Maintenance therapy with oral decitabine plus cedazuridine after allogeneic stem cell transplantation for myelodysplastic syndrome

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Abstract

Disease relapse remains the primary challenge for patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) for myelodysplastic syndromes. Maintenance therapies with hypomethylating agents are under investigation for use in mitigating relapse in high-risk patients. In this retrospective study, we assessed the safety and efficacy of oral decitabine-cedazuridine maintenance in 18 high-risk myelodysplastic syndromes patients post-HSCT. A total of 66.7% (N=12) received decitabine/cedazuridine (35/100 mg) on days 1 and 3, while 33.3% (N=6) received therapy on days 1-3. Patients completed a median of six treatment cycles (range, 1-20), with one third of patients completing all planned cycles. No unexpected adverse events were observed, with the primary toxicity being myelosuppression. Grade 1-2 upper respiratory tract infections occurred in four patients, and fungal pneumonia in one patient. Overall, patients achieved a median 2-year relapse-free survival of 66.7% (95% confidence interval [CI]: 40.4-83.4) and 2-year overall survival of 72.2% (95% CI: 45.6-87.4), with relapses occurring predominantly in *TP53*-mutated cases. Prospective clinical trials are essential to confirm the best tolerated dose with potential to improve transplant outcomes.

Introduction

For patients with myelodysplastic syndromes (MDS) undergoing allogeneic hematopoietic stem cell transplantation (HSCT), disease relapse remains the most common reason for transplant failure,[1,2] and treatment of relapse remains extremely challenging.[3] While results have been mixed, maintenance with hypomethylating agents (HMA) post-HSCT show improvement in disease-free and overall survival (OS) in several phase II studies, with findings supported by recent systematic reviews and meta-analyses.[4,5] However, all studies combine patients with MDS and acute myeloid leukemia (AML) despite differing disease biology, making it difficult to draw meaningful conclusions regarding efficacy in individual patient populations.

HMA including azacitidine and decitabine have been shown to potentiate the graft-*versus*-leukemia effect by inducing $CD8^+$ cytotoxic T-lymphocyte activity.[6] When combined with their expansive effect on T-regulatory cells and hence reduction of graft-*versus*-host disease (GVHD),[7] thus these agents are physiologically promising in mitigating GVHD as well as disease relapse post-HSCT through alteration of the alloreactive response.[8] Our group published a large phase III randomized controlled trial (RCT) investigating the use of azacitidine 32 mg/m^2 post-HSCT in patients with high-risk MDS/AML, finding no significant difference in relapse-free survival (RFS) or OS, although tolerability was shown.[9] However, our recent case control study showed significant improvement in cumulative incidence of relapse (CIR) and consequently RFS in high-risk AML and MDS patients, defined as adverse-risk category by European Leukemia Net (ELN) 2010[10] for AML and Revsised International Prognostic Scoring System (IPSS-R) score >4.5 for MDS, respectively.[11] In addition, a recent meta-analysis including 14 studies comparing HMA to observation alone concluded an improvement in OS, RFS, non-relapse mortality (NRM), rates of chronic GVHD and CIR.[5] There is data suggesting that decitabine might have superior effect on 3-year relapse incidence when compared with azacitidine (8.5% *vs*. 25%; *P*=0.019), albeit with higher rates of grade 3/4 neutropenia

and myelosuppression.[12] Despite the aforementioned trials, there remains a paucity of real world data regarding which HMA to choose, the ideal dosing schedule, efficacy and tolerability.[13]

Decitabine/cedazuridine is Food and Drug Administration-approved for *de novo* and secondary MDS, based on phase II data published in 2022.[14] In addition to potentiation of the graft-*versus*-leukemia effect, decitabine has been shown to enhance natural killer (NK) cell-mediated antibody-dependent cellular toxicity against AML blasts.[15] In the maintenance setting, this is an attractive potential therapeutic option given its oral administration (35-100 mg administered days 1-5 of 28 days). Herein we report the safety, and efficacy outcomes of off-protocol use of oral decitabine/cedazuridine maintenance in the post-transplant setting for patients with high-risk MDS at our institution.

Methods

Study population

Patients >18 years of age with MDS who initiated oral decitabine 35 mg - cedazudirine 100 mg (35/100 mg) maintenance within 180 days post-HSCT between January 2020 and January 2023 were identified retrospectively. Patients included were in complete morphologic remission (CR), defined as <5% bone marrow blasts, at the time of initiation of maintenance, and were minimal residual disease (MRD)-negative by multi-parametric flow cytometry (MFC). Patients had no active GVHD and active infection at time of maintenance initiation. All patients had achieved stable donor hematopoiesis prior to initiation of maintenance defined as absolute neutrophil count (ANC) >1.0x10^9/L and platelets >50 K. All donor types and conditioning regimens were included (Table 1). GVHD prophylaxis was post-transplant cyclophosphamide, tacrolimus and mycophenolate in all patients. Patients with active GVHD requiring treatment or uncontrolled infection were excluded.

