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SHORT REPORT

Low-dose decitabine plus venetoclax as post-transplant maintenance for high-risk myeloid malignancies

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Abstract

Relapse remains a major cause of treatment failure following allogeneic stem cell transplantation (allo-SCT) for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). We retrospectively investigated low-dose decitabine and venetoclax (DEC/VEN) as post-transplant maintenance in 26 older patients with AML and MDS. The cumulative incidence of day 100 gIII-IV acute graft versus host disease (GVHD) and 1-year moderate-severe chronic GVHD was 5% and 26%, respectively. One patient relapsed 14 m after transplant. The 1-year non-relapse mortality and survival were 11% and 84%, respectively. DEC/VEN is a safe and potentially effective strategy to reduce the risk of post-transplant relapse.

KEYWORDS
decitabine, maintenance chemotherapy, myeloid leukemia, post-transplant, venetoclax

1 | INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) is potentially curative for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). However, the post-transplant relapse rate ranges from 40% to 70%, particularly with reduced intensity conditioning, and remains a major cause of treatment failure for these patients [1–3]. Strategies to mitigate this risk are urgently needed. The combination of venetoclax (VEN) with a hypomethylating agent (HMA) such as azacitidine (AZA) or decitabine (DEC) has shown promising anti-leukemia activity in older or unfit patients with AML and is now being investigated in younger patients as well [4]. Several studies have also shown that HMA/VEN can serve as an effective salvage regimen for relapsed/refractory (r/r) AML, including post-transplant relapse [5]. However, data on the safety and efficacy of HMA/VEN, as post-transplant maintenance to prevent relapse, is limited and needs further investigation. Within that context, we report our experience of administering low-dose DEC/VEN as post-transplant maintenance in patients with high-risk myeloid malignancies.

2 | METHODS

Patients with high-risk myeloid malignancies who received post-transplant maintenance with DEC/VEN, at the University of Alabama at Birmingham between March 2021 and September 2023, were identified through electronic methods. DEC was administered at 10 mg/m^2 on days 1–3 per cycle and VEN was given at a target dose of 200 mg on days 1–28 for AML and days 1–14 for MDS. The VEN target dose of 200 mg was selected to reflect a 50% reduction from its pre-transplant treatment dose. As there was no data to help determine the dose of post-transplant DEC, when combined with VEN, an arbitrary one-third reduction in the dose of DEC was made. Further studies showed that a reduced dose of DEC given for 3 days was feasible, in combination with VEN [3]. The dose of VEN was reduced to 20 mg when administered

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TABLE 1 Baseline characteristics.

	n = 26
Age (median, range)	64 years (34 – 71 years)
Females (%)	58%
Non-Hispanic Whites (%)	65%
Disease (%)	
AML	77%
MDS	23%
Risk Stratification (%)	
AML (ELN 2017)	
Intermediate	20%
Poor	80%
AML (ELN 2022)	
Intermediate	10%
Poor	90%
MDS (R-IPSS)	
Very-high	33%
High	33%
Therapy-related	33%
Disease Risk Index (%)	
High	85%
Intermediate	15%
Status at transplant (%)	
AML	
CR1 (MRD-)	65%
CR1 (MRD+)	20%
CR2 (MRD-)	10%
CR3 (MRD+)	5%
MDS	
CR	33%
Stable disease	50%
Hematological improvement	17%
TP53 (%)	31%
Multi-hit (%)	75%
Other Molecular Mutations (%)	
ASXL1	66%
RUNX1	59%
IDH1/2	31%
DNMT3A	31%
SRSF2	26%
FLT3-ITD	8%
Donor type (%)	
Matched-related	19%
Matched-unrelated	69%
Haploidentical	12%
Conditioning (%)	
Reduced-intensity	92%
Myeloablative	8%
GVHD prophylaxis (%)	
Tacrolimus/Methotrexate	62%
Post-transplant cyclophosphamide-based	38%

with voriconazole or posaconazole or 100 mg when administered with fluconazole or isavuconazium. The cycle length was 4 weeks. Maintenance was recommended to continue at least till the 1-year post-transplant date with the option of extending therapy based on tolerance.

