | | | |
| Matched unrelated donor | 27 (56) | 16 (67) | 11 (46) | |
| Matched sibling | 17 (35) | 5 (21) | 12 (50) | |
| Haploidentical | 3 (6) | 3 (13) | 0 (0) | |
| Mismatched (9/10) | 1 (2) | 0 (0) | 1 (4) | |
| Conditioning regimen | | | | * |
| MAC | 23 (48) | 3 (13) | 20 (83) | |
| RIC | 25 (52) | 21 (88) | 4 (17) | |
| **Selected time intervals (median, range)** | | | | |
| Diagnosis to AlloHCT (weeks) | 14.5 (3 – 50) | 17 (3 – 50) | 14 (6 – 23) | |
| AlloHCT admission duration (days) | 28 (17 – 47) | 28 (17 – 47) | 27 (23 – 34) | |
| Allotransplant to last follow-up (weeks) | 47 (0 – 224) | 31 (0 – 99) | 90 (15 – 224) | * |
| Diagnosis to last follow-up (weeks) | 63.5 (19 – 238) | 54 (19 – 113) | 102 (31 – -238) | * |

*AML*, acute myeloid leukemia; *AHD*, antecedent hematologic disorder; *ELN*, European leukemia network; *NPM1*, nucleophosmine; *FLT3*, fms like tyrosine kinase3; *ITD*, internal tandem duplication; *TKD*, tyrosine kinase domain; *HDAC*, high dose ara-C; *IDAC*. intermediate dose ara-C; *HCT-CI*, hematopoietic stem cell transplant comorbidity index; *IHD*, ischemic heart disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *CKD*, chronic kidney disease; *GO,* gemtuzumab ozogamicin; *AlloHCT*, allogeneic hematopoietic cell transplantation; *MAC*, myeloablative conditioning; *RIC*, reduced intensity conditioning

*Statistically significant difference

cytogenetics. Compared to patients in the intensive therapy group, patients in the aza-ven group were more often transplanted from matched unrelated donors (67% vs. 46%) and received more often reduced intensity conditioning regimens (88% vs. 17%).

Three patients in the aza-ven group received post-transplant maintenance therapy (azacitidine, $n=1$; azacitidine + venetoclax, $n=2$), compared to 8 patients in the intensive group (sorafenib, $n=5$; midostaurin, $n=1$; azacitidine + venetoclax, $n=2$).

## Outcomes

### Entire cohort

The median follow-up was 8 (range, 0 to 25) months in the aza-ven group and 23 (range, 4 to 56) months in the intensive group.

The estimated median RFS was not reached in the aza-ven group and was 19.3 months (CI 95% 1–38) in the intensive group. The 12 months RFS was 58% and 54%, in the aza-ven (Fig. 1A) and the intensive group (Fig. 1B), respectively.

The estimated median overall survival of the aza-ven group was not reached and the 12 months OS rate was 63.2% (Fig. 2A). The estimated median survival of the intensive group was 50 months (CI 95% 5–96) and the 12 months OS rate was 70.8% (Fig. 2B).

The estimated 12 month non-relapse mortality (NRM) was 19.1% in the aza-ven group, and 11.8% in the intensive group. Relapse was the major cause of death in both groups (Table 2).

The cumulative incidence of aGVHD at 6 months was 58% in the aza-ven group and 62% in the intensive group. The cumulative incidence of cGVHD at 12 months was 40% and 42%, respectively (Table 2).

### Aza-ven group analysis

In a subgroup Cox regression analysis of the aza-ven group, adverse ELN 2017 risk category and HCT-CI score ≥ 3 were predictive of decreased RFS, both in UVA and in MVA (HR

