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mSMART

Mayo Stratification for Myeloma And Risk-adapted Therapy

Management of Cytokine Release Syndrome (CRS) and Immune Cell Associated Neurotoxicity Syndrome (ICANS)

- Idecabtagene vicleucel (ABECMA) and Ciltacabtagene autoleucel (CARVYKTI) are approved by FDA for relapsed, refractory myeloma
    - After 4 prior lines of therapy AND
    - Exposure to proteasome inhibitor, IMiDs, and anti-CD38 antibody
- Package insert and REMS (Risk Evaluation and Mitigation System) provides guidelines for product specific management of CRS and ICANS
- This consensus opinion specifically addresses general principles of management of acute and subacute adverse events
- Early communication and referral to CAR-T treatment center is recommended to facilitate efficient coordination to get patient to treatment

v1 //last reviewed Mar 2023.

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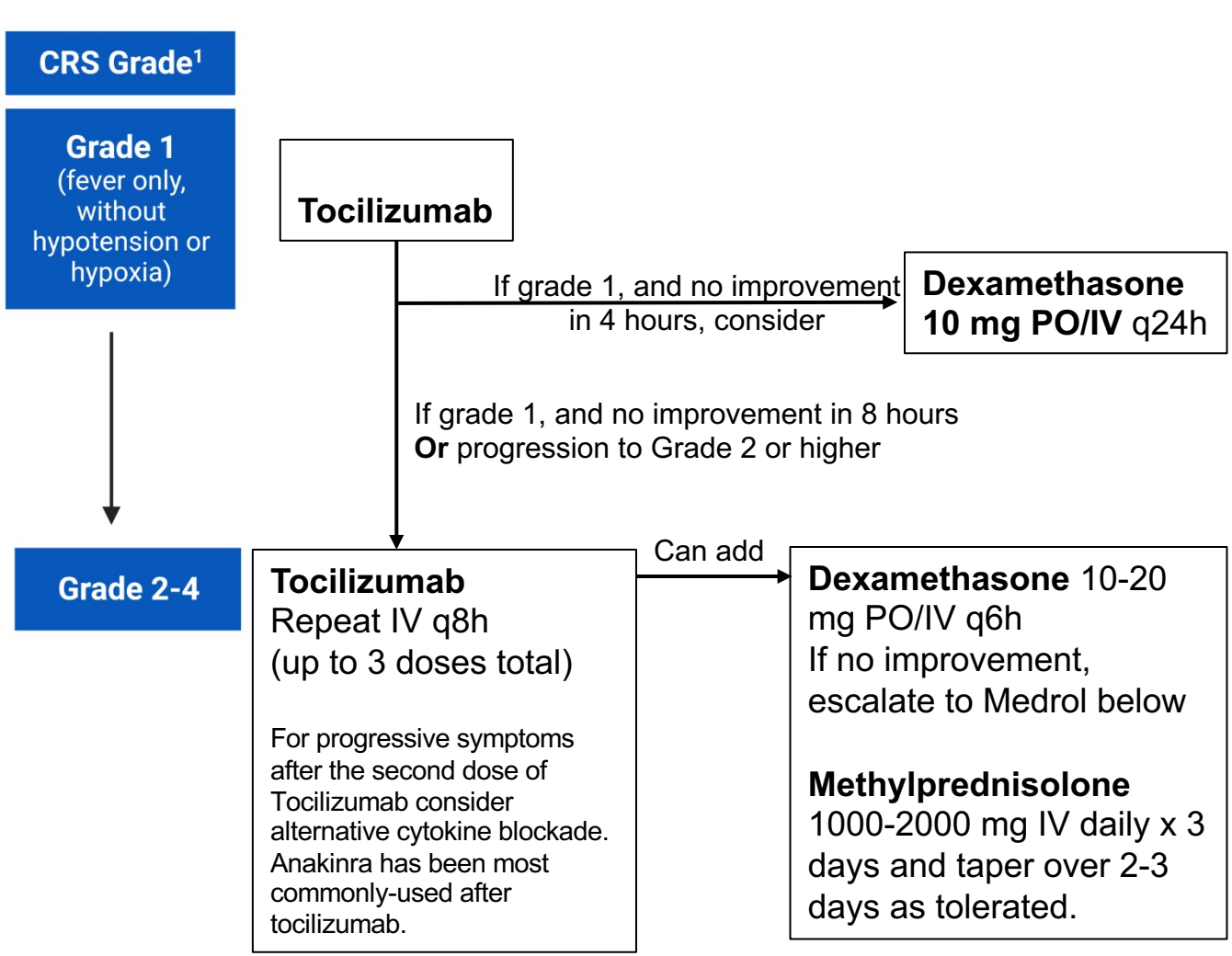
Management of CAR-T associated CRS



