Can we cure relapsed/refractory Hodgkin lymphoma without a stem cell transplant?

Matthew G. Mei and Alex F. Herrera

Division of Lymphoma, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA, USA

Correspondence: A.F. Herrera
aherrera@coh.org

Received: February 1, 2023.
Accepted: March 28, 2023.
Early view: April 6, 2023.

https://doi.org/10.3324/haematol.2023.282731
©2023 Ferrata Storti Foundation
Published under a CC BY-NC license

A remarkable development in the treatment of classic Hodgkin lymphoma (cHL) has been the striking efficacy observed when PD-1 blockade is combined with cytotoxic chemotherapy. In this issue of Haematologica, Ding and colleagues publish results of a single-arm trial testing the safety and efficacy of tislelizumab, gemcitabine, and oxaliplatin (T-GemOx) in relapsed and/or refractory (R/R) cHL.[1] All 30 evaluable patients responded, and only one patient did not achieve complete remission (CR). To date, this is the third published data set of combined PD-1 blockade and combination chemotherapy in R/R cHL featuring a best CR rate exceeding 90%. However, in addition to its role in the evolving story of PD-1 blockade and chemotherapy in cHL, this study also provides a potential glimpse into the future, as no patient was consolidated with autologous stem cell transplant (autoSCT), yet the 12-month progression-free survival (PFS) was 96%.

Published trials of PD-1 with chemotherapy in the R/R setting include pembrolizumab with gemcitabine, vinorelbine, and liposomal doxorubicin (pembro-GVD), as well as nivolumab with ifosfamide with carboplatin, ifosfamide, and etoposide (NICE).[2,3] The high CR rate with T-GemOx is consistent with the data from pembro-GVD and NICE, as all three studies featured best CR rates exceeding 90%. Nonetheless, pembro-GVD and NICE were tested strictly in the second-line setting with a goal of bridging patients to curative autoSCT. These are the first prospective data evaluating PD-1 blockade with chemotherapy beyond second-line treatment and also as a destination treatment without consolidative autoSCT. T-GemOx was administered to a patient population that was significantly more heavily pre-treated than those in the pembro-GVD and NICE trials, nearly half of whom (43.3%) had received at least two prior lines of therapy, and 16.7% of whom had undergone prior autoSCT. Even still, in this high-risk group of R/R cHL patients, the best CR rate and 12-month PFS both exceeded 95% with a median follow-up of 15.8 months, remarkable results that are comparable to those obtained with pembro-GVD and NICE.

The results of this trial raise at least two important questions. One is whether or not there is, in fact, an optimal choice of anti-PD-1 antibody and specific cytotoxic chemotherapies, and the other is whether or not anti-PD-1 combined with chemotherapy could potentially represent curative therapy in the R/R setting without subsequent consolidative autoSCT. Pembro-GVD, NICE, and T-GemOx all use different anti-PD-1 agents and very different chemotherapy backbones, yet return very similar results. As patients enrolled on this trial were more heavily pre-treated than in NICE and pembro-GVD, both of which restricted enrollment to patients after one prior line of therapy, is it possible that there is something special about T-GemOx in comparison to the other two regimens? Tiselizumab is specifically engineered to decrease FcγR binding on macrophages via a mutated Fc region with a single-agent CR rate of 62.9%. This is numerically higher than the CR rates observed with either nivolumab or pembrolizumab.[4-6] Gemcitabine and oxaliplatin have immunogenic properties including, but not limited to, depletion of myeloid-derived suppressor cells and promotion of cytotoxic lymphocyte-driven responses,[7] mechanisms which may augment synergy with PD-1 blockade. However, a trial comparing these regimens head-to-head is impractical, and off-protocol use of T-GemOx is restricted by the fact that tislelizumab is currently not approved for use outside China. GemOx is also not a widely used standard salvage regimen for R/R cHL, although the various regimens used in studies of anti-PD1-based salvage therapy reflect the lack of a clear standard chemotherapy salvage backbone in cHL. One important question that will be answered definitively with a randomized trial is whether the addition of PD-1 blockade to salvage chemotherapy improves efficacy compared to chemotherapy alone as initial salvage therapy for R/R cHL (Co-operative Group Trial EA4211; https://clinicaltrials.gov/ct2/show/NCT05711628).

