Assessing the Emerging Role of Checkpoint Inhibition and Other Immune Therapies in Lymphoma

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Overview
This activity is designed to inform physicians about the emerging role of checkpoint inhibition and other immune therapies in the treatment of lymphoma.

Target Audience
This activity is directed toward hematologists, medical oncologists, nurses, and nurse practitioners who manage and treat patients with lymphoma. Surgical oncologists, radiation oncologists, pathologists, fellows, physician assistants, and other healthcare providers interested in the treatment of lymphoma are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Describe the unmet needs in the treatment of patients with lymphoma
- Review recent developments in the field of immunology with respect to lymphoma treatment
- Review current and emerging clinical trial information concerning the use of investigational immunotherapeutic approaches for lymphoma treatment

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The American Cancer Society estimates a diagnosis of 81,080 new cases of lymphoma (Hodgkin lymphoma [HL, 8,500 cases] and non-Hodgkin lymphoma [NHL, 72,580 cases]), and an estimated 21,270 deaths from lymphoma this year.[1] While most patients with HL can be successfully treated with chemotherapy, radiotherapy, or combined chemoradiotherapy, these treatment options are associated with important short and long-term toxicities such as infertility, cardiovascular damage, and secondary malignancies. Though some patients are cured, there remains an unmet need for treatments in patients who develop refractory disease after stem cell transplant.[2]

An enhanced understanding of the interaction between the immune system and tumors has led to the development of novel and powerful forms of cancer immunotherapy in the recent few years. Recognition of negative regulatory immune checkpoints, such as the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed-death 1 (PD-1) pathways, has led to the discovery of novel therapies targeting these specific pathways. These treatments predominately involved the development of monoclonal antibodies (mAbs) directed against the immune receptors or ligands, and are capable of reversing tumor-induced immune-suppression, thereby, effectively enhancing the antitumor response at the priming (CTLA-4) or tissue effector (PD-1) phase.[3]

Checkpoint inhibitors have emerged as an important therapeutic class in several malignancies including hematologic. Based on the success of PD-1 blocking mAbs in the treatment of solid tumors, phase 1 studies evaluating the efficacy of these agents were initiated in several hematologic malignancies as well. For example, one of the studies tested the safety and activity of the anti-PD-1 mAb nivolumab in patients with relapsed or refractory (R/R) lymphoid malignancies including non-HL (NHL), and classical HL (cHL).[4]

In May this year, the US FDA granted accelerated approval to nivolumab for the treatment of patients with cHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and posttransplantation brentuximab vedotin.[5] The approval was based on two single-arm, multicenter trials of nivolumab in adults with relapsed or refractory cHL. In patients previously treated with autologous stem cell transplant (ASCT) and posttransplantation brentuximab vedotin (BV), treatment with single-agent nivolumab demonstrated good response; the median time-to-response was 2.1 months, and the estimated median duration of response (DOR) was 8.7 months.[5] Most recently, data from the Checkmate 205 study that evaluated the efficacy and safety of nivolumab in pts with cHL who had received BV after progression following ASCT was presented at the ASCO 2016 annual meeting. In this study, treatment with nivolumab demonstrated durable responses, high response rate (66% by independent radiologic review committee), and acceptable safety profile. Progression free survival (PFS) and overall survival (OS) data were also encouraging in this heavily pretreated population. Additionally, good efficacy was observed in patients with no prior BV response.[6]

Another anti-PD-1 mAb checkpoint inhibitor, pembrolizumab, has demonstrated similarly impressive results in cHL. In a recently described phase Ib study enrolling extensively pre-treated cHL patients who had undergone five or more prior lines of therapy, and had received prior BV (NCT01953692, KEYNOTE-013), treatment with pembrolizumab demonstrated an overall response rate of 66% was reported.[7,8] Most recently, at the 2016 ASCO Annual Conference, data from the KEYNOTE-087 study which aimed to confirm clinical activity of pembrolizumab in cHL pts were presented. In this study, ORR was 80% with pembrolizumab in patients with prior BV therapy failure and 70% in R/R cHL patients who had undergone ASCT and subsequent BV therapy.[9]