Management Considerations

Grade 1

- For treatment centers with capability for outpatient monitoring and rapid escalation of inpatient care when needed, initial monitoring can be done outpatient.
- Assess for infections

Grade 2 - 4

- Inpatient monitoring
- Monitor cytokine panel and consider alternative cytokine blockade
- Monitor cardiac, renal, hepatic functions, coagulopathy. If dysfunction not attributed to other causes, manage as refractory CRS.
- Vigilant monitoring for infections

- Consider disease debulking during CAR-T manufacturing whenever possible to reduce CRS risk.
- Proactive intervention should be given early in the onset of CRS to reduce the likelihood of progression to higher grade.
- Prophylactic cytokine blockade is being studied and not standard of care at this time.

1. Lee DW et al. BBMT 2019; 25: 625-638. PMID:30592986.

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Options for Management of severe CRS & IEC-HS*

Additional medications have been used to manage CAR-T associated severe CRS, IEC-HS (Immune effector cell associated hyperinflammatory syndrome). Use may be off label usage and not covered by insurance.

Medication	Starting Dose	Comment(s)
Anakinra	100 mg subQ BID	• IV doses can be given if concerns for subQ absorption. • Dose up to 48 mg/kg/day and 3500 mg/day IV for 3 days have been tolerated in infection and COVID-19. • Max dose: 100 mg bolus, 2mg/kg/hr IV.
Siltuximab	11mg/kg IV over 1-hour x 1	• If cytokine blockade in IL-6 strongly consider.
Basiliximab	20 mg IV x1	• If cytokine blockade in IL-2 strongly consider • Assess response after 6 to 8 hours; for robust responses additional doses can be given 4 days after the first.
Etoposide	150 mg/m^2 IV twice a week	• Not exceeding a cumulative dose of 2 grams.
Ruxolitinib	5mg po BID with a max of 20 mg po BID	
Etanercept	25 mg subQ 2 times a week	
Cyclosporine	trough of 200 to 250	
Emapalumab	1 mg/kg IV 2 times a week	• Non-formulary treatment and may increase administration time. • If cytokine blockade in IFN-γ strongly consider. • Max Dose: 10 mg/kg IV 2 times a week.
Cyclophosphamide**	1 g/m^2 IV	
ATG (rabbit)**	2 mg/kg/day IV	

** For refractory, potentially fatal severe CRS or IEC-HS where high expansion of CAR-T is detected, lymphotoxic agents such as high dose cyclophosphamide or ATG may be considered.

*Hines M; Knight T; McNerney K, et al TCT 2023.

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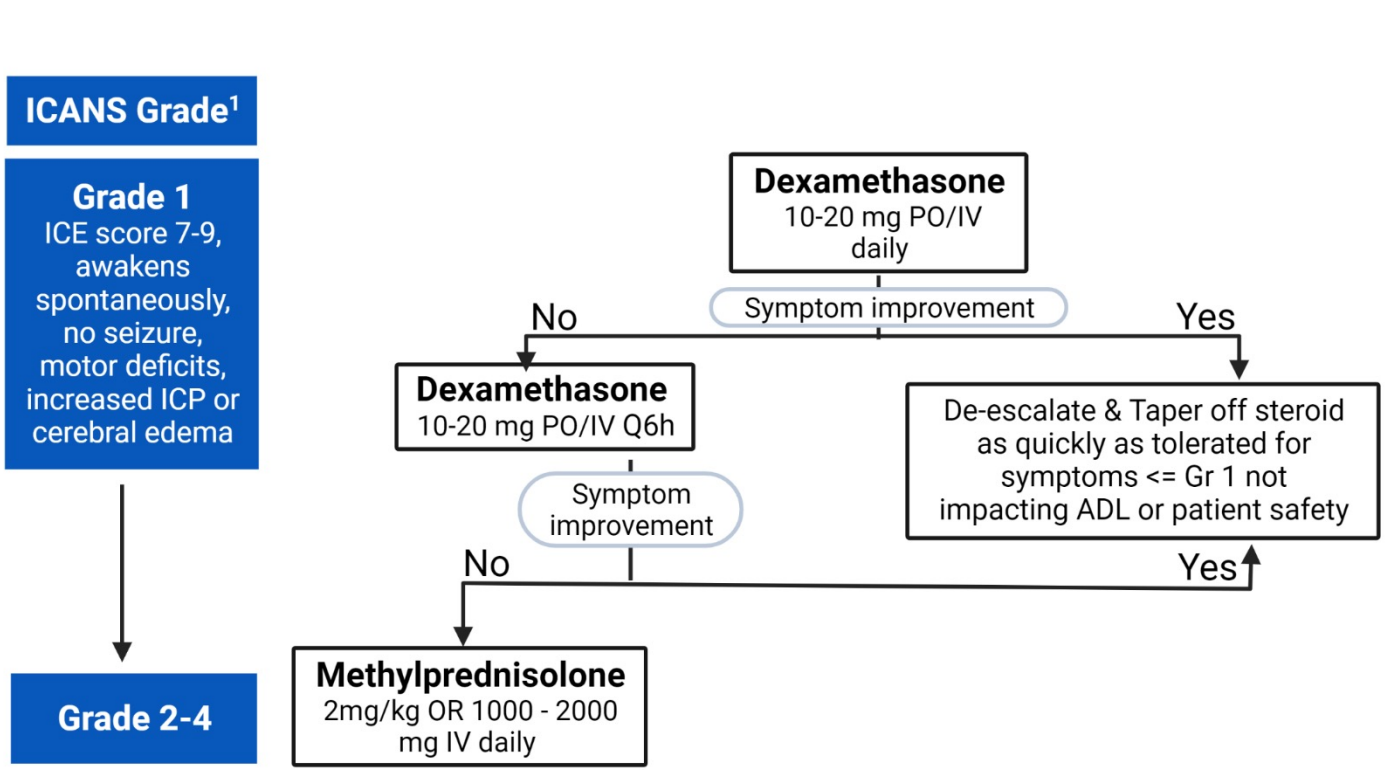
Management of ICANS associated with CAR-T