Treatment plan

At our institution, most patients with high-risk features for relapse are invited to participate in clinical trials investigating the efficacy and safety of promising agents used as maintenance in the post-transplant setting. However, during this study period, there was no clinical trial for post-HSCT maintenance in the high-risk MDS cohort, hence patients were treated off protocol. Decision regarding time to initiation of therapy post-HSCT was at the physicians' discretion. As per departmental guidelines, physicians aimed to give maintenance treatment for either 8 or 12 cycles total, unless disease relapse or toxicity was observed. The dosing schedule administered was decitabine/cedazudirine 35/100 mg given on days 1, 2 and 3, or days 1 and 3 of a 28-day cycle, pending tolerability and physician discretion. Dose delays and reductions were managed at the discretion of the treating clinician.

Table 1. Demographics of the study cohort.

Baseline characteristics	Values
Age in years, median (range)	62.5 (28-76)
Sex, N (%) Male Female	 12 (66.6) 6 (33.3)
TP53 mutated, N (%)	8 (44)
BM blast count % at diagnosis, median (range)	5 (2-15)
IPPS-R, high and very high risk, N (%)	9 (50)
Pre-HSCT BM blast count %, median (range)	2 (1-4)
Stem cell source, N (%) Bone marrow Peripheral blood stem cells	 1 (5) 17 (95)
Conditioning regime, N (%) Fludarabine/melphalan-based Busulfan-based Fludarabine-TBI	 3 (17) 14 (78) 1 (5)
Donor type, N (%) Matched unrelated donor Matched sibling Haploidentical	 10 (56) 7 (39) 1 (5)

BM: bone marrow; %: percent; IPSS-R: Revised International Prognostic Scoring System; HSCT: hematopoietic stem cell transplant; TBI: total body irradiation.

Safety and response evaluation

All patients had bone marrow evaluations around day +30, +100, day +180, at 1 year and at 2 years according to departmental guidelines. Patients had bone marrow evaluation outside of these time points if deemed necessary by their treating physician. Response was categorized using modified International Working Group criteria for MDS. The depth of response was determined by MRD status using MCF, with an estimated lower limit of detection 0.02%, next-generation sequencing (NGS, estimated sensitivity of 0.01%) and persistence of cytogenetic abnormalities.

All patients were included in safety and efficacy analyses. Adverse events (AE) were recorded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

Clinical characteristics and safety and laboratory data were summarized descriptively. The primary outcome of this study was relapse-free survival (RFS, defined as time from HSCT to disease relapse or death from any cause). Secondary endpoints included CIR, graft failure (GF) and OS. PFS and OS were estimated by Kaplan-Meier method. CIR and NRM were estimated in the competing risks framework treating each other as a competing event. The study was approved by the institutional review board of The University of Texas MD Anderson Cancer Center.

Results

Patient and disease characteristics

We identified 18 consecutive MDS patients who were evaluable for this analysis, with baseline characteristics described in Tables 1 and 2. Median age was 62.5 years (range, 28-76 years). The study cohort was high-risk with half of the patients (N=9) classified as high or very-high-risk disease according to IPSS-R.[16] *TP53* mutation was identified by NGS in 44% of patients (N=8). One third of the patients (N=6) were in the poor or very poor cytogenetic risk groups according to R-IPSS. The median pre-HSCT blast count was 2% (range, 1-4) with all patients exhibiting stable disease prior to transplantation.

Post-transplant maintenance

Oral decitabine/cedazuridine (35/100 mg) was administered on days 1 and 3 every 4-6 weeks in 12 of the 18 patients (66.6%). The remaining six patients received oral decitabine/cedazuridine (35/100 mg) days 1-3.

The median time to maintenance initiation after transplant was 68.5 days (range, 41-155 days). Of 18 patients, 77.7% (N=14) were able to start maintenance therapy within 3 months post-HSCT. All patients were in morphologic CR at time of maintenance initiation, without acute GVHD or active infection. The median number of treatment cycles administered was 6 (range, 1-20). One third of the 18 patients (N=6) completed all planned cycles, with one patient continuing therapy and receiving 20 cycles in total at the time of this evaluation. Four patients received only one cycle of treatment. Among 14 evaluable patients, the median time between cycle 1 and cycle 2 was 41.5 days (range, 28-78 days). For patients who completed eight cycles, the median time from the initiation of treatment to the completion of the eighth cycle was 326 days (range, 321-370 days), corresponding to an interval of 5.8 weeks between cycles. For those who completed 12 cycles, the median time from the start of treatment to the 12th cycle was 478 days (range, 441-515 days), with a median interval of 5.6 weeks between cycles. One patient, who had received 20 cycles and remained on treatment at the time of analysis, continued dosing every 4 weeks, with a total time on therapy of 640 days. Reasons for discontinuation were completion of therapy (N=6), graft failure (N=1), cytopenias (N=1), infection (n=2), disease relapse (N=4), financial reasons (N=1), other pathology (N=1). At the time of last follow-up, two patients remained on treatment, while 16 were off treatment.

