PHARMACOLOGY

Immune checkpoint inhibitors (ICI)

- PD-1
  - Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), Cemiplimab (Libtayo®)
- PDL-1
  - Atezolizumab (Tecentriq®), Avelumab (Bavencio®), Durvalumab (Imfinzi®)
- CTLA-4
  - Ipilimumab (Yervoy®)

T-cells originate in the bone marrow and develop to full maturity in the thymus. In the maturation process, T-cells can begin to express unique protein complexes on their surface, known as T-cell receptors (TCRs). These TCRs are responsible for recognizing and binding antigens presented by other cells via the major histocompatibility complexes (MHC).[1]

Because T-cells play an important role in recognition and destruction of antigens, it is important that they are able to recognize foreign and harmful cells from self.[2] T-cell activation is regulated through a variety of immune checkpoint pathways and these checkpoints are vitally important in preventing T-cells from becoming autoreactive, which can result in damage and destruction of one's own tissues.[2] In cancer, tumor cells that would normally be recognized by T-cells have developed ways of avoiding detection by utilizing these checkpoint pathways to further downregulate and prevent T-cell activation.[2]

PD-1 and CTLA-4 are both checkpoint pathways and the blockage of these pathways (or the ligand in the case of PDL-1) leads to increased T-cell activity.[3] This results in greater recognition and destruction of tumor cells. However, as previously mentioned, the blockage of these pathways increases the risk of T-cells becoming autoreactive. When this occurs, T-cells may attack healthy cells resulting in adverse inflammatory effects in any organ system.

PD-1 is primarily found in peripheral tissue while CTLA-4 is primarily found in lymphoid tissue and is thus present earlier in the immune response cascade. The exact mechanism for immune-related adverse events (IRAEs) is unclear but the increased production of autoantibodies, increased circulating inflammatory cytokines, and an increase in complement-mediated inflammation are all proposed pathways. Patients treated with CTLA-4 inhibitors typically have more severe IRAEs.[4] Colitis and hypophysitis occur more commonly with CTLA-4 inhibitors, whereas pneumonitis and thyroiditis are more frequent with PD-1 and PDL-1 inhibition.[4] There are conflicting data as to whether or not the development of IRAEs is associated with greater treatment efficacy and it is also unclear whether or not immunosuppressants (e.g. glucocorticoids) utilized to treat IRAEs reduce the clinical efficacy of the agents.[4]

Time to IRAE is agent and organ of toxicity dependent, but typically develop within a few weeks to months. Dermatologic events typically develop early (around 3 weeks) whereas gastrointestinal, pulmonary, and endocrine adverse events have an average range of 7 to 11 weeks.[4]

These agents are approved to treat a variety of cancers including melanoma, non-small-cell lung cancer, Hodgkin's lymphoma, gastric cancer, urothelial carcinoma, and squamous-cell carcinoma of the head and neck.[4]

Bi-specific T-cell engagers (BITE)

- Blinatumomab (Blincyto®)

Bi-specific T-cell engagers consist of 2 variable protein domains connected with a peptide linker.[5] One end of the molecule binds to a specific receptor found on T-cells and the other variable domain binds to proteins found on the tumor cell. The simultaneous binding allows for T-cell recognition and destruction of tumor cells.

In the case of blinatumomab, which is FDA approved to treat acute lymphoblastic leukemia, one portion will bind to CD3 positive cytotoxic T-cells while the other will bind to CD19, which is a surface antigen expressed in over 90% of B-cell precursor ALL blasts.[5]

Blinatumomab is administered over 28 days and patients may be sent home with medication infusing over 24 hours, 48 hours, or 7 days.[6] Infusion and toxicities are commonly seen early in therapy and glucocorticoids are commonly given as prophylaxis for the inflammatory sequelae that may result from administration.[6]

The destruction of B-cells can result in cytokine release syndrome (CRS) and neurological toxicities such as immune effector cell-associated neurotoxicity syndrome (ICANS). Target cell lysis releases inflammatory cytokines that can activate macrophage and endothelial cells to further release cytokines thus generating an inflammatory process that overwhelms homeostatic mechanisms.[7]

Cytokine release syndrome presents with a wide range of symptoms including fever, fatigue, and myalgias – however, it can progress to an uncontrolled systemic inflammatory response syndrome requiring vasopressors, intubation, and resulting in multi-organ system failure.[7] The pathophysiology of CRS is incompletely understood, but is thought to result from the release of cytokines – namely IL-6, IL-10, and interferon-Y. These cytokines then further activate the immune system via macrophages and endothelial cells.[7]

ICANS is also commonly seen in patients who receive immune modulating therapies. Its presentation can vary from mild symptoms including headaches and fatigue to severe and life-threatening conditions including seizures, elevated intracranial pressure, and coma.[8] Similarly to CRS, the pathophysiology is poorly understood, but considering ICANS may arise concurrently or separately from CRS suggests a slightly different pathway. It is believed the blood brain barrier becomes disrupted via inflammatory pathways allowing cytokine passage into the central nervous system and generating inflammation.[8]

T-cell infusions

- 5 FDA approved CAR T-cell therapy (October 2021) [9]
    - Kymriah™ (tisagenlecleucel)
    - Yescarta™ (axicabtagene ciloleucel)
    - Tecartus™ (brexucabtagene autoleucel)
    - Breyanzi® (lisocabtagene maraleucel)
    - Abecma® (idecabtagene vicleucel)

Chimeric antigen receptor (CAR) T-cell therapy utilizes a patient's own T-cells and engineers them to better recognize antigens expressed on tumor cells.[9] T-cells are harvested from the patient, sent to a laboratory that genetically modifies the T-cells to express antigen receptors specific to tumor cells, and

these new T-cells are then multiplied. Lymphodepleting chemotherapy is given to remove the patient's own ineffective T-cells, and the modified antigen receptor T-cells are then infused back into the patient.

Similar to BITE molecules, the most common and concerning side effects of CAR T-cell therapy are CRS and ICANS. CRS typically occurs within 3 – 5 days of infusion. ICANS can occur concurrently, however it may also occur without CRS and may occur even after CRS has subsided. While uncommon, ICANS can even occur up to 4 weeks after treatment.[10]

Patients who receive CAR T-cell therapy are required to remain close to their cancer hospital for several weeks following infusion and often receive wallet cards that can be helpful for providers who may be treating potential toxicities.

References:

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