[1]*ASTCT 2019 guideline, Lee DW et al. BBMT 2019; 25: 625-638. PMID:30592986.*

Management considerations

Grade 1
- ICANS during CRS- Tocilizumab can be given for CRS
- Neurologic presentation impacts patient safety- Initiate steroids
- Dysphasia alone at presentation- Monitor without steroid
- Seizure prophylaxis- Add keppra

Grade 2-4
- Neurologic evaluation to rule out raised ICP, seizures, cerebral edema and infections

- Cerebral edema should be co-managed with Neurology ICU specialists. Consider adding mannitol and lymphotoxic agents.

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Management of Late Onset Neurotoxicity

- Typical onset 1-3 months post CAR-T infusion.
- Clinical course can be prolonged. Spontaneous improvement can be seen, but can take months to > 1 year.
- Understanding of optimal management continue to evolve. Management in discussion with CAR-T treatment center is recommended.

Cranial nerve palsies

- Typically bilateral in presentation
- MRI finding of cranial nerve inflammation can be seen
- Steroid for severe manifestation

Parkinsonism

- Mitigation strategy with disease debulking prior to CAR-T and early intervention for CRS has reduced incidence in clinical trials
- Supportive care
- Sinemet and aggressive treatment such as systemic and or intrathecal lymphotoxic drugs have not been associated with improvement, and should be considered weighing severity of symptoms and side-effects of treatments

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Management of Post CAR-T Cytopenia

	Evaluations	Management
Month 1 Grade 3 or higher cytopenia can be common depending on cytopenia prior to CAR-T and CRS severity	Rule out persistent or recurrent inflammation: • CRP, ferritin, bone marrow biopsy Rule out nutritional deficiencies: • Iron studies, pernicious anemia eval, copper, zinc Rule out infection: • PCR for CMV, EBV, parvovirus B19, HHV6	• If IEC-HS identified, consider anakinra, add steroid if refractory. Escalate immunosuppressive agents if refractory. • If nutritional deficiencies or infections identified, treat as appropriate • Continue blood count monitoring and transfusion support • Variable success with growth factor and thrombopoietin mimetics
Month 3 Anticipate cytopenia improvement to grade 2 or less	Rule out nutritional deficiencies and infections as above if not tested earlier Rule out persistent or recurrent inflammation: • CRP, ferritin Rule out MDS, T-MN • Bone marrow biopsy with cytogenetic testing	• If MDS and T-MN is ruled out, consider stem cell boost in patients with grade 3 or higher cytopenia and who have stem cells available

- Antibacterial prophylaxis should be given during prolonged neutropenia
- Antifungal prophylaxis should be given in month 1 post CAR-T and continued if patient is receiving chronic immunosuppressive medications
- Antiviral prophylaxis and PJP prophylaxis should be continued until CD4 T cells count is persistent >200. (This can take 1 year or longer.)
- Prophylactic IVIG, 400 mg/kg IV, should be given monthly for IgG<400 mg/dL, or for patients with IgG<600 mg/dL and have frequent infections.