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Checkpoint blockade before allogeneic transplantation in pediatric lymphoma warrants a dedicated safety strategy. Comment on: “Immune checkpoint therapy in pediatric and adolescent lymphomas”

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Hoogstra and colleagues provide a timely review of immune checkpoint therapy in pediatric and adolescent lymphomas.¹ Programmed cell death protein 1 (PD-1) blockade has reshaped treatment for classic Hodgkin lymphoma and may have a role in selected programmed death-ligand 1-expressing non-Hodgkin lymphoma subtypes. However, several strategies described in the review use checkpoint inhibition not as definitive therapy, but as a bridge to allogeneic hematopoietic cell transplantation (allo-HCT). In ACCELERATE ALCL (ClinicalTrials.gov identifier: NCT07013562), nivolumab-based reinduction is followed by reduced-toxicity conditioning and allo-HCT; in a second study (ClinicalTrials.gov identifier: NCT03719105), pembrolizumab is used as rescue treatment for patients with aggressive natural killer (NK)-cell leukemia (ANKL) or peripheral T-cell lymphoma before allo-HCT. The NIVO-ALCL experience further suggests that nivolumab has clinical activity but is not, as monotherapy, a durable curative alternative to allo-HCT in relapsed/refractory ALK-positive anaplastic large cell lymphoma.¹ Children may therefore increasingly approach transplantation after recent PD-1 exposure, yet the potential implications for transplant safety are not addressed in detail. We therefore comment on two issues: the safety of sequencing PD-1 blockade with allo-HCT, and the distinction between ANKL and extranodal NK/T-cell lymphoma (ENKTL).

Adult data raise concern about this therapeutic sequence. An early multicenter series of allo-HCT after PD-1 blockade reported severe and occasionally fatal hyperacute graft-versus-host disease (GVHD), a steroid-requiring noninfectious febrile syndrome, and hepatic veno-occlusive disease.² In an international retrospective cohort of 209 patients with classic Hodgkin lymphoma, grade 3–4 acute GVHD occurred in 15% by day 180 and chronic GVHD in 34% by 2 years. Post-transplant cyclophosphamide-based prophylaxis was associated with superior progression-free and GVHD-free, relapse-free survival, although a causal benefit cannot be established from a nonrandomized cohort.³ Timing may also be important: a French national study reported severe acute GVHD in 41.7% of patients

transplanted within 30 days of the last PD-1 dose, compared with 2.7% beyond 30 days and none beyond 60 days.⁴ The reverse sequence can also be hazardous. PD-1 blockade for relapse after allo-HCT produced high response rates but frequent, sometimes steroid-refractory GVHD,⁵ and pooled data have similarly identified meaningful GVHD risk when checkpoint inhibitors are administered either before or after transplantation.⁶ Because the review also describes pembrolizumab for anaplastic large cell lymphoma relapsing after allo-HCT,¹ this risk is directly relevant to pediatric practice.

These data cannot simply be transferred to children. Pediatric patients differ from adults in thymic output, donor sources, frequent use of haploidentical grafts with post-transplant cyclophosphamide, cumulative prior treatment exposure, and immune reconstitution after transplantation. Pediatric protocols incorporating checkpoint inhibition before allo-HCT should therefore prospectively record the interval between the last checkpoint-inhibitor dose and conditioning, GVHD-prophylaxis strategy, hyperacute GVHD, early noninfectious inflammatory syndromes, sinusoidal obstruction syndrome/veno-occlusive disease, and non-relapse mortality. When disease control permits, washout intervals of 60 days or longer⁴ merit prospective evaluation rather than being assumed to represent established pediatric practice. In Epstein-Barr virus (EBV)-driven NK/T-cell disease arising in the setting of chronic active EBV infection, checkpoint inhibition may further amplify a pre-existing inflammatory state; secondary hemophagocytic lymphohistiocytosis may be difficult to distinguish from early post-transplant inflammatory complications. This issue may be particularly relevant in East Asian settings, including Taiwan, where EBV-associated NK/T-cell neoplasms are encountered more frequently than in many Western populations.

A second point concerns the discussion of rare mature T/NK-cell lymphomas, in which ANKL is considered alongside ENKTL and the TSIM, MB, and HEA molecular subtypes (Figure 6 of their review) are presented in that context.¹ However, ANKL and ENKTL are distinct entities in the fifth edition of the World Health Organization

classification.⁷ ANKL is characterized by recurrent JAK-STAT pathway and epigenetic-modifier alterations⁸ and is often fulminant, with a therapeutic window before transplantation measured in weeks. Although both are EBV-associated NK-cell neoplasms, these molecular subtypes were defined in ENKTL,⁹ as were the widely cited responses to PD-1 blockade after L-asparaginase failure.¹⁰ Extrapolation of ENKTL molecular subclasses and checkpoint-inhibitor efficacy to ANKL should therefore be framed as hypothesis-generating rather than as evidence of established benefit.

As checkpoint therapy moves earlier in pediatric lymphoma treatment, the central question is not only whether children respond, but also how checkpoint exposure influences subsequent allogeneic immunity. Prospective pediatric studies that sequence checkpoint blockade and allo-HCT should treat this interaction as a primary safety question.

References

1. Hoogstra DJ, Xavier AC, Harker-Murray P, et al. Immune checkpoint therapy in pediatric and adolescent lymphomas. *Haematologica*. 2026;111(10):3220-3234.
2. Merryman RW, Kim HT, Zinzani PL, et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. *Blood*. 2017;129(10):1380-1388.
3. Merryman RW, Castagna L, Giordano L, et al. Allogeneic transplantation after PD-1 blockade for classic Hodgkin lymphoma. *Leukemia*. 2021;35(9):2672-2683.
4. Kaphan E, Bettega F, Vallet N, et al. PD-1 blockade and allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma, a matter of time: a national study on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire. *Haematologica*. 2024;109(10):3373-3378.
5. Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood*. 2017;130(2):221-228.
6. Ijaz A, Khan AY, Malik SU, et al. Significant risk of graft-versus-host disease with exposure to checkpoint inhibitors before and after allogeneic transplantation. *Biol Blood Marrow Transplant*. 2019;25(1):94-99.
7. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748.
8. Dufva O, Kankainen M, Kelkka T, et al. Aggressive natural killer-cell leukemia mutational landscape and drug profiling highlight JAK-STAT signaling as therapeutic target. *Nat Commun*. 2018;9(1):1567.
9. Xiong J, Cui BW, Wang N, et al. Genomic and transcriptomic characterization of natural killer T cell lymphoma. *Cancer Cell*. 2020;37(3):403-419.e6.

10. Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood*. 2017;129(17):2437-2442.