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Pembrolizumab: The Nut Cracker

Abstract

Anti-programmed cell death-1 (PD-1)/PD ligand-1 immune checkpoint inhibitors (ICIs) are the newest class of drugs approved for various advanced cancers. Pembrolizumab, an anti-PD1 inhibitor, is approved for treating advanced-stage solid malignancies and refractory lymphomas. Recently, it has been approved as tumor agnostic therapy for microsatellite instability-high advanced-stage disease. In all these studies, pembrolizumab has shown dramatic efficacy with lesser Grade3/4 immune-related adverse events. Contemporarily, immunotherapy paved the way for diagnostic assays and immunotherapy-related response assessment criteria definitions. No published Indian experience with ICIs exists other than isolated case reports. This article aims to review on pembrolizumab mechanism, its indications, and safety. The description of other ICIs is beyond the scope of this review.

Keywords: *Advanced stage solid cancers, immune checkpoint inhibitors, lymphomas, pembrolizumab*

Gangothri Selvarajan

Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Introduction

The ability of cancer cells to evade immunity is the eighth hallmark of cancer.[1] The tumor cells survive by nil antigen expression and higher immune checkpoint expression.[1,2] Pembrolizumab, a monoclonal antibody, plays a vital role in boosting the cancer immunity cycle.

Discovery

In 1891, William Coley reported long-term regression of inoperable cancers when Coley's toxin (heat-inactivated *Streptococcus*) was administered.[1] In 1959, the concept that the immune system has the capability of killing malignant cells evolved.[1] In 1992, Tasuku Honjo discovered that mutation in programmed cell death 1 (PD-1) augments T-cell activity and inhibits the hematogenous dissemination of cancer cells. This anti-PD1 character was named as immune checkpoint inhibition.[1,2]

Phase I trials of the first anti-PD-1 antibody, nivolumab in advanced solid cancers, showed durable response rates.[3] Simultaneously, the promising results of pembrolizumab (anti-PD-1) in KEYNOTE-001 study among advanced melanoma cases with previous ipilimumab exposure cemented the role of immune checkpoint inhibitors (ICIs) in oncology.

Mechanism of Action

PD-1 protein (or CD279) is primarily expressed on the surface of activated T-cells, myeloid cells, and B-cells. It has two ligands, programmed cell death ligand 1 (PD-L1) and PD-L2. PD-L1 is broadly expressed on various organs, while PD-L2 is restricted to dendritic cells, macrophages, B-cells, and T-helper 2 cells.[4] Cancer cells express both PD-L1 and PD-L2. Binding of PD-1 to PD-L1/L2 induces phosphorylation of PD-1 cytoplasmic immunoreceptor tyrosine-based inhibition motif recruiting SHP2 phosphatase. SHP2 then dephosphorylates the T-cell receptor, leading to a reduction of target cell killing.[4] Pembrolizumab (MK-3475, lambrolizumab) is a humanized IgG4 kappa monoclonal antibody against PD-1. By blocking PD-1, the signals mentioned above are suppressed, and apoptosis is induced in tumor cells.[4]

Pembrolizumab distribution and metabolism in the body are not well characterized, and neither is its drug interactions. Its terminal half-life is 26 days.[5] There are no dose modifications with renal or hepatic dysfunction. It has no carcinogenic or infertility effects. The drug crosses the

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Address for correspondence:
Dr. Gangothri Selvarajan, Department of Medical Oncology, Cancer Institute (WIA), 28, Sardar Patel Road, Adyar, Chennai - 600 036, Tamil Nadu, India.
E-mail: gangothri11@gmail.com

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placenta, and animal studies have demonstrated fetal harm. Hence, it is contraindicated in pregnancy, and contraception is advised. Similarly, breastfeeding is to be avoided.[6,7] Contraindicated in autoimmune disease since it can induce a disease flare, and the autoimmune therapy might reduce its efficacy.[8]

Uses

Approval by the US Food and Drug Administration (based on landmark trials)

The indications for pembrolizumab are incorporated in Table 1.[9-14]

KEYNOTE 522 suggests that adding pembrolizumab to neoadjuvant chemotherapy is beneficial in stage II/III triple-negative breast cancer (pCR 64.8% vs. 51%).[15-17] In the PURE-01 study of muscle-invasive bladder cancer, pT0 rate was 37% and the pT1 rate was 55%, irrespective of variant histology.[18]

Drug Controller General of India and Central Drugs Standard Control Organization approval

Drug Controller General of India and Central Drugs Standard Control Organization have approved pembrolizumab in metastatic melanoma and the first/second-line treatment of nonsmall cell lung carcinoma as a single agent.