Safety and toxicity

No unexpected AE were observed. The most common toxicity was cytopenias, including grade 4 neutropenia (50%) and thrombocytopenia (33.3%). No significant differences in tolerability or toxicity between the dose schedules was identified. Platelet and ANC dynamics after the first cycle for all 18 patients are shown in Figure 1. Following the initiation of decitabine/cedazuridine maintenance, ANC nadired at 24 days (range, 5-50) with a median of 0.5 cells/uL (range, 0.04-7.26). Platelet counts nadired at day +15 (range, 12-65) with a nadir of 37 K (range, 4-177 K). Four patients had treatment delays due to cytopenias (N=2), COVID-19 infection (N=1) and recent surgery (N=1), with a mean delay of 11.94 days (range, 14-112 days).

Dose reduction due to toxicity or tolerability occurred in only two patients. The first patient reduced the dose to one tablet on day 1 but was able to successfully increase to days 1 and 3 after cycle 4. The second patient reduced dosing to days 1 and 3 for cycles 2-4 and then required a further reduction to day 1 only for subsequent cycles. Other toxicities during cycle 1 included nausea (N=3, grade 3 in one patient) and joint pain (N=1). Throughout the treatment period, grade 1-2 upper respiratory infections occurred in four patients, requiring treatment delay in 50% (N=2). One patient developed fungal pneumonia whilst on treatment. One patient taking decitabine/cedazuridine on days 1 and 3 experienced secondary graft failure following cycle 1, failed to respond to CD34-selected boost and died of graft failure at day +138 post-HSCT.

Outcome analyses

With a median follow-up of 31.3 months for survivors, five of 18 (28%) patients experienced relapse. Among these, three patients relapsed during maintenance therapy, leading to its discontinuation (Figure 2). The remaining two patients

Table 2. Disease and treatment characteristics of each myelodysplastic syndrome patient in the cohort.

Patient	Age in years at HSCT	IPSS-R at diagnosis	Cytogenetics at diagnosis	NGS status at diagnosis	Conditioning intensity (MAC *vs.* RIC) and regimen	Initiation of maintenance after HSCT in days	N of cycles	Days between flow MRD positivity and relapse	Days between transplant and relapse	Last status
1	57	7.5	45,XY,del(5)(q22q33),-20,-21,+r	*TP53*	MAC Fludarabine/ melphalan 140/TBI 200Gy	87	1	-	95	Died after relapse at day 222
2	76	7	46,XY,del(7)(q22)[1]/45,idem,-5,der(12) add(12)(p11.2)add(12)(q24.3),der(19) t(12;19)(p13;q13.2)[17]/46,XY[2]/ FISH(+) for *ETV6*(12p13),7q31.	*TP53, STAG2*	RIC Fludarabine/melphalan 100	51	5	98	273	Died after relapse at day 378
3	62	5.5	46,XY	*TP53*	RIC, Fludarabine/TBI 300Gy	61	1	-	-	Death due to secondary graft failure at day 138
4	66	2.5	46,XX,add(1)(p36.2),add(5)(q11.2) [4]/46,XX[16] FISH(+): loss of 2 copies of *EGR1*/del(5q)	*TP53*	MAC Fludarabine/busulfan/ thiotepa	59	8	-	-	Alive in CR at day 738
5	28	3.5	47,XY,+8[7]/46,XY[13]	*CEBPA, RUNX1,TET2*	MAC Fludarabine/melphalan 140	47	10	-	-	Alive in CR at day 819
6	59	5	46,XY[11]//46,XX[9	*ASXL1, SRSF2, TET2, STAG2*	MAC Fludarabine/busulfan/ thiotepa	111	1	53	152	Alive in CR following second transplant at day 1,126
7	69	8.5	45,XY,-3,add(4)(p14),der(5)t(5;17) (q11.2;p13),add(6)(q21),add(8) (p11.2),+add(9)(p12),-12,-13,der(17) t(3;17)(q12;p11.2),+mar[20]	*TP53, PRPF40B*	MAC Fludarabine/busulfan/ cladribine/venetoclax	76	12	-	-	Alive in CR at day 1,420
8	35	4	47,XX,+9[19]/XX[1]	*SMC1A*	MAC Fludarabine/busulfan/ cladribine/thiotepa/ venetoclax	72	8	-	-	Alive in CR at day 1,421
9	57	8.5	41-46,X,-Y,-5,add(7)(q22),+8,-13,add(1) (p11.2),add(19)(q13.2),-20,+0-4mar(cp17)/46,XY[3]8/3/20:45,X,-Y[3]/47~49,idem,del(5)(q13q33),del(7) (q22q34),+8,del(13)(q12q22),add(14) (p11.2),-18,add(19)(p13.3),-20,del(20)(q11 .2q13.3),+1~4mar[cp10]/46,XY[7]/FISH(+)	*TP53*	MAC Fludarabine/busulfan/ thiotepa	64	3	-	192	Died after relapse at 319

Continued on following page.