DEC/VEN was offered to consecutive patients who were > 30 days post-transplant with an absolute neutrophil count of > 1000/μL and a platelet count of > 100,000/μL, without any evidence of grade II-IV acute graft versus host disease (GVHD) requiring systemic therapy and with adequate organ function per the treating physician. High-risk AML was defined as any poor-risk AML by ELN 2017 or intermediate-risk AML by ELN 2017 that was either measurable residual disease (MRD) positive or in second remission or beyond. High-risk MDS was defined as any high or very-high-risk MDS by R-IPSS stratification or any therapy-related MDS.

MRD was assessed using flow cytometry validated to a sensitivity level of 0.1% and was uniformly performed in all patients pre and post-transplant. Post-transplant MRD time points followed standard operating procedures and included day 30 post-transplant for patients that were MRD+ prior to transplant, day 100 post-transplant for patients that were MRD- prior to transplant, and 1-year post-transplant for all patients. Additional time points could be included depending on the clinical scenario.

Variables of interest included age, gender, race and ethnicity, disease risk stratification, disease status at transplant, donor type, conditioning intensity, and GVHD prophylaxis. Outcomes of interest included time to starting maintenance therapy, duration of maintenance therapy, any adverse events while on maintenance therapy, dose adjustments, cumulative incidence (CI) of acute and chronic GVHD, relapse rate, non-relapse mortality (NRM), and overall survival (OS).

Summary statistics, including the median and range for continuous variables and frequencies and percentages for categorical variables, were calculated. Probabilities of engraftment, GVHD, relapse, and NRM were calculated using CI estimates adjusting for competing factors. The OS rate was determined using Kaplan-Meier estimates.

3 | RESULTS

We identified 44 patients that met eligibility criteria out of which 26 (59%) received post-transplant DEC/VEN for AML and MDS (Table 1).

The only reason for not proceeding with maintenance therapy was patient refusal. The median follow-up was 14 m (range 3–36 m). The median age was 64 years (range 34–71 years). There were 15 (58%) females and 17 (65%) non-Hispanic whites (NHWs). Twenty patients had AML and six had MDS. Of patients with AML, 16 had poor risk and four had intermediate-risk disease per ELN 2017. Twelve patients (46%) received HMA as pre-transplant therapy (AML = 6, MDS = 6). At the time of transplant, 17 patients with AML were in CR1 (CR1 = 10, CRi1 = 7), two were in CR2 (CR2 = 1, CRi2 = 1) and one was in CR3. Five patients with AML had MRD+ at the time of transplant (CRi1 = 4, CR3 = 1). Of patients with MDS, two had very high and two had high-risk disease per R-IPSS. Two patients had therapy-related MDS. The disease risk index was high in 22 (85%) patients and intermediate in four (15%) patients. Two patients with MDS had CR, three had stable disease and one had hematological improvement at the time of transplant. Overall, eight patients (31%) had a TP53 mutation. Two patients (8%) had an FLT3-ITD mutation and started DEC/VEN due to intolerance to FLT3 inhibitors. Donor type was matched-related in five, matched-unrelated in 18, and haploidentical in three patients. All patients received peripheral blood stem cell transplantation. Twenty-four patients received reduced-intensity conditioning. GVHD prevention consisted of tacrolimus and methotrexate in 16 and post-transplant cyclophosphamide-based (PTCy) in 10 patients. For patients receiving tacrolimus (TAC) and methotrexate (MTX), TAC was started on day −3 and continued until day +180 (with gradual taper initiated at day+100 if no GVHD). The MTX dose was 5 mg/m^2 per dose. For patients receiving PTCy-based prophylaxis, PTCy was dosed at 50 mg/kg on day +3 and day +4, TAC was started on day +5 and continued until day +180 (with gradual taper initiated at day+100 if no GVHD) and mycophenolate mofetil was started on day +5 until day +35 at a dose of 15 mg/kg every 8 hours (maximum of 1 gm per dose). The target trough level for TAC was 5–10 ng/mL. The taper/stop plan was changed if the patient developed GVHD. Clinically significant GVHD was treated with prednisone 1–2 mg/kg/day (or methylprednisolone equivalent) in addition to continuing or resuming therapeutic tacrolimus. Donor lymphocyte infusion (DLI) was administered at the emergence of MRD or after disease control was achieved in patients who relapsed post-transplant.

