Unfamiliar Immune-Oncology terms

CRS- Cytokine release syndrome is an exaggerated toxic immune system response that occurs after administration of chimeric antigen receptor (CAR) T cells. The patient's own T cells are collected and re-engineered in a lab by placing CAR proteins onto T cell surfaces then re-infused into the patient. These CAR proteins are designed to bind the T cells to tumors and attack. The treatments induce massive release of cytokines IL-6, IL-10, and interferon-Y from T cells that further activate macrophages and endothelial cells, causing a cascade of inflammation that kill tumors but also causes systemic toxicity. Clinically, the syndrome resembles sepsis, in that it presents with fever, fatigue, and myalgias that can progress to an uncontrolled systemic inflammatory response syndrome resulting in multi-organ system failure (CNS toxicity, renal, liver, respiratory failure, decreased cardiac output, arrythmias, DIC with low fibrinogen, cytopenias, vomiting/diarrhea, hypotension, lactic acidosis). The patient's condition may require vasopressors, and/or intubation. Characteristically there is very marked elevation of inflammatory markers CRP (C-reactive protein) and ferritin, as well as splenomegaly beyond what is typically seen with sepsis. In the emergency setting, supportive treatments (fluids, oxygen, vasopressors, etc.) plus broad spectrum antibiotics for sepsis is appropriate but concomitant urgent treatment for CRS with IL-6 inhibitor tocilizumab and dexamethasone should also be considered after consult with oncologist. [1,2,3]

HLH- Hemophagocytic lymphohistiocytosis is a very rare adverse effect of checkpoint immunotherapy. Primary HLH was first described as a rare primary genetic defect in pediatric patients leading to hyperactive cytotoxic macrophages and lymphocytes. Marrow depression from cytokines plus histiocyte phagocytosis of bone marrow cells (RBC, WBC, platelets) on bone marrow biopsies contribute to pancytopenia. Natural killer (NK) cells that usually kill pathologic target cells are defective and therefore can't terminate the inflammatory cascade. Acquired forms of HLH have been recognized, where defective NK cells triggered by malignancies, infections or autoimmune disorders also cause cytokine release. With checkpoint immunotherapy HLH, the removal of normal immune system inhibition by checkpoint inhibitor drugs causes overstimulation of cytotoxic T lymphocytes by defective NK cells, with similar systemic and bone marrow effects. HLH resembles CRS (CYTOKINE RELEASE SYNDROME) in that both can have fever, tachycardia, splenomegaly and multi-organ system failure (hypotension, neuro, cardiopulmonary, renal, liver failure, cytopenias, DIC with low fibrinogen), very elevated ferritin and lactate levels. HLH differs in that there is also hypertriglyceridemia, hemophagocytosis, and lowered NK cell function. Treatment of HLH includes high-dose glucocorticoids, etoposide, methotrexate and cyclosporine. However, the efficacy of these on HLH due to checkpoint immunotherapy is not well known due to the rarity of the condition. Expert consultation is advised since HLH has high mortality. [4,5]

ICANS- Immune effector cell-associated neurotoxicity syndrome is a complication of CAR T cell treatment. It is believed the blood brain barrier becomes disrupted via inflammatory pathways allowing CAR T cell and cytokine passage into the central nervous system and generating inflammation. Presentation can vary from mild symptoms including headaches and fatigue to severe and life-threatening conditions including seizures, elevated intracranial pressure, and coma. Expressive aphasia may predict severe neurotoxicity more accurately than other mild symptoms. [1]

ICE (Immune effector cell–associated encephalopathy) tool for CAR-T cell neurotoxicity is part of the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for ICANS. The 10 point scale gives 1 point for correct responses to year, month, city, hospital, ability to name 3 objects,

ability to follow simple command, ability to write a standard sentence (e.g., "Our national bird is the bald eagle"), and ability to count backwards from 100 by 10. ICANS grading corresponds to the score, with a low score of 0 associated with severe grade 4 ICANS, and a score of 7-9 corresponds to grade 1 ICANS. The ICE score is also considered with measure of level of consciousness, seizure, focal weakness, or evidence of increased ICP. In all cases the worst score determines the grade. Grades 1/2 are treated with fluids, seizure prophylaxis, avoiding CNS depressants, and a dose of dexamethasone 10 mg. Grades 3/4 are treated similarly but in ICU setting and a higher dose of dexamethasone 20 mg if seizure present. [1]

PRCA – pure red cell aplasia is a rare normocytic anemia, with low reticulocyte count, and absent hemoglobin containing cells in bone marrow. It can be seen with immune checkpoint inhibitors and is felt to have an autoimmune mechanism with antibodies against RBC precursors or erythropoietin. Treatment includes corticosteroids, IVIG and cyclosporine, and 10 year survival is 80%. [4]

RPLS-Reversible Posterior Leukoencephalopathy Syndrome, formerly known as PRES (posterior reversible encephalopathy syndrome) is marked by headache, visual disturbances, altered mental status and seizures. It is often seen with marked elevation of systemic blood pressure, and diagnosis is supported by edema of white matter in both posterior parietal-occipital lobes on MRI. It can be caused by many conditions including pre-eclampsia, septicemia, renal failure, immunosuppressants, chemotherapy and rarely checkpoint inhibitors. Postulated pathological mechanisms include HTN associated hyperperfusion and edema of brain, toxin effect on blood brain barrier by medications, renal failure, sepsis or pre-eclampsia. There is a high association between PRES/RPLS and auto immune disease, thus making immune checkpoint inhibitors more vulnerable. Treatment revolves around controlling BP and removing offending agent or condition. [6,7]

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