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MRD negative CR after azacitidine and venetoclax in a young patient with AML, unfit for intensive induction followed by ASCT

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ABSTRACT

A subset of AML patients are unfit for 7+3 induction at the time of diagnosis. Present case highlights the use of azacitidine and venetoclax in a patient with intermediate risk AML with WT-1 mutation,deemed unfit for intensive induction in view of poor general condition and comorbid illness. After venetoclax and azacitidine patient was negative for measurable residual disease but developed cerebellar toxicity after high dose cytarabine. He underwent successful matched sibling allogeneic stem cell transplant and is presently on routine follow up. This case report suggest possible role of this combination even in young patients unfit for intensive induction.

1. Introduction

AML is commonly occurring hematological malignancy in adults. Common presenting complaint includes weakness, bleeding and infections. Median age of diagnosis is 68 years for AML [1] in US and 40 years based on real world data from India [2]. In view of underlying immunocompromised status up to half of the patients present with active infection at the time of the diagnosis, thus making initial treatment very challenging, a balance between delaying treatment while treating infection versus simultaneous treatment for both is a challenging decision to be taken on case-to-case basis. Azacitidine and venetoclax have shown promising results in elderly AML, a particularly common but tough subset of AML to treat, in view of comorbid illness and increased mortality due to 7+3 induction. Present case discusses the successful management of a 19-year male with AML intermediate risk based on 2017 ELN risk stratification criteria [3] with WT-1 mutation and PTPN11 mutation with fungal pneumonitis, infective endocarditis and secondary hemophagocytic lymphohistiocytosis (HLH) with azacitidine and venetoclax induction resulting in MRD negative complete remission (CR) and subsequently went on to receive matched sibling peripheral stem cell transplant as consolidation.

2. Case report

19 years male presented in emergency with history of fever for 1 week and CBC showing increased WBC with possibility of acute leukemia, he was admitted for these complaints elsewhere and flow cytometry done was suggestive of AML.COVID PCR was negative, while galactomannan report and molecular panel for AML characterization were awaited.

At time of initial assessment in emergency at our hospital patient was febrile, had tachycardia and tachypnea and VBG showed metabolic acidosis. Repeat COVID PCR sent and blood cultures were sent. CBC showed HB-7.9 gm/dl, TLC-52,090 cells/mm^3, Platelet-52,000/mcl. Bone marrow and PBF were reviewed suggestive of Non-M3 AML and flow cytometry was repeated, which reconfirmed the diagnosis of AML. Intravenous antibiotics were stepped up and empirical liposomal amphotericin was started and nasal oxygen started and patient admitted in intensive care unit.

Repeat COVID PCR was negative, patient was shifted to HEPA filter room next day on nasal oxygen, fever spikes persisted. Hydroxyurea started and PICC line insertion done for intravenous access. Repeat CECT thorax was done and compared with previous CT done one week back, it showed increase in lung infiltrates. After infectious disease

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expert consultation dose of liposomal amphotericin was increased to 5 mg/kg. Next day patient's blood culture was negative and procalcitonin was normal. Oxygen requirement was reduced. Serum galactomannan was elevated, so liposomal amphotericin was continued. With treatment breathlessness decreased but fever persisted but decreased in frequency.

Next day he developed high grade fever, tachycardia and swelling in left upper limb. Left upper limb doppler-suggestive of partial thrombosis in cephalic vein, however deep veins were normal. 2D echocardiography (ECHO) showed vegetations on tricuspid valve leaflet and in the given clinical context suggesting possible infective endocarditis. Transesophageal ECHO was not done in view of poor general condition. Liposomal amphotericin continued and polymyxin B started empirically. Liver Function test (LFT) also showed hyperbilirubinemia without transaminitis.

Results of AML prognostication panel by real time PCR was negative for molecular alteration in PML-RARA,AML1-ETO,CBFB-MYH11,BCR-ABL,FLT3-ITD/TKD,NPM-1 and c-KIT. Comprehensive leukemia panel for 57 gene by NGS was sent.

