blood commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Hill et al, page 1447

Is antiviral therapy against HHV-6B beneficial?

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In this issue of *Blood*, Hill et al used a post hoc analysis of a randomized, placebo-controlled trial of brincidofovir (BCV) for prophylaxis against cytomegalovirus (CMV) to study the effect of this drug against human herpesvirus 6B (HHV-6B).[1] BCV is a lipid conjugate of cidofovir, which can be given orally and IV and has a better safety profile than cidofovir. BCV has in vitro activity against HHV-6B. It has been studied as prophylaxis against CMV and treatment of adenovirus infections, the latter primarily in children undergoing high-risk allogeneic stem cell transplants.

In the study by Hill et al, BCV was given orally twice weekly until 14 weeks after hematopoietic stem cell transplantation (HSCT). The authors selected patients, who started study therapy early after HSCT and who had received at least 6 doses of BCV. The main findings of the study were that patients receiving BCV were less likely to reactivate HHV-6B and that they had lower viral loads. The effect was strongest in patients with risk factors for developing viral infections, including CMV and HHV-6B. Furthermore, the authors found that rash was reported less frequently in patients receiving BCV despite there being more acute graft-versus-host disease (GVHD) grades II to IV in the BCV-treated group. There was no difference in HHV-6–associated disease entities such as encephalitis and pneumonia, but the power of the study to detect any such effects was very low due to the sample size.

The role of HHV-6 as a clinically important virus after allogeneic HSCT remains murky despite several studies performed over the last couple of decades. There is no doubt that HHV-6 is a cause of encephalitis, which can be fatal and, if the patient survives, frequently results in long-term sequelae.[2-4] Cohort studies have implicated HHV-6 in the development of acute GVHD grades II to IV, pneumonia, and bone marrow suppression, especially platelet recovery. HHV-6 has also been associated with increased mortality after allogeneic HSCT.[5-8] Despite the reports of these complications associated with HHV-6 replications, HHV-6B in blood is not routinely monitored at many transplant centers, likely due to the lack of effective therapy. The efficacy of antiviral therapy has been difficult to assess despite HHV-6 sensitivity to several drugs in vitro, including ganciclovir, foscarnet, and cidofovir. Controlled studies assessing antiviral drugs' effect on HHV-6 measured as either viral load or disease manifestations have not been conducted. Further complicating the picture, HHV-6 can be integrated in the genome, making interpretation of polymerase chain reaction results difficult in some patients.

The study by Hill et al is interesting for several reasons. First, it can be seen as proof of concept that BCV can inhibit HHV-6B replication, reducing the plasma viral load below the level where the risk for the most severe complication, namely encephalitis, increases.[2,9] Second, the authors found a reduction in the frequency of patients developing rash in the BCV-treated group, whereas the proportion of patients diagnosed with GVHD grades II to IV was higher in the BCV group. This apparent inconsistency was likely because the rash was directly caused by HHV-6B itself as it is well known that the virus causes exanthema subitem in small children. On the other hand, gastrointestinal toxicity probably caused by BCV was likely interpreted as GVHD.

What will be the next steps? Clinical development of oral BCV has been discontinued while development of the IV form is ongoing. It would be logical to study IV BCV as a possible preventive agent for HHV-6B encephalitis, the most severe manifestation of infection, although the relative rarity of this entity will make such studies challenging.

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REFERENCES

1. Hill JA, Nichols WG, Marty FM, et al. Oral brincidofovir decreases the incidence of HHV-6B viremia after allogeneic HCT. *Blood*. 2020; 135(17):1447-1451.

2. Zerr DM, Gooley TA, Yeung L, et al. Human herpesvirus 6 reactivation and encephalitis in allogeneic bone marrow transplant recipients. *Clin Infect Dis*. 2001; 33(6):763-771.

3. Ogata M, Satou T, Kadota J, et al. Human herpesvirus 6 (HHV-6) reactivation and HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: a multicenter, prospective study. *Clin Infect Dis*. 2013;57(5): 671-681.

4. Scheurer ME, Pritchett JC, Amirian ES, Zemke NR, Lusso P, Ljungman P. HHV-6 encephalitis in umbilical cord blood transplantation: a systematic review and meta-analysis. *Bone Marrow Transplant*. 2013;48(4):574-580.

5. Zerr DM, Corey L, Kim HW, Huang ML, Nguy L, Boeckh M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis*. 2005; 40(7):932-940.

6. Phan TL, Carlin K, Ljungman P, et al. Human herpesvirus-6B reactivation is a risk factor for grades II to IV acute graft-versus-host disease

after hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Biol Blood Marrow Transplant*. 2018;24(11):2324-2336.

7. Cone RW, Hackman RC, Huang ML, et al. Human herpesvirus 6 in lung tissue from patients with pneumonitis after bone marrow transplantation. *N Engl J Med*. 1993;329(3):156-161.

8. Hill JA, Vande Vusse LK, Xie H, et al. Human herpesvirus 6B and lower respiratory tract disease after hematopoietic cell transplantation. *J Clin Oncol*. 2019;37(29):2670-2681.

9. Ogata M, Satou T, Kawano R, et al. Plasma HHV-6 viral load-guided preemptive therapy against HHV-6 encephalopathy after allogeneic stem cell transplantation: a prospective evaluation. *Bone Marrow Transplant*. 2008;41(3):279-285.

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LYMPHOID NEOPLASIA

Comment on Pedrosa et al, page 1458

Go with the flow: simplified MRD in LMIC ALL

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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. ■

REFERENCES

1. Pedrosa F, Coustan-Smith E, Zhou Y, et al. Reduced–dose intensity therapy for pediatric lymphoblastic leukemia: long-term results of the Recife RELLA05 pilot study. *Blood*. 2020;135(17):1458-1466.

2. Coustan-Smith E, Ribeiro RC, Stow P, et al. A simplified flow cytometric assay identifies