MINI REVIEW

Approved Programmed Cell Death-1 Inhibitors in Hodgkin Lymphoma: The first Breakthrough of Immune Checkpoint Inhibitors in Hematologic Malignancies

Jun Gong

Department of Medicine, Division of Hematology/Oncology, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA

ABSTRACT

Despite the high cure rates with initial therapy in classical Hodgkin lymphoma (cHL), refractory disease and relapse still occur in this malignancy and emphasize the need for additional therapeutic strategies in this setting. Although programmed cell death-1 (PD-1) inhibitors have yet to be as widespread in implementation in the treatment of hematologic malignancies as they have been in solid tumors, the arrival of PD-1 inhibitors in this arena has been highlighted by the recent U.S. Food and Drug Administration (FDA) approvals of nivolumab and pembrolizumab in relapsed/refractory cHL. FDA approvals of PD-1 inhibitors for other hematologic malignancies have recently followed as well. The future remains promising for this class of agents as results from ongoing investigations involving immune checkpoint blockade as monotherapy or as part of combination regiments are eagerly awaited in a number of other hematologic malignancies.

Key words: Hematologic malignancy, Hodgkin lymphoma, immune checkpoint inhibitor, programmed cell death-1 inhibitor

EPIDEMIOLOGY

In 2018, there will be about 8500 new cases of Hodgkin lymphoma (HL) and an estimated 1050 deaths from this cancer in both men and women in the U.S.[1] HL historically represents a curable malignancy with an approximate 90% cure rate with conventional treatment in early-stage HL and 70% cure rate with standard therapies in advanced-stage disease.[2] However, about 25% of patients will have refractory disease to initial therapy or relapse after frontline therapy, and only half of the patients with relapsed disease can be cured with salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT).[2]

STANDARD OF CARE

The current standard treatment strategies for classical Hodgkin lymphoma (cHL) favor a risk-adapted initial therapeutic approach. For early-stage (stage I-IIA), favorable cHL, combined modality therapy (CMT) with two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 20 Gray (Gy) of involved-field radiation therapy (IFRT) is a widely-recognized standard treatment.[2,3] For early-stage, non-bulky, unfavorable cHL, CMT remains a standard therapy with options including ABVD for four cycles followed by 30 Gy IFRT, two cycles of escalated bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone (BEACOPP) with two cycles of ABVD followed by 30 Gy IFRT, or 3–6 cycles of ABVD alone when integrating a positron-emission tomography (PET) response-adapted approach.[2,3]

For early-stage, bulky, unfavorable cHL, CMT in the form of 4–6 cycles of ABVD followed by 30 Gy IFRT or two cycles of escalated BEACOPP with two cycles of ABVD followed by 30 Gy IFRT are favored treatment options.[2,3] Finally,

Address for correspondence:
Jun Gong, Department of Medicine, Division of Hematology/Oncology, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA. E-mail: jun.gong@cshs.org

for advanced-stage (stage IIB-IV), six cycles of ABVD, six cycles of AVD with brentuximab vedotin (BV), six cycles of escalated BEACOPP followed by RT for residual PET-positive masses ≥2.5 cm, or two cycles of ABVD followed by four cycles of AVD (if PET-negative) or six cycles of BEACOPP-14 (if PET-positive) represent standard frontline options.[2,3]

RELAPSED/REFRACTORY DISEASE

For primary refractory disease, which is defined as non-response or progressive disease (PD) during induction or within 90 days of completing initial therapy, HDT and ASCT are currently the favored treatment of choice.[3] For late relapses (>1 year after initial complete response [CR]), it has been standard practice to rechallenge with the same chemotherapeutic regimen as received in the frontline setting.[3] For patients who relapse within 12 months, salvage chemotherapy followed by ASCT is often utilized, although no standard salvage regimen is recognized.[2,3] Given the relatively low CR rates seen with salvage chemotherapeutic regimens, it is recognized that many patients often proceed to ASCT with suboptimal disease control.[2,3] Of note, BV as monotherapy has a U.S. Food and Drug Administration (FDA) indication in this space for disease that has progressed after ASCT or after 2 prior chemotherapy treatments for those who cannot receive a transplant. Despite high cure rates with initial therapy, approximately 5–10% of HL patients demonstrate refractoriness to frontline therapy and 10–30% of patients will relapse after achieving an initial CR, highlighting the need for further development of active agents in the relapsed/refractory setting.[3]