One week after admission patient continued to be hypoxic on supplemental oxygen requirement. Patient was unfit for intensive induction in view of active infection and poor general condition hence after discussing guarded prognosis with parents and patient, he was started on azacitidine (Day +1) with decision to add venetoclax based on availability.Venetoclax at the time of managing this case was unavailable in India and needed to be imported on case to case basis. At night patient developed worsening breathlessness and shifted to ICU, was started on non-invasive ventilation.

On Day + 2 in view of worsening breathlessness a decision to add anidulafungin was made. Azacitidine was given at reduced dose and venetoclax started at 100 mg. Patient continued to have fever,tachycardia, tachypnea and worsening LFT (T.Bilirubin-3.94 mg/dl, D.Bilirubin-3.67 mg/dl, I.Bilirubin-0.27 mg/dl with normal SGPT and SGOT and mildly elevated alkaline phosphatase)-so possibility of HLH was suspected. A sA single dose of hydrocortisone was given to assess steroid responsiveness to see for steroid responsiveness.

On Day +3 patient had improvement in tachycardia, tachypnea and fever. Ferritin was 4160 ng/ml. Day +4 chemotherapy continued with monitoring. On Day +5 bilirubin worsened to 5.92 mg/dl with repeated fever spikes and worsening breathlessness but in view of active fungal pneumonitis and possible risk of mycotic aneurysm steroids were not given and alternatively IV immunoglobulin started.Azacitidine and also 2nd dose of IV immunoglobulin given on next Day (+6).

Day +7 LFT Worsened (Total bilirubin-9.78 mg/dl, Direct-9.19 mg/dl, Indirect-9.19 mg/dl) and serum ferritin increased to 10,459 ng/ml. Dose of venetoclax reduced and last dose of azacitidine given. After discussing risk of mycotic aneurysm and absence of any established alternate treatment for HLH, patient was given Methylprednisolone following which he had improvement in breathlessness and was afebrile. LFT improved with serum bilirubin in the range of 5–6 mg/dl over the next 3 days. Methylprednisolone was changed to dexamethasone from 3rd day. Over a period of next few days bilirubin got further reduced . Blood and platelet transfusion of irradiated and leucodepleted products continued as per CBC reports. Dual antifungal completed for 14 days. On day +22 platelet count > 20,000/mcl suggestive of platelet recovery. On Day +30 ANC > 500 cells/mm^3. Blood investigation on Day +32 showed Hb-9.0 gm/dl, TLC-1820 cells/mm^3 Platelet-175,000/mcl and LFT was normal so patient was discharged from hospital.

NGS 57 gene comprehensive leukemia panel suggested presence of mutation in WT1 and PTPN11 genes. Cytogenetics suggestive of metaphases with normal karyotype.

Patient assessed after one week of discharge on day +39 on outpatient basis, CBC was suggestive of count recovery without abnormal cells in peripheral smear. Bone marrow smear examination showed morphological complete remission and MRD by flow cytometry was negative.

3. Further brief course

Patient given 1st cycle consolidation Cytarabine, but developed cerebellar toxicity 24 h after last dose of cytarabine, managed conservatively, with near complete recovery with mild slurring of speech.

He had normal cytogenetics with WT-1 and PTPN11 mutation belonging to intermediate risk based on ELN criteria.

He had younger 10/10 HLA matched sibling donor .He received peripherally harvested unmanipulated 8.4 million/kg CD34+ stem cell after FLU-BLU-MEL conditioning and followed by MTX- cyclosporine as GVHD prophylaxis. He had platelet engraftment on day+11 and neutrophil engraftment at day+14. Grade 3–4 mucositis was managed with symptomatic treatment and ryles tube feeding. Febrile neutropenia was managed with appropriate antibiotics based on culture report.His repeat bone marrow on day +30 was in morphological remission and was MRD negative. He is doing well at day+365, with 99.8% full donor chimerism. He is off immunosuppression and on active surveillance.

