United States. *Transplant Cell Ther*. 2022; 28(9):581.e1-581.e8.

3. Rejeski K, Perez A, Iacoboni G, et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL. *J Immunother Cancer*. 2022;10(5):e004475.

4. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant*. 2019; 54(10):1643-1650.

5. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Blood*. 2021;138(24): 2499-2513.

6. Jain T, Olson TS, Locke FL. How I treat cytopenias after CAR T-cell therapy. *Blood*. 2023;141(20):2460-2469.

7. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to evaluate the severity of adverse events of anticancer therapies. *Actas Dermosifiliogr (Engl Ed)*. 2021;112(1):90-92.

8. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. *Blood Adv*. 2020; 4(15):3776-3787.

https://doi.org/10.1182/blood.2023021305

CLINICAL TRIALS AND OBSERVATIONS

Comment on Armand et al, page 878

Pembrolizumab: a key for some, but not all, HL

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In this issue of *Blood*, Armand et al describe the long-term outcomes of a phase 2 study of the immune checkpoint inhibitor pembrolizumab in patients with relapsed/refractory classic Hodgkin lymphoma (HL).[1]

Although most patients with HL are cured with multiagent chemotherapy, a substantial minority remain in need of other therapies. Fortunately, the discovery and subsequent therapeutic exploitation of the programmed cell death 1 pathway has led to agents such as pembrolizumab becoming available for patients with a variety of cancers, including HL. In the initial report, with a median follow-up of 10.1 months, the objective response rate (ORR) was 69.7% (complete response [CR], 22.7%).[2] Response rates were similar regardless of prior autologous stem cell transplant (ASCT) and/or brentuximab vedotin exposure, and were consistent among the one-third of patients with primary refractory disease.[3] Many patients with HL are young adults (the median age of KEYNOTE-087 participants was 35 years at enrollment) and often deal with relapsed lymphoma in the face of other major life events, such as marriage, parenthood, or establishing careers. For such patients, when their lymphoma does not respond to chemotherapy, understanding long-term outcomes from pembrolizumab provides important context for decision-making.

Now with a median observation period exceeding 5 years, the median duration of response (DOR) remained steady at 16.6 months, and the 5-year progression-free survival (PFS) and overall survival rates were 14.2% and 70.7%, respectively. Unsurprisingly, the 58 patients who achieved CR to pembrolizumab had the most favorable outcomes, with median DOR not reached. A key question for patients with HL achieving CR following pembrolizumab in this setting is whether to proceed to stem cell transplant. This question is challenging to study prospectively, and observations from studies such as this can be informative (with the caveat that the study was neither designed nor appropriately powered to provide definitive answers). Of the 58 patients who achieved CR, 10 ultimately underwent allogeneic stem cell transplant (5 proceeding directly to transplant, and the others requiring further therapy for relapsed disease), and the median DOR and PFS were 13.6 and 36.9 months, respectively. Among the 48 patients who did not proceed to transplant, the median DOR was not reached, and the median PFS was 56.5 months. Although allocation to transplant was nonrandomized, the favorable outcomes observed among the patients who did not undergo allogeneic stem cell transplant are encouraging and suggest that observation of patients achieving CR may be reasonable.

The data set also provides useful data regarding pembrolizumab retreatment. Per protocol, patients who achieved CR and received ≥6 months of therapy and ≥2 doses after CR were allowed to discontinue treatment before 2 years, with those who experienced subsequent disease progression able to receive retreatment for up to an additional 17 cycles. Among 20 such patients, the ORR (73.7%) and CR (36.8%) rates following retreatment were similar to those observed with initial treatment in the overall population, and the median PFS was 17.2 months, with no new safety signals observed.

Important unanswered questions remain, such as the role of ASCT following checkpoint inhibitor therapy. Observational series suggest a potential chemosensitization effect from checkpoint inhibitors, with a US academic collaborative group reporting favorable outcomes for patients undergoing ASCT after checkpoint inhibitor use.[4] The 18-month PFS was 86%, and prior response to checkpoint inhibitor appeared to be a better predictor of outcome than positron emission tomography status before transplant. The role of allogeneic stem cell transplant after checkpoint inhibitors (and vice versa) also remains an open question. In a pooled analysis of allogeneic stem cell transplant after checkpoint inhibitor, rates of grade 3 to 4 acute graft-versus-host disease were increased, but chronic graft-versus-host disease and nonrelapse mortality rates were similar.[5] However, the use of posttransplant cyclophosphamide may mitigate some of the immune activation from checkpoint inhibitors and improve their safety in this setting.[6] Conversely, the use of checkpoint inhibitors after allogeneic stem cell transplant, although effective, does appear to result in

aggressive graft-versus-host disease, with resistance to immunosuppression and deaths reported, meaning they should be used with caution.[7] The toxicity of checkpoint inhibitor use after allogeneic stem cell transplant brings into sharp focus the importance of identifying patients likely to achieve durable responses to pembrolizumab without allogeneic stem cell transplant. It is also reassuring to know that if transplant is deferred, retreating patients who previously achieved CR is feasible and is a viable bridging strategy to transplant. Checkpoint inhibitors have substantially improved the outcomes of patients with HL, but the optimal treatment setting, sequencing, and combinations require further investigation.

