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LYMPHOID NEOPLASIA

Comment on Pedrosa et al, page 1458

Go with the flow: simplified MRD in LMIC ALL

James A. Whitlock | The Hospital for Sick Children

In this issue of *Blood*, Pedrosa et al[1] provide long-term results of a pilot study in children with precursor B-cell ALL conducted in a Brazilian center in a limited-resource setting. This pilot study incorporated a previously described simplified flow cytometric methodology for minimal residual disease (MRD) assessment in B-lineage ALL adapted for use in limited-resource settings to assess response at days 19 and 26.[2,3]

Children diagnosed with acute lymphocytic leukemia (ALL) in low- and middle-income countries (LMICs) do not enjoy the outstanding outcomes presently available to children with ALL in first-world countries. Factors contributing to this disparity in outcomes include abandonment of care (ie, patients who drop out of treatment prior to completion),[4] limited access to essential medications,[5] and limitations in supportive care measures contributing to excessive toxicity and poor outcomes associated with the use of intensive chemotherapy regimens employed in the first world setting.[6] Optimal management of childhood ALL in first-world countries also includes the use of diagnostic tests, such as immunophenotyping by flow cytometry, fluorescence in situ hybridization (FISH) to detect common recurring cytogenetic abnormalities associated with favorable or unfavorable outcomes, and assessment of MRD by flow cytometry.[7]

End-induction MRD assessment is the single strongest prognostic factor in predicting outcome in childhood ALL.[8] However, the sophisticated equipment and complex technical requirements for multiparametric flow cytometry as used in resource-rich settings, together with limited resources for personnel and reagents, place routine MRD assessment beyond the reach of many pediatric cancer programs in limited-resource settings. The lack of advanced diagnostic testing capabilities in many LMICs precludes optimal risk-stratification and therapy refinement for children with ALL, contributing to unnecessary overtreatment of some children with lower-risk ALL and a corresponding increased risk of treatment-related toxicity and mortality. Thus, the validation of a simplified MRD assay as feasible in the LMIC setting with sufficient predictive power to achieve clinically relevant risk stratification in childhood ALL would represent a significant step forward.

MRD results obtained with this simplified flow cytometry approach were combined with clinical features, immunophenotype, and a limited genetic analysis to identify a population of patients predicted to be at very low risk (VLR) of disease recurrence. These patients, representing about one-fifth of the total ALL population at the treating center, received a reduced-intensity, antimetabolite-based treatment protocol, which minimized myelosuppressive agents commonly used in first-world protocols, such as cyclophosphamide and cytarabine, that contribute to infections and other treatment-related toxicities.

The outcomes achieved with this risk-stratified, reduced-intensity approach for VLR patients enrolled in the Recife RELLA05 pilot study were outstanding, with a very high rate of remission induction, estimated 5-year event-free and overall survival rates of 92% and 96%, respectively, and a 5-year cumulative relapse risk of only 4%. These results rival or surpass those previously reported in similar settings. Importantly, the toxicity associated with this approach was also remarkably low, with an overall toxic death rate of <1%. Abandonment of therapy was not an issue, as all patients completed treatment.

Many challenges remain in improving outcomes for childhood ALL in LMICs. The approach used in the Recife RELLA05 is relevant for only about one-quarter of the childhood ALL population in LMICs; more effective, less toxic approaches are needed for children with higher-risk disease, for whom greater treatment intensity, with its risks of treatment-related toxicities and morbidity, is presently required. It must also be acknowledged that even the simplified MRD assessment approach used in this study may be beyond the reach of some LMIC centers treating childhood ALL, as may the polymerase chain reaction–based genetic analyses used to identify common gene fusions with prognostic significance; FISH analysis may be more attainable for this purpose in the LMIC setting. Nevertheless, these results clearly document that a simplified MRD assessment is feasible in the LMIC setting and informs a risk-adapted approach that identifies a very low-risk subset of the childhood ALL population with excellent outcomes following minimally intensive chemotherapy. Pedrosa and colleagues have established a new benchmark of success for LMIC pediatric cancer programs and their twinning collaborators in improving outcomes for their children with low-risk ALL.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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Comment on Yoshida et al, page 1467

CD28 fusions: an opportunity for young ATL?