Patient	Age in years at HSCT	IPSS-R at diagnosis	Cytogenetics at diagnosis	NGS status at diagnosis	Conditioning intensity (MAC *vs.* RIC) and regimen	Initiation of maintenance after HSCT in days	N of cycles	Days between flow MRD positivity and relapse	Days between transplant and relapse	Last status
10	58	5.5	47,XX,+8[20]. FISH(+) +(8q)>2/8/21 (BM:14%): 47,XX,+8[19]/ 46,XX[1]>6/4/21:FISH(+) for KMT2a(MLL)	*BCOR, DNMT3A, IDH1, U2AF1*	MAC Fludarabine/busulfan/ thiotepa	87	20	-	-	Alive in CR at day 1219
11	64	1	46,XX	*SF3B1,TET2*	MAC Fludarabine/busulfan/ thiotepa	65	12	-	-	Alive in CR at day 954
12	65	2	46,XX,del(5)(q13q33) [14]/46,XX[6]>3/ 16/22:46,XX,del(5) (q13q33)[9]/46, idem,del(11) (p15p13)[11]	*TP53, SF3B1*	MAC Fludarabine/busulfan/ thiotepa	148	3	-	-	Alive in CR at day 935
13	68	5.5	46,XY,del(7)(q22q320[17]/46,XY[3]/ FISH(+) for del 7q>10/7/21:6,XY,add(7) (q22)[12]/46,XY[4]/FISH(+) for 7q31	*ASXL1, BRINP3, CSF3R, RUNX1, U2AF1*	MAC Fludarabine/busulfan/ thiotepa	50	1	-	-	Alive in CR at day 985
14	42	4	46,XX,inv(3) (p13q27),-5,add(20)(p11.2), +mar[13]/46,XX[7]/ FISH(+) for del 5q	Negative	MAC Fludarabine/busulfan/ cladribine/thiotepa/ venetoclax	155	7	-	-	Alive in CR at day 730
15	66	3.5	46,XY,del(15) (q22q26.1)	*ASXL1, JAK2*	MAC Fludarabine/busulfan/ cladribine/thiotepa/ venetoclax	101	8	-	-	Alive in CR at day 890
16	66	6	46,XY	*ASXL1, DNMT3a, NPM1, PHF6,U2AF2.*	MAC Fludarabine/busulfan/ cladribine/thiotepa/ venetoclax	90	10	-	-	Alive in CR at day 731
17	61	2	46,XY	*ASXL1,CBL, CSF3R,ETV SETBP1, SH2B3, TP53,U2AF1, ZRSR2*	MAC Fludarabine/ busulfan/thiotepa	42	2	-	176	Death after relapse at day 266
18	63	4	46,XY	*DDX41, DNMT3a*	MAC Fludarabine/ busulfan/thiotepa	63	3			Alive in CR at day 1,288

HSCT: hematopoietic stem cell transplant; NGS: next-generation sequencing; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; MRD: minimal residual disease; TBI: total body irradiation; Gy: gray; CR: complete remission; FISH: fluorescence *in situ* hybridization

relapsed after discontinuing treatment: one at day +152 and other on day +176 after transplant. The first patient completed one cycle of therapy but discontinued due to ongoing pancytopenia at the sixth week post-transplant. Notably, bone marrow assessment at that time showed no evidence of disease. However, the patient relapsed on day 56 after the first cycle of maintenance. The second patient completed three cycles of maintenance therapy but had to discontinue due to veno-occlusive disease. This patient relapsed 55 days after cessation of maintenance therapy. The median time to relapse was 176 days after transplant (range, 95-273) with 40% (N=2/5) relapses occurring in the first 6 months. All relapses occurred in the first year post-HSCT. Among those who relapsed during maintenance, all had *TP53* mutation and complex cytogenetics at diagnosis. As per the inclusion criteria, all patients were MRD negative by MCF at the time of maintenance initiation. However, of the five patients who relapsed, two had persistent mutations identified by NGS prior to starting maintenance therapy, indicating a high risk of relapse. Further patient characteristics for relapsed patients are reflected in Table 2.

At the time of data cutoff, 72.2% (N=13) patients were alive and disease-free, including three with *TP53* mutations. The 2-year RFS was 66.7% (95% confidence interval [CI]: 40.4-83.4) and 2-year OS was 72.2% (95% CI: 45.6-87.4) as shown in Figure 3.

