Indian Journal of Pediatrics (January 2024) 91(1):35–36
https://doi.org/10.1007/s12098-023-04920-2

EDITORIAL

Management Principles and Advances in Therapies of Pediatric Acute Leukemia: A Comprehensive Snapshot

Shuvadeep Ganguly[1] · Yaddanapuddi Ravindranath[2] · Sameer Bakhshi[1]

Received: 18 October 2023 / Accepted: 25 October 2023 / Published online: 10 November 2023

Childhood acute leukemia accounts for 40–50% of pediatric malignancies in India [1]. Over the last five decades, advances in chemotherapy regimens, supportive care and hematopoietic stem cell transplantation (HSCT) have drastically improved the survival outcomes of pediatric acute leukemia worldwide. The last two decades saw a deeper understanding of biology, identification of therapeutic targets, and incorporation of targeted therapies in the management. The collection of articles in this symposium on acute leukemia provide a comprehensive review on management strategies of clinically challenging aspects as well as recent advances in the therapies of childhood acute leukemia. The articles also describe the challenges faced in resource-constrained settings and offer pragmatic solutions for such clinical scenarios.

The cure rates of pediatric acute lymphoblastic leukemia (ALL) approaches 90% in high-income countries; while there exists a survival gap in low-middle income countries (LMICs) like India (45–81%) [1]. The survival gap is for the most part due to healthcare resource limitations, although, some studies also indicate that the proportion of patients with high-risk ALL (T-ALL, higher age, Philadelphia positive) may be higher in India [1, 2]. Even in the presence of resource constraints, it is often cost-effective to evaluate for newly recognised entities like Philadelphia-like ALL in India by adopting a stepwise diagnostic algorithm to facilitate early enrolment of clinical trials for these children [2].

The intensive and prolonged therapy for ALL is often fraught with challenges like management of drug-related toxicities and infections which leads to treatment abandonment in LMICs. This often leads to inability to maintain desired treatment intensity; possibly accounting for comparatively higher proportion of relapse (20–40%). Krishnan et al. underscore the importance of maintaining adequate treatment intensity, especially during the maintenance phase. The utility of routine evaluation of common pharmacogenomic variants (especially common polymorphism in Indian population like *NUDT15*3*) and dose titration of anti-metabolites guided by pharmacogenomics should be prospectively evaluated to limit toxicities and maintain overall treatment intensity [3]. Furthermore, the review by Suryaprakash et al. encourages adopting treatment strategies like steroid prophase before first lumbar puncture, using Capizzi-methotrexate instead of high-dose methotrexate, based on available resources to limit treatment related toxicities without compromising outcomes [4]. Healthcare burden at tertiary care centres may also be reduced by shared care approach, where, majority of maintenance therapies including intrathecal therapies may be done at a local healthcare centre, in conjunction with primary treating oncology centre.

Relapsed ALL, especially early medullary relapses, continues to have poor prognosis despite newer therapies. In a retrospective analysis by Arya et al. among children with ALL treated with a uniform protocol in India, the cumulative relapse rate was 17.9%, where the proportion of isolated marrow relapse (57.5%) was highest and more than two-thirds (67.5%) relapses were on-therapy [5]. Sidhu et al. provided a comprehensive summary on the management of relapsed ALL. The primary goal in the management of relapsed ALL is attaining a second complete remission with negative minimal residual disease (MRD) status followed by consolidation with HSCT/CD19 CAR T-cell therapy. In this regard, use of newer agents like blinatumomab and inotuzumab ozogamicin has considerably expanded the treatment options in B-ALL to attain negative MRD status. The use of drug-response profiling to select appropriate choice of therapy especially in chemo-refractory disease is an attractive choice, which needs further prospective evaluation [6]. On the other hand, for relapsed Ph+ ALL, the contribution

✉ Sameer Bakhshi
sambakh@hotmail.com

[1] Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All Institute of Medical Sciences, New Delhi, India

[2] Department of Pediatrics, School of Medicine, Wayne State University, Detroit, USA

of BCR-ABL tyrosine kinase domain (TKD) mutations as resistance mechanisms is lower in children than in adults. Hence, even though TKD mutations should be routinely evaluated in relapsed Ph+ ALL, same tyrosine kinase inhibitor may also be used in relapse in absence of any such mutations [2].

