Short Course Venetoclax with standard chemotherapy is effective in Early T cell precursor acute lymphoblastic leukemia

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May 27, 2022

Abstract

Early T cell precursor acute lymphoblastic leukemia is a relatively new, high risk subgroup of acute lymphoblastic leukemia characterized by unique immune-phenotype and disease biology. ETP ALL cells share similarities with hematopoietic stem cells and myeloid progenitor cells. These patients have lower rates of complete remission overall survival. Venetoclax is an orally bioavailable BCL 2 inhibitor. We report the treatment outcomes of 2 patients with ETP ALL who achieved MRD negative remission with short course of venetoclax.

Introduction

Early T cell precursor acute lymphoblastic leukemia (ETP ALL) is a relatively new, high-risk subgroup of acute lymphoblastic leukemia (ALL) characterized by unique immune-phenotype and disease biology. ETP ALL cells share similarities with hematopoietic stem cells and myeloid progenitor cells [1]. Immunophenotypically it is characterized by $CD1a^-$, $CD8^-$, $CD5^-$ (dim), and positivity for 1 or more stem cell or myeloid antigens [2]. As compared to patients with non ETP-ALL, these patients have lower rates of complete remission (73% vs 91%; $P = .03$) and overall survival (OS)(20 months versus not reached, $P = .008$). ETP ALL has been shown to be BCL 2 dependent and is sensitive to in vitro inhibition by BCL2 inhibitors [3]. Venetoclax is an orally bioavailable BCL 2 inhibitor approved for use in acute myeloid leukemia, chronic lymphocytic leukemia and multiple myeloma [4]. Response of relapsed refractory T cell ALL with venetoclax based therapy have been reported in literature. We present the treatment outcomes of 2 patients with ETP ALL treated with venetoclax.

Case 1

A 18 year old male presented with history of fever and headache for 3 days duration. Complete blood count showed haemoglobin of 6.6 g/dL, white blood cells 1.3 x 10^9/L, platelet count 10 x 10^9/L and 49% blasts in differential count. Bone marrow examination showed 89% blasts. Flow cytometry analysis was suggestive of ETP – ALL [CD7(bright), CD33+, CD 38+, hetergenous dim to moderate CD5, 64% blasts positive for CD34, cCD3 positive. Negative expression was seen for CD1a, CD2, CD3, CD4, CD8, CD10, CD13, CD15, CD16, CD19, CD34, c CD41, CD56, cCD 79a, cMPO and cTdT). Molecular markers were negative. He had complex karyotype (46, XY, add(10)(q26), del(11)(q13q23),del(12)(q13),-15,-17, add(20)(q13.3), del(20)(q13.1), +mar1, +mar2[10]). Baseline cerebrospinal fluid examination was normal. He was started on Berlin-Frankfurt-Meunster (BFM) 95 ALL protocol. Day 8 blast count was 0.35 x10^9/L. He developed febrile neutropenia with probable fungal pneumonia. Post induction bone marrow examination showed persistence of 10% blasts. He was started on HR 1 protocol of BFM 95 along with oral venetoclax x 7 days (100 mg day 1, 200 mg day2, 300 mg day3, and 100 mg with oral posaconazole from day 4 to day 7). Post HR1, he developed febrile neutropenia with fungal pneumonia. Repeat bone marrow examination on day 28 showed morphological remission with negative minimal residual disease MRD (<0.01%). He received HR 2

protocol with venetoclax (100 mg for 7 days along with oral posaconazole). Following recovery, he underwent matched sibling donor allogeneic stem cell transplant. Conditioning was given with cyclophosphamide 60 mg /kg x 2 days on D-5, D-4 followed by myeloablative total body irradiation – 200 Gy twice a day x 3 days on D-3, D-2 and D-1. Graft versus host disease prophylaxis was given with tacrolimus and short course methotrexate on D1, 3, 6 and 11. He achieved neutrophil engraftment on day + 15 and platelet engraftment on day + 9. Day+ 30 chimerism was 100 % donor. Day +60 bone marrow evaluation showed morphological remission and negative MRD (<0.01%). He developed tacrolimus toxicity in the form of severe tremors and seizures. MRI brain and CSF analysis were normal. Tacrolimus tapering was started on day + 88 and tacrolimus was stopped on day + 100. At present he has completed 2 years 1 month of follow-up and is on weekly 15 mg methtrxate for chronic skin graft versus host disease (GVHD).