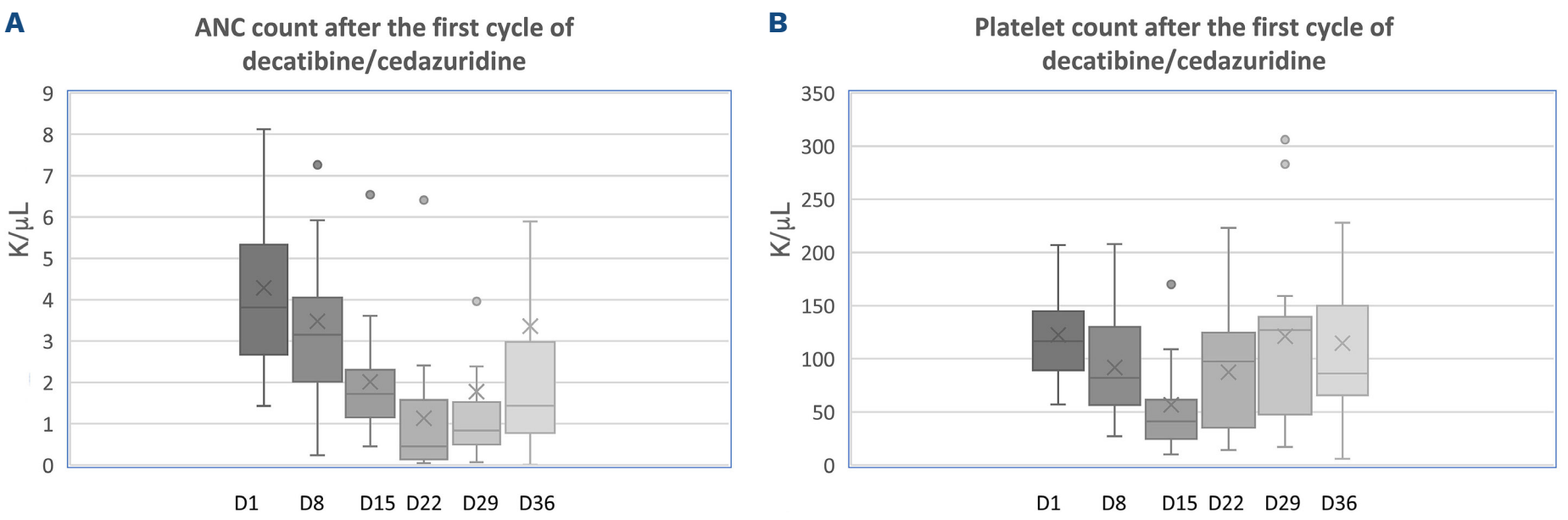

Figure 1. Peripheral blood counts for patients on cycle 1 of decitabine/cedazuridine maintenance. Counts on days 1, 8, 15, 22, 29, 36 of cycle 1 have been presented. (A) Median absolute neutrophil count (K/µL). (B) Median platelet counts (K/µL). The bars in all plots represent median values with error bars representing the interquartile range between the 25% and 75% quartiles. D: day.

