PD-1 blockade for diffuse large B-cell lymphoma after autologous stem cell transplantation

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Key Points

• Pembrolizumab can be safely given as consolidation after ASCT for R/R DLBCL.
• The 18-month PFS observed in this trial does not support a larger confirmatory study.

Disease relapse remains the leading cause of failure after autologous stem cell transplantation (ASCT) for patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). We conducted a phase 2, multicenter, single-arm study of the anti–PD-1 monoclonal antibody pembrolizumab given after ASCT in patients with chemosensitive DLBCL, hypothesizing that it would improve the progression-free survival (PFS) at 18 months after ASCT (primary endpoint) from 60% to 80%. Pembrolizumab was administered at 200 mg IV every 3 weeks for up to 8 cycles, starting within 21 days of post-ASCT discharge. Twenty-nine patients were treated on this study; 62% completed all 8 cycles. Seventy-nine percent of patients experienced at least one grade 3 or higher adverse event, and 34% experienced at least one grade 2 or higher immune-related adverse event. Overall, 59% of patients were alive and progression free at 18 months, which did not meet the primary endpoint. The 18-month overall survival was 93%. In conclusion, pembrolizumab was successfully administered as post-ASCT consolidation in patients with R/R DLBCL, but the PFS did not meet the protocol-specific primary objective and therefore does not support a larger confirmatory study. This trial was registered at www.clinicaltrials.gov as #NCT02362997.

Introduction

The leading cause of treatment failure after high-dose chemotherapy and autologous stem cell transplantation (ASCT) for patients with chemosensitive relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) remains disease relapse. Although DLCBL, with the exception of primary mediastinal B-cell lymphoma (PMBCL), does not classically harbor genetic amplification at 9p24.1 leading to overexpression of PD1 ligands (PD-L1 and PD-L2), early results with PD-1 blockade in the R/R setting suggested a potential benefit across B-cell non-Hodgkin lymphoma subtypes, including a 36% overall response rate.1,2 Administering PD-1 blockade after ASCT is ideal for multiple reasons: (1) this setting is characterized by a minimal disease state; and (2) there exists a preponderance of lymphocytes after immune reconstitution that are the target for PD-1 blockade. PD-1 blockade early after ASCT could therefore leverage the remodeling immune landscape to decrease disease relapse.
Because most relapses after ASCT occur within the first year following transplantation, maintenance with PD-1 blockade is likely to offer the most benefit during this early phase of immune reconstitution. Any benefits from such a strategy are likely to be durable, as previous studies using PD-1 blockade suggest that responses continue after discontinuation of drug treatment despite a half-life of only 14 to 22 days. We consequently conducted a phase 2 study administering maintenance anti–PD-1 antibody pembrolizumab after ASCT for patients with R/R DLBCL.

Methods

This phase 2, investigator-initiated, open-label, multicenter trial enrolled patients at 6 centers in the United States. The study accrued patients in 3 cohorts, 1 for classical Hodgkin lymphoma (cHL), 1 for DLBCL, and 1 for T-cell lymphoma. The current article presents the results of the DLBCL cohort. Patients aged ≥18 years with R/R DLBCL (per World Health Organization 2008 guidelines) or PMBCL who had received ≥3 lines of previous therapy and underwent ASCT who had chemosensitive disease (defined as partial response or better to salvage therapy, per International Harmonization Project criteria) were eligible. Patients could not have received previous anti–PD-1 therapy. Subjects who were enrolled before ASCT were required to re-screen and meet all eligibility criteria after transplantation. Treatment was started within 60 days of ASCT once participants had appropriate hematologic recovery (grade 2 or lower per Common Terminology Criteria for Adverse Events version 4.0) with a goal of starting pembrolizumab 200 mg intravenously every 3 weeks for 8 cycles within 21 days of hospital discharge. Dose modification was not allowed; however, subsequent dosing could be delayed up to 12 weeks for toxicity. Participants could not receive any additional therapy (including radiotherapy, chemotherapy, or immunotherapy) after ASCT. Drug was permanently held for grade 4 treatment-related adverse events (AEs) and selected grade 3 immune-related AEs. The primary endpoint was progression-free survival (PFS) at 18 months after ASCT, following the International Harmonization Project 2007 criteria using PET and CT scans.

