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Clinical Development of PD-1 Blockade in Hematologic Malignancies

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Abstract

Clinical development of Immune checkpoint inhibitors targeting the programmed cell death 1 (PD-1) pathway has led to clinical benefits for patients with multiple solid tumor and hematologic malignancies and has revolutionized modern oncology. High response rates to PD-1 blockade in patients with classical Hodgkin lymphoma and certain subtypes of non-Hodgkin lymphoma highlight an intrinsic biologic sensitivity to this strategy of treatment. Despite early success of checkpoint inhibitor and immunomodulatory drug combinations in phase II studies in multiple myeloma, safety concerns in patients treated with the combination of immunomodulatory drugs and checkpoint inhibitors in myeloma have stalled drug development in this space. Novel combination approaches exploring PD-1 inhibitors with epigenetic modifiers in leukemia are underway.

Keywords

immune checkpoint inhibitors; hematologic malignancies; leukemia; lymphoma; myeloma

Introduction

As the key mediators of host immunosurveillance, effector T cells are tasked with the maintenance of host immune homeostasis through elimination of intracellular pathogens and neoplasia while also minimizing autoimmune responses and collateral damage to host tissues. At the level of the tissue microenvironment, T cell activation or inhibition requires co-stimulatory or co-inhibitory signaling following T cell receptor (TCR) recognition of its cognate peptide presented in the context of major histocompatibility complex (MHC) I or II receptor on the cell surface. A host of co-stimulatory and co-inhibitory ligand-receptor interactions known as immune checkpoints then ultimately determine T cell fate within the spectrum of activation or inhibition by modulating a balance between expansion, exertion of cellular cytotoxicity and memory formation versus anergy, exhaustion or senescence¹.

Clinical development of monoclonal antibodies that block immune checkpoints cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death 1 receptor (PD-1), and

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programmed death-ligand 1 (PD-L1) has resulted in FDA approvals for use of these agents in multiple solid and hematologic tumors. Herein, we focus on the current status of clinical development of PD-1 pathway inhibitors for the treatment of hematologic malignancies.

The PD-1 Pathway

Biology of PD-1 and its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC)

Programmed cell death 1 receptor (PD-1, CD279) is a type I transmembrane immunoreceptor expressed by activated T cells, natural killer (NK) cells, and B cells cells^{2,3,4}. To prevent immune-related damage to self after binding of TCR to MHC-peptide, T cell activation is inhibited through binding of PD-1 on T cells to its ligands PD-L1 (B7-H1, CD274) and/or PD-L2 (B7-DC, CD273) that are normally expressed on peripheral tissues. PD-1 ligands PD-L1 and PD-L2 are known to be expressed in the tumor microenvironment by both tumor cells{Dong, 2002 #2406;Zou, 2008 #2630} and non-tumor immune and stromal cells{Curiel, 2003 #3251;Zou, 2008 #2630;Wu, 2009 #3249;Nazareth, 2007 #3254;Flies, 2011 #998;Dong, 2002 #2406}.

Binding of PD-1 to its ligands act to inhibit cytotoxic T cell activity via an intracellular signaling cascade involving several kinases downstream of PD-1⁵. Continued PD-1 signaling is important in development of T cell exhaustion, a state in which T cells lose their capacity for cytotoxicity⁶. Antitumor activity following blockade of the PD-1 axis suggests PD-1 signaling is important for immune escape and tumor persistence, an idea supported by clinical efficacy of PD-1 pathway blockade in multiple tumor types and several hematologic cancers.

PDL1 is encoded on the long arm of chromosome 9p under the control of an AP1 sensitive promoter region downstream of JAK-2-STAT signaling cascade. Expression of PD-L1 is upregulated by many cytokines, most potently by interferon- γ (IFN- γ)⁸. Interferon-mediated upregulation of PD-L1 and PD-L2 is an important feature of several hematologic cancers that reside in a pro-inflammatory tumor microenvironment, including acute myeloid leukemia¹¹ and multiple myeloma^{12,13}. In addition to cytokine-mediated mechanisms of inducible PD-L1 overexpression, oncogenic viruses relevant to lymphomagenesis such as EBV are directly capable of driving PD-L1 expression via downstream effects of latent membrane protein-1 (LMP-1) on nuclear factor kappa B (NF- κ B) signaling and the AP-1 sensitive promoter of *PD-L1*^{14,15}. PD-L1 can also be overexpressed by STAT3 upregulation via upstream activation of ALK¹⁶. Correlative analysis of ongoing trials in hematologic malignancies is needed to explore the contribution of these and other mechanisms to response and resistance to PD-1 pathway inhibition.