Beyond HL, there are also emerging data suggesting that checkpoint blockade therapy with PD-1-blocking antibodies may be effective in NHL.[10] In a phase II single-arm international study of checkpoint inhibitor pidilizumab in R/R diffuse large B-cell lymphoma (DLBCL) or primary mediastinal B-cell lymphoma after ASCT, the overall response rate was 51%. Subsequently, pidilizumab was evaluated in combination with rituximab in a phase II single-arm open label study, and an overall response rate of 66% was reported.[7,11]

Another emerging concept surrounds combining immune checkpoint inhibitors with immuno-modulators or targeted agents, based on the rationale that small molecules directed at various signaling pathways involved in malignancy affect immune responses. Preclinical data combining anti-PD-L1 antibodies and the bruton's tyrosine kinase inhibitor ibrutinib has shown promising activity in lymphoma, which, in turn, has opened the doors for clinical studies evaluating the combination of immunotherapy with immunomodulators or targeted agents such phosphoinositide (PI) 3-kinase inhibitors and others.[7] Currently, atezolizumab (MPDL3280A), an anti-PDL1 (PD-1 ligand) antibody, is being evaluated in combination with the anti-CD20 antibody obinutuzumab in patients with R/R follicular lymphoma (FL) and DLBCL (NCT02220842).[12]

Several other novel checkpoint inhibitors or other immunotherapies are in various stages of development. Beyond PD1 antibodies, a checkpoint inhibitor currently being investigated in lymphoma includes antibodies directed against lymphocyte-activation gene-3 (LAG-3) (NCT02061761).[13] Additional immunotherapeutic approach being investigated in lymphoma includes the chimeric antigen receptor (CAR) T-cell therapy, which uses autologous infusion of genetically engineered T cells that express chimeric antigen receptors targeting surface antigens, such as CD19. CAR T-cell therapy is currently being investigated for lymphoma treatment based on the promising preliminary data.[14]

There are several novel therapeutic options including different immunotherapy approaches that are currently being investigated in lymphoma, and the standard of care for lymphoma will continue to evolve as new agents are approved. Some of the challenges that the practitioners may face in the future may include determining the most optimal approach (sequencing/combination) and personalizing

treatment based on predictive biomarkers such as PD-L1 as they become available.

Dr. Anas Younes, MD, a medical oncologist and Chief of Memorial Sloan Kettering's Lymphoma Service at New York, NY provided his insights and point on view on the emerging role of checkpoint inhibition and other immune therapies in lymphoma.

Moderator: What are some of the unmet needs in the treatment of lymphoma?

Dr Younes: It depends on the disease subtype. There are a lot of areas of unmet medical needs in lymphomas. Let us discuss Hodgkin lymphoma, as an example. So even though we can cure up to 80 to 85 percent of all patients with Hodgkin lymphoma with currently available modern therapy, the unmet medical need here is to further improve the cure rate, and to reduce treatment related toxicity. So we definitely want to cure all patients, not just 85 percent. But also we need to improve the safety of the curative regimens. It is well-established that chemotherapy and radiation therapy do have side effects. Some of them are delayed effects, including cardiovascular complications and second malignancies. Immunotherapy could fit in that role by not only improving the cure rate but could potentially improve the safety of the curative regimens.

The same applies to non-Hodgkin lymphoma as well. One of the most curable subtypes of non-Hodgkin lymphoma is the diffuse large B-cell lymphoma, where standard R-CHOP Chemotherapy can cure about 50 percent of the patients. So incorporating new, effective drugs in the RCHOP regimen is highly desirable and needed. And the question is, of course, that everyone wants to find an answer to is whether additional immune therapy-based treatment, on top of what we already have, let's say rituximab, would do the trick and would improve the cure rate, and that's an area under investigation by many investigators in the centers.

