Daratumumab induced Minimal Residual Disease Negative Remission in CD 38 (dim) Positive Pediatric Acute Myeloid Leukemia

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Abbreviations

AML	Acute myeloid leukemia
MRD	Minimal residual disease
HSCT	Hematopoietic stem cell transplant

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Dear Editor,

Despite recent advancements, the survival in pediatric acute myeloid leukemia (AML) continues to remain dismal.[1] Various molecular and genetic alterations and minimal residual disease (MRD) are frequently used

for risk stratification. Salvage intensive chemotherapies have been recommended to bring remission before proceeding to hematopoietic stem cell transplant (HSCT). These come with prolonged duration of neutropenia and higher infective mortality.[2] There is need for identification of novel therapeutic targets.

Leukemic blasts commonly express CD38, daratumumab, a recombinant monoclonal antihuman CD38 antibody approved for myeloma therapy, has been suggested to be also potent in acute lymphoblastic leukemia.[3] We report possibly first case of pediatric AML who achieved MRD negative remission with single agent daratumumab.

A 2 years old male presented with history of recurrent fever, which was not responding to conventional antibiotics. Routine blood investigations revealed anemia with hypereosinophilia. CBC revealed hemoglobin 8.3g/dl, white blood cell counts 32.5 x 10^9/microlit and platelet count of 320 x 10^9/microlit. Absolute eosinophil count was 10.6 x 10^9/microlit. USG abdomen documented abdominal lymphadenopathy and splenomegaly. Hematology opinion was sought for eosinophilia. Child underwent a lymph node biopsy under sedation and in same sitting a bone marrow aspirate and biopsy were performed. Bone marrow revealed 71% blasts. The flowcytometry scatter parameters and antigenic expression profile of bone marrow along with morphology are consistent with Acute Myeloid Leukemia with CD 38 (dim expression) and aberrant expression for CD56. Abdominal lymph node biopsy was suggestive of round cell tumor with histomorphology and immunostaining were consistent with hematolymphoid (Myeloblast) malignancy. Ki67 was 70%. Cytgenetics revealed tetraploidy (XXXY) on chromosomal analysis. He was administered induction chemotherapy ADE as per AAML0531 protocol. Child attained morphologic remission but MRD assessment revealed 0.57% clonal cells. He went on to receive phase II of ADE therapy. Subsequent cycles were continued as per protocol. At end of intensification II protocol bone marrow MRD assessment revealed 0.48% clonal cells in April 22. There was delay in subsequent therapy. BMA at this point revealed 7% blasts. These clonal cells had dim CD 38+ expression.

Parents were counselled regarding need for allogeneic bone marrow transplantation. Gemtuzumab ozogamicin is not available in India. Daratumumab at a dose of 16 mg/kg was started in view of CD 38 expression. After 4 weekly doses of daratumumab, child attained MRD negative (<0.1) remission. BMT was delayed due to logistic issues and lack of consent from family. Therefore, weekly doses of daratumumab were continued. MRD remained negative even after 1 month (After 8 doses of Daratumumab) in June 22 <0.1%. Dosing schedule was changed to once in 2 weeks after this.

At the time when he was due to for 10^{th} dose of daratumumab, he complained of right leg pain which worsened with restricted movement and local tenderness. MRI hip and leg showed marrow edema with periosteal reaction in right tibia suggestive of myeloid leukemia changes. Histobiopsy from tibial lesion and bone marrow both revealed florid relapse. MRD was 21.9%.

Child underwent a salvage chemotherapy with FLAG and attained morphologic remission. MRD at this time was 1.72%. He underwent a haploidentical (donor sister) hematopoietic stem cell transplant in Oct 22. At present child is 5 months post BMT with MRD negative status and 100% donor chimerism.

Most AML blasts show high CD38 expression without obvious correlation with cytomorphological and genetic characteristics.[4] Daratumumab is a fully human IgG1-kappa monoclonal antibody that directly binds to CD38 has been confirmed to be safe and effective in patients with relapsed and refractory multiple myeloma.[5] Daratumumab has multiple mechanisms of action Daratumumab significantly induces antibody dependent phagocytosis in AML and shows interference with AML cell trafficking in vivo in a xenograf transplantation model.[6]

Previous reports on daratumumab in acute lymphoblastic leukemia have used a dose of 16 mg/kg which is typical myeloma protocol.[7] MRD negative remission induction is fast as happened with this child who attained MRD negative remission after 4 weekly doses. This remission was sustained for 10 weeks which provides a very good window to proceed with HSCT as curative therapy. One important consideration is that our child had a dim CD 38 expression. Daratumumab promotes antitumor immune responses, rather than targeting the cancer directly [10]. Daratumumab can inhibit cytotoxic T-lymphocyte–associated antigen 4