Classical Hodgkin lymphoma (CHL)

Early phase clinical trials of PD-1 pathway blockade highlighted that certain lymphomas, especially classical Hodgkin lymphoma (cHL), harbor an intrinsic susceptibility to PD-1 pathway blockade. Hodgkin lymphoma is defined by the presence of the Hodgkin Reed Sternberg (HRS) cell among a robust inflammatory infiltrate and is cured with chemotherapy or combined modality therapy in most cases. However, a need exists for cHL

patients who relapse or are refractory to existing therapies. In several pre-clinical studies in cHL, near universal overexpression of PD-L1 on the HRS cell likely driven by 9p24.1 amplification were noted, suggesting a biologic importance to the PD-1 pathway in cHL¹⁷.

Supporting the importance of PD-1 signaling to the pathogenesis of cHL, a significant efficacy signal was apparent in the phase I clinical trials of nivolumab (Opdivo, Bristol-Myers Squibb), a humanized IgG1 kappa monoclonal antibody, and pembrolizumab (Keytruda, Merck), a humanized IgG4 kappa monoclonal antibody, both of which block the interaction of PD-1 with its ligands PD-L1 and PD-L2. Responses to PD-1 blockade were directly related to the degree of amplification of 9p24.1¹⁸. In the CheckMate039 phase I clinical trial (nivolumab), relapsed/refractory (R/R) cHL patients had an overall response rate (ORR) of 87% with 17% reaching a complete response (CR), and 70% with a partial response (PR)^{19,20}. Among 31 patients with cHL with relapse after brentuximab vedotin (BV) and autologous stem cell transplant (ASCT) or prior ineligibility for treatment with BV, the ORR was 58%, CR rate 19%, and PR rate 12% with median follow-up of 24.9 months²¹. The phase II study of pembrolizumab, KEYNOTE-087, evaluated 210 patients among three cohorts, in whom the overall response rate was 69%, and the overall CR rate was 22.4%²². The ORR was 73.9% in R/R cHL patients with progressive lymphoma after ASCT and BV, 64.2% in patients with chemo-resistant disease ineligible for ASCT, and 70.0% in BV-naïve patients with relapsed disease after ASCT. These important studies led the Food and Drug Administration (FDA) to grant accelerated approval to nivolumab and pembrolizumab for the treatment of Hodgkin lymphoma.

Ongoing studies are evaluating use of PD-1 blockade for cHL in the frontline setting and in a variety of patient populations including those who are transplant ineligible, early stage unfavorable disease, and in patients older than 60. Interim results from a phase I/II study of nivolumab plus BV as first salvage after upfront chemotherapy before ASCT showed a CR rate of 63% among 59 patients, a rate much higher than expected with either agent as a monotherapy²³. In sum, PD-1 pathway blockade is very likely to transform the treatment landscape for cHL patients in the coming years.

Non-Hodgkin lymphoma (NHL)

Substantial heterogeneity exists among non-Hodgkin lymphomas. Within this large group of malignancies there have been some responses to PD-1 pathway blockade. PD-L1 upregulation via genetic aberrations involving 9p24.1 are found commonly in primary mediastinal B cell lymphoma (PMBL)²⁴, primary testicular lymphoma²⁵, plasmablastic lymphoma, HHV-8 associated primary effusion lymphoma, and primary central nervous system lymphomas^{25,26}, and several of these tumors have been sensitive to PD-1 blockade. Promising activity of pembrolizumab for PMBL was observed in a phase Ib study with 41% responding to treatment among 17 patients²⁴. Chronic viral infection with EBV also plays a role in PD-L1 upregulation, and high response rates to PD-1 blockade in extranodal NK/T cell lymphoma²⁷, EBV(+) and EBV(−) lymphoproliferative disorders have been reported.

