Review Article

Pembrolizumab in systemic and cutaneous T-cell lymphoma

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Abstract: Suppression of antitumor immunity through programmed death-1 (PD-1) interaction between lymphoma cells and the tumor environment plays a key role in lymphoma cell survival. Pharmacologic disruption of the PD-1 axis using antibodies against PD-1 or its ligands has demonstrated significant antitumor activity in solid tumors with similar evidence emerging in hematologic malignancies. Pembrolizumab, an immune checkpoint inhibitor of the PD-1/programmed death-ligand 1 (PD-L1) axis, has significant clinical activity in patients with mycosis fungoides (MF) and Sézary syndrome (SS). The promising findings of pembrolizumab in MF and SS warrant further investigation of PD-1 blockade in the treatment of systemic and cutaneous T-cell lymphomas.

Keywords: Checkpoint blockade; anti-PD-1 therapy; pembrolizumab; T-cell lymphoma

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Introduction

Programmed death-1 (PD-1) is a critical pathway that regulates T-cell over-activation by attenuating the immune response and maintaining self-tolerance. Tumors can exploit this intrinsic immune checkpoint to escape immune surveillance and selectively block antitumor immune responses. High expression of PD-1 ligands (PD-L1 and, to a lesser extent, PD-L2) on tumor cells has been found to correlate with poor prognosis in various cancer types, suggesting that the PD-1 pathway plays a critical role in tumor immune evasion. PD-L1 expression can be found in T cell lymphomas, and translocations of both PD-L1 and PD-L2 have been observed in cutaneous T cell lymphoma (CTCL) (1-3). Moreover, the lesional skin and circulating Sézary cells in CTCL often exhibit PD-1 expressing T-cells representing either malignant or non-neoplastic T cells (3-5). Therefore, PD-1 and its ligands may be viable targets for therapeutic intervention in PTCL and CTCL, allowing for reversal of tumor-induced T-cell suppression, thereby augmenting antitumor immune activity. Pembrolizumab is a highly selective humanized monoclonal antibody of the immunoglobulin G4/kappa isotype designed to block interaction between PD-1 and its ligands.

Unique among cancers, it is important to highlight that the malignant cells in T-cell lymphomas can express PD-1, most notably angioimmunoblastic T cell lymphoma, certain subtypes of peripheral T-cell lymphoma (PTCL) and CTCL (5,6). Therefore, there does exist a theoretical concern that PD-1 blockade could directly activate the cancerous cells and accelerate tumor growth, as proposed in early murine studies (7).

Clinical studies in PTCL and CTCL

Clinical activity

Limited published data is available for pembrolizumab in the treatment of PTCL and CTCL. In a phase 2, single-arm study coordinated by the Cancer Immunotherapy Trials Network (CITN) (*Table 1*), pembrolizumab demonstrated significant clinical activity in pretreated patients with

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Table 1 Summary of phase 2 study of pembrolizumab in mycosis fungoides and Sézary syndrome

Trial	Key points
Objective	To explore the clinical activity of pembrolizumab in patients with mycosis fungoides and Sézary syndrome
Methods	MF/SS patients stages IB-IV treated with at least 1 prior systemic therapy
	Pembrolizumab administered at 2 mg/kg every 3 weeks for up to 2 years
	Primary endpoint: overall response rate as determined by consensus global response criteria; secondary endpoints: safety, tolerability, time to response, duration of response, and progression free survival
Results	24 patients enrolled; median age 67 (range, 44–85) years; 23 patients stage IIB or higher including 15 patients with Sézary syndrome
	Median follow-up time 40 weeks (range, 9–60 weeks)
	Objective response rate (ORR) was 38% with 1 complete response (CR) and 8 partial responses (PR)
	Median time to response was 11 weeks (range, 8–41 weeks)
	89% responses ongoing at a median of 32 weeks of duration
Adverse events	Similar to those immune-mediated toxicities seen in prior studies of pembrolizumab
	Immune-mediated skin flare reaction noted in six patients (two grade 2 and four grade 3), all of whom had Sézary syndrome

Pembrolizumab for treatment of relapsed/refractory mycosis fungoides and Sézary syndrome: clinical efficacy and safety in a CITN multicenter phase 2 study (8). MF, mycosis fungoides; SS, Sézary syndrome.

mycosis fungoides (MF) and Sézary syndrome (SS) (8). Overall response rate (ORR) was 38% in 24 evaluable patients. Median time to response was 11 weeks. Responses were durable, with 89% of responses ongoing at a median of 32 weeks duration. In this small sample size, there was no apparent correlation of $CD8^+$ T cells, PD-1, PD-L1, and PD-L2 expression levels in the skin or blood compartments with clinical responses.

Nivolumab, a PD-1 inhibitor with a similar efficacy and toxicity profile to pembrolizumab, has demonstrated efficacy in T-cell lymphoma, as seen in a phase I, open-label, dose-escalation study in patients with relapsed or refractory hematologic malignancies (1). Of 16 CTCL and 5 PTCL patients evaluable, ORR was 13% and 40%, respectively.

Safety

In the phase 2 study of MF/SS, pembrolizumab was generally well-tolerated but immune-mediated toxicities were observed at rates similar to those seen in the treatment of other malignancies. Of the 24 patients treated with pembrolizumab, immune-related serious adverse events included a case of grade 2 pneumonitis and a grade 3 steroid-refractory duodenitis. Notably patients with SS frequently experienced an immune-mediated skin flare reaction (six patients, two grade 2 and four grade 3) that improved with additional treatment.

In the phase 1b trial with nivolumab, 79 patients with various hematology malignancies were treated with nivolumab monotherapy (1). The majority of the drug-related adverse events were grade 1 or 2, and the incidence of severe or life-threatening events attributable to nivolumab was low across all disease cohorts. Immune-mediated toxicities were limited to anticipated events and were mostly manageable.

Summary and future studies

The promising findings of pembrolizumab in MF/SS support further investigation of PD-1 blockade in the treatment of PTCL and CTCL. Preliminary data suggest synergistic effects of PD-1 inhibitors used in combination with immunomodulatory agents. A phase 2 study of pembrolizumab in combination with gamma interferon, a key antitumor cytokine that strengthens cytotoxic effector responses, is under development (NCT03063632). Similarly, other combined approaches are being studied: pembrolizumab with romidepsin (NCT03278782), pembrolizumab with decitabine and

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pralatrexate (NCT03240211), nivolumab with brentuximab vedotin (NCT02581631), and nivolumab with ipilimumab (NCT01592370). Translational correlative studies are highly encouraged in these clinical trials to identify biomarkers of clinical outcome and to optimize the combination strategies with checkpoint inhibitors. These studies will guide use of PD-1 blockade within the landscape of PTCL and CTCL therapy.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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