Conflict-of-interest disclosure: C.Y.C. reports consulting/advisory/honoraria for Roche, Janssen, Gilead, AstraZeneca, Lilly, TG Therapeutics, BeiGene, Novartis, Menarini, Daizai, AbbVie, Genmab, and BMS; and research funding from BMS, Roche, AbbVie, MSD, and Lilly. ■

REFERENCES

1. Armand P, Zinzani PL, Lee HJ, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. *Blood*. 2023;142(10):878-886.
2. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*. 2017;35(19):2125-2132.
3. Zinzani PL, Chen R, Armand P, et al. Pembrolizumab monotherapy in patients with primary refractory classical Hodgkin lymphoma who relapsed after salvage autologous stem cell transplantation and/or brentuximab vedotin therapy: KEYNOTE-087 subgroup analysis. *Leuk Lymphoma*. 2020;61(4):950-954.
4. Merryman RW, Redd RA, Nishihori T, et al. Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma. *Blood Adv*. 2021;5(6):1648-1659.
5. Dada R, Usman B. Allogeneic hematopoietic stem cell transplantation in r/r Hodgkin lymphoma after treatment with checkpoint inhibitors: feasibility and safety. *Eur J Haematol*. 2019;102(2):150-156.
6. Nieto JC, Roldán E, Jiménez I, et al. Posttransplant cyclophosphamide after allogeneic hematopoietic cell transplantation mitigates the immune activation induced by previous nivolumab therapy. *Leukemia*. 2020;34(12):3420-3425.
7. Ito A, Kim SW, Matsuoka KI, et al. Safety and efficacy of anti-programmed cell death-1 monoclonal antibodies before and after allogeneic hematopoietic cell transplantation for relapsed or refractory Hodgkin lymphoma: a multicenter retrospective study. *Int J Hematol*. 2020;112(5):674-689.

https://doi.org/10.1182/blood.2023021050

RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Keith et al, page 918

The incredible ULK improves β-thalassemia

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In this issue of *Blood*, Keith and colleagues show the miR-144/451 locus is a genetic modifier of β-thalassemia by regulating removal of free α-globin via the autophagy kinase ULK1 (Unc-51–like autophagy-activating kinase 1).[1] miR-144/451 is the highest expressed miR locus in terminal erythroid differentiation, and its disruption in a β-thalassemia mouse model releases inhibition of the Cab39/Strad/LKB1 complex. Increased expression of Cab39/Strad/LKB1 activates adenosine monophosphate–activated protein kinase (AMPK), sometimes referred to as the "cellular fuel gauge." Increased AMPK signaling reduces mammalian target of rapamycin complex 1 (mTORC1)-mediated repression of ULK1 and directly activates ULK1 to give it super strength to degrade free α-globin, which, if it accumulates, is so toxic that it triggers apoptosis (see figure). The role of AMPK in this pathway suggests existing drugs that increase AMPK activity[2] could be repurposed as part of a β-thalassemia combination therapy.

β-Thalassemia, caused by a deficit in the production of the β-globin component of hemoglobin, is one of the most common monogenic diseases. In most patients, clinical management still largely depends on supportive treatment with red blood cell transfusions and iron chelation.[3] Hydroxyurea is used to increase γ-globin expression as this fetal β-like globin combines with free α-globin to form fetal hemoglobin, increasing functional hemoglobin levels and reducing toxic levels of unpaired α-globin. Until recently, allogenic bone marrow transplantation remained the only curative treatment; however, its usefulness is largely limited to a minority of patients who have HLA-matched sibling donors.[4]

Most emerging therapies for β-thalassemia aim to supplement reduced β-globin levels, by either inducing expression of the γ-globin genes or replacing the damaged or missing β-globin genes using lentiviral vectors.[5] One particularly elegant strategy is to delete an erythroid-specific enhancer of *BCL11A*, one of the main γ-globin repressors,[6] to reduce its expression in erythroblasts.

Although increasing β-like globin leads to increased functional hemoglobin, it is important not to overlook its role in reducing the excess of the free α-globin chains, which are the primary culprit in β-thalassemia pathology as they cause ineffective erythropoiesis. Mae West was wrong in the case of α-globin: too much of a good thing is not always wonderful. Reduction of α-globin levels as a therapy for β-thalassemia has been previously suggested (eg, by removal of an α-globin enhancer[7] to reduce α-globin protein levels). Evidence from clinical studies shows a reduction of α-globin expression to 75% to 25% of normal is effective, safe, and tolerable and provides sustainable beneficial effects in patients with β-thalassemia.[8] Natural modifiers, such as coinherited α-thalassemia, can modify a genotype associated with transfusion-dependent β-thalassemia into a clinical phenotype of β-thalassemia intermedia, a