The Highs and Lows of Immune-Checkpoint Blockade in Lymphoma

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Abstract

Immunologic approaches to treating patients with cancer have shown promise, and immune-checkpoint blockade has been particularly successful. In many solid tumors, the presence of intratumoral immune cells has been predictive of a response to therapy, and blockade of inhibitory signals that dampen an effective antitumor response has resulted in clinical benefit for patients. Lymphoid malignancies, including Hodgkin lymphoma and non-Hodgkin lymphoma, are cancers of the immune system, and in these diseases, the malignant cells interact with the immune system and commonly provide signals that regulate immune function. Therefore, many of the immunologic lessons learned from solid tumors may not directly translate to lymphoid malignancies, and the mechanisms of effective antitumor responses in these diseases

may be different. In Hodgkin lymphoma, for example, immune-checkpoint blockade has resulted in response rates of 65% to 75%. In contrast, in non-Hodgkin lymphoma, responses to immune-checkpoint blockade in phase II trials have been seen in fewer than 10% of patients, and the reasons for this substantial difference are largely unknown. Combination approaches are likely needed, particularly in the various subtypes of non-Hodgkin lymphoma, and combinations that include cytotoxic agents seem more effective than combinations of immunologic therapies. Successful therapeutic combinations in lymphomas may require an approach that simultaneously blocks inhibitory immune signals, provides direct activation of the immune response, and directly inhibits the malignant clone.

Introduction

The goal of immunotherapy in lymphoma is to optimize immune function and effectively target tumor cells. The tumor microenvironment in most subtypes of lymphoma typically comprises a rich immune infiltrate of T cells, natural killer cells, macrophages, dendritic cells, and neutrophils (1). Despite the presence of immune cells in the tumor microenvironment, the malignant B cells of the lymphoma persistently proliferate, and the disease progresses. Previous studies have identified multiple immunologic barriers to an effective immune response in B-cell malignancies. These include the presence of regulatory and suppressive immune cells, immunosuppressive ligands, and cytokines, and inadequate presentation of tumor antigens (2–7). For immune therapy to be effective, these immunologic barriers must be overcome, and the immune response must be appropriately activated.

Previous research has focused on activating the immune response in lymphoma; however, arresting inhibition and suppression of the immune response by blocking immune-checkpoint signaling is far more effective (8). Blockade of PD-1 signaling has been particularly effective, as PD-1 signaling regulates effector T-cell function. PD-1 is upregulated as T cells are activated and binds to two ligands, namely, PD-L1 (CD274) and PD-L2 (CD273). Signaling through PD-1 results in inhibition of T-cell

function, immune exhaustion, and subsequently in T-cell apoptosis. Intratumoral T cells that are persistently activated by the presence of tumor antigens express PD-1 and tumor cells increase expression of PD-L1 and PD-L2 as a mechanism to avoid eradication by activated T cells. Blockade of PD-1 using monoclonal antibodies prevents the inhibitory signal via PD-1 and potentially results in sustained activation of intratumoral T cells that target the malignant clone (8).

PD-1 Blockade in Hodgkin Lymphoma Is Effective and Responses Are Durable

Reed-Sternberg cells, the signature cell of Hodgkin lymphoma, overexpress PD-L1 and PD-L2, the ligands for PD-1, as a result of copy-number gain or amplification at chromosome 9p24.1 (2, 7, 9). The presence of Epstein–Barr virus (EBV), which is commonly seen in Hodgkin lymphoma, also promotes the upregulation of PD-L1 and PD-L2 (9). The intense expression of PD-1 ligands on Reed-Sternberg cells, as well as on macrophages surrounding the tumor cells, may account for the suppression of an effective immune response by an extensive infiltrate of immune cells in the tumor microenvironment in Hodgkin lymphoma (10). Blockade of the inhibitory signals provided by PD-1 ligands is, therefore, a particularly attractive strategy in Hodgkin lymphoma.

