Case Report

Venetoclax and Decitabine for T/Myeloid Mixed-Phenotype Acute Leukemia Not Otherwise Specified (MPAL NOS)

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T/myeloid mixed-phenotype acute leukemia not otherwise specified (MPAL NOS) is an uncommon and aggressive leukemia without well-established treatment guidelines, particularly when relapsed. Venetoclax plus a hypomethylating agent offers a promising option in this situation since studies support its use in both acute myeloid and, albeit with fewer data to date, acute T-cell-lymphoblastic leukemias. We report the successful eradication of T/myeloid MPAL NOS relapsed after allogeneic stem cell transplant with venetoclax plus decitabine. A consolidative allogeneic stem cell transplant from a second donor was subsequently performed, and the patient remained without evidence of disease more than one year later. Further investigation is indicated to evaluate venetoclax combined with hypomethylating agents and/or other therapies for the management of T/myeloid MPAL NOS.

1. Introduction

Mixed-phenotype acute leukemia (MPAL) is characterized by leukemic blasts expressing antigens of more than one lineage to such a degree that it is not possible to assign one lineage with certainty. MPAL and acute undifferentiated leukemia (which shows no lineage-specific antigen) constitute a group of acute leukemias of ambiguous lineage. MPAL are uncommon, accounting for <5% of acute leukemias [1, 2]. MPAL/T/myeloid NOS (T/myeloid MPAL) fulfills criteria for both T-cell and myeloid lineage without specific genetic abnormalities such as BCR-ABL1 or KMT2A rearrangement and is one of 5 MPAL subtypes recognized by 2016 World Health Organization classification [3]. T/myeloid MPAL is considered a high-risk acute leukemia, and limited data guide its management at diagnosis and relapse [4]. Venetoclax plus a hypomethylating agent (HMA) was approved for use by the Food and Drug Administration in November 2018 for older or relatively frail patients with newly diagnosed acute myeloid leukemia (AML) [5]. We report here the first, to our knowledge, successful application of venetoclax plus HMA for relapsed T/myeloid MPAL.

2. Case Report

A previously healthy 65-year-old man presented to an outside hospital with fatigue, folliculitis, easy bruising, vision changes, and decreased hearing. He had a normal coagulation screen; however, he was found to have cytopenias with a white blood cell count of 5.5 K/µL that included approximately 50% blast forms, hemoglobin of 10.0 g/dL, and platelet count of 78 K/µL. Marrow showed 70–80% blasts
positive for CD34, terminal deoxynucleotidyl transferase (TdT), CD3, myeloperoxidase (MPO), and CD5, and negative for PAX-5 and c-Kit (Figure 1). Flow cytometry (FC) demonstrated the blasts to express markers specific for myeloid (cytoplasmic MPO) and T-lymphoid (cytoplasmic CD3) lineages. Blasts were also positive for CD5, CD7, CD10, CD34, CD11b, CD33, and TdT on FC. Cytogentic examination were normal, and no abnormalities were identified on 200 interphase cells examined by fluorescence in-situ hybridization: specifically, analysis showed no evidence of 3q21.3q26.2 translocation or inversion, deletion 5q31, monosomy 7, deletion 7q31, RUNX1T1-RUNX1 translocation, KMT2A rearrangement, CBFB rearrangement, or monosomy 7, deletion 7q31, RUNX1T1-RUNX1 translocation, KMT2A rearrangement, CBFB rearrangement, or PML/RARA translocation. Next generation sequencing identified the following mutations: DNMT3A c.2206C>T (variant allele frequency (VAF) 43.9%); DNMT3A c.1755dup (VAF 36.5%); IDH1 c.394C>T (VAF 44.0%); CBL c.1227+2T>C (VAF 51.6%); and NOTCH 1 c.5023_5025del (VAF 13.9%). Together, findings established the diagnosis of T/myeloid MPAL. Cerebrospinal fluid was negative by cytology and FC.

Induction treatment was given with 3 half cycles (1A, 1B, and 2A) of cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (hyper-CVAD) and intrathelial (IT) prophylaxis [6]. This achieved a complete remission (CR), with bone marrow biopsy after cycle 1A, showing no evidence of disease by morphology or FC and no circulating blasts in the peripheral blood. He was transferred to our facility for consideration of consolidation stem cell transplantation. A repeat bone marrow exam was performed and demonstrated continued remission. The patient proceeded to a matched related donor allogeneic stem cell transplantation (allo-SCT) from his brother with reduced intensity conditioning (RIC) (flu darabine 30 mg/m² daily for 3 consecutive days (Flu) and 200 cGy total body irradiation (TBI)) with tacrolimus and mofetil, and sirolimus GvHD prophylaxis [9]. Engraftment occurred on day 19 after transplantation, and no grade ≥1 GvHD has been observed to date. At his most recent follow-up 1 year after his 2nd allo-SCT he remains in CR by morphology and FC. A 2nd cycle was given, with venetoclax dose-reduced to 100 mg daily. A full 28 days of venetoclax was administered with recovery of neutrophils and platelets on day 37. Other than cytopenias, the regimen was well tolerated. He proceeded to a 2nd SCT from a matched unrelated donor allograft with Flu/TBI RIC and cyclosporine, mycophenolate mofetil, and sirolimus GVHD prophylaxis [9]. Engraftment of neutrophils occurred on day 19 after transplantation, and no grade ≥1 GVHD has been observed to date. At his most recent follow-up 1 year after his 2nd allo-SCT he remains in CR by morphology and FC with CD3, CD33, and CD56 compartments entirely of donor origin.