4. Discussion

Presence of infection at the time of diagnosis with AML is commonly seen in clinical practice. Based on a retrospective study around 40% of patients have fever at the time of presentation, and 31% have documented infections. Presence of infection is associated with significant increase in induction mortality as compared to those without baseline infection [4].

HLH is a severe hyperinflammatory syndrome induced by aberrantly activated macrophages and cytotoxic T cells. Based on a study by Karen Delavigne [5] in a series of 343 patients treated with intensive chemotherapy over 5 year period, 32 patients (9.3%) had clinical presentation consistent with HLH. Possible etiology of secondary HLH was infection in 75% patients. The most common infections in this study were bacterial followed by fungal and viral. Also diagnosis of HLH in AML is challenging because most of the classical criteria of HLH seems unsuitable when applied to acute leukaemia.

In the present case patient had imaging suggestive of possible fungal pneumonitis and elevated galactomannan and background of newly diagnosed acute myeloid leukaemia in the absence of culture proven bacterial sepsis. This patient was febrile throughout the initial course and also had borderline altered LFT at the time of admission, but after start of azacytidine and venetoclax patient had worsening LFT and persistence of fever, Serum ferritin >10,000 ng/ml inspite of dual antifungal and adequate antibacterial coverage leading to clinical suspicion of HLH. Dramatic response with normalization of hyperbilirubinemia and fever resolution and decrease in ferritin level after starting steroids makes alternate diagnosis less likely. Treatment of HLH with AML is challenging and IV immunoglobulin, steroids and cyclosporine have been tried alone or in combinations. Diagnosis of HLH with AML is also associated with inferior survival [5].

A phase 3 trial VIALE-A [6] in previously untreated patients who were ineligible for intensive chemotherapy, randomized patients to azacitidine plus venetoclax versus azacytidine alone and at a median follow-up of 20.5 months, the median overall survival was significantly better at 14.7 months in the azacitidine–venetoclax group as compared to 9.6 months in the control group .The incidence of complete remission was significantly higher with azacytidine–venetoclax than with the control regimen (36.7% vs. 17.9%), as was the composite complete remission (complete remission or complete remission with incomplete hematologic recovery) (66.4% vs. 28.3%)

Patient in this case report was young but ineligible for intensive chemotherapy in view of active infection and so the combination of venetoclax and azacitidine was used. Tumor lysis syndrome with combination of venetoclax and azacitidine was a concern when initially used in AML but incidence is low when adequate precaution is taken and another concern is risk of drug interactions. All possible precaution were taken as per package insert and review article [7] and dose was modified

for liver abnormality.

Patient belonged to intermediate risk based on ELN 2017 risk stratification criteria [3] in view of normal cytogenetics with WT-1 and PTPN11 mutation. The prognostic significance of WT-1 mutation is not well defined but studies show inferior survival in presence of this mutation [8]. He became MRD negative by flow cytometry after one cycle azacytidine and venetoclax. MRD assessment with WT1 expression was not used because of its low sensitivity and specificity [9].The percentage of patients with AML who achieve an MRD value $< 0.1\%$ with combination of azacitidine and venetoclax appears to be around 6–21% based on trial results [10,11].

Patient developed ataxia and slurring of speech without change in sensorium one day after completion of last dose of high dose cytarabine. Renal and liver function test were normal at the time of symptoms and also MRI brain was normal. Diagnosis of cytarabine induced cerebellar toxicity was made, the reported incidence of severe cerebellar toxicity due to high dose cytarabine in leukaemia and lymphoma is close to 8%, while incidence of fatal or irreversible toxicity is around 1% based on a retrospective study [12] of 418 patients. Patient had near complete neurological recovery with mild slurring of speech at time of discharge.

He successfully underwent matched sibling allogeneic stem cell transplant. Repeat evaluation with bone marrow at day +30 suggested morphological complete remission and MRD from bone marrow was negative. He is now on routine follow up and doing well.

This case report suggest possible role of Azacitidine and venetoclax even in young patients unfit for intensive induction.

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