The use of PD-1 blocking monoclonal antibodies such as nivolumab and pembrolizumab in patients with relapsed and refractory Hodgkin lymphoma has resulted in high clinical response rates, and the responses seen with this approach appear durable (11–15). Initial phase I clinical trials of these agents suggested that 65% to 87% of patients with Hodgkin lymphoma responded to this treatment (11, 12). Subsequent phase II trials confirmed a response rate of approximately 70% in all

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subgroups of patients, despite previous chemotherapy or stem cell transplantation (13–15). Although most results have been reported with PD-1 antibodies, similar promising clinical benefit has been seen with antibodies directed against PD-L1, suggesting that blockade of either the receptor or ligand benefits the patient (16). Because of the high response rate to PD-1 blockade in Hodgkin lymphoma, it has been difficult to identify biomarkers that predict response. An analysis of patients treated on the phase II clinical trial of nivolumab found that although the response rates did not differ, patients with amplification or copy-number gain at chromosome 9p24.1 had the highest expression of PD-L1 and the most durable progression-free survival (7).

The Challenge of PD-1 Blockade in Other Lymphomas

Although responses to PD-1 blockade in Hodgkin lymphoma have been seen in more than two thirds of patients, clinical outcomes with PD-1 blockade in other types of lymphomas have been far less impressive (17–19). Response rates to nivolumab or pembrolizumab in patients with diffuse large B-cell lymphoma or indolent lymphomas have been very disappointing. The only subgroups of patients with durable responses are those with diseases with amplifications or copy-number gain of the PD-L1/2 locus or presence of EBV (20–23). Diseases such as primary mediastinal large B-cell lymphoma, mediastinal gray zone lymphoma, or primary CNS lymphoma frequently have amplifications of chromosome 9p24.1. In these rare entities, responses have been seen in more than a third of patients. In primary mediastinal B-cell lymphoma, for example, an overall response rate of 41% has been documented (20).

In contrast, clinical trials of PD-1 blockade in patients with diffuse large B-cell lymphoma or follicular lymphoma have shown very modest response rates and in the small subset of responding patients, the response durations have been short (18, 19). In patients with follicular lymphoma treated with single-agent pembrolizumab, only 2 of 18 patients responded. Similarly, in patients with relapsed or refractory diffuse large B-cell lymphoma treated with nivolumab alone, a response rate of only 10% was reported (18). In the subset of patients with primary refractory diffuse large B-cell lymphoma who were ineligible for a stem cell transplant, the response rate was 3% (18). In patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, no responses were seen in 16 patients (19). However, in patients with Richter's transformation, approximately 40% of the patients benefited from PD-1 blockade (19). In clinical trials in patients with multiple myeloma using antibodies targeting PD-1 as a single agent, no responses were seen (17). This suggests that genetic or viral drivers of PD-L1 and PD-L2 expression are associated with clinical benefit and responses are seldom seen when these are absent.

The Mechanisms That Account for the Efficacy of PD-1 Blockade in Lymphoma Are Unclear

The general assumption in B-cell malignancies is that PD-1$^+$ T lymphocytes present within the tumor microenvironment have an exhausted phenotype and are commonly suppressed by PD-L1/2–expressing tumor cells. Although it has been shown

that some PD-1$^+$ T cells in the tumor microenvironment are indeed exhausted, many PD-1$^+$ cells are in fact activated and not functionally exhausted (24). T follicular helper cells are commonly present in some lymphomas and highly express PD-1 (24). These cells seem fully functional and proliferate or produce cytokines when stimulated. Furthermore, inhibition of PD-1 signaling may occur at different sites than expected. PD-1 ligands are not only expressed on the tumor cell surface; they may be shed, and soluble PD-L1 and PD-L2 can be detected in patient serum. These soluble forms of PD-1 ligands are biologically active and can suppress T cells at distant sites (5). Thus, some of the binding of PD-1 blocking antibodies may occur in the periphery, rather than at the site of lymphoma, resulting in reduced therapeutic efficacy at sites involved by malignant B cells.