Table 1: Food and Drug Administration-approved indications for pembrolizumab

Type of malignancy	Clinical trial evidence
Unresectable or metastatic melanoma	KEYNOTE-001 and 006 (↑PFS/OS)
Melanoma - Adjuvant therapy	KEYNOTE-054 (↑RFS in stage III)
Metastatic NSCLC with no EGFR/ALK rearrangement - First-line therapy	KEYNOTE 024 (TPS≥50%) KEYNOTE 042 (↑OS without chemo) KEYNOTE189 (nonsquamous) KEYNOTE 407 (squamous) (↑OS with chemo, TPS ≥1%)
Metastatic NSCLC - Single agent/second line	KEYNOTE 010 (TPS ≥1%), ↑DOR, OS and ORR
Locally advanced or metastatic UC progressed on platinum-based chemotherapy	KEYNOTE 045 (↑OS)
UC progressed <12 months of neoadjuvant/adjuvant chemotherapy. Platinum ineligible with locally advanced or metastatic UC	*KEYNOTE 052 (↑ORR, DOR)
High-risk NMIBC BCG unresponsive CIS (cystectomy ineligible/unwilling)	*KEYNOTE 057 (single-arm trial) ↑ORR/CR and DOR
First line in advanced renal cell carcinoma with axitinib	KEYNOTE 426 (in first-line versus sunitinib) ↑PFS/OS
First line in recurrent/metastatic head and neck squamous cell carcinoma	KEYNOTE 058 (with chemo ↑OS)
Recurrent/metastatic head and neck squamous cell carcinoma as second line	KEYNOTE 048 (↑OS)
Recurrent locally advanced or unresectable IIIB or metastatic Merkel cell carcinoma without any prior therapy	*KEYNOTE017 (Phase II) (↑PFS, ORR, and DOR
Hepatocellular carcinoma progressed on or after treatment with sorafenib or intolerant to it	*KEYNOTE 224 (↑ORR and DOR) single-arm open-label study It is indicated in HBV and HCV seropositive patients with Child-Pugh Class A liver impairment
Second line in recurrent or metastatic cervical carcinoma patients	*KEYNOTE 158 (↑ORR, DOR)
Recurrent or metastatic gastric and gastroesophageal adenocarcinomas progressed on or after ≥2 lines of therapy	*KEYNOTE 059 (cohort 1 as a single agent) (↑ORR, DOR)
Mismatch repair deficient (dMMR) solid tumors when unresectable or metastatic, progressed after prior treatment, make pembrolizumab a biomarker defined tumor site -agnostic approval from FDA	*KEYNOTE 16 and 164 (colorectal cancers) (↑ORR and DOR) *KEYNOTE 158 (noncolorectal) basket study
Hodgkin's lymphoma - Refractory or relapsed after ≥3 lines of therapy (including auto-SCT)	*KEYNOTE O87 Nonrandomized open-label trial (↑ORR and DOR)
Primary mediastinal large B cell lymphoma - Refractory or relapsed after ≥2 lines of therapy	*KEYNOTE 170 (↑ORR and DOR)
Progression on ≥2 lines of therapy in small cell lung carcinoma	*KEYNOTE 158 cohort G (basket study) KEYNOTE 028 cohort C1 (↑ORR and DOR)