Perhaps the more provocative and compelling question is whether or not a subset of patients with R/R cHL can be

cured without consolidative autoSCT. As modern salvage regimens built around PD-1 blockade deliver unprecedented rates of complete metabolic response, a previously unimaginable possibility has now become one of the most critical unanswered questions in cHL. The long-term durable remission rate when PD-1 blockade is used as monotherapy in later lines of therapy is low.[8-10] Will the combination of PD-1 blockade with moderate dose, but not high-dose chemotherapy, be sufficient for cure? How much chemotherapy is enough? As consolidative autoSCT was not performed for patients treated with T-GemOx, the results presented by Ding and colleagues are an incremental but important step in exploring long-term outcomes of anti-PD1-based salvage therapy without autoSCT. However, a relatively short median follow-up, that is shorter than the planned two years of tislelizumab maintenance, means that these results can only be taken as an early provocative signal of a potential pathway towards cure without autoSCT in R/R cHL. Other efforts in this area are ongoing; there is a cohort of the pembro-GVD study evaluating ongoing pembrolizumab maintenance without planned autoSCT (clinicaltrials.gov: NCT03618550), and brentuximab vedotin and nivolumab are being studied in the second-line setting specifically for patients who are ineligible for or who refuse autoSCT (clinicaltrials.gov: NCT04561206). Further optimization of therapy in R/R cHL will likely be bolstered by incorporation of more quantitative measures of disease burden such as tumor metabolic volume and circulating tumor DNA, both of which have shown significant promise in refining prognostication in cHL and may enable response-adapted approaches.[11,12] In spite of the above limitations, Ding and colleagues have conducted an important trial which continues to build upon the remarkable story of combining PD-1 blockade and chemotherapy while potentially helping to usher in curative therapy for R/R cHL without autoSCT.

Disclosures

AFH has received research funding from BMS, Merck, Genentech Inc./F. Hoffmann-La Roche Ltd., Gilead Sciences, Seattle Genetics, AstraZeneca and ADC Therapeutics, and consultancy fees from BMS, Merck, Genentech Inc./F. Hoffmann-La Roche Ltd., Kite Pharma/Gilead, Seattle Genetics, Karyopharm, Takeda, Tubulis, AstraZeneca, Genmab, Regeneron, Pfizer, Abbvie, Adicet Bio and Caribou. MM has received research funding from BMS, Incyte and Morphosys, consultancy fees from Novartis, Seattle Genetics, CTI, Janssen, EUSA, and has been a member of the Speakers' Bureau for Morphosys and for Seattle Genetics.

Contributions

MGM and AFH wrote and edited the manuscript.

References

1. Ding K, Liu H, Ma J, et al. Tislelizumab with gemcitabine and oxaliplatin in patients with relapsed or refractory classic Hodgkin lymphoma: a multicenter phase II trial. Haematologica. 2023;108(8):2146-2154.
2. Moskowitz AJ, Shah G, Schöder H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. J Clin Oncol. 2021;39(28):3109-3117.
3. Mei MG, Lee HJ, Palmer JM, et al. Response-adapted anti-PD-1-based salvage therapy for Hodgkin lymphoma with nivolumab alone or in combination with ICE. Blood. 2022;139(25):3605-3616.
4. Song Y, Gao Q, Zhang H, et al. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. Leukemia. 2020;34(2):533-542.
5. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol. 2016;17(9):1283-1294.
6. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol. 2016;34(31):3733-3739.
7. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell. 2015;28(6):690-714.
8. Chen R, Zinzani PL, Lee HJ, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood. 2019;134(14):1144-1153.
9. Armand P, Kuruvilla J, Michot J-M, et al. KEYNOTE-013 4-year follow-up of pembrolizumab in classical Hodgkin lymphoma after brentuximab vedotin failure. Blood Adv. 2020;4(12):2617-2622.
10. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. J Clin Oncol. 2018;36(14):1428-1439.
11. Yhim H-Y, Eshet Y, Metser U, et al. Risk stratification for relapsed/refractory classical Hodgkin lymphoma integrating pretransplant Deauville score and residual metabolic tumor volume. Am J Hematol. 2022;97(5):583-591.
12. Kurtz DM, Soo J, Co Ting Keh L, et al. Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA. Nat Biotechnol. 2021;39(12):1537-1547.