Even in diseases in which PD-1 blockade is effective, the mechanisms that account for the benefit are unclear. In Hodgkin lymphoma, the majority of patients exhibit loss or downregulation of MHC class I or II molecules (6, 7). Although it is assumed that immune cells effectively target the tumor when PD-1 signaling is inhibited, the immune mechanisms by which tumor-related antigens are presented to the immune system are deficient or lost in most patients with Hodgkin lymphoma. In patients with Richter's transformation, who also respond well to PD-1 blockade, PD-1 expression appears increased on the malignant B cells rather than T cells (19). In this case, PD-1 blockade may have a direct effect on the malignant cell rather than on the immune system.

Effective Combination Therapies Include Cytotoxic Agents

To build on the efficacy of PD-1 blockade, combination studies have been performed. Generally, the combination strategies have taken one of two approaches. Either an additional immunologic therapy has been administered in combination with nivolumab or pembrolizumab, or these agents have been combined with a cytotoxic drug. The cytotoxic agents have either been in the form of an antibody drug conjugate or chemotherapy.

For example, to further modulate the immune response in lymphoma, nivolumab has been combined with ipilimumab, a monoclonal antibody targeting CTLA-4, similar to the approach taken in treating malignant melanoma (25). In Hodgkin lymphoma, this resulted in a response rate of 74%, but this response rate was not substantially greater than that seen with nivolumab alone (25). In other lymphomas, the combination of nivolumab and ipilimumab resulted in a response rate of 20% that did not appear to be an improvement over either agent alone (25). Other immunologic agents such as bispecific antibodies, rituximab, and killer cell immunoglobulin-like receptor antibodies have also been tested in combination with PD-1 blocking antibodies, but the incremental improvement in outcome appears modest (26, 27). Small-molecule inhibitors that modulate immune function have also been used. Ibrutinib, a Bruton tyrosine kinase inhibitor, also modulates IL2-inducible T-cell kinase function and promotes a T helper type 1 (Th1)–predominant immune response. Ibrutinib has been tested in combination with nivolumab in a variety of lymphoma subtypes, but the response rates have appeared similar to ibrutinib alone in most lymphomas except in Richter transformation, for which responses seemed more similar to

nivolumab. In all subtypes, ibrutinib appears to add little to the combination with checkpoint blockade (28).

In contrast, the addition of antibody drug conjugates, such as brentuximab vedotin, to PD-1 blockade appears to substantially improve response rates. In relapsed Hodgkin lymphoma, this combination has demonstrated overall response rates of greater than 80% with complete responses in more than 60% of patients (29, 30). Particularly in patients with Hodgkin lymphoma in first relapse, two thirds of patients treated with the combination underwent a stem cell transplant without requiring additional therapy (29). Additional studies are in progress combining PD-1 blockade with chemotherapy combinations such as AVD (doxorubicin, vinblastine, dacarbazine) chemotherapy for Hodgkin lymphoma and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy for large cell lymphoma (31). In these studies, response rates have been high, but whether this approach is better than standard chemotherapy will require randomized clinical trials. Overall, however, it does appear that the combination of PD-1 blockade targeting immune function and agents that directly target the malignant cell may be the most promising.

The Road Ahead

Although PD-1 blockade in Hodgkin lymphoma has been successful (Table 1), with very high response rates that appear durable, the challenge remains that patients commonly progress after this therapy. It is clear that immunologic memory to lymphoma-associated antigens is not generated by simply blocking PD-1 signaling. Even though the malignant clone is initially suppressed by the immune system, over time malignant Reed–Sternberg cells survive, and patients subsequently relapse despite immune-checkpoint blockade (13, 15). Much work is needed to understand how to induce immune recall

when tumor antigens are sensed by the immune system. Future treatment may therefore focus on therapies that improve tumor antigen presentation. Clinical trials using agents that induce immunogenic cell death of the Reed–Sternberg cells may help to achieve this (32, 33). To accomplish this, cytotoxic agents such as anthracyclines or radiotherapy are being tested in combination with PD-1 blockade.