Diffuse large B cell lymphoma (DLBCL) represents a heterogeneous group of aggressive malignancies derived from mature B lymphocytes. A retrospective series of 1253 samples

from patients with DLBCL showed only 11% were PD-L1 positive and those patients with PD-L1 had a poor prognosis²⁸. In addition, DLBCL patients with a high International Prognostic Index (IPI) score and elevated soluble PD-L1 (sPD-L1) have an inferior prognosis, with a 3 year overall survival of 40.9% in patients with high sPD-L1 compared with 82.1% in those without elevated sPD-L1²⁹. In a signal-seeking phase Ib study, 36% of unselected patients with DLBCL responded to treatment with nivolumab³⁰.

PD-1 can also be upregulated on peripheral T cell lymphomas derived from T follicular helper cells (T_{FH}) including angioimmunoblastic T cell lymphoma (AITL), follicular T cell lymphoma, and nodal peripheral T cell lymphoma with T_{FH} phenotype³¹. A phase II study in mycosis fungoides/Sézary syndrome (MF/SS) demonstrated a response rate of 38% in 24 patients³².

Evaluation for biomarkers predictive of response to PD-1 pathway blockade in lymphoma may aid in optimal patient selection for prospective clinical trials. Markers of immune exhaustion LAG-3 (lymphocyte activation gene 3) and TIM-3 (T-cell immunoglobulin and mucin-domain containing-3) have been found to be co-expressed in T cell infiltrates in NHL, and these may represent viable targets alone or in combination with PD-1 blockade^{33,34}. Biomarkers of poor response to therapy also warrant attention; beta-2 microglobulin (B2M) mutations and loss of MHC-I expression are relevant in melanoma resistant to PD-1 pathway blockade³⁵. Correlation of these biomarkers with outcome after checkpoint blockade in cHL or NHL have not yet been reported, although it is known B2M mutations and loss of MHC-II are frequent findings in cHL.

Multiple Myeloma

Multiple myeloma (MM) is a clonally heterogeneous hematologic malignancy derived from terminally differentiated B cells known as plasma cells which secrete clonal monoclonal immunoglobulin paraproteins and whose effects in the bone marrow tumor microenvironment cause systemic multifactorial cellular and humoral immunodeficiency. The MM bone marrow tumor microenvironment is characterized by profound immunosuppression related to inhibitory cytokines^{36–40}, suppressive cells such as myeloid-derived suppressor cells^{41,42}, and regulatory T cells^{43–45}, and known active PD-1/PD-L1 signaling¹². In contrast to plasma cells in premalignant states, MM cells express PD-L1 driven by IFN-gamma, toll-like receptor, Akt, and Ras signaling^{12,46}, and its expression is functionally associated with reduced susceptibility to effector T cell killing¹². PD-1 is expressed on marrow infiltrating T cells, and PD-1 ligands are expressed and upregulated on malignant plasma cells in MM⁴⁷. Multifactorial immunosuppression within the MM tumor microenvironment inhibits MM-specific tumor infiltrating T cells, which retain the capacity for recognizing and killing MM cells *ex vivo*, suggestive of a potential benefit to reversing local immunosuppression in the tumor microenvironment⁴⁷. A large retrospective study recently found that MM patients with a high mutational and neoantigen burden in MM have inferior PFS and outcomes⁴⁸, a potentially provocative result given that sensitivity to immune checkpoint blockade was observed among patients with high mutation burden solid tumors.