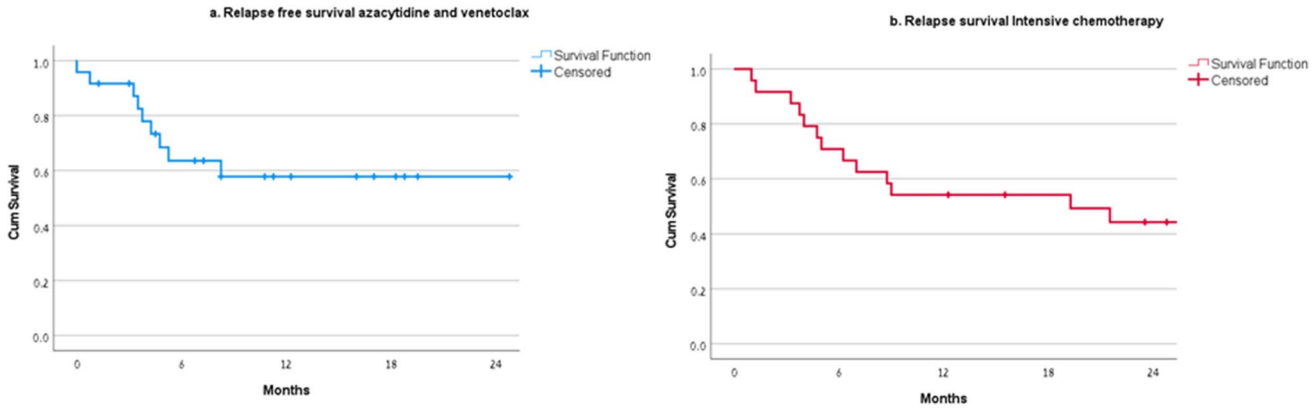


**Fig. 1** Relapse-free survival of the aza-ven group (**A**) and the intensive group (**B**)

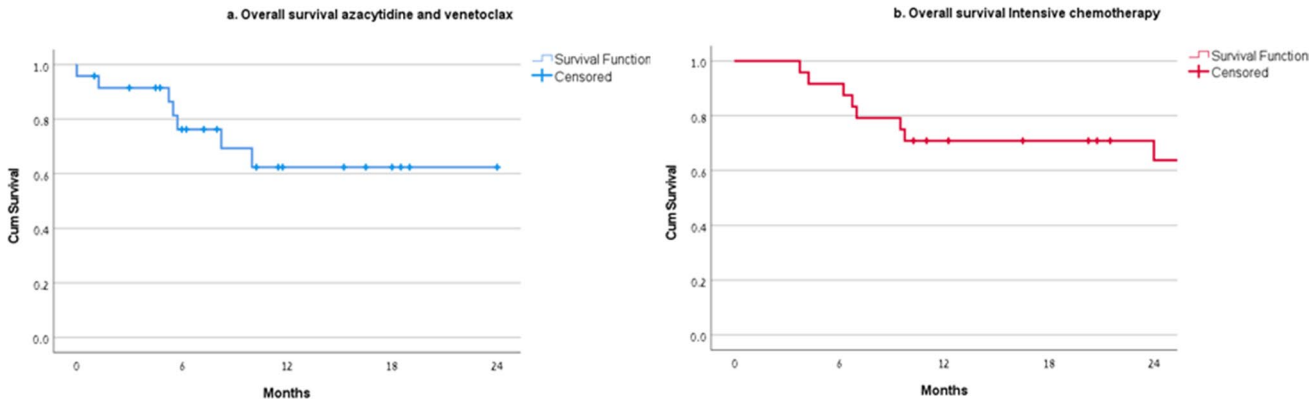


**Fig. 2** Overall survival of the aza-ven group (**A**) and the intensive group (**B**)

10.56, CI 95%1.64–68.1, $p = 0.013$ and HR 6.43, CR 95% 1.34–30.75, $p = 0{,}02$, respectively; Table 3).

Graft source (alternative vs. matched donor) and HCT-CI score $\geq 3$ were predictive of decreased OS in UVA (HR 19.45, CI 95% 1.66–228.13, $p = 0.018$ and HR 5.93, CI 95% 1.13–31.05, $p = 0.03$, whereas age, ELN2 2017 risk stratification, GVHD, and maintenance therapy were not. In MVA, neither of these factors retained their predictive value.

Of note, neither aGHVD nor cGHVD as time-dependent variables were predictive of RFS or OS (Table 3).

## Discussion

Herein, we report the post-transplant outcomes of 24 AML patients transplanted in CR1 after first-line therapy with azacitidine plus venetoclax. With a median follow-up of 8 (range 0 to 25) months, 62.5% were alive and in remission. We also describe outcomes of a second group of 24 patients treated with intensive induction therapy prior to transplant. Although a direct comparison of outcomes between these two distinct groups is not possible due to different baseline patient characteristics, short-term outcomes, including RFS, OS, and GVHD rates seem similar. In subgroup analysis of the aza-ven group, HCT-CI score and ELN risk category were predictive of RFS in both UVA as well as MVA.