Case 2

A 19-year-old male presented to us with fever and abdominal pain for 2 days duration. His hemogram showed haemoglobin - 10.6g/dL, white blood cell count 44.2 x 10^9/L, platelet count 90 x 10^9/L with 88% blasts in differential count. Bone marrow examination showed hypercellular marrow with 87% blasts. Flow cytometry analysis showed CD7, CD38 positive, heterogenous dim to moderate cCD3 and CD5. Dim expression for CD33. Negative expression was seen for CD1a, CD2, CD3, CD4, CD8, CD10, CD13, CD15, CD16, CD19, CD34, c CD41, CD56, cCD 79a, cMPO and cTdT suggestive of ETP ALL. Molecular markers were negative and karyotype was normal. Baseline cerebrospinal fluid evaluation was normal. He was started on BFM 95 regimen. Day 8 blast count was 12.51 x 10^9/L. He continued to have blast in peripheral blood until day 22 of therapy. Hence, he was started on oral venetoclax x 7 days (100 mg day 1, 200 mg day2, 300 mg day3, and 100 mg with oral posaconazole from day 4 to day 7) in addition to continuation of BFM regimen. He had cytopenias for 2 weeks after completion of therapy and post induction bone marrow evaluation on D 49 of therapy showed morphological remission with positive MRD (0.99%). He received HR1 protocol of BFM 95 with oral venetoclax (100 mg for 7 days along with oral posaconazole). Post HR1 bone marrow showed < 1 % blasts with negative MRD (<0.01%). Patient did not have a matched sibling donor. Matched unrelated donor search showed 6 fully matched donors in India. However, none of the donors were willing for donation in the setting of corona virus pandemic. He underwent haploidentical allogeneic stem cell transplant with father as donor. Conditioning was done with fludarabine 30 mg/m2 x 3 days on D-6, D-5 and D-4 followed by total body irradiation – 200 Gy twice a day x 3 days on D-3, D-2 and D-1. GVHD prophylaxis was with tacrolimus, MMF and post-transplant cyclophosphamide. Neutrophil engraftment was on day+ 13 and platelet engraftment was on day +10. He had persistently low tacrolimus trough levels and developed Grade IV acute GVHD of gut on D+ 25 of transplant. He responded to IV methylprednisolone. Tacrolimus was changed to cyclosporine. Chimerism analysis at D+ 30 showed 99.14% donor. Day +60 bone marrow evaluation showed morphological remission and negative MRD (<0.01%). At present he has completed 1 year 10-month follow-up and is doing well on Ruxolinitib for liver and gastrointestinal GVHD.

Discussion

ETP- ALL has been characterised by chemo-refractoriness and bad disease biology.

High percentage of persistent minimal residual disease and poor overall survival has been reported in ETP ALL patients treated with GRAALL 2003 and GRAALL 2005 protocol. However, response adapted treatment stratification and use of allogeneic stem cell transplant in CR1 has been shown to abrogate the negative effects of chemo-resistance in ETP ALL [5]. Patients with ETP ALL have low rates of CR with standard chemotherapy. In a small series from India only 1 of 6 patients of ETP- ALL could achieve complete remission after initial chemotherapy [6].

Novel therapeutic agents studied in ETP ALL include dasatinib (patient with NUP214-ABL1 aberration), ruxolitinib (JAK/STAT pathway), daratumumab (anti CD38 antibody), gemtuzumab ozagamycin(anti CD 33 antibody conjugate) and venetoclax (BCL-2 inhibitor)[7]. Table 1 summarises the reports of venetoclax use in ETP ALL [8-10]. In a study from MD Anderson Cancer Center, 13 patients of relapsed refractory T cell ALL which included 5 patients of ETP ALL were treated with venetoclax in combination with various

chemotherapy regimens [11]. The median dose given was 200 mg with a total duration of 21 days in combination with HyperCVAD, fludarabine+ cytarabine + idarubicin, decitabine, nelarabine and asparaginase. Prolonged cytopenias were observed with dose of 400 mg/day or duration of therapy > 14 days. 60% of patients achieved complete remission. No association between bone marrow response and dose was observed. The median OS was 7.7 months. Only 1 ETP ALL patient achieved MRD negativity. Only 2 patients were alive at 1 year and both had ETP ALL. Duration of remission achieved with venetoclax was short lived. In our study we used 100mg on day 1, 200 mg on day 2, 300 mg on day 3 and 100 mg with oral posaconazole from day 4 to day 7 onwards in combination with BFM 95 regimen. Both patients attained complete remission after 1 course of venetoclax combination chemotherapy. One patient achieved MRD negativity after 1 course of venetoclax and the other patient achieved MRD negativity after 2^{nd} course of venetoclax. In a study by El-Cheikh J et al, 3 patients of relapsed refractory T cell ALL were treated with venetoclax and BFM based therapy [12] . 2 patients achieved CR.