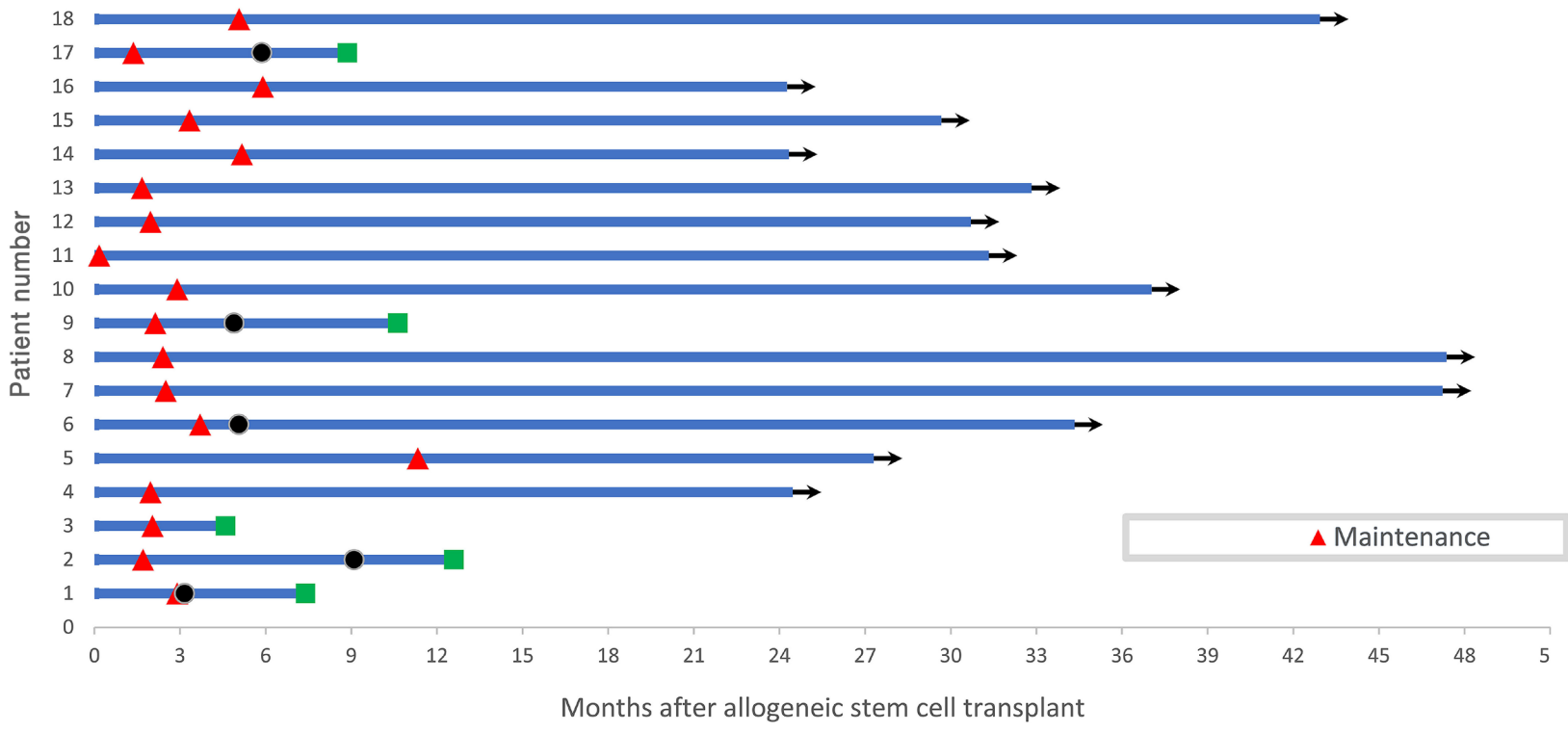

Figure 2. Swimmer plot for the cohort (N=18), including time to death or last known alive. Each row identifies a unique patient received maintenance with decatibine and cedazudirine. ▲: initiation of maintenance treatment; ●: disease relapse after transplant; ■: death; ➡: continues to be alive.

Minimal residual disease monitoring on maintenance treatment

Prior to the initiation of maintenance therapy, all evaluable patients by MCF for MRD (N=16) were MRD negative. Flow cytometry MRD positivity preceded relapse post-HSCT in 40% (N=2/5) relapsed patients. Of the three patients who relapsed while on maintenance therapy, two developed MRD positivity prior to relapse. All three patients required the initiation of further therapy, including the addition of venetoclax, and increase in the decitabine dose.

Molecular monitoring on maintenance therapy

Prior to maintenance therapy initiation, NGS positivity was detected in 18.8% of evaluated patients (N=3/16), with *TP53* mutations detected in all three. Of these, 66.7% (N=2/3 patients) relapsed, developing MRD positivity by MFC at 175 and 94 days post-HSCT respectively, and are described above. The remaining patient exhibited NGS positivity (*TP53*, variant allele frequency [VAF] 2-5%) following completion of 12 cycles of maintenance, but remains in clinical and morphologic remission 1,110 days post-HSCT. At the time of last follow-up, 62.5% of patients (N=10/16 evaluated) maintained NGS negativity following maintenance treatment. Maintenance therapy did not convert any patients with NGS positivity to negativity.

Acute and chronic graft-*versus*-host disease

The cumulative incidence of acute GVHD grade 2-4 at day 100 was 27.78%. Only one patient developed chronic GVHD.

Discussion

To our knowledge this study is the first to report the tolerability and efficacy of oral decitabine/cedazudirine in a homogenous population of real-world patients with high-risk MDS post-HSCT. While HMA agents including azacitidine, guadecitabine and decitabine have been studied in the post-HSCT maintenance setting, the use of HMA post-transplant has not been fully established. There is significant variation in dosing and administration across studies, and all studies combined AML and MDS patients when reporting outcomes.

The choice of maintenance agent post-HSCT must balance tolerability - ensuring minimal impact on quality of life - against efficacy in a patient population which has already undergone extensive prior treatment. Consideration should also be given to minimizing further genomic instability related to therapy. Unique to the HSCT setting, it is crucial to minimize any risk of GVHD or graft failure. Earlier trials investigated the use of subcutaneous (SC) administration of HMA preparations. Phase I dose finding studies in a cohort of 45 patients with high-risk MDS and AML concluded that 32 mg/m^2 of 5-azacitidine for 5 consecutive days was the optimal tolerated dose, associated with relapse incidence of 53%.[17] However, subsequent randomized phase III data published by our group did not show an improvement in RFS or OS with SC azacitidine maintenance in patients with high-risk MDS/AML. Notably, 40% of patients withdrew and only 27.6% of patients were able to complete their planned 12 cycles of treatment.[9] This study also included outdated risk categories, which may have impacted the ability to derive benefit in the high-risk setting. Other retrospective studies in the post-HSCT AML setting have shown conflicting results.[18] The personalization of therapy accounting for disease risk and mitigate toxicity may be important, as demonstrated by improved relapse rates and time to relapse in prospective cohort analysis of high-risk patients with AML.[19] Our recently published matched cohort analysis confirmed these findings, indicating that SC azacitidine may reduce relapse rates, and improve PFS and OS in subsets of high-risk MDS/AML patients defined by IPSS-R and ELN 2010 criteria.[11] Some benefit has also been shown with the use of oral azacitidine (CC-486), with a relapse rate of 21%,