Despite evidence suggesting importance of the PD-1 pathway in MM, there was no clinical activity seen in the 27 patients treated with nivolumab on the CheckMate 039 study³⁰. Pre-clinical data supported a synergistic role for immunomodulatory drugs (IMiDs) with PD-1 pathway blockade in patients with myeloma, as IMiDs polarize T cells toward a Th1 phenotype and promote NK cell cytotoxicity^{42,49}, inhibit regulatory T cells (T_{reg})⁵⁰, and downregulate PD-L1 on tumor cells^{42,49}. Preliminary results of PD-1 pathway blockade combined with IMiDs were encouraging. The phase I study of pembrolizumab with lenalidomide and dexamethasone (KEYNOTE-023, NCT02036502) showed a response to therapy in 20/40 evaluable patients (ORR 50%) with 5 patients reaching VGPR, and 14 patients achieving PR⁵¹. In the lenalidomide-refractory patients, the ORR to pembrolizumab plus lenalidomide and dexamethasone was 38% (11/29)⁵¹. In patients with detectable bone marrow plasma cells by flow cytometry, 100% expressed PD-L1, while PD-L2 expression was variable⁵¹. The phase II study of pembrolizumab plus pomalidomide and dexamethasone showed an ORR of 60%, with 8% of patients achieving a strict complete remission. In patients previously refractory to both proteasome inhibitors and IMiDs the response rate was 68%⁵².

Building on these results, two phase III studies of pembrolizumab in combination with lenalidomide and dexamethasone (KEYNOTE-185, NCT02579863) or pomalidomide and dexamethasone (KEYNOTE-183, NCT02576977) and one phase III study of pomalidomide and dexamethasone vs. nivolumab, pomalidomide, and dexamethasone vs. nivolumab, elotuzumab, pomalidomide and dexamethasone (CheckMate 602, NCT02726581) were initiated. However, on June 12, 2017, following a review of data by the studies' data monitoring committee, the FDA requested a stop to new accrual to these studies due to increased patient deaths on the trial arms receiving experimental therapy with pembrolizumab in combination with immunomodulatory drugs lenalidomide or pomalidomide⁵³. An investigation of the nature of these deaths are underway, and on July 3, 2017, the FDA required that all patients on these trials be discontinued from further treatment⁵⁴. Interim analysis of the KEYNOTE-183 data using a data cutoff date of June 2 showed a higher relative risk of death for patients in these studies receiving pembrolizumab plus pomalidomide and dexamethasone over pomalidomide and dexamethasone (HR 1.61, (5% CI 0.91–2.85), and an objective response rate of 34% compared to 40% in the control arm⁵⁵. In the KEYNOTE-185 study, the hazard ratio of the pembrolizumab-containing investigational arm was 2.06 (95% CI: 0.93–4.55), and an ORR of 64% in the investigational arm compared with ORR 62% in the control arm⁵⁵. Until further analysis can be performed other studies including PD-1 and PD-L1 blocking antibodies in myeloma have been placed on hold by the FDA as a precaution⁵⁴. In addition, durvalumab trials in combination with immunomodulatory agents in patients with chronic lymphocytic leukemia (CLL) or lymphoma were also placed on hold⁵⁶. The pembrolizumab phase III results in MM highlight a critical need to explore immune regulation at the interface between malignant plasma cells and the tumor microenvironment. Further analysis and followup of patients accrued to both the pembrolizumab and other IMiD/anti-PD-1 or anti-PD-L1 trials will hopefully elucidate if there are patient or disease factors that predict for benefit or toxicity of this therapy in MM.

Leukemia

PD-1 pathway blockade is currently under exploration for treatment of myeloid hematologic cancers, often in combination with other epigenetic and immunomodulatory agents. In contrast to lymphoma, there have been limited clinical results reported to date of PD-1 pathway blockade in patients with leukemia. However, pre-clinical data suggest a potential role for the PD-1 pathway in patients with myeloid malignancies. In myelodysplastic syndromes (MDS), PD-L1 is expressed by CD34+ blasts in a significant subset of patient samples (~36%), while stroma and non-blast cellular components express PD-1⁵⁷. In acute myeloid leukemia (AML), PD-L1 expression on AML cells is negatively correlated with outcome⁵⁷⁻⁵⁹. Although PD-L1 expression is low on most cases of de novo AML, interferon-induced PD-L1 expression increases on AML blast cells during treatment, and PD-L1 expression is higher in patients with relapsed AML than in de novo patients^{11,58,60}. Pre-clinical mouse models also point towards the PD-1/PD-L1 pathway in immune evasion by AML.⁶¹⁻⁶⁴ Hypomethylating agents (HMAs) upregulate immune checkpoints⁵⁷, further suggesting an appealing treatment strategy of combination epigenetic therapy and immunotherapy for myeloid malignancies. HMAs also trigger expression of endogenous retroviruses in multiple human tumor types, activating a cellular viral defense program mediated by interferon- β , and strongly potentiating checkpoint blockade in mouse models^{65,66}. A phase II study is underway in MDS evaluating nivolumab or ipilimumab combined with 5-azacitidine⁶⁷. Nivolumab as a single agent had no activity in MDS, but early data showed an overall response rate of 69% for combination azacitidine and nivolumab in patients previously failing azacitidine⁶⁷. Preliminary clinical data for nivolumab in combination with azacitidine in patients with relapsed or refractory AML also suggest promising overall response rates (ORR) of 34% (N=53) in this high risk patient population.⁶⁸ There are several trials underway evaluating nivolumab in combination with other agents in precursor B acute lymphoblastic leukemia (B-ALL) (NCT02879695) and acute myeloid leukemia (AML) (NCT 02532231). Pembrolizumab trials are underway in B-ALL and T acute lymphoblastic leukemia (T-ALL) (NCT02767934), AML (transplant-ineligible) (NCT02771197), and R/R CLL (NCT02332980).