↑Improved, *Accelerated approval by FDA based on tumor response rate and durability of response. OS – Overall survival; PFS – Progression-free survival; ORR – Overall response rate; DOR – Duration of response; NMIBC – Nonmuscle invasive bladder cancer; CIS – Carcinoma *in situ*; TPS – Tumor proportion score; SCT -stem cell transplant; HBV – Hepatitis B virus; HCV – Hepatitis C virus; FDA – Food and Drug Administration; BCG – Bacillus Calmette-Guérin; UC – Urothelial carcinoma; EGFR – Estimated glomerular filtration rate; ALK – Anaplastic lymphoma kinase

Table 2: Immune checkpoint inhibitor-related adverse events with immune checkpoint inhibitors depending on the site

Site	Incidence (%)
Dermatological	40-60
Gastrointestinal	5-10
Endocrine	6
	<1% severe
Pulmonary	4-5
Neurologic	<5
Fatigue	16-24
Hematologic	<1
Renal	2
Ocular	<1
Cardiac	<0.5

IRAE – Immune checkpoint inhibitor-related adverse events; ICI – Immune checkpoint inhibitor

Dose and Administration Instructions

The fixed (200 mg every 3 weeks) and weight-based (2 or 10 mg/kg) dosing demonstrates similar pharmacokinetic and toxicity profiles.[19]

Pembrolizumab, in solution or lyophilized powder, should be reconstituted with sterile water along the walls of the vial and by gentle swirl. Do not shake the vial. Discard the solution if discoloration and particulate matter. If so, discard it. Withdraw the required volume and transfer into an intravenous bag containing 0.9% sodium chloride injection USP or 5% dextrose injection USP. Mix by gentle inversion. Infuse the solution over 30 min. Store the reconstituted solution at room temperature for <6 h and under refrigeration (2°C–8°C) for < 24 h.

Toxicities

ICI has demonstrated a wide range of immune-related adverse effects (irAEs) as listed in Table 2. Toxicities are a reflection of the drug regimen combined with it and varieties of malignancies treated.[20]

Fatal toxicities such as pneumonitis, infections, myocarditis, colitis, hemorrhagic/thrombotic, and neurologic toxicities have been reported.[21] Others such as Stevens–Johnson syndrome and toxic epidermal necrolysis and infusion-related reactions can be fatal. Hyper-acute graft-versus-host disease and hepatic veno-occlusive disease can occur post allogeneic stem cell transplant.[22,23]

For Grade 1 toxicity, use oral prednisone 0.51 mg/kg/day.[22,23] For any Grade 2, withhold ICI and give oral or intravenous prednisone 12 mg/kg/day based on symptoms. Discontinue ICI if > Grade 1 hypophysitis, pneumonitis, or sarcoidosis and if any Grade 3 or more toxicities. Depending on the grade of toxicity, wean off-steroids at 2–4 weeks if moderate or 4–8 weeks if severe and resume therapy when the adverse reaction remains at Grade 1 or less. Permanently discontinue ICI for grade 4 or any life-threatening adverse event. Infliximab, mycophenolate mofetil, tocilizumab as well as plasmapheresis or immunoglobulin may be considered in steroid-refractory cases. Consider rituximab or cyclophosphamide in case of hematologic toxicity.[22,23]

Take Home

The broad activity of pembrolizumab against various malignancies implies that immune escape is indeed a crucial step in cancer survival. The optimal duration of treatment is still unknown – whether 2 years or until progression. The Food and Drug Administration has accepted supplemental Biologics License Applications for 400 mg every 6 weeks dosing schedule for pembrolizumab across several indications. This dose schedule will be more convenient for patients.[24]

The cost of treatment with pembrolizumab varies from 2 to 10 lakhs (INR) per dose, depending on the schedule and patient body weight. irAEs will add to the cost of treatment. These events complicate the decision on the sequence of management.

Conclusion

Many upcoming trials will highlight the role of ICIs in the era of targeted therapies. Translational research is needed to develop predictive biomarkers, elucidate the mechanisms of resistance, and formulate rational combined modality treatment. Although immuno-oncology is promising, there are still unanswered questions from curative point of view as well as in pediatric cancers.

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Conflicts of interest

There are no conflicts of interest.

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