The median time to initiate maintenance therapy was 63 days (range 48–200 days) post-transplant. The median number of cycles administered was 7 (range 2–24). Grade III-IV neutropenia, anemia, and thrombocytopenia occurred in six, one, and two patients, respectively. Two patients had febrile neutropenia and one patient had candida esophagitis. Five patients required a reduction or interruption in the dose of VEN due to adverse events. In four cases, the VEN duration was shortened by 1 week resulting in the resolution of toxicity. In the fifth case, the VEN duration was shortened by 1 week and the cycle length was extended from 28 days to 35 days, resulting in resolution of toxicity.

The CI of day 100 grade II-IV and III-IV acute GVHD was 13% and 5%, respectively. There were no grade IV cases. The 1-year CI of moderate-severe cGVHD was 26%. By day + 180, 12 patients were able to taper off TAC completely. To date, one patient relapsed 14 m after transplant and was unable to achieve disease control. No patient received DLI, either prophylactically or preemptively. The 1-year NRM was 11%. The 1-year OS for the entire cohort was 84% (Figure 1). The cumulative incidence of relapse was 17% in patients declining maintenance therapy.

4 | DISCUSSION

In our analysis, we report that the combination of low-dose DEC/VEN was associated with a low rate of post-transplant relapse in older patients with high-risk AML or MDS. We also find that the combination was well-tolerated with regard to hematological toxicities as well as the risk of GVHD.

Post-transplant HMA maintenance has been extensively investigated. Preclinical studies demonstrated that DEC could ameliorate GVHD without compromising on the graft versus leukemia effect [6]. These promising results led to a randomized trial of post-transplant maintenance with AZA in high-risk AML or MDS. Unfortunately, AZA maintenance did not improve outcomes, compared to placebo, for these patients [2]. On the other hand, a phase II trial comparing G-CSF/DEC to placebo, as post-transplant maintenance for AML, demonstrated a reduction in the incidence of relapse with the G-CSF/DEC [7].

The tolerability of VEN, as post-transplant maintenance, has also been demonstrated in small studies. As a single agent, VEN 400 mg resulted in a 1-year OS rate of 70% in patients with high-risk AML [1]. Given that the single-agent activity of VEN in r/r AML is modest and that combination of HMA/VEN serves as the current standard of care for older patients with AML, post-transplant maintenance with HMA/VEN is actively being investigated. In a phase I study of AZA 36 mg/m^2 on days 1–5 and VEN 400 mg on days 1–14, in 22 patients with high-risk MDS/AML receiving reduced intensity transplant, the 1-year OS was 79%. These patients also received 7 days of VEN during conditioning therapy [8]. In another study of low-dose DEC (15 mg/m^2 on days 1–3) and VEN (200 mg on days 1–21), in 20 patients with high-risk MDS/AML, the 2-year OS was 85.2% with no excessive GVHD and manageable myelosuppression [3]. Our study adds to the evidence that the combination of DEC/VEN is safe to administer. Although our DEC dose is lower, compared to the study by Wei et al., our VEN duration is higher and the cycle length is shorter. Despite these differences, these studies still demonstrate tolerability and early signs of efficacy of post-transplant DEC/VEN maintenance. Further investigation on the dosing and duration of VEN is warranted.

