blood advances

More evidence for low-dose IL-2 for chronic GVHD in children

John E. Levine

Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Comment on Wobma et al, page 4647

In this issue of *Blood Advances*, Wobma et al report that subcutaneous low-dose interleukin-2 (LD IL-2) reversed chronic graft-versus-host disease (cGVHD) manifestations in children and young adults who were treated outside of the context of a clinical trial.[1] In this report of real-world data (RWD), 15 patients whose cGVHD was long standing (median, 8 months from diagnosis) and not responding despite multiple treatments (median, 3 prior therapies) were treated with LD IL-2 for a median of 15 months. LD IL-2 treatment was safe; there were no serious adverse events attributed to LD IL-2, and although 4 patients did not tolerate the maximum dose of 1×10^6 IU/m^2 per day because of malaise (n = 3) or renal impairment (n = 1), 13 of 15 patients received at least 4 weeks of treatment and were evaluated for response. Most patients responded in at least 1 target organ (85%, 11 of 13) with an impressive complete response rate (46%, 6 of 13) in a disease in which complete responses are rare especially when symptoms have been resistant to treatment for a long duration.[2,3] Children aged as young as 1 year experienced benefit and importantly, responses were observed across the full spectrum of cGVHD targets such as the liver, gastrointestinal tract, joints, and even in particularly hard-to-treat manifestations such as sclerotic skin and lung GVHD.

Limitations of this study include the small number of patients treated and the unstructured handling of therapies before and during LD IL-2 treatment. Nonetheless, the results were consistent with the response rates (61%-82%) reported in clinical trials by the same group[4,5] and appear promising compared with the 3 drugs (ibrutinib, belumosudil, and ruxolitunib) approved by the Food and Drug Administration (FDA) for cGVHD in patients who are at least 12 years old.[6]

The efficacy of LD IL-2 appears to derive from the selective expansion of functional, regulatory T cells (Tregs) by inhibiting both spontaneous and Fas-induced apoptosis.[7] This effect is preferential for Tregs because they constitutively express high amounts of the high-affinity IL-2 receptor and their differential reliance on the STAT5 pathway that is critical to the activation of numerous genes important for cell function.[8] Age-related differences in the immune system, including T-reg expansion, natural killer cell activation, and presence of thymic tissue may contribute to enhanced LD IL-2 efficacy in young patients.[5]

Interest in RWD reflects the challenge that comes from trying to generalize "clean" clinical trial results to a "dirty" world and, thus, reports of real-world experiences can help clinicians contextualize structured clinical trial results. Ideally, RWD reflect routine care without attempts to homogenize who is treated and how treatment is delivered. Recently, the International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology published recommendations for RWD studies including that it should be determined a priori whether a study is exploratory or testing a hypothesis and that the data sources and population should be different from those used to generate the hypotheses tested.[9] In this study, the real-world experience reported is that of the same group that designed the clinical trials. Some variables, such as the starting dose of IL-2, are appropriately controlled. Others, such as the decision to start LD IL-2 in some patients but not others may reflect the adoption of study design aspects as institutional practice and thus limit the application of the results to the more general population of children with treatment-resistant cGVHD. Thus, LD IL-2 as a treatment for cGVHD requires further study outside of single-center trials. Fortunately, a multicenter study of LD IL-2 for children with cGVHD has been approved by the Children's Oncology Group and will, hopefully, begin enrolling patients in 2023. A third study with positive results should be sufficient to establish LD IL-2 as a treatment for cGVHD in children, especially those aged <12 years who have not yet received any FDA-approved treatments.

Conflict-of-interest disclosure: J.E.L. reports research support from Equillium, Incyte, MaaT Pharma, and Mesoblast; consulting fees from bluebird bio, Editas, Equillium, Inhibrx, Kamada, Mesoblast, Sanofi, and X4 Pharmaceuticals; and royalties from a GVHD biomarker patent.

References

1. Wobma HM, Kapadia M, Kim HT, et al. Real-world experience with low-dose IL-2 for children and young adults with refractory chronic graft-versus-host disease. *Blood Adv*. 2023;7(16):4647-4657.
2. Vigorito AC, Campregher PV, Storer BE, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. *Blood*. 2009;114(3):702-708.
3. Sarantopoulos S, Cardones AR, Sullivan KM. How I treat refractory chronic graft-versus-host disease. *Blood*. 2019;133(11):1191-1200.
4. Koreth J, Kim HT, Jones KT, et al. Efficacy, durability, and response predictors of low-dose interleukin-2 therapy for chronic graft-versus-host disease. *Blood*. 2016;128(1):130-137.
5. Whangbo JS, Kim HT, Mirkovic N, et al. Dose-escalated interleukin-2 therapy for refractory chronic graft-versus-host disease in adults and children. *Blood Adv*. 2019;3(17):2550-2561.
6. Zeiser R, Lee SJ. Three US Food and Drug Administration-approved therapies for chronic GVHD. *Blood*. 2022;139(11):1642-1645.
7. Matsuoka K, Koreth J, Kim HT, et al. Low-dose interleukin-2 therapy restores regulatory T cell homeostasis in patients with chronic graft-versus-host disease. *Sci Transl Med*. 2013;5(179):179ra143.
8. Klatzmann D, Abbas AK. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. *Nat Rev Immunol*. 2015;15(5):283-294.
9. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf*. 2017;26(9):1033-1039.

https://doi.org/10.1182/bloodadvances.2023010756