(CTLA-4) and programmed cell death protein 1 (PD-1) to promote T-cell expansion and enhance T-cell activation, resulting in prolonged survival and delayed disease recurrence in patients with advanced solid tumors and hematologic malignancies.[8] Therefore, it is possible that other mechanism of action may have been useful in inducing remission. This opens up possibility of its usage in CD 38 dim/negative negative AML also. Daratumumab and venetoclax combination has been added to a preparative regimen among 20 children with chemorefractory acute myeloid leukemia who underwent haploidentical HSCT yielding a 2-year EFS of 44%.[9]

Present report highlights efficacy of daratumumab as a single agent in inducing short lived MRD negative remission in a child with dim CD 38 expression.

References

1. Chaudhary S, Ganguly S, Palanichamy JK, Singh A, Pradhan D, Bakhshi R, Chopra A, Bakhshi S. Mitochondrial gene expression signature predicts prognosis of pediatric acute myeloid leukemia patients. Front Oncol. 2023 Feb 9;13:1109518. doi: 10.3389/fonc.2023.1109518. PMID: 36845715
2. Madney Y, Aboubakr S, Khedr R, Hafez H, Ahmed N, Elsheshtawy K, Elanany M, Salahelden A, Shalaby L, Galal Behairy O. Carbapenem-Resistant *Enterobacteriaceae* (CRE) among Children with Cancer: Predictors of Mortality and Treatment Outcome. Antibiotics (Basel). 2023 Feb 17;12(2):405. doi: 10.3390/antibiotics12020405. PMID: 36830314
3. Cerrano M, Bonifacio M, Olivi M, Curti A, Malagola M, Dargenio M, Scattolin AM, Papayannidis C, Forghieri F, Gurrieri C, Tanasi I, Zappasodi P, La Starza R, Fracchiolla NS, Chiusolo P, Giaccone L, Del Principe MI, Giglio F, Defina M, Favre C, Rizzari C, Castella B, Pizzolo G, Ferrara F, Chiaretti S, Foà R. Daratumumab with or without chemotherapy in relapsed and refractory acute lymphoblastic leukemia. A retrospective observational Campus ALL study. Haematologica. 2022 Apr 1;107(4):996-999. doi: 10.3324/haematol.2021.279851.
4. Keyhani, A. et al. Increased CD38 expression is associated with favorable prognosis in adult acute leukemia. Leuk Res. 24, 153–159 (2000)
5. Jeyaraman P, Bhasin A, Dayal N, Pathak S, Naithani R. Daratumumab in dialysis-dependent multiple myeloma. Blood Res. 2020 Mar;55(1):65-67. doi: 10.5045/br.2020.55.1.65.
6. Farber M, Chen Y, Arnold L, Möllmann M, Boog-Whiteside E, Lin YA, Reinhardt HC, Dührsen U, Hanoun M. Targeting CD38 in acute myeloid leukemia interferes with leukemia trafficking and induces phagocytosis. Sci Rep. 2021 Nov 11;11(1):22062. doi: 10.1038/s41598-021-01300-8. PMID: 34764342; PMCID: PMC8586007.
7. Vakrmanová B, Nováková M, Říha P, Žaliová M, Froňková E, Mejstříková E, Starý J, Hrušák O, Šrámková L. CD38: A target in relapsed/refractory acute lymphoblastic leukemia-Limitations in treatment and diagnostics. Pediatr Blood Cancer. 2022 Sep;69(9):e29779. doi: 10.1002/pbc.29779. Epub 2022 May 20. PMID: 35592935.
8. J. Krejcik, T. Casneuf, I.S. Nijhof, B. Verbist, J. Bald, T. Plesner, K. Syed, K. Liu, N.W. van de Donk, B.M. Weiss, T. Ahmadi, H.M. Lokhorst, T. Mutis, A.K. Sasser, Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expan- sion, and skews T-cell repertoire in multiple myeloma, Blood 128 (3) (2016) 384–394.
9. Klimentova M, Shelikhova L, Ilushina M, Kozlovskaya S, Blagov S, Popov A, Kashpor S, Fadeeva M, Olshanskaya J, Glushkova S, Pershin D, Balashov D, Maschan A, Maschan M. Targeted Therapy With Venetoclax and Daratumumab as Part of HSCT Preparative Regimen in Children With Chemorefractory Acute Myeloid Leukemia. Transplant Cell Ther. 2023 Feb;29(2):127.e1-127.e9. doi: 10.1016/j.jtct.2022.11.022.