PROGRAMMED CELL DEATH-1 (PD-1)/PD-L1 AXIS IN HODGKIN LYMPHOMA

Several inhibitors of PD-1 and programmed death-ligand 1 (PD-L1) have been FDA approved in the treatment of a number of solid tumors; however, their implementation into the standard treatment paradigm for hematologic malignancies have not so readily occurred.[4] It was not until preclinical and clinical studies involving integrative copy number analysis and transcriptional profiling that identified the putative role of the PD-1/PD-L1 axis in malignant cell evasion of immune surveillance when targeting of this axis with PD-1 blockade represented a viable therapeutic strategy in cHL.[5] In this seminal study, the immunoregulatory genes PD-L1 and PD-L2 were identified as key targets of the 9p24.1 amplification in HL cell lines. These findings were also found in primary HL tumors where a positive association between 9p24.1 copy number and PD-1 ligand expression was observed. The extended 9p24.1 amplification region also included the JAK2 locus whereby JAK2 amplification further induced PD-1 ligand transcription. Ultimately, these findings established 9p24.1 amplification as a cHL-specific structural alteration that increased both expression of PD-L1/PD-L2 and their induction by JAK, which further corroborated proof-of-principle in targeting either of these pathways in cHL.

FDA-APPROVED PD-1 INHIBITORS

On May 17, 2016, the PD-1 inhibitor nivolumab received the first approval for an agent in this class in the treatment of a hematologic malignancy based on CheckMate 039 and CheckMate 205 trials in HL.[6,7] CheckMate 039 was a phase I study with dose escalation and expansion cohorts in relapsed or refractory HL.[6] A total of 23 patients were enrolled, the majority of whom had been treated with ≥3 prior lines of therapy, received BV and received ASCT. The expansion cohort received nivolumab at 3 mg/kg every 2 weeks, and the primary endpoint was safety. Nivolumab was relatively tolerated with grade≥3 adverse events being seen in five patients including myelodysplastic syndrome, pancreatitis, and pneumonitis. Promising response rates were observed in this heavily pre-treated population of HL [Table 1].

CheckMate 205 was a single-arm phase II trial investigating nivolumab at 3 mg/kg every 2 weeks in 80 patients with relapsed/refractory HL.[7] Again, the majority of patients had received ASCT (93%) and BV (88%), and the median number of prior lines of therapy was 4 (range 4-7). In this heavily pretreated population, nivolumab showed promising response rates (primary endpoint was overall response rate) and a tolerable toxicity profile [Table 1]. On March 6, 2018, nivolumab received an FDA label update to include a dosing regimen of 480 mg intravenous every 4 weeks in addition to the previously available 240 mg every 2 weeks dosing for relapsed/refractory cHL after ASCT and BV or ≥3 lines of prior therapy (includes ASCT).

On March 15, 2017, pembrolizumab was first approved in a hematologic malignancy based the KEYNOTE-087 trial in relapsed/refractory cHL.[8] In 210 patients with cHL, the majority of which who had received ≥3 prior lines of therapy (86.7%), pembrolizumab showed durable responses (primary endpoint was overall response rate and safety) and a tolerable safety profile [Table 1]. The FDA approval for pembrolizumab in cHL is for patients who have relapsed after 3 or more prior lines of therapy at 200 mg every 3 weeks until PD, intolerability, or up to 24 months.

IMPLICATIONS AND FUTURE DIRECTIONS

The breakthrough of PD-1 inhibitors into the arena of hematologic malignancies has been underscored with the recent FDA approvals of nivolumab and pembrolizumab in

Table 1: FDA-approved PD-1 inhibitors in Hodgkin lymphoma

Study	Setting	Experimental Arm	Control Arm	Efficacy	Toxicities	Ref
Nivolumab						
CheckMate 039 (phase I)	≥1 prior treatment (including ASCT)	3 mg/kg every 2 weeks (*n*=23)	N/A	ORR 87%, 17% CR, 70% PR	Grade 3 AEs 22%	[6]
CheckMate 205 (phase II)	≥1 prior treatment (including BV and ASCT)	3 mg/kg every 2 weeks (*n*=80)	N/A	ORR 66.3% (95% CI 54.8–76.4)	Most common grade 3–4 AEs: neutropenia (4 (5%)) and increased lipase concentration (4 (5%))	[7]
Pembrolizumab						
KEYNOTE-087 (phase II)	Previously treated with ASCT or AV	200 mg every 3 weeks (*n*=210)	N/A	ORR 69.0% (95% CI 62.3–75.2%) CR 22.4% (95% CI 16.9–28.6%)	Most common grade 3–4 AEs: neutropenia (2.4%), dyspnea (1%), and diarrhea (1%)	[8]

