Article published online: 2024-07-10

Minimal Disseminated Disease Continues to Impact Outcomes Even in the Era of Targeted Therapy in Childhood ALK+ Anaplastic Large Cell Lymphoma, What More Do We Have to Offer?

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South Asian J Cancer

Abstract

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Keywords

- ALK
- anaplastic large cell lymphoma
- minimal disseminated disease
- minimal residual disease
- targeted therapy

Over the last four decades, outcomes of pediatric anaplastic large cell lymphoma (ALCL) have plateaued despite use of multiagent chemotherapy and targeted therapy. Historically, ALCL99 study has been the largest trial in pediatric ALCL which enrolled 420 children treated on a uniform chemotherapy backbone[1] with reported 10-year progression-free

DOI https://doi.org/10.1055/s-0044-1788541 ISSN 2278-330X

How to cite this article: Dhariwal N, Srinivasan S Minimal Disseminated Disease Continues to Impact Outcomes Even in the Era of Targeted Therapy in Childhood ALK+ Anaplastic Large Cell Lymphoma, What More Do We Have to Offer?. South Asian J Cancer 2024;00(00):00–00

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

survival (PFS) of 70%. In this study, data on minimal disseminated disease (MDD) was available for 162 patients of which 87 (54%) were $MDD_{positive}$; defined as positive polymerase chain reaction (PCR) for nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) in peripheral blood (PB) and/or bone marrow (BM). In a post hoc analysis, MDD along with small--cell/lymphohistiocytic histology (SC/LH) were found to be independently prognostic. When risk stratified according to MDD and SC/LH morphology, the high-risk (HR) group having both these factors had a significantly inferior PFS in comparison to the low risk (LR) ($MDD_{negative}$ without SC/LH pattern) and intermediate risk (IR) (either $MDD_{positive}$ or SC/LH pattern; 10-year PFS LR vs. IR vs. HR being 86% vs. 75% vs. 40%; $p < 0.0001$).

The recently concluded ANHL12P1 study was a phase II randomized control trial with a primary aim to determine the toxicity and efficacy of addition of crizotinib (CZ)[2] or brentuximab vedotin (BV)[3] to standard ALCL99 chemotherapy backbone in children with newly diagnosed ALK+/CD30+ ALCL. Though this study failed to show improvement in outcomes beyond the highest reported in pediatric ALCL, of interest was that patients with $MDD_{positive}$ (defined as > 10 copies of NPM-ALK fusion transcript/10^4 ABL1 in PB/BM) continued to have significantly inferior outcomes in comparison to those with $MDD_{negative}$ in both CZ arm (2-year event-free survival [EFS]: 58.1% vs. 85.6%; $p = 0.0058$) and BV arm (2-year EFS: 89.0% vs. 52.6%; $p = 0.00043$); impact of SC/LH morphology was not studied here. Hence, MDD continues to remain prognostic even with the addition of targeted therapy. Depending on the method used, the incidence of $MDD_{positive}$ patients in ALCL varies between 30 and 50%. Though there is a high concordance of both qualitative and quantitative NPM-ALK PCR between BM and PB, use of better techniques like digital PCR can improve the sensitivity of detection and facilitate uniform measurement across different laboratories.[4,5]

Minimal residual disease (MRD) determined following chemotherapy using similar methods, has also been shown to have prognostic relevance. Damm-Welk et al,[6] in a cohort of 180 patients showed that $MRD_{positive}$ (determined by qualitative PCR done before the second course of chemotherapy) status significantly impacted outcomes in addition to MDD determined at diagnosis (5-year EFS: 82% in $MDD_{negative}$, 69% in $MDD_{positive}/MRD_{negative}$ and 19% in $MDD_{positive}/MRD_{positive}$, $p < 0.001$). Similar results were shown by Rigaud et al in a cohort of 138 French patients.[7] Both these studies employed a chemotherapy-only backbone. With MRD strongly impacting outcomes, the effect of targeted therapy in achieving MRD clearance in ALK+ ALCL needs further evaluation.

These static outcomes of pediatric ALCL with diverse regimens mandate evaluation of other prognostic factors as well. Mathew et al[8] showed a significant impact of whole-body metabolic tumor volume and interim response on outcomes of pediatric ALCL with a novel vinblastine nonhigh dose methotrexate regimen (Modified MCP−842). Whether integration of targeted therapy in this regimen or switching to an ALCL99-like regimen can improve outcomes in these patients needs to be determined.

Patients with $MDD_{positive}/MRD_{positive}$ ALCL have a dismal EFS and ways for early treatment modification to improve outcomes for this HR subgroup is worth exploring. Limited case series and reports have shown checkpoint inhibitors like nivolumab[9] and next-generation ALK inhibitors like ceritinib, alectinib, and lorlatinib[10] to induce durable remission in $MDD_{positive}/MRD_{positive}$ ALCL. A single case report of combination of CZ and BV used as a bridge to autologous stem cell transplant and CD30 CAR-T cell therapy in a case of refractory ALCL showed partial remission with the combination; the safety and efficacy of this combination in this HR $MDD_{positive/MRDpositive}$ cohort needs evaluation in larger cohorts. Though prolonging maintenance therapy beyond 1 year has not shown any survival benefit in ALCL99,[11,12] whether this benefits the $MDD_{positive}/MRD_{positive}$ subset remains unanswered. Data from BFM (Berlin-Frankfurt-Muenster)[13] and ALCL99[14] studies have shown efficacy of allogenic hematopoietic stem cell transplant (HSCT) as consolidative therapy for relapse/refractory ALCL. Exploiting the graft-versus-leukemia effect of allogenic HSCT in treating $MDD_{positive}/MRD_{positive}$ ALCL has not been previously explored and investigating this would be worthwhile. CD30 CAR-T cells[15,16] have already been explored in the setting of relapse ALCL and could be another therapeutic option for this HR group.

Conflict of Interest

None declared.

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