Lucy B. M. Cook and Aileen G. Rowan | Imperial College London

In this issue of *Blood*, Yoshida et al identify concurrent fusions of CD28 with CTLA4 and ICOS in younger Japanese patients with adult T-cell leukemia/lymphoma (ATL).[1]

With chemotherapy-based treatment approaches, overall survival in ATL has not significantly improved in the nearly 40 years since human T-cell lymphotropic virus and ATL were first described.[2] Therefore, the identification of a novel, measurable, and druggable target is exciting.

The median age at presentation with ATL is ~70 years in Japanese patients, whereas ATL arising in patients living in the United States, Europe, the Caribbean, and South America occurs at age 45 to 55 years.[3] It is not understood whether the differences in age at presentation reflect differences in disease biology, underlying host genetics, immune response to the tumor or virus, or environmental factors.

Yoshida et al hypothesize that the tumors of younger patients with ATL would contain distinct genetic alterations, similar to other cancers that present in younger individuals, such as ETV6-RUNX1 fusion seen in childhood acute lymphoblastic leukemia. They identify concurrent CTLA4-CD28 and ICOS-CD28 fusions in 37.5% of ATL cases (3 of 8 cases) in those age <50 years, the presence of which did not affect survival. This is in contrast to earlier reports of peripheral T-cell lymphoma (PTCL) and ATL, where the presence of both fusions was rare.[4,5]

CD28 and ICOS are costimulatory molecules that potentiate T-cell activation on binding their respective ligands CD80/CD86 and ICOSL. In contrast, ligation of the coinhibitory CD28 homolog CTLA4 inhibits T-cell activation through binding ligands of CD28 with higher affinity, sequestering CD80/CD86 and initiating an inhibitory signaling cascade. The CTLA4-CD28 fusion consists of the extracellular and transmembrane domains of CTLA4 and the intracellular signaling domain of CD28, whereas the ICOS-CD28 fusion combines only the signal peptide from ICOS with the extracellular and intracellular domains of CD28. In other PTCL tumors, this ICOS-CD28 fusion was associated with CD28 overexpression and ICOS haploinsufficiency.[6]

Yoshida et al demonstrate in vitro that the expression of CTLA4-CD28 and, to a lesser degree, CTLA4-ICOS fusions could induce cellular proliferation when cocultured with cells expressing CD80 and CD86. In ATL cases with both fusions present, immunohistochemistry demonstrated that ATL tumor cells express CD80 and macrophages in the tumor microenvironment express CD86, suggesting that both intra- and intercellular actions could drive cellular proliferation in vivo. The authors report that cases with fusions had gene expression signatures associated with AKT and RAF signaling and, strikingly, LAG3 downregulation, which is known to negatively downregulate T-cell proliferation. Finally, the in vitro CD80/CD86-driven proliferation of cells expressing CTLA4-CD28 fusion could be suppressed with a CTLA4-blocking antibody in a dose-dependent manner.

Chemotherapy alone rarely cures ATL, and there is a desperate need for new and better therapies and for an understanding of how to apply our current therapies more effectively. For example, mogamulizumab is associated with better responses in leukemic rather than nodal disease, even more so in the presence of CCR4-activating mutations.[7] Similarly, responses to combination therapy with zidovudine and interferon-α are significantly better in leukemic rather than nodal ATL.[8,9] This work suggests that there may be a rationale for targeting cases with CD28 fusions with an anti-CTLA4 antibody and/or targeting its downstream effectors, such as the phosphatidylinositol 3-kinase pathway.

Of course, these observations were made in a small number of cases, and it remains unclear why these dual fusions were not observed in a larger Japanese cohort,[4,10] which also included a small number of cases who presented at age <50 years. It is logical that these fusions should be investigated systematically in cohorts arising in the United States, South America, and Europe, where so-called young ATL is frequently seen. Presumably because of the small number of cases here, the age cutoff at 50 years is arbitrary, but in a larger cohort, perhaps a true biological entity may be defined. Understanding these biological differences and how to best select treatments and apply new therapies will be crucial to improving survival outcomes.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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