HMA agents primarily target DNA hypermethylation, thereby disrupting myeloid maturation and differentiation with a relatively favorable toxicity profile [11]. Venetoclax induces apoptosis by BCL2 inhibition [12]. Venetoclax-based combination therapy, mainly with HMAs or low-dose cytarabine (LDAC), has been shown to be safe and efficacious in AML, in both upfront as well as salvage setting [13]. In the study conducted by Dinardo et al., the addition of

**Table 2** Patient outcome and GVHD

| Response at last follow-up | Azacitidine-venetoclax group ($n=24$) | Intensive treatment group ($n=24$) |
|---|---|---|
| Complete remission | 15 (62.5%) | 10 (42%) |
| Progressive disease | 2 (8.3%) | 5 (21%) |
| Death and cause | 7 (29.2%) | 9 (37%) |
| -Relapse | 4 (16.7%) | 6 (25%) |
| -GVHD | 0 | 0 |
| -Infection | 2 (8.3%) | 0 |
| -Secondary malignancy | 1 (4.2%) | 3 (12%) |
| GVHD | | |
| 6 months aGVHD cumulative incidence | 58% | 62% |
| 12 months cGVHD cumulative incidence | 40% | 42% |
| Grade ≥ 2 aGVHD | 7/13(53.8%) | 13/18 (72.2%) |
| cGVHD grade | | |
| -Mild | 5 | 8 |
| -Moderate | 1 | 3 |
| -Severe | 1 | 6 |

*GVHD*, graft versus host disease; *aGVHD*, acute GVHD; *cGHVD*, chronic GVHD

venetoclax to azacitidine increased the proportion of patients achieving a composite of CR or CR with incomplete hematologic recovery to 66.4%, compared to 28.3% in the placebo group [5]. Importantly, almost half of patients achieved their response prior to their second cycle of treatment. In our study, 46% of patients underwent alloHCT after just one or two cycles of aza-ven, having achieved CR.

Data regarding post-transplant outcomes after azacitidine and venetoclax treatment are limited. Pratz et al. presented in abstract form outcomes of 31 older AML patients included in phase 1/2 clinical trials who received first-line venetoclax–based therapy who underwent alloHCT. Post-transplant 1 year OS and PFS rates were 68% and 55%, respectively [14], similar to the rates observed in the present study. A real-life report of venetoclax-based combinations demonstrated a CR/Cri rate of 60% among AML patients ineligible for intensive chemotherapy [15]. The added drug was either a HMA or low-dose cytarabine (LDAC). Only 10 of the 133 patients included in the study underwent allogeneic HSCT, which was associated with improved survival. A study published by Sandhu et al. described post-transplant outcomes of 32 patients who received HMA and venetoclax as first-line treatment ($N=13$) or for relapsed/refractory disease ($N=19$) [16]. Although almost a third of patients were not in CR/Cri at transplant, results were encouraging, with a 1-year DFS and OS rates of 43.8% and 62.5%, respectively. Compared to these previous reports, the present study includes a rather homogenous study cohort, comprised of 24 patients who underwent allogeneic HSCT at CR1 after receiving only azacitidince and venetoclax.

In a study of 63 patients who received first-line HMA with venetoclax on or off clinical trials, the authors conducted a theoretical comparison with intensive induction chemotherapy using the AML SCORE calculator to evaluate each patients' response and early death, revealing non-inferior response rates and lower death rates with the HMA and venetoclax combination [17].

For years, the mainstay of treatment for patients with AML has been intensive chemotherapy. As such, only younger fit patients have received curative–intent therapy, including alloHCT. Furthermore, high-risk features such as complex karyotype convey inferior remission rates with conventional chemotherapy [18]. Only 10–44% of patients with complex karyotype AML older than 60 years achieve CR with this approach [19]. In comparison, the efficacy of HMA-based therapy seems less dependent on leukemia cytogenetic characteristics [20], and this regimen causes a low rate of organ toxicity [5, 21]. Therefore, older patients with comorbidities and/or adverse-risk cytogenetics may now achieve CR and undergo allHCT. Indeed, Pollyea et al. recently showed that transplant confers a survival advantage in patients who responded to initial azacitidine and venetoclax therapy [22]. In the future a wider range of transplant-eligible AML patients, perhaps also the young and fit could potentially achieve remission and undergo transplant without traditional intensive chemotherapy, following the footsteps of tyrosine kinase inhibitor–based therapy in Philadelphia positive acute lymphoblastic leukemia [23, 24].

Our study has several limitations. First, due to the retrospective nature of the study, there is inherent selection bias, since all patients achieved CR after first-line treatment and

