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AML with Extramedullary Relapse after Allogeneic Stem Cell Transplant Treated Successfully with Decitabine and Venetoclax: A Case Report

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CASE PRESENTATION

AML Diagnosis and allo-HSCT: A 64-year-old man with intermediate-risk AML reached CR1 after 2 courses of induction chemotherapy and 1 cycle of consolidation with high-dose cytarabine. He then underwent a 10/10 HLA-matched allogeneic stem cell transplant from his ABO-compatible brother prepped with fludarabine (30 mg/m^2 T-5 to T-2) and busulfan (4800 microMol*min T-5 to T-1). GVHD prophylaxis consisted of tacrolimus and methotrexate (10 mg on T +1, 5 mg on T +3, T+6, T+11). He received post-transplant maintenance therapy with low-dose azacitidine (32 mg/m^2 on days 1-5 of a 28 day cycle) for 12 months, which was complicated by transiently decreased donor chimerism at T +6 months (CD3 89%, CD33 97%). Tacrolimus was then tapered rapidly, which was followed by onset of stage 1, grade II acute graft-versus-host disease of the liver, managed successfully with systemic corticosteroids and sirolimus. Disease reassessments by bone marrow biopsy through T +2 years showed continued CR1 with > 99% total donor chimerism.

Extramedullary Relapse: At T +51 months, the patient underwent endoscopy for evaluation of recent onset abdominal pain, nausea, vomiting, and diarrhea. Visual examination of the gastric body and jejunum was remarkable for scattered congestion, erythema, friability, and granularity. Biopsy of the gastric body confirmed involvement by acute myeloid leukemia without evidence of other pathologies including graft vs. host disease. The patient underwent full restaging (**Table 1**) with bone marrow biopsy (which showed a minute population of blasts by flow cytometry) and lumbar puncture (positive for AML blasts). PET imaging (**Figure 1**) showed avidity throughout the upper GI tract, including the distal esophagus, stomach, duodenum, and jejunum.

MANAGEMENT

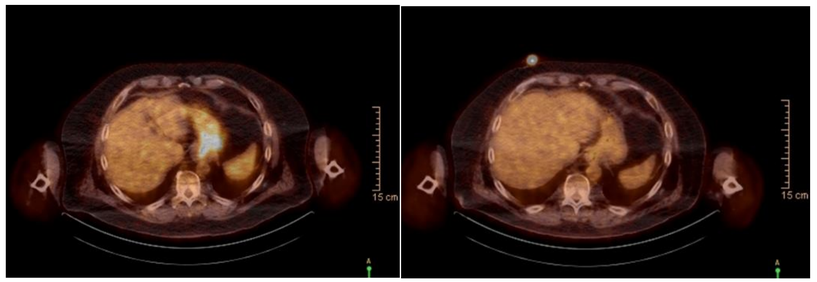
The patient received twice weekly intrathecal chemotherapy (methotrexate alternating with cytarabine) resulting in clearance of CSF blasts. Further intrathecal treatment was deferred due to subdural hematoma after placement of an Ommaya reservoir. Systemic therapy consisted of decitabine 20 mg/m^2 daily x5 days every 28 days and Venetoclax 400 mg daily after standard ramp-up. Serial restaging studies (representative restaging shown in **Table 1**) showed complete remission with incomplete count recovery in the marrow, blast clearance in the CSF, and near-resolution of PET avidity, suggesting either normal physiologic activity or low-level residual disease (**Figure 1**). He remains in CR after 8 cycles of therapy.

Table 1. Initial staging, re-staging at relapse, and post-relapse response assessments

Event	Result
Diagnosis (12/2018)	**Bone marrow:** 50% blasts; *NGS:* TET2 (30%), U2AF1 (30%), GATA2 (30%); *cytogenetics*: ring chromosome 12 **CSF:** not analyzed
Relapse (7/2023)	**Bone marrow:** 0.05% blasts by flow cytometry; NGS and cytogenetics not performed **CSF:** 6.2% blasts by flow **Stomach:** atypical blasts (CD34+, CD38+, CD56+, CD117+, HLA-DR+); *NGS*: FLT3-ITD, TET2, U2AF1** **PET:** hypermetabolic activity in distal esophagus, stomach, duodenum, and proximal jejunum
Restaging (1/2024)	**Bone marrow:** no increased blasts by histology or flow cytometry **CSF:** no blasts detected by slide review or flow cytometry **PET:** mild avidity in proximal stomach (suspect physiologic uptake)

*NRAS also detected in stomach, ASXL1 also detected in small bowel; **No allele frequencies reported.

Figure 1. Transverse PET images at relapse and after 5 cycles of decitabine + venetoclax



DISCUSSION

Gastrointestinal extramedullary relapse after allo-HSCT: The reported incidence of extramedullary relapse (ER) following allo-HSCT for AML ranges from < 1% to over 20% (Clark) and tends to occur later than bone marrow relapse (median onset T + 17 months, range T +1 to T +121 months post-transplant) (Kogut).[1] Most frequent sites of post-transplant ER (in decreasing order of frequency) are skin, breast, bone, testis, serosa, gynecological tract, and bladder (Cunningham 2006).[2] Gastrointestinal relapse is especially uncommon, representing only 4% of post-transplant ER (Cunningham 2006).[2] Due to the rarity of extramedullary relapse in the gastrointestinal tract, post-transplant patients presenting with gastrointestinal complaints may experience delays in diagnosis and treatment due to suspicion that their symptoms reflect more common complications such as medication toxicity, infection, or graft vs. host disease.[3]

Treatment Approach: Published treatment outcomes for extramedullary relapse after allogenic stem cell transplant are largely limited to cohort studies and case reports, with variable results.[4-7] The combination of a hypomethylating agent (HMA, *i.e.,* azacitidine or decitabine) plus venetoclax has emerged recently as standard of care in the frontline setting for AML patients unfit for intensive induction chemotherapy; however, its utility in the relapsed (and extramedullary) settings is less established. The phase 3 trial that led to the FDA approval of venetoclax in combination with a HMA in the front-line setting for AML excluded patients with CNS involvement did not report whether extramedullary cases were enrolled.[8] Studies of HMA + venetoclax in the relapsed setting include very few patients with ER, and only a portion of relapsed cases had a prior allo-HSCT.[9-11] Recently, a retrospective study of HMA + venetoclax in patients with AML relapsed after allo-HSCT demonstrated an overall response rate of 48%, with prolonged MRD-negative resmissions in some patients.[11]

Alternative treatment approaches considered for this patient included (a) second allogeneic transplant (deferred due to comorbidities acquired in the post-transplant period), (b) donor lymphocyte infusion (deferred due to history of GVHD and corticosteroid intolerance), (c) hypomethylating agent plus FLT3 inhibitor (deferred due to undetermined FLT3 allele frequency and detection in a non-validated tissue), and (d) clinical trial (as patient was ineligible for open trials at our institution).

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