ASCT: Autologous stem cell transplantation, ORR: Overall response rate, CR: Complete response, PR: Partial response, AEs: Adverse events, BV: Brentuximab vedotin, CI: Confidence interval

relapsed/refractory HL. These immunotherapeutic agents occupy a needed space in the treatment paradigm of HL. Pembrolizumab is notably available in the late-line treatment setting of cHL in those who have not received or may not be candidates for ASCT, in contrast to the nivolumab FDA label in relapsed/refractory cHL. Results from confirmatory phase III trials are pending for these agents, but findings thus far show promising efficacy and a well-tolerated safety profile.

Future directions for checkpoint inhibitors in hematologic malignancies will likely involve expansion to other tumor types, and in combination strategies to make use of the tolerable safety profiles of these agents. Indeed, based on the positive results of the KEYNOTE-170 phase II trial, pembrolizumab became the first PD-1 inhibitor approved for non-Hodgkin lymphoma on June 13, 2018, specifically in refractory primary mediastinal large B-cell lymphoma (PMBCL) or those with PMBCL who have relapsed after 2 or more prior lines of therapy.[9] This was based on pre-clinical and clinical data supporting that PMBCL, similar to cHL, frequently exhibits 9p24.1/PD-L1/PD-L2 copy number alterations associated with overexpression of PD-L1 and PD-L2. Investigations are ongoing regarding the efficacy of immune checkpoint inhibitors as monotherapy or as part of combination regimens in other hematologic malignancies including diffuse large B-cell lymphoma, follicular lymphoma, T-cell non-Hodgkin lymphomas, multiple myeloma, chronic lymphocytic leukemia, acute myeloid leukemia, and myelodysplastic syndromes based on preexisting rationale supporting PD-1 ligand overexpression in these cancer subtypes.[10,11]

CONCLUSION

The FDA approvals of nivolumab and pembrolizumab in the treatment of relapsed/refractory cHL have been important breakthroughs for immune checkpoint inhibitors in hematologic malignancies. Aside from the promising efficacy and well-tolerated safety profile of PD-1 inhibitors in relapsed/refractory cHL, pembrolizumab has just been approved in relapsed/refractory PMBCL and the number of trials investigating checkpoint inhibitors in other hematologic malignancies is picking up considerable momentum. Final results from these ongoing investigations are eagerly awaited and will be critical in assessing whether this class of immunotherapeutic agents will be firmly established in the treatment paradigm of hematologic malignancies.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
2. Diefenbach CS, Connors JM, Friedberg JW, Leonard JP, Kahl BS, Little RF, *et al.* Hodgkin lymphoma: Current status and clinical trial recommendations. J Natl Cancer Inst

2017;109:djw249.
3. Ansell SM. Hodgkin lymphoma: 2018 update on diagnosis, risk-stratification, and management. Am J Hematol 2018;93:704-15.
4. Gong J, Chehrazi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: A comprehensive review of registration trials and future considerations. J Immunother Cancer 2018;6:8.
5. Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E, *et al.* Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116:3268-77.
6. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, *et al*. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311-9.
7. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, *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;17:1283-94.
8. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, *et al.* Phase II study of the efficacy and safety of pembrolizumab for relapsed/Refractory classic hodgkin lymphoma. J Clin Oncol 2017;35:2125-32.
9. Zinzani PL, Thieblemont C, Melnichenko V, Bouabdallah K, Walewski J, Majlis A, *et al.* Efficacy and safety of pembrolizumab in relapsed/refractory primary mediastinal large B-cell lymphoma (rrPMBCL): Updated analysis of the Keynote-170 phase 2 trial. Blood 2017;130:2833.
10. Jelinek T, Mihalyova J, Kascak M, Duras J, Hajek R. PD-1/PD-L1 inhibitors in haematological malignancies: Update 2017. Immunology 2017;152:357-71.
11. Wang Y, Nowakowski GS, Wang ML, Ansell SM. Advances in CD30-and PD-1-targeted therapies for classical hodgkin lymphoma. J Hematol Oncol 2018;11:57.

How to cite this article: Gong J. Approved Programmed Cell Death-1 Inhibitors in Hodgkin Lymphoma: The first Breakthrough of Immune Checkpoint Inhibitors in Hematologic Malignancies. Clin Res Hematol 2018;1(1):1-4.