Our results did not demonstrate an increased risk of GVHD with this maintenance strategy. In fact, the rate of grade III-IV aGVHD was much lower than what was reported with TAC/MTX in BMTCTN 1703 [9]. The risk of moderate and severe cGVHD was not increased in our study. Studies evaluating HMA/VEN maintenance in the post-transplant setting have reported a low incidence of cGVHD [3, 8]. In vivo administration of DEC has been shown to mitigate the risk of GVHD [6] and more recently Garcia et al. observed that B-cell expansion post-transplant was not as robust in patients receiving AZA/VEN

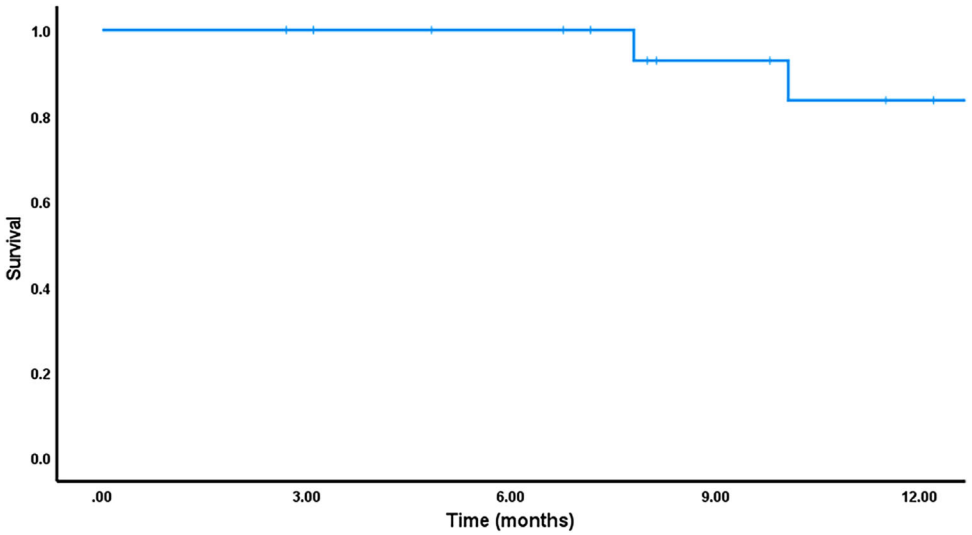

FIGURE 1 Overall survival of patients receiving post-transplant decitabine and venetoclax maintenance chemotherapy.

maintenance and perhaps this could explain the lower rates of cGVHD with this strategy [8] Results from VIALE-T are awaited to provide more insight into the risk of GVHD with post-transplant HMA/VEN maintenance [10].

Our patients were older with a median age of 64 years and nearly all received reduced-intensity conditioning. Additionally, our patients represented a high-risk subset based on cytogenetic and molecular abnormalities. Despite this, we were able to introduce maintenance in a timely manner at a median of 63 days. Furthermore, the median number of cycles administered was 7 but this may increase with longer follow-up. To date, no patient has discontinued the combination due to toxicity, and the majority of dose reductions were in the duration of VEN. This highlights the tolerability of this regimen in an older population. Limitations of our study include the small sample size as well as a relatively short duration of follow-up. The ongoing VIALE-T phase III trial will further shed light on the optimal schedule of maintenance chemotherapy, along with its efficacy [10].

5 | CONCLUSION

Post-transplant maintenance therapy for myeloid malignancies remains an area of unmet need. We have seen several trials, with variable results, for patients with a targetable mutation [11, 12]. Limited opportunities exist for those without actionable mutations and therefore low-dose chemotherapy regimens, such as HMA/VEN, are an area of interest. Our preliminary data suggests that the combination of low-dose DEC/VEN is a safe and potentially effective strategy to reduce the risk of post-transplant relapse in patients with high-risk AML or MDS. Adverse effects mainly included manageable cytopenias with no increase in risk of GVHD. The efficacy of the combination appears to be promising but needs longer follow-up as well as confirmation in large, randomized studies.

AUTHOR CONTRIBUTIONS

Katherine Parks, Kendall Diebold, and Omer Jamy contributed to the conception of the presented study and data collection and analysis. Katherine Parks, Kendall Diebold, Donna Salzman, Antonio Di Stasi, Zaid Al-Kadhimi, Manuel Espinoza-Gutarra, Ravi Bhatia, and Omer Jamy contributed to drafting, revising, and approving the manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

IRB approval was obtained.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

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