In contrast to B-ALL, the management of T-ALL continues to be even more challenging due to comparatively less treatment options at relapse. Identification of early-T-cell precursor ALL (cCD3 positive, CD1a negative, CD8 negative with dim/negative CD5) with poor response to initial chemotherapy is important at diagnosis [7]. Jeha S summarized the newer targeted therapies in relapsed T-ALL which are in active exploration. Agents like bortezomib, daratumumab and venetoclax ± navitoclax have shown promising responses. Although long term data on their outcomes are yet to mature, their long-term safety profile in other hematological disorders and early efficacy results warrants their incorporation in management of relapsed T-ALL [8]. Advances in base editing technology has led to the development of base-edited CD7 CAR T-cells, with recent trials in relapsed T-ALL.

The outcome of pediatric acute myeloid leukemia (AML) continues to be dismal due to high proportion of relapses (40%) despite attaining initial remission status (80%). Use of salvage chemotherapy regimens like outpatient-based ADE (Cytarabine, Daunorubicin, Etoposide), FLAG (Fludarabine, Cytarabine, with granulocyte-colony stimulating factor) to attain second remission and simultaneously limiting treatment related toxicities remains a challenge [9]. Al-Antary et al. provide a snapshot on the therapeutic landscape of relapsed pediatric AML. Currently, the only targeted agent with regulatory approval among children is Gemtuzumab ozogamicin in addition to chemotherapy in newly diagnosed cases, and even as mono-therapy in relapsed disease; although hepato-toxicity is a concern. Sorafenib also demonstrated safety and efficacy for FLT3/ITD+ (Fms-like tyrosine kinase-3 internal tandem duplication) AML in children, and is commonly incorporated in treatment paradigm. In contrast to adults, the frequency of mutations in methylation-related genes in pediatric AML is lower, with unclear utility of hypomethylating agents for single agent therapy. On the other hand, the combination of venetoclax with chemotherapy has shown good response and is worth further exploration [10].

However, it should be borne in mind that the newer therapies including HSCT are often not-affordable for majority of Indian households. Hence, the role of low-dose chemotherapy for symptomatic management, and palliative and supportive care for patients with relapsed/refractory disease are of no less importance in areas of resource constraints [6]. The support of government-led public health insurance programs for therapies like HSCT is likely to change the outlook in the future. The evolution of collaborative trials under Indian Pediatric Oncology group (InPOG) is likely to shape the clinical research landscape on pediatric acute leukemia in India in the coming years. This needs to be nurtured so as to explore cost-effective therapies suited to address unique needs in LMICs.

Declarations

Conflict of Interest None.

References

1. Ganguly S, Kinsey S, Bakhshi S. Childhood cancer in India. Cancer Epidemiol. 2020;71:101679.
2. Ganguly S, Sasi A, Pushpam D, Bakhshi S. Philadelphia chromosome positive and philadelphia-like acute lymphoblastic leukemia in children and adolescents: current management, controversies and emerging concepts. Indian J Pediatr. 2023. https://doi.org/10.1007/s12098-023-04782-8.
3. Krishnan S, Mahadevan A, Mungle T, Gogoi MP, Saha V. Maintenance treatment in acute lymphoblastic leukemia: a clinical primer. Indian J Pediatr. 2023. https://doi.org/10.1007/s12098-023-04687-6.
4. Suryaprakash S, Inaba H. Acute lymphoblastic leukemia with central nervous system involvement-challenges in management. Indian J Pediatr. 2023. https://doi.org/10.1007/s12098-023-04731-5.
5. Arya LS, Kotikanyadanam SP, Bhargava M, et al. Pattern of relapse in childhood ALL: challenges and lessons from a uniform treatment protocol. J Pediatr Hematol Oncol. 2010;32:370–5.
6. Sidhu J, Gogoi MP, Krishnan S, Saha V. Relapsed acute lymphoblastic leukemia. Indian J Pediatr. 2023. https://doi.org/10.1007/s12098-023-04635-4.
7. Chopra A, Bakhshi S, Pramanik SK, et al. Immunophenotypic analysis of T-acute lymphoblastic Leukemia. A CD5-based ETP-ALL perspective of non-ETP T-ALL. Eur J Haematol. 2014;92:211–8.
8. Jeha S. Relapsed/Refractory T-acute lymphoblastic Leukemia - current options and future directions. Indian J Pediatr. 2023. https://doi.org/10.1007/s12098-023-04745-z.
9. Garg A, Ganguly S, Vishnubhatla S, Chopra A, Bakhshi S, Outpatient ADE (cytarabine, daunorubicin, and etoposide) is feasible and effective for the first relapse of pediatric acute Myeloid Leukemia: a prospective, phase II study. Pediatr Blood Cancer. 2020;67:e28404.
10. Al-Antary ET, Gupte A, Ravindranath Y. Targeted therapies in pediatric acute myeloid leukemia - evolving therapeutic landscape. Indian J Pediatr. 2023. https://doi.org/10.1007/s12098-023-04741-3.