Combinations of venetoclax with other chemotherapeutic agents have been studied in relapsed refractory ALL. Navitoclax is a novel inhibitor of BCL-XL and in combination with Venetoclax has shown synergistic effect in phase 1 study in patients with relapsed/refractory B and T cell acute lymphoblastic leukemia [13]. The overall rate of combined complete response, CR with incomplete marrow recovery or incomplete platelet recovery was 49%. Responses of combination therapy of venetoclax(800 mg followed by 400 mg with azoles)with decitabine in relapsed T cell ALL post allogeneic stem cell transplant have also been described[14, 15]. Patient had also achieved MRD negativity. Individualized therapy based on drug response profiling of leukemia cells with venetoclax and bortezomib was done in 3 patients of relapsed refractory ETP ALL. 1 patient achieved CR and 2 PR. All patients underwent transplant and achieved remission [16]. Currently a phase I/II study is undergoing in MDACC of venetoclax in combination with low dose chemotherapy in relapsed refractory T cell ALL(NCT03808610). We used a short low dose regimen with posaconazole which was well tolerated and achieved good results in our patients.

Conclusion

Combination therapy of short course venetoclax with BFM 95 regimen is an effective regimen for treating patients with ETP ALL.

References

1. Wada H, Masuda K, Satoh R,et al. Adult T-cell progenitors retain myeloid potential. Nature. 2008;452(7188):768-72.

2. Jain N, Lamb AV, O'Brien S, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. Blood. 2016;127(15):1863-9.

3. Chonghaile TN, Roderick JE, Glenfield C, et al. Maturation stage of T-cell acute lymphoblastic leukemia determines BCL-2 versus BCL-XL dependence and sensitivity to ABT-199. Cancer Discov. 2014;4(9):1074-87.

4. Juarez-Salcedo LM, Desai V, Dalia S. Venetoclax: evidence to date and clinical potential. Drugs Context. 2019;8:212574.

5. Bond J, Graux C, Lhermitte L, et al. Early Response-Based Therapy Stratification Improves Survival in Adult Early Thymic Precursor Acute Lymphoblastic Leukemia: A Group for Research on Adult Acute Lymphoblastic Leukemia Study. J Clin Oncol. 2017;35(23):2683-91.

6. Iqbal N, Sharma A, Raina V, et al. Poor Response to Standard Chemotherapy in Early T-precursor (ETP)-ALL: A Subtype of T-ALL Associated with Unfavourable Outcome: A Brief Report. Indian J Hematol Blood Transfus. 2014;30(4):215-8.

7. Castaneda Puglianini O, Papadantonakis N. Early precursor T-cell acute lymphoblastic leukemia: current paradigms and evolving concepts. Ther Adv Hematol. 2020;11:2040620720929475.

8. Starza RL, Cambò B, Pierini A, et al. Venetoclax and Bortezomib in Relapsed/Refractory Early T-Cell Precursor Acute Lymphoblastic Leukemia. JCO Precision Oncology. 2019(3):1-6.

9. McEwan A PO, Viiala N. Relapsed/Refractory ETP-ALL Successfully Treated With Venetoclax and Nelarabine as a Bridge to Allogeneic Stem Cell Transplant. Hemasphere. 2020; 4(3):e379(Jun 8).

10. Numan Y, Alfayez M, Maiti A, Alvarado Y, et al. First report of clinical response to Venetoclax in Early T-cell Precursor Acute Lymphoblastic Leukemia. JCO precision oncology. 2018; 2(10.1200).

11. Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical Experience With Venetoclax Combined With Chemotherapy for Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk. 2020;20(4):212-8.

12. El-Cheikh J, Moukalled NM, El Darsa H, et al. Feasibility of the Combination of Venetoclax and Asparaginase-based Chemotherapy for Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk. 2018;18(10):e441-e4.

13. Alexander T, Pullarkat AV, Jabbour EJ, et al. Venetoclax and Navitoclax in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma. Blood. 2018;132(Supplement 1):3966.

14. Rahmat LT, Nguyen A, Abdulhaq H, Prakash S, Logan AC, Mannis GN. Venetoclax in Combination with Decitabine for Relapsed T-Cell Acute Lymphoblastic Leukemia after Allogeneic Hematopoietic Cell Transplant. Case Rep Hematol. 2018;2018:6092646.

15. Farhadfar N, Li Y, May WS, Adams CB. Venetoclax and decitabine for treatment of relapsed T-cell acute lymphoblastic leukemia: A case report and review of literature. Hematol Oncol Stem Cell Ther. 2020.

16. Zhang X, Li J, Jin J, Yu W. Relapsed/refractory early T-cell precursor acute lymphoblastic leukemia was salvaged by venetoclax plus HAG regimen. Ann Hematol. 2020;99(2):395-7.

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