BONE MARROW TRANSPLANT AND CELLULAR THERAPY GUIDELINE

Management of Neurotoxicity from CAR-T Therapy

BACKGROUND

Neurotoxicity from CAR-T therapy can occur as part of cytokine release syndrome (CRS) or as an independent process. The underlying pathophysiology for neurologic toxicity from CAR-T therapy is not fully understood. CAR-T cells in the CNS may play a role. However, the heightened systemic inflammatory and cytokine state resulting from CAR-T therapy may also be a factor, as other therapies associated with increased cytokine levels have also been associated with neurologic toxicities, such as high-dose interleukin-2 (IL-2) and blinatumomab.

The symptoms and manifestations of neurotoxicity are broad and range from confusion/altered mental status to seizures. Routine monitoring is critical in patients receiving CAR-T therapy to identify neurologic symptoms early and neurology should be consulted for any patients that exhibit early signs/symptoms of neurotoxicity. Early interventions should be employed to prevent worsening, especially if therapies are already indicated such as corticosteroids.

Neurotoxicity grading should follow CTCAE v4.03.

****Note that tocilizumab has no clear role in managing CAR-T-induced neurotoxicity, largely because tocilizumab is not thought to penetrate the central nervous system (CNS). If neurotoxicity occurs with concomitant CRS then tocilizumab should be employed per CRS management algorithm to treat CRS, but for neurotoxicity in the absence of CRS, tocilizumab should generally not be used.****

Neurotoxicity Treatment Algorithm

Signs/Symptoms	Management
Grade 1-2 neurotoxicity, excluding seizures	
- Non-life threatening symptoms which may include: moderate headaches not responding to oral medications, confusion, dizziness, hallucinations, tremor, or psychiatric changes. - Grade 1: Symptoms are mild and do not substantially impair function. - Grade 2: Symptoms are moderate and may impair function such as conducting instrumental activities of daily living (IADL's) like self-administering medications or using a telephone, but NOT activities of daily living (ADL's) such as dressing, walking or bathing. - **Any generalized seizures should be managed as grade 3 or greater events (see below).**	- Notify covering providers, including oncology oncology (CAR-T) attending physician. - Ensure other etiologies have been excluded as much as possible, such as infection or toxicity from other medications. - If not already admitted, admit to inpatient for grade 2 or rapidly worsening grade 1. - Daily neurological exam including mini-mental status exam. - Consider urgent MRI brain with and without contrast. - Consider lumbar puncture to evaluate for infection. If sufficient material is available these samples may also be used for CAR T cell and cytokine analysis.
Grade 3 neurotoxicity or any non-sustained / non-recurrent generalized seizures	
- Symptoms may be severe and impair ADL's (listed above). Symptoms may include confusion/altered mental status, disorientation, aphasia, tremor, stupor, loss of consciousness, hallucinations, unstable	- Notify covering providers, including oncology fellow and oncology (CAR-T) attending - If not already admitted, admit to inpatient floor bed with seizure precautions. Consider stepdown / ICU, particularly if event is a seizure.

balance, cranial nerve deficits, or psychiatric changes. - Any non-sustained / non-recurrent generalized seizures should be managed as a grade 3 neurological event. - Likely or definite strokes should be managed as a grade 4 neurological event.	- **Neurological exam at least every 8 hours plus daily mini-mental status exam.** - **Consult neurology service.** - Obtain urgent MRI brain with and without contrast if feasible. - Obtain lumbar puncture to evaluate for infection if feasible. If sufficient material is available these samples may also be used for CAR T cell and cytokine analysis. - **Give corticosteroids as indicated below for any grade 3 neurotoxicity or for generalized seizures of any duration.** - **Dexamethasone:** **Adults: 10 mg IV q6h** **Pediatrics: 0.1 mg/kg (Max 10 mg) IV q6h** - **Continue corticosteroids until symptoms have improved to Grade 1 or resolved completely.** - **If seizure activity, add levetiracetam 500 mg PO BID and/or other antiepileptics as appropriate.**
Grade 4 neurotoxicity, any recurrent / sustained generalized seizures, or any stroke	
- Life threatening symptoms including recurrent or sustained generalized seizures, or obtundation. - Likely strokes should be managed as grade 4 neurological events until if and when stroke is excluded as a probable diagnosis.	- Notify covering providers, including oncology fellow and oncology (CAR-T) attending. - Manage as grade 3 event as above, but admit to ICU. - If stroke is felt to be possible, call CODE STROKE and notify Brain Attack Team (BAT) team.

References:

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124(2):188-195.
2. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood* 2016;127(26):3321-3330.