All patients signed informed consent. The study was registered at clinicaltrials.gov (NCT02362997), Institutional Review Board approved, monitored by an independent Data and Safety Monitoring Board, and conducted in accordance with the principles of the Declaration of Helsinki. Merck & Co. (Kenilworth, NJ) provided study drug and funding. Data collection and analysis were independently performed by investigators. PFS and overall survival rates were estimated as the proportion of evaluable patients alive and progression-free, or alive, respectively, at 18 months after ASCT. We hypothesized that pembrolizumab could improve the 18-month progression-free rate from 60% to 80%. Eighteen-month PFS 60% was determined based on previous studies of DLBCL after ASCT. With a sample size of 30 patients, the treatment would be considered promising if ≥22 of 30 patients remained progression free at 18 months. This design had a power of 87%, at a significance level of 0.09 as calculated by using the exact binomial method. We also calculated Kaplan-Meier estimates of PFS and overall survival; PFS was defined as time from transplantation to death from any cause, relapse, or progression, with patients censored at the last time seen alive and progression free, and overall survival was defined as the time from study entry to death from any cause, with patients censored at the last time seen alive.

Results and discussion

Thirty-one subjects were enrolled, and two subjects withdrew consent before starting treatment. Clinical characteristics of the 29 eligible subjects are shown in Table 1. The median age was 57 years (range, 22-76 years). Eight patients were primary refractory to first-line therapy. Median International Prognostic Index.
Figure 1. PFS, overall survival, and examples of tumor characteristics pre- and posttreatment. PFS in all evaluable patients (n = 29) (A) and patients stratified according to disease response before ASCT (partial remission [PR], n = 11; CR, n = 18) (B). (C) Representative IHC for pretransplant (pre) samples and posttransplant (post) relapse biopsy samples (original magnification ×200) showing CD3 (white), PD-1 (red), and 4',6-diamidino-2-phenylindole (DAPI; blue) with corresponding quantification of CD3+ infiltrates and PD-1 staining in 4 patients. (D) Representative IHC for pretransplant samples and posttransplant relapse biopsy samples (original magnification ×200) showing Pax5 (pink), CD68 (orange), PD-L1 (green), and DAPI (blue) with corresponding quantification of CD68+PD-L1+ infiltrates in 4 patients.
In addition, a phase 2 study of nivolumab, which was not evidence suggesting that its target is delta-like protein 1 and not of pidilizumab has recently been reconsidered, with more recent blockade has, in fact, very limited activity in unselected DLBCL.13

Our results suggest that deploying PD-1 blockade post-ASCT does not seem to increase its therapeutic benefit in this disease.

Pretreatment (from diagnosis or relapse) and postprogression biopsy samples were available for 4 patients whose disease progressed during the study. Although most postprogression biopsy results demonstrated lower CD3+ T-cell infiltrates compared with pretreatment ones, according to both density and percentage of total cellularity, PD-1 expression on the remaining CD3+ cells was roughly unchanged (Figure 1C). PD-L1 expression was observed predominantly on CD68+ macrophages and did not significantly differ between time points (Figure 1D), a finding previously described in the de novo setting without significant prognostic implication.14,15 To investigate alternative mechanisms of resistance, samples were also analyzed for MHC class II expression, as well as its ligand LAG3. The relative expression of MHC class II on PAX5+ tumor cells was increased in postprogression samples (P = .04) (supplemental Figure 1). There was no corresponding increase in LAG3 expression on infiltrating T cells (supplemental Figure 2). These results argue that relapse in this context may not be related to alteration in expression of PD-1 or PD-L1. It is possible that LAG-3/MHC II–mediated inhibition could participate in the mechanism of relapse; however, full elucidation of those mechanisms will definitely require further studies.