Moderator: What impact can checkpoint inhibitors have in the treatment of lymphomas in general?

Dr Younes: There are two goals that we keep in mind when we try to incorporate new agents, such as checkpoint inhibitors, in the treatment of patients with lymphoma. And if we can't improve the cure rate, the second alternative goal is to improve the overall outcome of treatment, especially in non-curable lymphomas such as the follicular lymphomas and the mantle cell lymphomas by prolonging the duration of remission, for example. And also when we want to change a treatment strategy, we always keep in mind the potential safety of these regimens. And immune checkpoint inhibitors will need to be tested to determine whether they can achieve our goals.

Moderator: Results from the phase 2 Checkmate 205 study[6] that evaluated nivolumab therapy in classical Hodgkin's lymphoma were presented recently at this year's ASCO. Would you be able to share some of the key takeaways from this study?

Dr Younes: As you probably remember, there were two highly cited phase 1 trials with checkpoint inhibitors, and those were with pembrolizumab and nivolumab. And the Hodgkin lymphoma part was sort of a subset of patients in a larger phase 1 trial that included different types of hematologic malignancies, including myelodysplastic syndrome, multiple myeloma, and non-Hodgkin lymphoma, and Hodgkin lymphoma.

In the phase 1 trial of nivolumab, the initial report included 23 patients with Hodgkin lymphoma, and remarkably, 87 percent of the patients responded with about 17 percent achieving complete response. Approximately 70 percent of the patients who responded had a prior exposure to brentuximab vedotin, which up till then was the only FDA-approved agent for the treatment of relapsed Hodgkin lymphoma. Although the number of Hodgkin lymphoma patients was only 23, this data generated tremendous interest and enthusiasm that led to the phase 2 trial that you're referring to, which is the Checkmate 205 study. The data that was reported at ASCO was specific for Hodgkin lymphoma patients who had failed both autologous transplant and brentuximab vedotin.

The trial included 80 patients and the overall response rate was 66 percent and the complete response rate was 9 percent. So it confirmed in a way the data that was reported initially from the phase 1 trial. And based on this data, in May 2016, the FDA gave approval for nivolumab for the treatment of patients with relapsed Hodgkin lymphoma after failing both autologous transplant and brentuximab vedotin.

Moderator: Data from phase 2 KEYNOTE-087 study[9] evaluating pembrolizumab therapy in classical Hodgkin's lymphoma were also presented recently at this year's ASCO. How do these compare with Checkmate 205 study?

Dr Younes: Yes, and remarkably a similar story. Initially pembrolizumab was tested in a multi-cohort phase 1 trial that included also Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, and myelodysplasia. And like nivolumab, in a small number of patients, 29 patients treated in that phase 1 trial, 29 patients had relapsed Hodgkin lymphoma, and the overall response rate was 66 percent, and the complete response rate was 21 percent and in patients who relapsed or were exposed to brentuximab vedotin, the response rate was also high with pembrolizumab, was 66 percent.

So, again, based on this very promising data, a phase 2 trial, the registration trial, was initiated and also had multiple cohorts. In reference to prior autologous transplants, brentuximab vedotin, brentuximab was given before after transplant and so forth. But at ASCO, 30 patients—this was still ongoing trial—30 patients were treated with pembrolizumab, 200 mg intravenously given every three weeks. And the overall response rates from this ongoing trial was 70 percent and the CR rate was 20 percent. If you look at the data again for nivolumab phase 2 trial and then the pembrolizumab, the ongoing trial, it's remarkable similarity with nivolumab overall response rate 66 percent, pembrolizumab overall response rate was 70 percent. It's amazing the similarities between these two agents.

Moderator: Can brentuximab vedotin be potentially used in combination with PD-1/PD-L1–targeted agents and at what stage of the treatment. Why or why not?

