Off-label Venetoclax in combination with Hypomethylating Agents for Post-Allogeneic Stem Cell Transplant Acute Myeloid Leukemia Relapse

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Declarations

Conflicts of interest

All authors declare no conflict of interest.

Ethics approval

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.

Authors' contributions

FS, MS, NSF and FO designed the study. FS and MS assessed patients for eligibility and collected data. FS analysed data and designed tables and figures. FS, MS, NSF and FO contributed to manuscript development. All authors approved the final manuscript for submission. NSF and FO equally contributed to the manuscript.

To the Editor,

Relapse of acute myeloid leukemia (AML) after hematopoietic stem cell transplantation (HSCT) remains the greatest cause of unsuccess and mortality after transplant nowadays. In recent years, the pro-apoptotic agent venetoclax, a B-cell lymphoma-2 (BCL-2) inhibitor, and venetoclax-based combinations, especially with hypomethylating agents (HMA), have improved outcomes of newly diagnosed and relapsed/refractory AML (R/R), inducing higher remission rates and increasing overall survival (1-2). Reported CR/CRi rates from the first trials range from 19% as single agent up to 67% in combination with HMA with a median time to response of 1-2 cycles which was confirmed by the phase III trial VIALE-A (3). Data on safety and efficacy of venetoclax-based combinations as salvage therapy after HSCT is scarce, with few retrospective reports with heterogeneous venetoclax-based combinations (4-5) or as part of other r/r AML patients cohorts (6). Composite CR/CRi/~~morphologic~~morphological leukemia-free state rate range around 35-40%, with a median OS around 6 months and with a high rate of infectious complications and hematological toxicity with necessity of dose adjustments or interruptions. Until venetoclax approval, azacitidine +/- DLI was the main treatment option that showed positive results both as prophylactic and therapeutic agent post HSCT, with good tolerability profile (7-9). We hypothesized that the addition of venetoclax to this combination could increase the response rate and reach a higher disease control. We hereby aim to report the experience of the combination of venetoclax with HMA +/- donor lymphocyte infusions (DLI) in post-HSCT AML patients at our center.

We conducted an observational retrospective study to report the response rates and safety profile of ~~V~~venetoclax therapy after HSCT, given in combination with HMA. All consecutive patients aged >18 years and receiving ~~V~~venetoclax in combination with HMA for post-transplant R/R AML were included. Venetoclax was administered off-label and added to eventual previous therapy with HMA. Data on underlying disease, previous lines of therapy, drug dosing, discontinuation, eventual DLI administration, adverse events, response, relapse and death were recorded. Bone marrow aspirate evaluation for response assessment was done monthly after start of therapy and standard response

criteria by the International Working Group (IWG) (10) were used for response assessment. Adverse events were defined according to the CTCAE version 5.0. As per institutional policy, venetoclax was discontinued in case of not disease-related grade 4 neutropenia or thrombocytopenia and restarted at neutrophil count recovery >500/mcl and platelet count recovery > 30.000/mcl; venetoclax was also discontinued in case of infection until infection resolution. In case of multiple neutropenic febrile episodes, grade >3 infection, persistent not disease-related cytopenia leading to multiple interruptions or worsening of ECOG performance status >2, venetoclax was permanently discontinued.

From September 2016 to March 2021 a total of 48 patients received a hematopoietic stem cell transplant for acute myeloid leukemia. Fourteen patients relapsed after transplant with a median time from transplant to relapse of 196 days (27 – 1442).

Eleven of these patients (5 female) have then been treated with the combination of ~~V~~venetoclax and HMA and their characteristic are summarized in Table 1. According to ELN risk, three patients (27%) had favorable risk (AML with NPM1 mutation), three (27%) adverse risk (1 complex karyotype, 1 del7, 1 FLT3+ high ratio NPM1-) and 5 (45%) intermediate risk (AML NOS). All but one patient had received chemotherapy-based induction; three patients were refractory to induction while five patients had relapsed during consolidation phase. Overall, disease phase at transplant was CR1 in four patients (36%), CR2 in five patients (45%) and active disease in 2 patients (18%). Two patients received ~~V~~venetoclax plus HMA before transplant, one due to chemo-refractoriness and the other as was judged unfit for intensive chemotherapy. Both obtained CR before transplant.

