Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Targeted inhibitors and antibody immunotherapies: Novel

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BASED ON ARTICLE

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INTRODUCTION

Leukaemias and lymphomas in children are heterogeneous diseases comprising roughly one-third of paediatric cancers. Although in acute lymphoblastic leukaemia (ALL), mature B-cell ALL and lymphoblastic lymphoma (LL) outcomes have increased to over 85% event-free survival (EFS), outcomes in anaplastic large-cell lymphoma (ALCL) and acute myeloid leukaemia (AML) still lag behind with EFS rates in the range of 55–75%. Moreover, the treatment for relapsed/refractory T-ALL, B-ALL, AML, ALCL etc becomes tricky and complicated. This article reviews the current status of drug development for leukaemia and lymphoma in children, excluding Hodgkin lymphoma (HL) and provides an overview of actionable targets with agents currently in development in paediatric settings, in AML, ALL and NHL, respectively.

Results: Bispecific and antibody–drug conjugates targeting CD19 and CD22 (blinatumomab and inotuzumab ozogamicin) play an important role in the treatment of relapsed and refractory B-cell precursor acute lymphoblastic leukaemia (BCP-ALL); antibodies targeting CD123 and CD38 are also under investigation for AML and T-ALL, respectively. Targeted therapy with small molecules is of primary importance for specific genetic subtypes, such as BCR-ABL-positive ALL, FLT3-ITD AML and anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma. KMT2A-directed targeted therapy with menin inhibitors holds promise to be of relevance in KMT2A-rearranged leukaemias, known to have dismal prognosis. Target inhibition in cellular pathways such as BCL-2, RAS, MEK, Bruton's tyrosine kinase, JAK-STAT or CDK4/CDK6 inhibition may be suitable for different diseases with common mutated pathways.

COMMENTARY

India has a unique problem of abundant patients and scarce resources. As a result of which we deal with a lot of fresh, relapsed and resistant diseases alike. Hemtopoietic Stem Cell Transplant (HSCT) is the current standard of care that we offer to all patients after the first relapse, especially in leukemias and some lymhomas; but management becomes complex and the options are limited after the second and

third relapses.

To summarize this study, CD38-targeting monoclonal antibodies (Daratumumab; Isatuximab) are approved to treat adults with multiple myeloma (MM). Preclinical data shows that CD38 is expressed in many paediatric haematological malignancies (strong expression in ALL and variable in AML). A phase I–II trial of daratumumab with standard 4-drug reinduction in children and young adults with relapsed or refractory (R/R) BCP or T-cell ALL and LL is ongoing. Rituximab, a monoclonal antibody that binds to CD20, is the standard of care in addition to chemotherapy in mature B-cell NHL and as single agent in post-transplant lymphoproliferative disease (especially EBV-positive). In ALL only 30 to 50% of BCP-ALL blasts express CD20. In a French trial in adults, adding rituximab to the ALL chemotherapy protocol, demonstrated an improved outcome for younger adults with CD20-positive, Philadelphia chromosome (Ph)-negative ALL.

Blinatumomab is a bispecific antibody approved by the FDA as monotherapy for the treatment of children with R/R BCP-ALL, or in the first or second CR with persisting positive minimal residual disease (MRD) (1). In Europe, blinatumomab is indicated for paediatric patients above the age of 1 year, with second or greater R/R BCP-ALL, or with high-risk first relapse BCP-ALL as part of the consolidation therapy. Inotuzumab ozogamicin (InO) is an anti-CD22 antibody. In a compassionate use program in children with R/R BCP-ALL, treatment with single-agent InO resulted in CR in 67% of patients (2). Current guideline is to limit InO to 2–3 cycles if a patient is a candidate for HSCT and to use non-alkylating chemotherapy.