Dr Younes: Everybody wants to know the answer for this question because if you look at brentuximab vedotin as single agent in patients who relapsed at autologous transplant, overall response rate is 74 percent and the CR rate is about 34 percent. And now we have PD-1 inhibitors giving a high response rate, 66 or 70 percent, with slightly lower CR rate. We have two highly active agents and the question, are they combinable?

The trials are ongoing right now in different settings. One setting is in relapsed after frontline therapy before autologous stem cell transplant, and the second one is after autologous stem cell transplant. So, these trials are ongoing and if the combination can be given within safety, then I think this may become a new doublet that one could build on to develop future treatment regimens.

Moderator: What is the potential of rationale for combining checkpoint inhibitors with other therapies in lymphoma? Do we have any data so far supporting any such combinations?

Dr Younes: There's no data to support. These are ongoing clinical trials. So, for example, checkpoint inhibitors are being combined with frontline regimens like ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or AVD (ABVD modified regimen without the inclusion of bleomycin). In untreated patients with Hodgkin lymphoma they're being combined with radiation therapy; in patients with follicular lymphoma, the PD-L1 inhibitor is being combined with CHOP-based regimens in newly-diagnosed diffuse large B-cell lymphoma. Same thing being combined with bendamustine-based regimens in untreated follicular lymphoma. There's combination with lenalidomide and rituximab or obinutuzumab in relapsed follicular lymphoma.

These trials are ongoing using different combination regimens, and everybody is interested to find out how these regimens will perform in terms of safety and efficacy. So it will take about a year or two before we find support.

Moderator: Do we have any data supporting the role of CAR-T cell therapy in the treatment of lymphoma?

Dr Younes: A very important question. Can we further activate engineered T cells to be more effective killers, especially in the settings where CAR-T cell has not shown very high efficacy, for example, in diffuse large B cell lymphoma, CAR-T cells have shown modest efficacy but not as striking as in ALL. And the question, is it because T cells are not optimally activated? And if so, can we further activate engineered T cells by adding checkpoint inhibitors?

Clinical trials are currently being conducted to ask this question. The other question that comes to mind is, yes, we may be able to activate T cells, and we may enhance their efficacy, but do we also increase the toxicity of CAR-T cells knowing that CAR-T cells have some unusual toxicity profile? I don't know, we'll find out. I mean the trials are being done and everybody is keeping eye on both efficacy and safety of this approach.

Moderator: What does the future hold for checkpoint inhibitors specifically with respect to treatment of lymphoma and patient selection?

Dr Younes: The future is a) add on to preexisting regimens, and b) develop sort of chemotherapy-free combination strategies. For example, combining checkpoint inhibitors with lenalidomide or bispecific targeted antibodies. We have a trial combining ibrutinib plus PD-1 inhibitors. And there are several versions of this combination going on in different, again centers, and so forth. So not only we're looking at adding checkpoint inhibitors to traditional chemotherapy regimens, we are also combining them with small molecules or other immune therapy drugs to determine the safety and efficacy of these new regimens.

Moderator: Besides checkpoint inhibitors and CAR-T cell therapy, what are some of the other promising/emerging immunotherapeutic approaches that have shown promise in lymphoma?

Dr Younes: We talked about CAR-T cells and how they are also promising. And checkpoint inhibitors are very promising. And now there's also emergence of bispecific antibodies, BiTE antibodies, BiTE blinatumomab was the first one approved by the FDA for the treatment of ALL. But there are now newer versions of these bispecifics that are sort of a larger molecules that have a longer half-life, so they can be given by short intravenous infusions rather than by the continuous infusion as is the case with blinatumomab. And then, as mentioned before, there are now attempts to combine multiple immune therapy modalities—CAR-T cells plus checkpoint inhibitors, or bi-specific antibody plus checkpoint inhibitors, or checkpoint inhibitors plus small molecules. Most of these combinations are based on solid preclinical data, and we are all awaiting the results of the clinical trials.