In conclusion, pembrolizumab after ASCT in patients with R/R DLBCL is feasible, with potentially higher hematologic toxicity compared with the recently reported cHL arm of this trial.10 These differences are likely attributable to differences in previous treatment regimens when comparing disease subtypes. Alternatively, it could reflect an accentuated toxicity of pembrolizumab in this specific context, although the rate of severe neutropenia was lower in the cHL arm of the trial, arguing against a general post-ASCT immuno-oncology phenomenon. The 18-month PFS rate did not meet the protocol-specified primary objective and therefore does not support a larger confirmatory study in R/R DLBCL. Future studies of PD-1 blockade in the post-ASCT setting should likely focus on specific subsets of DLBCL (eg, PMBCL,16 Epstein-Barr virus–positive DLBCL,17,18 T-cell histioocyte-rich large cell lymphoma18), which may be especially sensitive to PD-1 blockade.

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Authorship

Contribution: M.J.F. collected data, analyzed and interpreted data, and wrote the manuscript; P.A., Y.-B.C., and R.M.J. designed research, performed research, collected data, analyzed/interpreted data, performed statistical analysis, and helped in manuscript preparation; and R.A.R., E.J., R.W.M., K.C.C., A.F.H., P.D., Y.N., A.S.L., D.C.F., S.Y.N., O.O.O., A.S.F., A.I.K., J.L.C., C.A.J., E.D.J., J.L.W., J.B., S.S.P., J.R., S.J.R., and M.A.S. performed research, analyzed data, and helped in manuscript preparation.
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References

1. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a Phase Ib study. J Clin Oncol. 2016;34(23):2698-2704.
2. Merryman RW, Armand P, Wright KT, Rodig SJ. Checkpoint blockade in Hodgkin and non-Hodgkin lymphoma. Blood Adv. 2017;1(26):2643-2654.
3. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study [published correction appears in Blood. 2017;130(16):1800-1808]. Blood. 2017;130(16):1800-1808.
4. Elassaiss-Schaap J, Rossenu S, Lindauer A, et al. Using model-based “learn and confirm” to reveal the pharmaco kinetics-pharmacodynamics relationship of pembrolizumab in the KEYNOTE-001 Trial. CPT Pharmacometrics Syst Pharmacol. 2017;6(1):21-28.
5. Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti–PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res. 2015;21(19):4286-4293.
6. Cheson BD. The International Harmonization Project for response criteria in lymphoma clinical trials. Hematol Oncol Clin North Am. 2007;21(5):841-854.
7. Norris D, Stone J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Geneva, Switzerland: World Health Organization; 2008:22-23.
8. Armand P, Welch S, Kim HT, et al. Prognostic factors for patients with diffuse large B cell lymphoma and transformed indolent lymphoma undergoing autologous stem cell transplantation in the positron emission tomography era. Br J Haematol. 2013;160(5):608-617.
9. Chen YB, Hochberg EP, Feng Y, et al. Characteristics and outcomes after autologous stem cell transplant for patients with relapsed or refractory diffuse large B-cell lymphoma who failed initial rituximab, cyclophosphamide, adriamy cin, vincristine, and prednisone therapy compared to patients who failed cyclophosphamide, adriamycin, vincristine, and prednisone. Leuk Lymphoma. 2010;51(5):789-796.
10. Armand P, Chen YB, Redd RA, et al. PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation. Blood. 2019;134(1):22-29.
11. Armand P, Nagler A, Weller EA, et al. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic transplantation: a single-arm, phase II study. J Clin Oncol. 2013;31(33):4199-4206.
12. Stenner F, Renner C. Cancer immunotherapy and the immune response in follicular lymphoma. Front Oncol. 2018;8:219.
13. Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. J Clin Oncol. 2019;37(6):481-489.
14. McCord R, Bolen CR, Koeppen H, et al. PD-L1 and tumor-associated macrophages in de novo DLBCL. Blood Adv. 2019;3(4):531-540.
15. Xu-Monette ZY, Zhou J, Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. Blood. 2017;130(3):267-270.
16. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood. 2017;130(3):267-270.
17. Kim SJ, Hyeon J, Cho I, Ko YH, Kim WS. Comparison of efficacy of pembrolizumab between Epstein-Barr virus–positive and –negative relapsed or refractory non-Hodgkin lymphomas. Cancer Res Treat. 2019;51(2):611-622.
18. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res. 2013;19(13):3462-3473.