Additionally, it is clear that the malignant cell may generate an immunosuppressive microenvironment (34, 35). In lymphomas other than Hodgkin lymphoma, simply arresting the suppression of immune function may be insufficient. It may be more effective to target the malignant cell directly and allow for a "reprogramming" of the tumor microenvironment. Cytotoxic strategies that directly kill malignant cells and decrease the tumor burden may be successful. Using PD-1 blockade and other immune-checkpoint approaches post–autologous stem cell transplant may therefore be an appropriate approach (36). Additionally, combination strategies utilizing nivolumab or pembrolizumab in combination with R-CHOP as initial therapy for B-cell lymphomas are currently under way (37).

Furthermore, most of the immune-checkpoint combination strategies thus far have used monoclonal antibodies to block more than one inhibitory signal. Nivolumab has been combined with ipilimumab, targeting CTLA-4, in both Hodgkin lymphoma and B-cell non-Hodgkin lymphomas (25). Combination studies with nivolumab and LAG-3 antibodies are in progress. Further strategies currently being investigated include combination studies that utilize a PD-1 blocking antibody in combination with an agonistic antibody. The agonistic signal has been directed against CD27, ICOS, and 4-1BB. These studies are exploring the notion that along with inhibiting suppression of immune cells, concurrent stimulation may increase efficacy. An additional strategy to activate the immune system is to use vaccination to stimulate antigen-specific T cells. In non-Hodgkin lymphoma, including indolent lymphomas or

Table 1. Selected responses to PD-1 blockade in patients with Hodgkin and non-Hodgkin lymphoma

Agent(s)	Number of patients treated	Histology	Previous autologous stem cell transplant	Overall response	Reference
Nivolumab (phase I study)	23	Hodgkin lymphoma	78%	87%	11
Nivolumab (phase II study)	243	Hodgkin lymphoma	100%	69%	13
Pembrolizumab (phase I study)	31	Hodgkin lymphoma	71%	65%	14
Pembrolizumab (phase II study)	210	Hodgkin lymphoma	61%	69%	15
Nivolumab + ipilimumab	31	Hodgkin lymphoma	39%	74%	25
Nivolumab + brentuximab vedotin	62	Hodgkin lymphoma	0%	82%	29
Nivolumab + AVD chemotherapy	51	Hodgkin lymphoma	0%	84%	31
Nivolumab (phase I study)	54	Various non-Hodgkin lymphomas	18%	Follicular ($n = 10$), 40%; DLBCL ($n = 11$) 36%; CTCL ($n = 13$), 15%	17
Pembrolizumab (phase I study)	18	Primary mediastinal large B-cell lymphoma	33%	41%	20
Pembrolizumab (phase II study)	25	CLL/Richter transformation	0%	CLL, 0%; Richter, 44%	19
Nivolumab (phase II study)	87	DLBCL (ASCT-failed)	100%	10%	18
Nivolumab (phase II study)	34	DLBCL (ASCT-ineligible)	0%	3%	18

Abbreviations: AVD, doxorubicin, vinblastine, dacarbazine; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma.

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virally driven lymphomas, vaccines have shown real promise, particularly in patients with a low burden of disease who mount an adequate immune response.

All told, this is only the beginning of an exciting time to optimize antitumor immune responses in patients with lymphoma. As additional tools become available to target important signaling pathways in immune cells, rational combination approaches will have to be cautiously designed. It is likely that combination approaches will need to both inhibit the malignant clone and optimize the immune response. Effective immune modulation may require an approach that blocks inhibitory signals through receptors such as PD-1, provides a stimulatory signal to specifically activate the immune cell, and adds agents that directly inhibit or kill the malignant clone.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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