**Changing Acute Myeloid Leukemia into a Chronic Disease with Long-Term Venetoclax**

Dear Editor:

The survival rate for children with multiply recurrent acute myeloid leukemia (AML) continues to be low despite intensive therapy. Rasche and colleagues reported that children with two or more relapses of AML had an overall five-year survival rate of 31% (+/- 9) with hematopoietic stem cell transplantation and 15% (+/- 4) without. Those who opted for palliative treatment alone had a median survival time of 2 months1.

Venetoclax, an oral selective B-cell lymphoma-2 inhibitor, was first approved by the US FDA in 2016 to treat a specific subtype of chronic lymphocytic leukemia2. Venetoclax in combination with azacytidine or cytarabine (ARA-C) has been shown to be an effective treatment for pediatric patients with relapsed AML, especially those with FLT3 negative disease3-5. We present a case of a child with multiply recurrent AML who received venetoclax-containing treatment for palliation and is alive 4 years following his 2nd relapse.

Our patient is a 15-year-old male who initially presented at the age of 7 years with a four-day history of fever, leg pain, and refusal to walk. Laboratory testing showed an elevated white count, severe anemia, severe thrombocytopenia and myeloblasts were evident on the peripheral blood smear. Analysis of cerebrospinal fluid (CSF) did not detect any leukemia cells at presentation. Morphologic, flow cytometric, and molecular genetic analyses of the patient’s marrow were consistent with a diagnosis of M4/M5 AML. The leukemic blasts contained an X;10 translocation and were FLT3 negative leading to a low-risk classification. The patient was treated with multi-agent chemotherapy as per the Children's Oncology Group study AAML1031, arm A (cytarabine, daunorubicin, etoposide, mitoxantrone) and remission was achieved at the end of the first induction course.

Fifteen months after completing initial treatment, the patient experienced a marrow and central nervous system (CNS) relapse. Following two cycles of fludarabine and cytarabine, the patient’s disease went into remission and no minimal residual disease (MRD) was detected in the marrow. He then received a 5 of 6 HLA-matched cord blood transplant.

18 months post-transplant, the patient presented with proptosis and was found to have a chloroma involving the left maxillary sinus, left pterygoid and orbit. CSF had no detectable leukemic blasts, but the marrow was involved with 6.2% blasts that remained FLT3 negative (2nd relapse). He received emergent radiation therapy to the left orbital region. The patient and guardians facing a poor prognosis expressed their desire to pursue palliative treatment and declined intensive treatment in hopes of preserving a good quality of life.

Based on the results of studies from Liu and Wei, the patient was started on palliative regimen of continuous daily oral venetoclax (400 mg) and 7 days of low dose daily subcutaneous ARA-C (20 mg/m2/dose) every 28 days4,5. While the venetoclax continued long-term, the ARA-C was administered for only 6 cycles. There was no detectable circulating blast population in the peripheral blood shortly after the start of treatment and MRD analysis of the marrow was negative after the 6th cycle of ARA-C.

Nine months after starting venetoclax, the patient developed left-sided vision loss and was found to have grade 5 papilledema, retinal hemorrhages and a markedly thickened left optic nerve without chloroma. CSF analysis was positive for CNS disease (3rd relapse). While continuing the daily venetoclax, the patient received triple intrathecal (IT) chemotherapy (methotrexate, cytarabine, hydrocortisone) twice weekly for 7 doses, after which blasts were no longer detected in the CSF. Additional IT cytarabine was administered monthly for 5 doses and then every 3 months for 4 doses. The patient tolerated daily venetoclax well without significant adverse effects and maintained good quality of life except for vision-loss secondary to optic nerve infiltration by leukemia.

Then 3 years after starting venetoclax, patient presented with left leg pain and numbness, a subcutaneous lump in his scalp, and difficulty urinating. Patient was found to have experienced a 4th relapse (marrow, CNS and extramedullary) with a paraspinal chloroma causing spinal cord compression. Emergent radiation was directed to the chloroma and triple IT chemotherapy was again administered twice weekly for 4 doses after which the blasts were cleared from the CSF. Six cycles of subcutaneous ARA-C as administered previously was given again and daily venetoclax continued. From this point forward, the patient’s ambulation remained significantly impaired and 2 months after the 4th relapse, patient developed a “saddle” pulmonary embolus and anticoagulation was started.

Two months after the last cycle of ARA-C, a routine assessment of disease status again found leukemic blasts in the CSF but the marrow was not involved by leukemia (MRD negative). Monthly triple IT chemotherapy was given in addition to the daily venetoclax.

Oncologists should consider the regimen of oral venetoclax and subcutaneous ARA-C for patients with multiply relapsed, FLT3 negative AML seeking palliative treatment options. Venetoclax is easy to administer and does not require IV access or inpatient hospitalization. It was well tolerated in our patient, even after a prolonged treatment course, but clearly is not effective in preventing or treating CNS disease. Currently, our patient is alive 48 months post-second relapse (7.5 years post-diagnosis) with persistent CNS disease and disease-related morbidities.

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