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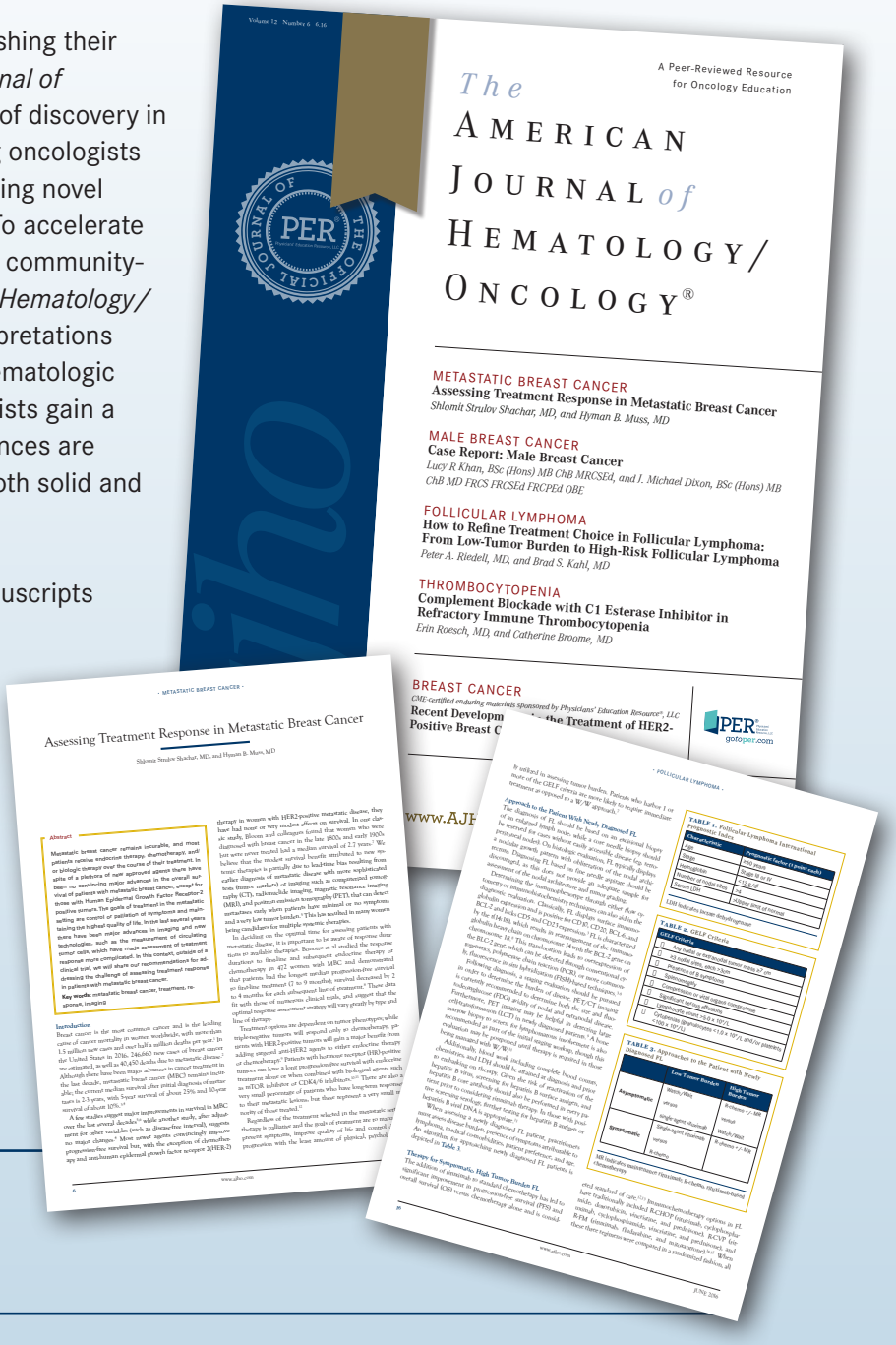

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