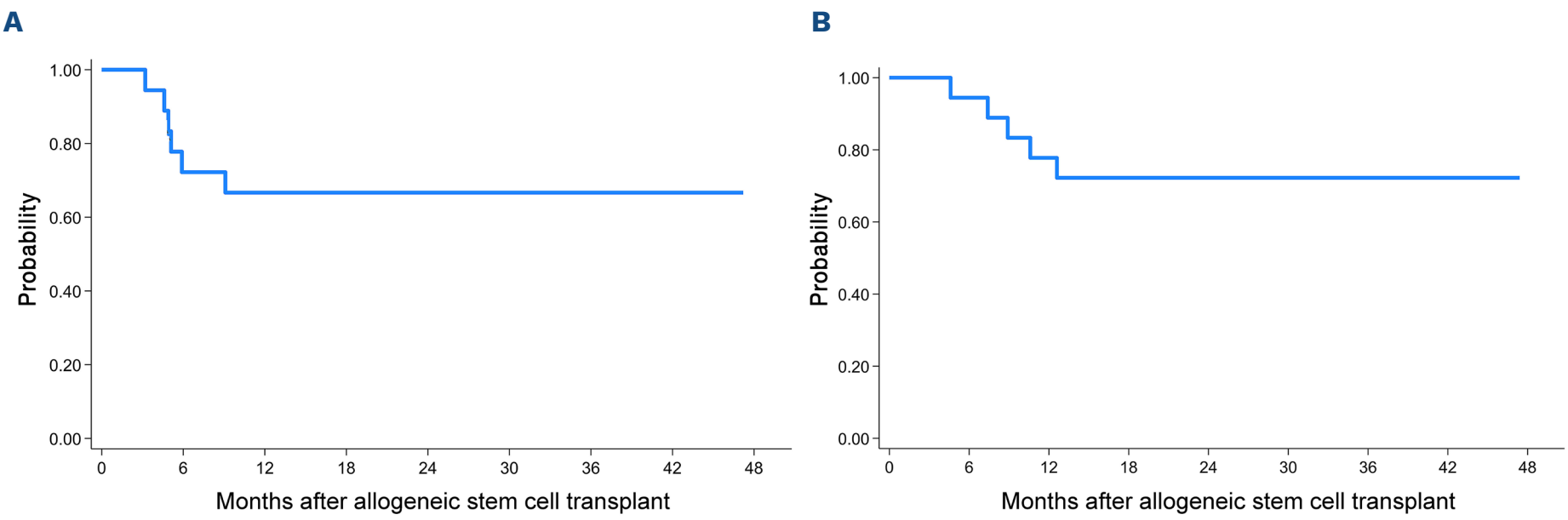

Figure 3. Kaplan-Meier estimate of progression-free survival and overall survival. (A) Progression-free survival. (B) Overall survival.

albeit in a single-armed study.[20] With promising phase I data, the awaited AMADEUS study compares oral CC-486 given for 14 days in 28 day cycles to placebo post-HSCT (*clinicaltrails gov. Identifier: NCT04173533*) with stratifications for age, donor type and conditioning intensity.

Decitabine has mainly been studied in SC preparations with noted benefit.[21-23] Most recently, decitabine (5 mg/m^2 on days 1-5 of each cycle) was combined with recombinant G-CSF in a randomized phase II trial enrolling 220 MRD-negative AML patients post-HSCT.[21] Compared with observation, maintenance therapy improved the 2-year cumulative relapse rates (15 *vs*. 38.3%; *P*<0.01), leukemia-free survival (81.9 *vs*. 60.7%; P<0.01) and OS (85.8 *vs*. 69.7%; *P*<0.01). This effect was maintained even when stratified by MRD status.[21] A retrospective comparison between SC azacitidine and decitabine in 136 patients with high-risk AML suggests decitabine's superior effect on 3-year relapse incidence (8.5% *vs*. 25%; *P*=0.019), albeit with higher rates of grade 3/4 neutropenia and myelosuppression.[12] Oral decitabine/cedurazine, has not yet been studied in this setting, although phase I/II prospective trial is underway (*clinicaltrials gov. Identifier: NCT06297629*) to assess the toxicity and efficacy of oral decitabine/cedurazine alone or in combination with DLI to improve relapse rates after HSCT. It is particularly attractive due to its oral bioavailability allowing for at-home administration and reducing the needs for hospital visits. As an HMA, it potentiates the graft-*versus*-leukemia effect by inducing cytotoxic CD8$^+$ T-cell activity, while also promoting the expansion of T-regulatory cells. Additionally, decitabine has been shown to enhance NK cell-mediated antibody-dependent cellular toxicity against AML blasts.[15]

