Venetoclax-Based Salvage Therapy for Post-Hematopoietic Cell Transplantation Relapse of Acute Myeloid Leukemia

Michael Byrne1, Nathalie Danielson2, Adrianne Rasche3, Rachel Hamers3, Katie A Colos4, Katie S Gatwood, Houston Wyatt, Kristin Fogo, Bhagirathbha Dholaria, Brian G Engelhardt5, P Brent Ferrell6, Madan Jagasia7, Adetola A Kassim5, Sanjay R Mohan, Bipin N Savani, Stephen A Strickland, Salyka M Sengsaydeek3, Michael R Savona3

1Department of Medicine, Division of Hematology/Oncology, Vanderbilt University Medical Center; Vanderbilt-Ingram Cancer Center, Nashville, TN; 2Tennessee Valley Health System Veterans Affairs Medical Center, Nashville, TN; 3Department of Nursing, Vanderbilt University Medical Center, Nashville, TN; 4Department of Pharmacy, Vanderbilt University Medical Center, Nashville, TN; 5Department of Cancer Biology, Vanderbilt University Medical Center, Nashville, TN.

Introduction

Acute myeloid leukemia (AML) is a biologically aggressive disease associated with poor clinical outcomes. FIt patients are generally treated with cytotoxic chemotherapy whereas elderly individuals may receive less intensive therapy.1,2 Patients with poor-risk features have limited life expectancies with only a small fraction surviving beyond five years.3 Allogeneic hematopoietic stem cell transplantation (HCT) is the only potentially curative therapy, however, post-HCT relapse is common and many of the same disease features that qualify patients for HCT also predict for relapse and shortened OS afterward. The management of patients with relapsed disease may be challenging. Overall response rates (ORR) with cytotoxic salvage therapy are variable, but far poorer after HCT.4 In a large registry analysis, only 15% of post-HCT relapsed AML patients achieved a complete remission of remission (CR). Less than 5% of patients who relapsed within six months, and 32% of patients who relapsed six months to two years after HCT were alive at three years.5 Venetoclax, is an orally bioavailable small-molecule inhibitor of the anti-apoptotic protein BCL-2. The initial trial of venetoclax as a single agent in relapsed/refractory (R/R) AML reported an ORR of 19%.6 Two subsequent studies in treatment-naive (TN) AML patients deemed not to be candidates for intensive cytotoxic chemotherapy demonstrated significant complete remission (CR) or CR with incomplete count recovery (CRi) rates of 50-70%. Based on these data, venetoclax was approved for use in combination with DNA methyltransferase inhibition (DNMTi) or low dose cytarabine (LDAC) for elderly/TN AML.7,8 Off-label venetoclax use, administered in combinations consistent with the FDA approval, is increasing. There is limited data surrounding the safety and use of venetoclax after HCT and no study has focused solely on this population. Here we report the outcomes of 21 AML patients who received venetoclax-based salvage chemotherapy for post-HCT relapse.

Methods

Following approval by the Vanderbilt University Medical Center and Tennessee Valley Healthcare System/Veterans Affairs Medical Center Institutional Review Boards, we retrospectively reviewed the medical records of patients who underwent allogeneic HCT for a myeloid malignancy and relapsed disease. Eligible patients began salvage chemotherapy with a venetoclax-based regimen between May 2018 and October 2019. Outcomes data was censored at the last clinic visit. Selection of the venetoclax paradigm, post-HCT relapse, and treatment schedules were at the discretion of the treating physician and were generally based on published prescribing information. Treatment responses were assessed based on the AML International Working Group criteria.9 Patient characteristics are summarized using descriptive statistics. Survival estimates were performed using Kaplan-Meier curve. Surviving patients were censored at their last clinic visit.

Results

Table 1. Patient characteristics. Summary of patient disease, and transplant characteristics. Abbreviations: AML: acute myeloid leukemia; CR: complete remission; CRi: complete remission with incomplete count recovery; DNMTi: chronic myeloid myeloctytic leukemia; HCT: hematopoietic cell transplantation; DNMT: full remission; HI-FN: hematopoietic improvement erythroid, myeloid, platelets, Fll: relapse; PR: primary induction failure; NSD: no response/dissease; PD: Progressive disease; VUS: Variant of uncertain significance; N/A: not applicable.

Figure 1. Venetoclax + DNMT/LDAC dosing. Eight patients had dosing interrupted/delayed due to peripheral cytopenias in the setting of BM aplasia. Dosing alterations were per discretion of the treating physician. Venetoclax dose was reduced, or administered as a single agent, or abandoned in favor of DNMTi monotherapy for maintenance of response. Two patients experienced dosing interruptions lasting >3 months and maintained their response.

Figure 2. Treatment response to venetoclax-based therapy. Bone marrow aspiration and biopsy was performed in 17/21 patients to assess treatment response. Twelve patients responded to salvage therapy: 5 CR, 3 CRi, 0 PR, 4 MLD. Two additional patients had a 75% reduction in PB blasts suggesting treatment effect, however, response could not be verified given the lack of a surveillance BM biopsy. Five patients with BM blasts did not achieve an FNG response and two patients, both with therapy related myeloid neoplasms, CR, and TP53 mutations had frank disease progression during the first cycle and did not undergo repeat BM biopsy. A total of 13 patients were assessed for treatment effect (11 with BM biopsy and two with frank PB progression) leading to a response rate of 63.2%.

Figure 3. Infectious complications with venetoclax-based salvage therapy. Most infections were observed in the early-onset patients treated with venetoclax. We began performing BMAs earlier in the treatment course, interrupted/reduced venetoclax dosing, and adopted a broad spectrum anti-fungal/anti-microbial prophylaxis strategy. The rate of infectious complications fell with this approach.

Figure 4: Overall survival (OS) measured from relapse to death/censorship: Fig 4A. The median OS of the entire cohort is 7.8 months (range: 0.2 to 12.1 months). Fig 4B. Patients who either had immunophenotyping experience superior survival relative to patients in CR/CRi (median OS: not reached vs. 6.7 months; P = 0.0054).

Conclusions

Venetoclax-based therapy is well-tolerated and led to responses in post-HCT patients where the outcomes are historically very poor. Of the 5 non-responding patients, 3 had TP53 mutations, which are generally thought to confer resistance to venetoclax-based therapies. Tailoring this therapy to post-HCT patients in the absence of TP53 mutations may improve response rates and duration of response.

Infectious complications are common causes of death in post-HCT relapsed AML patients. Early infectious complications are death from viral infections with significance in our cohort in the absence of fungal or bacterial infections. Identifying patients at risk for infection with broad spectrum anti-fungal and anti-bacterial prophylaxis coverage, frequent and early marrow assessment, and liberal dose modification strategies, the number of infectious complications was reduced from prior patients (7 deaths) treated to 4/10 patients (2 deaths) treated to date in 2019. With the use of venetoclax-based regimens post-HCT, adoption of these practices will likely improve outcomes and these should be formally explored for post-salvage maintenance therapy.

References