Efficacy of acute myeloid leukemia therapy without stem-cell transplantation in a child with blastic plasmacytoid dendritic cell neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), previously known as blastic natural killer (NK)-cell lymphoma, is a rare, aggressive tumor, which primarily affects the elderly (mean age 61-67 years), although it can occur at any age, including childhood.[1] The cell of origin, previously believed to be the NK cell,[2] is derived from plasmacytoid dendritic cell committed hematopoietic precursors. The World Health Organization has re-classified this tumor as a myeloid malignancy,[1] characterized by CD4 and CD56 positivity with high levels of membranous CD123 in tumor cells.[3] There is no consensus treatment. The recent article by Pagano *et al.*[4] highlights the varied treatment approaches and continued dismal outcome for 43 adults with BPDCN treated between 2005 and 2011. Their study revealed significantly higher complete remission rates following acute lymphoblastic leukemia (ALL)/lymphoma therapy, compared with acute myeloid leukemia (AML) therapy. Moreover, there was a survival advantage for patients who underwent allogeneic hematopoietic stem cell transplant (HSCT) compared to non-transplanted patients, though actuarial survival at two years was only 7%, consistent with previous reports.[5,6] In contrast, a review of 25 children with BPDCN, where the majority of patients received high-risk ALL (n=14) or non-Hodgkin's lymphoma (n=6) therapy, without HSCT, demonstrated significantly better outcomes for children with an overall survival of 72%.[7] This prompted the authors to suggest high-risk ALL chemotherapy with central nervous system prophylaxis as a therapeutic approach, with HSCT reserved for children with recurrent disease in second remission. We present a 2½-year old girl treated with AML therapy who remains in first continuous complete remission two years and two months from the end of therapy. Our case demonstrates that AML therapy, without HSCT, can be sufficient to treat this rare disease in children.

Our patient presented with a right infraorbital mass (Figure 1A) with an overlying purplish/brown skin discoloration, thought to be a chloroma. and a leukoerythroblastic blood film with cells resembling myeloblasts. Clinical examination revealed no hepatosplenomegaly or lymphadenopathy. Flow cytometry showed blast cells strongly positive for CD2, MHC Class II and CD45, weak expression of CD24, whilst CD3, CD7, CD10, CD13, CD19, CD33, CD34, CD41a, CD61 and TdT were negative. Bone marrow aspirate (BMA) and trephine were consistent with an initial diagnosis of AML (FAB M5a; Figure 1B). Conventional cytogenetics demonstrated a normal karyotype and molecular genetic studies revealed no FLT-3 ITD or *NPM1* mutations.

Her family consented to treatment on the Children's Oncology Group (COG) protocol AAML0531 comprising gemtuzamab ozogamicin, cytarabine, daunorubicin, etoposide, mitoxantrone and L-asparaginase.[8] She showed a rapid response with near complete resolution of the mass lesion within 24 hours. BMA at the end of induction cycle I demonstrated M1 remission. She had a matched sibling donor and HSCT was planned after cycle three of chemotherapy. However, HSCT was deferred due to significant cardiac dysfunction. She received a further two cycles of AML therapy, without anthracyclines.

Central pathology review by the COG using an expanded immunohistochemistry panel revealed CD56, CD123, TCL-1 positivity, weak CD4 expression and negativity for S100, MPO, CD163 and CD3, diagnostic of BPDCN. Re-review of her initial biopsies at our institution was consis-