Toxicity and Immune Related Adverse Events

Immune checkpoint blockade has been clearly associated with unique immune mediated toxicities. With single agent therapy, the side effect profile in hematologic malignancies has been similar to that seen in solid tumor patients; and side effects can be readily reversed with established algorithms for immunosuppression. Specific consideration to overlapping toxicities in combination studies of PD-1 pathway blockade and drugs routinely used in hematologic malignancies are beyond the scope of this review. Nevertheless, therapies that cause pneumonitis, such as radiation, brentuximab vedotin, bleomycin for treatment of Hodgkin disease, and IMiDs for treatment of MM highlight some of the potential challenges of discerning causality in the face of toxicity. Another specific scenario is in the setting of stem cell transplantation, a therapy unique to hematologic cancer. Several preclinical studies demonstrated augmentation of graft-versus-tumor (GVT) effects^{69,70}, as well as graft-versus-host-disease (GVHD)⁷¹. After four treatment related deaths were noted among 39 patients receiving PD-1 blockade before allogeneic stem cell transplant, the FDA added a

warning to the package insert for nivolumab⁷², urging vigilance for early evidence of GVH after allogeneic stem cell transplant such as severe acute GVHD, hepatic veno-occlusive disease, steroid-responsive febrile syndromes that may precede GVHD, and other immune-related phenomena⁴⁷. There are limited data to support use of PD-1 antibodies after allogeneic stem cell transplant and off-label use in this manner is increasing in frequency⁷³. Three retrospective series report that the high response rate to treatment with PD-1 blockade after allo-HSCT (ORR 77–95%) was accompanied by a rate of severe treatment emergent GVHD of 30–55%^{73–75}. A prospective trial of PD-1 blockade as a maintenance therapy after allo-HSCT is ongoing (NCT02985554).

Conclusions

Successes in cHL and subtypes of NHL have led to a surge of investigation into the potential benefits of PD-1 pathway blockade in distinct cohorts of patients with lymphoma. Development of PD-1/PD-L1 blockade in myeloma has been halted for the moment by safety issues that demand thoughtful scrutiny to protect patients and inform future clinical trials. Drug development of PD-1 in leukemias is underway with limited results to date, though preliminary data suggest that combination epigenetic therapy and PD-1 blockade may have some efficacy in myeloid malignancies. Safety issues have also been raised in the context of allogeneic SCT. These observations highlight a multitude of disease specific challenges facing investigators seeking to treat cancers of immune cell origins with therapies that potentially modulate the immune response.

Successes in immune checkpoint blockade have also fueled enthusiasm for other novel immunotherapies such as adoptive T cell therapy with chimeric antigen receptor T cells, novel antibody engineering products such as bispecific T cell engager proteins (BiTEs), and tumor vaccines or immunotherapies directed at shared tumor antigens or patient-specific neoantigens. Development of novel biomarkers predictive of response and failure of these therapies in hematologic malignancies is critical to expanding the number of patients who derive durable benefits and to evaluate for rationale to combine with immune checkpoint blockade in search of durable remissions or cures for a greater number of patients.

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