Toxicities of Targeted Agents and Immunotherapies for Cancer

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Key Article

- Gutierrez C, McEvoy C, Munshi L, et al. Critical Care Management of Toxicities Associated With Targeted Agents and Immunotherapies for Cancer. *Crit Care Med*. 2020;48(1):10-21.

Introduction

- We are facing a growing tidal wave of cancer patients in our EDs, any many of them are critically ill with complications directly related to their cancers, or, from toxicities of the therapies towards their cancers
- Cancer treatment options are evolving at a rapid pace, and with this, the toxicities that we see are also evolving rapidly
- Standard anti-cancer drugs present with toxicities related to immunosuppression and infection, however, the new immuno-oncology drug toxicities induce overwhelming inflammation and autoimmunity

Chemotherapy vs Targeted Therapy vs Immunotherapy

- Chemotherapy
    - We are all familiar with cytotoxic chemotherapy and the complications that can occur- tumor lysis syndrome, neutropenic infections/sepsis, etc.
- Targeted therapy
    - Class of agents that are developed against specific molecular targets identified in cancer cell growth and survival
    - Examples: tyrosine kinase inhibitors (TKIs), or monoclonal antibodies (mAbs) such as imatinib, dasatinib, etc.
- Immunotherapy
    - These drugs stimulate the immune system and engage it against the cancer
    - Examples of immunotherapies: immune checkpoint inhibitors (ICI) such as ipilimumab, pembrolizumab, durvalumab, immune effector cell (IEC) therapy such as chimeric antigen receptor (CAR) and T-cell receptor (TCR) therapy, and cancer vaccines

Infusion Reactions

- Immediate- mAbs infusions can be complicated by true anaphylaxis and anaphylactoid reactions. Treat with supportive care as you would any hypersensitivity reaction.
- Delayed- rare cases have been reported of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis with rituximab and cetuximab

Cytokine Release Syndrome (CRS) *aka "Cytokine Storm"*

- Marked inflammatory response after infusion of IECs (CAR or TCR), and can also occur after infusion of mABs
- Occurs within the first 7-14 days after T cell infusion, and is the most common serious toxicity experienced with CAR therapy
- **Hallmark signs: fever, hypotension, hypoxemia**
    - Up to 1 in 5 require vasopressor support
    - May lead to multisystem organ failure
        - Dysrhythmias, LV dysfunction
        - ARDS
        - Renal failure
        - Hepatic failure
        - DIC
- **These symptoms and signs are not easily differentiated from infection/sepsis and other complications, so must be simultaneously investigated**
- Generally, treatment is supportive. Anti-Interleukin (IL)-6 therapy (tocilizumab or siltuximab) is recommended for Grade 2 or higher CRS, with corticosteroids recommended in toxicities of Grade 3-4.
    - Monitoring and grading of CRS has evolved over time as we learn more about the syndrome. Guidelines and treatment protocols have also evolved, but be sure to adhere to institutional guidelines when available.

Pulmonary toxicities

- Pneumonitis
    - Associated with immune checkpoint inhibitors therapy, also TKIs and drugs targeting angiogenesis
    - No pathognomonic radiographic pattern has been described
    - **Pulmonary infection must still be ruled out- early bronch and BAL recommended**
    - Treatment: corticosteroids. For severe grade adverse events or no improvement after 48 hours, consider infliximab, mycophenolate mofetil, cyclophosphamide, or IVIG.
- Pulmonary thromboembolic complications
    - anti-VEGF antibodies and TKIs
- Pulmonary hypertension
    - TKIs

Neurotoxicity

- **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)**
    - 70-80% of patients receiving CARs
    - 30-40% of these cases severe
    - Mild: tremors, headache, mild aphasia, confusion, dysgraphia
    - Severe: global aphasia, seizures/status, coma, paresis, cerebral edema
    - ICANS assessment tool- standardized scoring system
    - Treatment: Must be discussed with primary oncologist
- ICI-related neurotoxicity: Seizures, PRES, aseptic meningitis, encephalitis, myositis, Guillain-Barre Syndrome, Myasthenia Gravis, transverse myelitis

Cardiac Toxicity

- CRS cardiotoxicity as above
- mABs
    - Coronary artery vasospasm
    - Stent thrombosis
    - Kounis syndrome- allergic thrombosis causing acute coronary syndrome (mAbs activate mast cells)
- ICI
    - Myocarditis- incidence is low, but may be under-reported. Symptoms start appx 30 days after therapy. High mortality- 50% in one retrospective observational study (Salem et al, Lancet Oncology 2018)
    - Other cardiac toxicities: Cardiomyopathy, pericarditis, dysrhythmias

Nephrotoxicity

- ICI associated with AKI, nephritis, and nephrotic syndrome
- Anti-VEGF, TKIs associated with nephritis and thrombotic microangiopathy

Other Considerations

- Endocrinopathies are known complications of ICIs- including hyper and hypothyroidism, hyperglycemia/DKA, hypophysitis, and adrenalitis
- Colitis is a very common adverse reaction experienced in patients on ICI, but does not often cause critical illness
- Underlying immune disorders can be uncovered/exacerbated by ICI therapy
- Secondary Hemophagocytic lymphohistiocytosis (HLH) has been described in CAR-T, ICI, and blinatumomab patients. Presentation similar to CRS and sepsis.
- Opportunistic infections have been reported in patients on targeted and immunotherapy, and the use of corticosteroids for treatment of adverse events in these patients leaves them at higher risk for infection.

Take Home Points

- The toxicities of targeted therapies and immunotherapy are wide-ranging and can cause critical illness

- Symptoms and signs can often mimic other life-threatening etiologies, so they must be considered in parallel
- Treatments strategies are based on grade of toxicity. Immunosuppression to treat the toxicity must be weighed against the loss of anti-tumor effects of the treatment
- A multidisciplinary approach involving the emergency physician, intensivist, oncologist, and other subspecialist is best