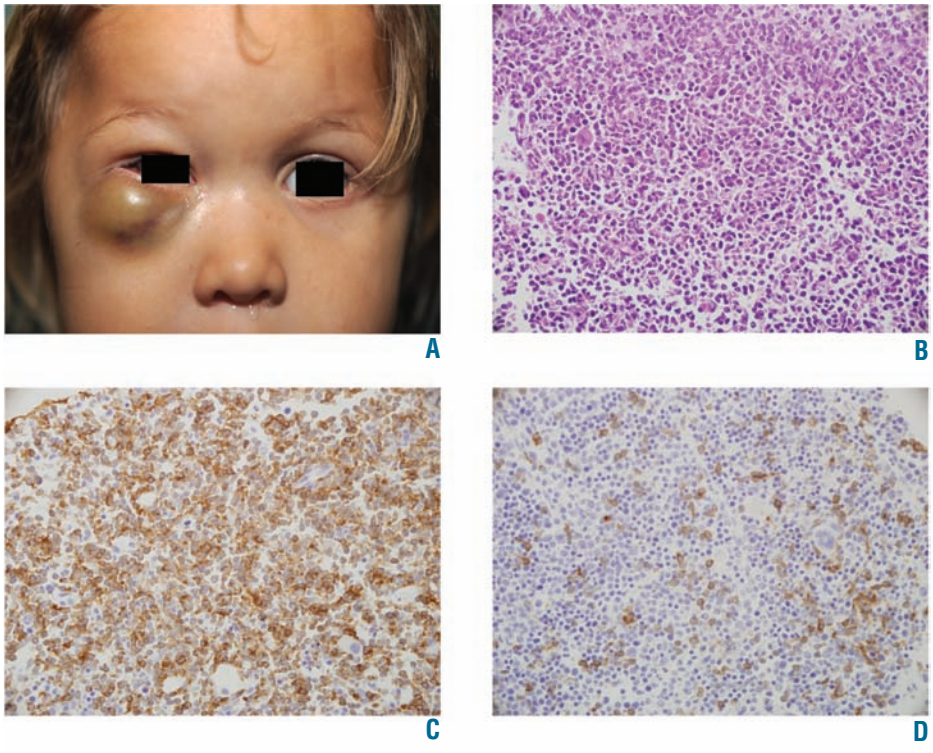

Figure 1. (A) Cutaneous manifestation of blastic plasmacytoid dendritic cell neoplasm at presentation. (B) H&E staining (original magnification 400x) of bone marrow biopsy at diagnosis, demonstrating sheets of small or intermediate cells and irregularly shaped hyperchromatic nuclei with scant cytoplasm. (C) Strong CD123 immunohistochemical staining of membranes in the majority of cells. (D) Smaller numbers of cells with CD56 membranous positivity on immunohistochemical staining.

tent with central review (Figure 1C and D) and the diagnosis was subsequently revised. BMA at the end of therapy revealed continued remission and she remains in continued remission two years and two months from the completion of therapy.

Our case highlights two important points. The first is the complexity of diagnosing this rare entity. BPDCN should be considered in the diagnosis of any child presenting with cutaneous lesions and blasts in the bone marrow. The panel of flow cytometry and immunohistochemical markers should include CD4, CD56 and CD123. Secondly, consistent with Pagano *et al.* and others,[9] AML therapy was effective in inducing a first remission. Whilst, 3 of the children reported by Jegalian *et al.* received AML therapy, 2 succumbed to therapy-related complications and one to progressive disease following relapse after 12 months,[10] precluding a meaningful assessment of efficacy for this approach in children. Our case demonstrates the feasibility of using AML therapy to successfully treat BPDCN in childhood. Whilst HSCT may not be a necessity following first complete remission, the optimal chemotherapeutic strategy remains unknown. To assess AML *versus* high-risk ALL therapy, a randomized controlled trial with central histopathological review is required, but the rarity of this disorder makes this unfeasible. An alternative approach is to establish a central registry, incorporating standardized international reporting, as has been successfully achieved for pleuropulmonary blastoma, another rare childhood malignancy (*http://www.ppbregistry.org/*).

Jordan R. Hansford,[1] Rishi S. Kotecha,[1,2,3] Gareth Jevon,[1,4,5] Catherine H. Cole,[1,2,5] and Nicholas G. Gottardo[1,2,3]

[1]Department of Hematology and Oncology, Princess Margaret Hospital for Children, Perth, WA; [2]School of Pediatrics and Child Health, University of Western Australia; [3]Telethon Institute for Child Health Research, Centre for Child Health Research, Perth, WA; [4]Department of Pathology, University of Western, Australia; and [5]PathWest, Perth, WA, Australia.

Correspondence: Nicholas G. Gottardo.
nick.gottardo@health.wa.gov.au
doi:10.3324/haematol.2012.082487

Funding: this study was carried out as part of our routine work.

Key-words: blastic plasmacytoid dendritic cell neoplasm, BPDCN, pediatric.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Facchetti F, Jones D, Petrella T, eds. Blastic plasmacytoid dendritic cell neoplasm. 2008 ed. Lyon: IARC Press; 2008.
2. Chan JKC, Jaffe ES, and Ralfkiaer E, eds. Blastic NK-cell lymphoma. 2001 ed. Lyon: IARC Press; 2001.
3. Petrella T, Comeau MR, Maynadie M, Couillault G, De Muret A, Maliszewski CR, et al. 'Agranular CD4+ CD56+ hematodermic neoplasm' (blastic NK-cell lymphoma) originates from a population of CD56+ precursor cells related to plasmacytoid monocytes. Am J Surg Pathol. 2002;26(7):852-62.
4. Pagano L, Valentini CG, Pulsoni A, Fisogni S, Carluccio P, Mannelli F, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica. 2012. Epub 2012/10/16. doi: 10.3324/haematol.2012.072645. PubMed PMID: 23065521.
5. Petrella T, Bagot M, Willemze R, Beylot-Barry M, Vergier B, Delaunay M, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. Am J Clin Pathol. 2005;123(5):662-75.
6. Reimer P, Rudiger T, Kraemer D, Kunzmann V, Weissinger F, Zettl A, et al. What is CD4+CD56+ malignancy and how should it be treated? Bone Marrow Transplant. 2003;32(7):637-46.
7. Jegalian AG, Buxbaum NP, Facchetti F, Raffeld M, Pittaluga S, Wayne AS, et al. Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic features and clinical implications. Haematologica. 2010;95(11):1873-9.
8. Hann IM, Stevens RF, Goldstone AH, Rees JK, Wheatley K, Gray RG, et al. Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of the Medical Research Council's 10th AML trial (MRC AML10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. Blood. 1997;89(7):2311-8.
9. Ham JC, Janssen JJ, Boers JE, Kluin PM, Verdonck LF. Allogeneic stem-cell transplantation for blastic plasmacytoid dendritic cell neoplasm. J Clin Oncol. 2012;30(8):e102-3.
10. Feuillard J, Jacob MC, Valensi F, Maynadie M, Gressin R, Chaperot L, et al. Clinical and biologic features of CD4(+)CD56(+) malignancies. Blood. 2002;99(5):1556-63.