**Table 3** COX Regression analysis for overall survival and relapse-free survival in the azacitidine and venetoclax group

| COX regression analysis | | P value |
|---|---|---|
| RFS | | |
| Univariate analysis (hazard ratio, CI 95%) | | |
| Age at transplant | 1.09 (0.9–1.33) | 0.38 |
| ELN 2017 risk stratification (adverse vs. favorable and intermediate risk groups) | 5.91 (1.44–24.27) | 0.014 |
| HCT-CI HCT-CI ≥ 3 vs. < 3 | 4.39 (1.08–17.81) | 0.038 |
| Graft source (alternative vs. matched) | 4.16 (0.82–21.17) | 0.09 |
| Acute GVHD as time-dependent variable | 1.09 (0.26–4.62) | 0.90 |
| Chronic GVHD as time-dependent variable | 0.14 (0.02–1.17) | 0.069 |
| Maintenance therapy post-transplant | 2.8 (0.57–14.35) | 0.20 |
| Multivariate analysis (hazard ratio, CI 95%) | | |
| Age at transplant | 0.94 (0.82–1.08) | 0.38 |
| HCT-CI ≥ 3 vs. HCT-CI < 3 | 6.43 (1.34–30.75) | 0.02 |
| ELN risk criteria | 10.56 (1.64–68.05) | 0.013 |
| OS | | |
| Univariate analysis (hazard ratio, CI 95%) | | |
| Age at transplant | 1.07 (0.87–1.31) | 0.55 |
| ELN 2017 risk stratification (adverse vs. favorable and intermediate risk groups) | 2.81 (0.63–12.62) | 0.18 |
| HCT-CI HCT-CI ≥ 3 vs. < 3 | 5.93 (1.13–31.05) | 0.03 |
| Graft source (alternative vs. matched) | 19.45 (1.66–228.13) | 0.018 |
| Acute GVHD as time-dependent variable | 0.47 (0.09–2.41) | 0.37 |
| Chronic GVHD as time-dependent variable | 0.17 (0.02–1.55) | 0.12 |
| Maintenance therapy post-transplant | 2.04 (0.22–18.62) | 0.53 |
| Multivariate analysis (hazard ratio, CI 95%) | | |
| Age at transplant | 1.13 (0.85–1.51) | 0.40 |
| HCT-CI ≥ 3 vs. HCT-CI < 3 | 3.28 (0.51–20.77) | 0.21 |
| Graft source (alternative vs. matched) | 16.58 (0.75–362.8) | 0.075 |

*OS*, overall survival; *AML*, acute myeloid leukemia; *ELN*, European leukemia network; *HCT-CI*, hematopoietic stem cell transplant comorbidity index; *GVHD*, graft versus host disease; *RFS*, relapse-free survival

were eligible for transplant. Yet, even though the aza-ven group had several characteristics which traditionally confer inferior outcomes (older age, secondary AML, and adverse cytogenetic features) [1, 18], outcomes were still similar to patients in the intensive group. OS and RFS in the latter group were comparable to those previously described in the literature [3]. Second, follow-up time in the aza-ven group was significantly shorter than the intensive group due to the novelty of this former combination, limiting the yield of chronic GVHD comparison. A further limitation is the lack of minimal residual disease (MRD) data for our patients, due to the lack of validated flow cytometry/next generation sequencing (NGS) MRD measurement for AML in Israel. Lastly, due to the distinct characteristics of the two groups, we were not able to conduct direct statistical comparisons.

In conclusion, for patients with AML who achieve CR1 after aza-ven therapy, alloHCT is a valid option, with short-term post-transplant outcomes that appear to be similar to those achieved after traditional intensive chemotherapy. Our results were collected in the real-world setting, and patients in the aza-ven group were older and had inherently worse leukemia characteristics, including more secondary AML and more adverse cytogenetic features. Therefore, future research is warranted to decipher the true spectrum of AML patients who could benefit from remission induction with this less intensive regimen prior to alloHCT.

**Author contributions** OP contributed to research design, acquisition of data, analysis and interpretation of data, drafted the manuscript and approved the submitted and final versions; SS contributed to research design, acquisition of data, analysis and interpretation of data, drafted the manuscript and approved the submitted and final versions; RR contributed to research design, acquisition of data, revised the manuscript critically and approved the submitted and final versions; AS contributed to research design, acquisition of data, revised the manuscript critically and approved the submitted and final versions; LS contributed to the acquisition of data, revised the manuscript critically and approved the submitted and final versions; BA contributed to the acquisition of data, revised the manuscript critically and approved the submitted

and final versions; OW contributed to research design, analysis and interpretation of data, revised the manuscript critically and approved the submitted and final versions; TS contributed to research design, analysis and interpretation of data, revised the manuscript critically and approved the submitted and final versions; RY contributed to the acquisition of data, revised the manuscript critically and approved the submitted and final versions; OA contributed to the acquisition of data, revised the manuscript critically and approved the submitted and final versions; PR contributed to research design, analysis and interpretation of data, revised the manuscript critically and approved the submitted and final versions; MY contributed to research design, analysis and interpretation of data, drafted the manuscript and approved the submitted and final versions;

**Data availability** Upon request, from corresponding author.

## Declarations

**Conflicts of interest** None.

**Ethics approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Consent for publication** Informed consent was obtained from all individual participants included in the study.

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