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615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Down Syndrome with Acute Myeloid Leukemia in an Adolescent Male Successfully Treated with Low Dose Ara-C in Combination with Hypomethylating Agent

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Introduction

Patients with Down syndrome (DS) are prone to developing hematological malignancies, with risk of acute myeloid leukemia (AML) being 150 -fold higher compared to the general population. DS patients with leukemia are likely to experience significant chemotherapy related toxicities, hence require dose modifications. The myeloid leukemia of Down Syndrome (ML-DS) typically reflects acute megakaryoblastic leukemia (AMKL) a rare subtype of AML. ML-DS typically evolves from transient aberrant/abnormal myelopoiesis (TAM), aka transient myeloproliferative disorder (TMD), a pre-leukemic syndrome that almost always precedes myeloid leukemia in Down syndrome. *GATA1*, the hallmark driver mutation of TAM, is found in all TMD/TAM cases. AML in DS can occur de-novo which represents a different entity, appears immunophenotypically as (non-AMKL) AML, but differs morphologically from the classical ML-DS. The de-novo type AML in DS is reported to have worse prognosis. Poor outcomes are due to increased chemosensitivity and resulting chemotherapy-related toxicities when treated on standard high dose Ara-C based AML regimens. There is currently a lack of consensus on standard-of-care AML therapy applicable to this population.

Methods

Case report, retrospective electronic medical record review with institutional board review exemption

Results

We report a case of a 25-year-old male with trisomy 21, presenting with a one-month history of low-grade fevers, fatigue, and upper back pain. Initial laboratories showed a white cell count of 6.6 K/uL, hemoglobin 11.9 gm/dL, platelets 352 K/uL. CT chest showed a large right-sided pleural effusion, pleural thickening and multiple sclerotic bone lesions concerning for malignancy. Positron emission tomography (PET) CT revealed multiple hypermetabolic foci in the pelvis, spine, ribs, and cervical lymph nodes. Thoracocentesis was completed and pleural fluid pathology revealed atypical cells, flow cytometry showed 18% blasts positive for CD38, CD45, CD117 and negative for CD34 and HLA DR indicative of a myeloid neoplasm. Bone marrow aspirate and biopsy showed 10% CD117 positive immature myeloid cells. Morphology was not megakaryoblastic. Bone marrow flow cytometry results were consistent with that of pleural fluid with CD117 and myeloperoxidase (MPO) positive blasts. Fluorescent in-situ hybridization was negative for fusions/rearrangements. Next generation sequencing (NGS) detected *NPM1* mutation and also a low level (variant allelic frequency <3%) *FLT3* p.Y599C mutation (not internal tandem duplication or tyrosine kinase domain). *GATA1* mutation was absent. A diagnosis of AML with *NPM1* mutation and staging CNS1 was confirmed.

Our patient was defined as DS and AML. Given innate fragility and higher chemo sensitivity in patients with DS, we elected to treat him off protocol with Cladribine and low dose Ara-C alternating with Decitabine. This regime was derived from an adult leukemia protocol. Cycle 1 was complicated by central line related occlusive thrombus requiring anticoagulation, slow count recovery, and a brief episode of febrile neutropenia managed with antibiotics. End of induction marrow evaluation was negative for minimal residual disease (MRD).

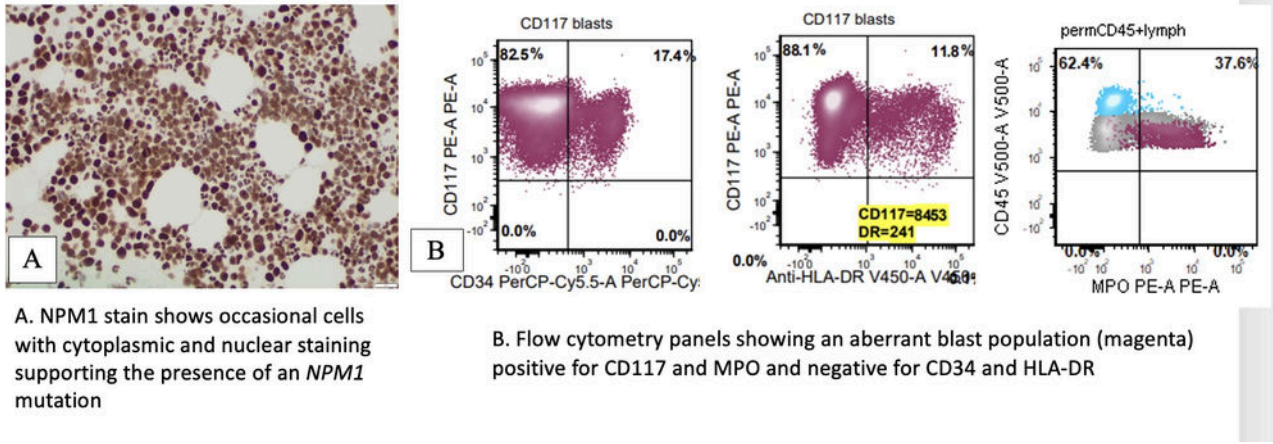
Flow cytometry on pleural fluid was also negative for abnormal blasts that were previously detected. Repeat molecular testing with NGS was negative for *NPM1*, *DNMT3A*, and *FLT3* mutations. The patient received a total of 8 cycles of chemotherapy.

On subsequent bone marrow evaluations, blasts remained <5% and MRD was negative. Interval PET scan showed significant improvement. Patient is currently more than a year off therapy and remains in remission.

Conclusion

Patients with DS and AML have a higher mortality due to increased risk of cardiotoxicity and infection from chemotherapy. There is a risk of either undertreatment or less commonly overtreatment leading to early mortality. Our case describes an adolescent male with DS and AML with pulmonary comorbidity who was successfully treated with a low-dose Ara-C regimen adapted from an adult protocol and had great clinical outcome. AML treatment in DS remains a challenge and further research is warranted to develop tailored regimens effectively balancing curative intent and reduced toxicity. This regimen could be considered in pediatric patients with Down Syndrome and other comorbidities.

Disclosures No relevant conflicts of interest to declare.



A. NPM1 stain shows occasional cells with cytoplasmic and nuclear staining supporting the presence of an *NPM1* mutation

B. Flow cytometry panels showing an aberrant blast population (magenta) positive for CD117 and MPO and negative for CD34 and HLA-DR

Figure 1

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