3. Discussion

Relapsed T/myeloid MPAL, including after allo-SCT, carries a poor prognosis with no established treatment protocols. Generally, strategies are extrapolated from studies of more common acute leukemias [4]. Consolidative second allo-SCT can be beneficial to select patients with relapsed AML [10]. In our case, a 2nd allo-SCT was considered a reasonable approach if CR without detectable disease could be achieved since the patient had a good functional status, few comorbidities, and a different matched donor. Venetoclax, an inhibitor of the antiapoptotic protein BCL-2, is a generally well-tolerated oncolytic with synergistic antileukemic activity when combined with an HMA [5]. Though limited prospective data detail the regimen’s use in the relapsed AML setting, it appears to have significant activity, with CR rates as high as 40% in a retrospective analysis of 219 patients.
with relapsed AML, myelodysplastic syndrome, or blastic plasmacytoid dendritic cell neoplasm [11]. Still fewer data exist on the use of venetoclax plus HMA in relapsed T-cell leukemias [12]. A series of 12 patients with relapsed T-cell leukemia treated with venetoclax plus various chemotherapies (included an HMA in 3) was recently published and showed an impressive response rate of 60% [13]. In addition, emerging data from recent and ongoing clinical trials have shown promising outcomes with venetoclax and an HMA in cases of acute myeloid leukemia with an IDH1/2 mutation; this may have particular relevance to our case in which a mutation in IDH1 was detected at diagnosis [14].

4. Conclusion

To our knowledge, this is the first report of venetoclax plus HMA for relapsed T/myeloid MPAL. The regimen was a successful bridge to 2nd allo-SCT and well-tolerated aside from prolonged cytopenias in the setting of repeated prior cytotoxic chemotherapy regimens. Regimens for MPAL are typically designed to treat both myeloid and lymphoid lineages; therefore, based on publications of retrospective series to date, venetoclax plus HMA offers a promising novel approach to this clinically challenging entity [11, 13]. Future research is required to further explore this strategy and combine venetoclax with other agents active in T/myeloid MPAL.

Disclosure

The contents of this paper do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] W. van den Ancker, M. Terwijn, T. M. Westers et al., “Acute leukemias of ambiguous lineage: diagnostic consequences of the WHO 2008 classification,” Leukemia, vol. 24, no. 7, pp. 1392–1396, 2010.
[2] J. H. Kurzer and O. K. Weinberg, “Acute leukemias of ambiguous lineage,” Surgical Pathology Clinics, vol. 12, no. 3, pp. 687–697, 2019.
[3] D. A. Arber, A. Orazi, R. Hasserjian et al., “The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia,” Blood, vol. 127, no. 20, pp. 2391–2405, 2016.
[4] O. Wolach and R. M. Stone, “Optimal therapeutic strategies for mixed phenotype acute leukemia,” Current Opinion in Hematology, vol. 27, no. 2, pp. 95–102, 2020.
[5] C. D. DiNardo, K. W. Pratz, A. Letai et al., “Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study,” The Lancet Oncology, vol. 19, no. 2, pp. 216–228, 2018.
[6] H. M. Kantarjian, S. O’Brien, T. L. Smith et al., “Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia,” Journal of Clinical Oncology, vol. 18, no. 3, p. 547, 2000.
[7] Y. Nieto, N. Patton, T. Hawkins et al., “Tacrolimus and mycophenolate mofetil after nonmyeloablative matched-sibling donor allogeneic stem-cell transplantations conditioned with fludarabine and low-dose total body irradiation,” Biology of Blood and Marrow Transplantation, vol. 12, no. 2, pp. 217–225, 2006.
[8] A. B. Halpern, M. Othus, E. M. Huebner et al., "Phase I/II trial of cladribine, high-dose cytarabine, mitoxantrone, and G-CSF with dose-escalated mitoxantrone for relapsed/refractory acute myeloid leukemia and other high-grade myeloid neoplasms," *Haematologica*, vol. 104, no. 4, pp. e143–e146, 2019.

[9] B. M. Sandmaier, B. Kornblit, B. E. Storer et al., "Addition of sirolimus to standard cyclosporine plus mycophenolate mofetil-based graft-versus-host disease prophylaxis for patients after unrelated non-myeloablative haemopoietic stem cell transplantation: a multicentre, randomised, phase 3 trial," *The Lancet Haematology*, vol. 6, no. 8, pp. e409–e418, 2019.

[10] B. Gyurkocza, R. Storb, T. R. Chauncey, D. G. Maloney, B. E. Storer, and B. M. Sandmaier, "Second allogeneic hematopoietic cell transplantation for relapse after first allografts," *Leukemia & Lymphoma*, vol. 60, no. 7, pp. 1758–1766, 2019.

[11] J. P. Bewersdorf, S. Giri, R. Wang et al., "Venetoclax as monotherapy and in combination with hypomethylating agents or low dose cytarabine in relapsed and treatment refractory acute myeloid leukemia: a systematic review and meta-analysis," *Haematologica*, vol. 60, 2020.

[12] L. T. Rahmat, A. Nguyen, H. Abdulhaq, S. Prakash, A. C. Logan, and G. N. Mannis, "Venetoclax in combination with decitabine for relapsed T-cell acute lymphoblastic leukemia after allogeneic hematopoietic cell transplant," *Case Reports in Hematology*, vol. 2018, 2018.

[13] G. Richard-Carpentier, E. Jabbour, N. J. Short et al., "Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia," *Clinical Lymphoma, Myeloma & Leukemia*, vol. 18, 2019.

[14] C. D. DiNardo, C. R. Rausch, C. Benton et al., "Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies," *American Journal of Hematology*, vol. 93, no. 3, pp. 401–407, 2018.