Given the biggest potential hurdle to long-term success is the prevention of relapse, identifying a tolerable agent that reduces relapse rates is paramount. According to Center for International Blood and Bone Marrow Transplantation (CIBMTR) data, in cohorts of high-risk patients with MDS who do not receive maintenance therapy, 3-year relapse rates are reported to be between 47-52%.[24,25] While our study is limited by its retrospective design and single-arm nature, a 1-year RFS of 66.7% compares favorably to that of patients with similar disease status who do not receive maintenance therapy post-HSCT. In this high-risk patient population, the most common reason for discontinuation of maintenance therapy was relapse, occurring in three patients despite being MRD negative by flow cytometry at time of maintenance initiation. All patients who relapsed had no molecular markers detectable by dedicated molecular MRD testing (*TP53*, N=4; *ASXL1* and *SRSF2*, N=1), but became MRD positive by flow cytometry while receiving maintenance therapy.

Selecting the optimal dose requires further assessment. Pusic *et al*. studied four decitabine doses in SC preparations (5, 7.5, 10 and 15 mg/m^2), administered for 5 days every 6 weeks, and found that 10 mg/m^2 was the most tolerable dose.[22] Similarly, we also found that the majority of patients receiving oral decitabine/cedurazine (35/100 mg) tolerated therapy, with no appreciable difference in toxicity found between administration on days 1-3 when compared to days 1 and 3. Myelosuppression is the major toxicity, although it was manageable with adjusted treatment cycles and did not result in severe infection. The majority of patients were able to initiate maintenance treatment within 3 months post HSCT, and tolerated treatment for a median of six cycles, with approximately 33.3% completing their intended treatment course of eight or 12 cycles (acknowledging that there was variation in planned duration between cycles across treating physicians). While adverse events were generally tolerable, one patient developed graft failure after the initiation of decitabine/cedurazine, which remains an important safety signal that requires monitoring in larger randomized controlled trials. Planned phase I/II data (*clinicaltrials gov. Identifier: NCT06297629*) will be helpful in examining dosing in a larger patient cohort.

The majority of patients in this study received myeloablative conditioning (MAC), which likely contributed to the observed low relapse rate seen in this population. The randomized BMTCTN0901 trial demonstrated improved OS in patients with both MDS and AML treated with MAC, when compared to reduced-intensity conditioning (RIC), with the significantly lower relapse rates offsetting its higher treatment-related mortality.[27] The small sample number of patients treated with RIC regimens in this study limits any conclusions with regarding the role of maintenance following RIC transplantation, although upcoming clinical trials (*clinicaltrials gov. Identifier: NCT04980404*) aim to address this.

Lastly, while this study was not designed to draw inferences regarding MRD monitoring, as high-sensitivity assays including deep-sequencing NGS and dedicated quantitative polymerase chain reaction for targeted mutations become standard of care, the potential role of maintenance may become much more nuanced. Although it is clear that the detection of molecular disease or MRD by flow cytometry post-HSCT is a poor prognostic factor, we identified one patient with NGS positivity who did not relapse, in line with recently published data out of Dana Farber.[26] This suggests that other factors such as conditioning intensity, patient and donor selection may influence disease progression. While one might hypothesize that VAF in molecular reassessment is important, recent publications in this area do not support this hypothesis.[26]

In conclusion, decitabine/cedazudirine for MDS in the post-HSCT setting demonstrated a promising efficacy profile with myelosuppression as the primary toxicity. The majority of patients were able to complete the proposed treatment plan, remaining on maintenance treatment for a median of six cycles, with only five of 18 patients relapsing at a median follow-up of almost 3 years. Prospective randomized trials are needed to determine the most tolerable dose as well as to gather meaningful information regarding patient

selection, optimal treatment duration and overall efficacy to improve HSCT outcomes.

Disclosures

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Contributions

PS, TLS, OP and BO performed data collection and analysis. PS and BO wrote the manuscript. AA, QB, TLS, OP, CH, YA, JR, UP, RC and EJS reviewed and edited the manuscript.

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Data-sharing statement

Individual participant data underlying the results reported in this article (including text, tables, and figures) will be shared after de-identification. Access will be granted to researchers who submit a methodologically sound and ethically approved proposal and obtain MDACC IRB approval for data sharing. Proposals can be submitted within 60 months following article publication. Requests should be directed to boran@mdanderson.org. Data requestors must sign a data access agreement to gain access.

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