After transplant, only one patient was treated due to molecular relapse, all other patients had overt hematologic relapse. Hypomethylating agent was ~~A~~azacitidine in all but one patient who received ~~D~~decitabine due to hyperleukocytosis. Full dose of ~~A~~azacitidine (75 mg/msq G 1-7 every 28 days) and ~~D~~decitabine (20 mg/msq for 5 days every 28 days) were used in all cases. Venetoclax was added to HMA after a median of 2 cycles of HMA (0-10), with three patients starting directly with the combination therapy; all patients had active disease at start of venetoclax, with 6 non-responders to HMA and 2 relapsing after 6 and 10 cycles of HMA. Venetoclax was administered continuously after

a short ramp-up phase in 28-day cycles until response and then for 21 out of 28 days for subsequent cycles. Dosage of venetoclax was 400 mg ~~die~~qd if the patient was not receiving antifungal azole-based therapy (4 cases), 50 mg ~~die~~qd if ~~P~~posaconazole was concomitantly administered (5 cases) or 200 mg ~~die~~qd if ~~I~~isavuconazole was concomitantly administered (2 cases). No signs of tumor lysis syndrome were observed at the start of venetoclax therapy. Five (45%) patients received DLI in combination with azacitidine and venetoclax with one infusion per cycle at incremental doses as per standard protocol. Reasons for not giving DLI were active GvHD (3 cases), no availability (1 case) and previous use of DLI for mixed chimerism (2 cases).

Nine (82%) patients experienced grade >3 toxicity (8 hematological, 3 infectious, 1 nausea and diarrhea). Five (45%) patients needed to stop venetoclax prematurely after a median time of 35 days (25-46); three of them had no response to venetoclax, while two proved to have benefited from therapy: at bone marrow evaluation at 30 days from the start of therapy, one (with molecular relapse) had CRi and reached again MRD negative status and the other reached CRi. Duration of response was 1 month for both patients; DLI had been used for both responders and for none of non-responders. Six patients did not meet permanent suspension criteria, but at least one temporary suspension due to hematological toxicity was required in four of them. Median duration of venetoclax therapy was 90 days (37-341). ~~Of~~Among these six patients, four patients had no response (three had received DLI), while other two patients responded. Time to best response was ~~, one had partial response~~ three months for one patient achieving PR and six months ~~after venetoclax beginning and one had a~~ for another patient obtaining ~~complete response~~CR with MRD negative status ~~reached six months after venetoclax beginning~~. Duration of response was 12 months for the ~~complete responder~~ patient in CR and 4 months for the patient in PR. Median OS was 122 days from start of venetoclax (Figure 1); seven patients died due to progressive disease, three patients are alive with active progressive disease and one patient (the only one with molecular relapse at the beginning) alive and continuing azacitidine and DLI after stopping venetoclax due to toxicity. Figure 2 sums up clinical history of each patient.

In conclusion, treatment options for post-transplant relapse are often limited and including patients in clinical trials should always be pursued if available. Until venetoclax approval, azacitidine +/- DLI was the main therapeutic resource available in the post-transplant setting (7-9), resulting in a manageable approach with low toxicity rates, but overall response rate <30% in case of active relapse. In our center, based on pre-transplant studies, we added off-label venetoclax to this combination in order to increase overall response rate. Previous reports of venetoclax use in r/r AML setting included heterogenous patient population with transplanted and non-transplanted patients (6) and hetereogenous venetoclax-based combinations in the post-HSCT setting (4-5). Response rates ranged from 20 to 40% with median OS around 6 months. Our report shows a more homogenoushomogeneous cohort of post-HSCT relapsed AML patients, all treated with the combination of venetoclax and HMA, plus DLI if feasible. As shown in our series, venetoclax-based combination could induce CR in 27% of these heavily pre-treated and high-risk patients. These results are still suboptimal, not exceeding those obtained with other post-transplant strategies, and post-HSCT AML relapse remains an unmet clinical need. The major challenge lied in optimizing venetoclax therapy due to the higher - especially hematological - toxicity rates encountered compered to historical pre-transplant cohorts, linked to lower bone marrow reserve after transplant. In fact, all but one patient received a discontinuous treatment, which can have a negative impact on the response rate itself. Lower doses or shorter courses of HMA and/or venetoclax may improve the tolerability of this combination. Only one patient, despite intermittent therapy, was able to achieve a durable CR, while another responding patient had to stop venetoclax due to toxicity and continued only on azacitidine and DLI combination. At the end of the study, all patients eventually had relapsed or were refractory to venetoclax thus suggesting a long-term disease control is difficult to obtain without a second HSCT. Overall survival remains poor for these patients.

Despite being venetoclax a possible new therapeutic options for post-HASCT AML, further studies focusing on appropriate patient selection and treatment schedule definition are needed in this patient population.

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Table 1 - Patients'~~'s~~ characteristics.

Female	5	
Male	6	
Median age	65 y	31-72
ECOG 0	9	
ECOG 1	2	
Median time from diagnosis to transplant	247	122-488
ELN risk		
favourab~~v~~le	3	
intermediate	5	
adverse	3	
Disease status at transplant		
CR1	4	
CR2	4	
PR2	1	
active disease	2	
Median time from transplant to relapse	196	27-1443
Median line before ~~V~~venetoclax	3	1-4
DLI		
yes	5	
no	6	