Brentuximab vedotin is a CD30-directed ADC approved for adult patients with HL and ALCL. A paediatric phase I–II trial recently showed an ORR of 53% for R/R ALCL and 47% for classical HL (3). Brentuximab vedotin with chemotherapy in children with newly diagnosed ALCL, reported a two-year EFS of 79.1% and a two-year OS of 97.0%without significant additional toxicity compared with standard chemotherapy. Midostaurin has strong inhibitory effects on FLT3. A phase I trial of midostaurin monotherapy was conducted in children with leukaemia, five of nine patients with AML and three of 13 patients with KMT2A-rearranged ALL had partial or complete responses (4). Sorafenib is a first-generation pan-kinase inhibitor used in AML maintenance in adults.

ALK inhibitors are investigated in the treatment of malignancies that are ALK or ROS fusion gene-driven, including ALCL. A variety of ALK inhibitors are available, including crizotinib, ceritinib, lorlatinib, alectinib, entrectinib and brigatinib. Imatinib, dasatinib and nilotinib are the first- and second-generation BCR-ABL inhibitors approved for paediatric patients with CML. Venetoclax restores the process of apoptosis by binding directly to the BCL-2 protein. It is FDA approved for adult patients with CLL or small lymphocytic lymphoma, and in combination with hypomethylating agents or low-dose cytarabine for the treatment of newly diagnosed AML in adults not eligible for intensive induction chemotherapy. A phase I/II study of venetoclax in combination with chemotherapy in paediatric patients with different diseases (ALL, AML, NHL, neuroblastoma and other tumours) showed preliminary efficacy in patients with leukaemia (5). A phase I study of venetoclax in combination with cytarabine, with or without idarubicin, in children and young adults with R/R AML showed overall responses in 69% of the 35 patients (6).

This study is especially relevant to the Indian scenario as HSCT is not always readily available due to resource constraints (7). Many of the above mentioned drugs are been freely used by our adult oncology counter-parts in routine clinical settings. With the correct background, research and knowledge we can

offer these drugs to our patients on the roadway to HSCT, or just to buy precious time. Many of the therapeutic options mentioned are not only time-buying but also have been proven to prolong disease free survival and over-all survival.

REFERENCES

1. F. Locatelli, G. Zugmaier, N. Mergen, P. Bader, S. Jeha, P.-G. Schlegel, et al Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia: results of the RIALTO trial, an expanded access study Blood Cancer J, 10 (7) (2020), p. 77
2. D. Bhojwani, R. Sposto, N.N. Shah, V. Rodriguez, C. Yuan, M. Stetler-Stevenson, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia Leukemia, 33 (4) (2019), pp. 884-892
3. F. Locatelli, C. Mauz-Koerholz, K. Neville, A. Llort, A. Beishuizen, S. Daw, et al. Brentuximab vedotin for paediatric relapsed or refractory Hodgkin's lymphoma and anaplastic large-cell lymphoma: a multicentre, open-label, phase 1/2 study Lancet Haematol, 5 (10) (2018), pp. e450-e461
4. C.M. Zwaan, S. Söderhäll, B. Brethon, M. Luciani, C. Rizzari, R.W. Stam, et al. A phase 1/2, open-label, dose-escalation study of midostaurin in children with relapsed or refractory acute leukaemia Br J Haematol, 185 (3) (2019), pp. 623-627
5. S.E. Karol, T.M. Cooper, H. Bittencourt, L. Gore, M.M. O'Brien, C. Fraser, et al. Safety, efficacy, and PK of the BCL2 inhibitor venetoclax in combination with chemotherapy in pediatric and young adult patients with relapsed/refractory acute myeloid leukemia and acute lymphoblastic leukemia: phase 1 study Blood, 134 (Supplement_1) (2019), p. 2649
6. S.E. Karol, T.B. Alexander, A. Budhraja, S.B. Pounds, K. Canavera, L. Wang, et al. Venetoclax in combination with cytarabine with or without idarubicin in children with relapsed or refractory acute myeloid leukaemia: a phase 1, dose-escalation study Lancet Oncol, 21 (4) (2020), pp. 551-560
7. Kulkarni U, George B. Access to hematopoietic stem-cell transplantation in India. J Postgrad Med. 2019 Jan-Mar;65(1):1-4. doi: 10.4103/jpgm.JPGM_391_18. PMID: 30693869; PMCID: PMC6380131.