Clinical Pharmacology & Toxicology Pearl of the Week

Immune Checkpoint Inhibitors: Pharmacology and Indications

Background

- ✓ Immune checkpoints are "secret handshakes" used by our own cells to tell T-cells not to attack ourselves
- ✓ Checkpoint inhibitors inhibit these handshakes, **allowing the T-cells to attack self-cells**
  - This results in a general 'turning up' of the immune system
- ✓ Immune checkpoint inhibitors are classified as CTLA-4, PD-1, and PD-L1 and have been approved for the treatment of numerous cancers
  - **They are monoclonal antibodies**
- ✓ Patients are often on more than one immune checkpoint inhibitor
- ✓ Due to their long duration of action, ask all oncology patients if they have ever received an immune checkpoint inhibitor

Mechanism of Action

- ✓ There are 3 types of immune checkpoint inhibitors: CTLA-4, PD-1, and PD-L1 inhibitors
  - They block either the CD8 T-cell receptors (CTLA-4, PD-1) that detect self-cells or block the PDL-1 ligand on self-cells that help CD-8 T-cells to avoid destroying self-cells.

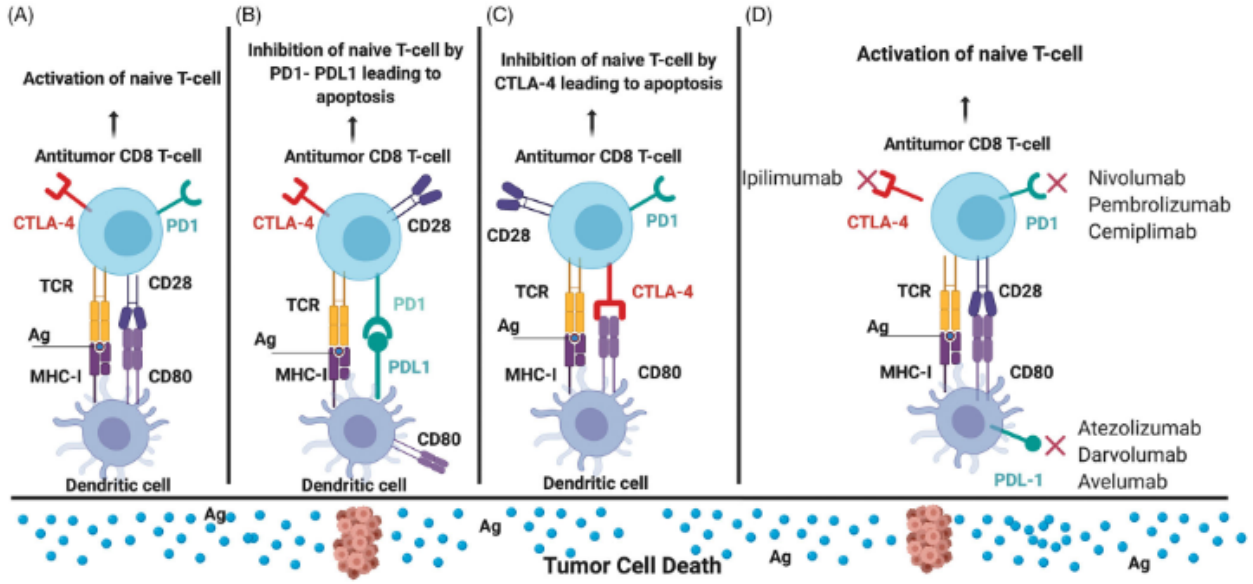

Figure 2. (A) Normal T lymphocyte activation, (B) Inhibition of T lymphocyte activation by the inhibitory pathway of PD1-PDL-1 interaction, (C) Inhibition of T lymphocyte activation by the inhibitory CTLA-4 pathway, (D) Site of action of immune checkpoint inhibitors, leading to T cell activation. (image created using Biorender.com). Ag: antigen; CD28: cluster of differentiation 28; CD8: cluster of differentiation 8; CD80: cluster of differentiation 80; CTLA-4: cytotoxic t-lymphocyte antigen 4; MHC-1: major histocompatibility complex 1; PD1: programmed cell death 1; PDL-1: programmed cell death ligand 1;TCR: t cell receptor.

Source: Lipe et al, Clin Toxicol 2021, 59(5):376-385

  - This allows CD-8 T-cells to activate against cancer cells that otherwise would identify as "self"

Pharmacokinetics

- Administration: IV/IM/SC
- Large molecule (>150kDa)
- Distribution: 3-8L/kg
- Metabolized via Fc receptor recycling
- Half-life: 11-30 days

Approved Uses

- ✓ Immune checkpoint inhibitors are currently used for many cancers, including melanoma, lung cancer, and uroepithelial cancers
- ✓ Uses are rapidly expanding

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Source: Postow et al, NJEM 2018, 378(2):158-168

See Part 2: Immune Checkpoint Inhibitors: Toxicity in subsequent Pearls of the Week

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultation service is also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK)

References:

1. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018 Jan 11;378(2):158-168. doi: 10.1056/NEJMra1703481. PMID: 29320654.
2. Lipe DN, Shafer S. CAR-T and checkpoint inhibitors: toxicities and antidotes in the emergency department. Clin Toxicol (Phila). 2021 May;59(5):376-385. doi: 10.1080/15563650.2021.1880008. Epub 2021 Feb 12. PMID: 33576256.
3. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, Berdelou A, Varga A, Bahleda R, Hollebecque A, Massard C, Fuerea A, Ribrag V, Gazzah A, Armand JP, Amellal N, Angevin E, Noel N, Boutros C, Mateus C, Robert C, Soria JC, Marabelle A, Lambotte O. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016 Feb;54:139-148. doi: 10.1016/j.ejca.2015.11.016. Epub 2016 Jan 5. PMID: 26765102.
4. https://www.esmo.org/content/download/124130/2352601/1/ESMO-Patient-Guide-on-Immunotherapy-Side-Effects.pdf
5. https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf