[Clinic or Hospital Logo]		
	SOP #	[Number]
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	Owner	[Name]
	Department	[Name]
	Tags	[Tags]
	Applicability	[Name of sites]

Management of Cytokine Release Syndrome Associated with Bispecific T-Cell Engagers

(Example 2)

Where Did This Resource Come From?	
Clinic/Hospital Type	Large community cancer center
What's Unique?	• This clinic administers step-up dosing in the outpatient setting. • Patients receive an *as needed* home dexamethasone prescription, regardless of the type of BTCE received. • Patients are instructed to monitor blood pressure, pulse oximetry, and temperature 3 times a day for 2-3 days following each step-up dose, then as clinically indicated. • Patients with Grade 1 CRS are typically treated in the outpatient setting.

1. Purpose

To provide a framework for the monitoring and management of CRS in patients receiving BTCE therapy.

2. Scope

This policy is applicable to all clinical staff at [site name].

3. Definitions

- **Bispecific T-Cell Engager (BTCE)**: Synthetic proteins that bind two distinct antigens: one targets the CD3 protein on T cells, and the other targets a specific cancer antigen, redirecting T cells to activate an antitumor immune response.
- **Step-Up Dose**: A dosing strategy that starts with a lower dose and gradually increases it to effectively prime the immune system while minimizing adverse effects.
- **Cytokine Release Syndrome (CRS)**: A potentially severe inflammatory response that occurs when immune effector cell therapy leads to the release of cytokines into the

bloodstream. This syndrome causes symptoms such as fever, hypotension, hypoxia, chills, tachycardia, dyspnea, nausea, rash, headache, and myalgia.

4. Patient and Caregiver Education

- Prior to initiating BTCE treatment, educate patients and caregivers about the potential symptoms of CRS, noting the higher likelihood of symptoms during step-up dosing phases, with the highest risk occurring at the first full treatment dose.
- Ensure patient has the following:
    - Thermometer
    - Pulse oximeter
    - Blood pressure machine
    - Prescription for as needed home dexamethasone
- Instruct patient on the importance of monitoring temperature, blood pressure, and pulse oximetry three times daily for 2-3 days following each dose of the step-up dosing, and as clinically indicated thereafter.
- Stress the need to contact healthcare providers if there are changes in the patient's condition.
- Provide the after-hours clinic phone number and instructions for when to seek emergency help or call 9-1-1.
- Patients should receive written materials about their specific therapy and a patient card listing the therapy name and emergency instructions.

5. Healthcare Team Education and Management

- Clinical staff must check the patient’s vitals before starting treatment. Abnormal readings require documentation of "okay to treat" by a qualified provider in the treatment plan.
- If contacted by a patient, use the nurse triage checklist to assess symptoms, and promptly communicate any abnormal CRS findings to the covering provider for further evaluation and management.
- If outpatient, admit to inpatient if Grade >1 (Grade 1 may be managed as an outpatient). During initial step-up therapy, the patient may need to be admitted to the inpatient service depending on the BTCE.
- **Table 1** describes the management strategies of CRS in patients receiving BTCEs.

Table 1. Management of CRS in Patients Receiving Bispecific T-Cell Engagers

CRS Grade	Supportive Care	Glucocorticoids	Anticytokine Therapy
Grade 1 Temp ≥ 100.4°F	Support with antipyretics and encourage hydration. • Acetaminophen 1000 mg by mouth every 8 hours PRN for elevated temperature • Monitor neurologic status. • Assess for infections with cultures and chest radiography (if able). • If grade 1, patient will check temperature and blood pressure every 2 hours while awake at home. Call clinic for advisement if blood pressure goes <10 mmHg below baseline AND <90 mmHg systolic, new orthostatic symptoms, weakness, confusion, dizziness or new hypoxia (<90%).	Dexamethasone 16 mg by mouth may be given and repeated daily if grade 1 CRS continues. • Consider for administration for refractory fever. Must be reviewed with clinical team or covering MD prior to administration. • Patient must be seen for clinical evaluation the same or next day.	May consider tocilizumab for high-risk patients (e.g., advanced age, high tumor burden, heart failure, pulmonary disease) or those with fever persisting > 48 hours. • Must be evaluated in clinic and reviewed with clinical team or covering MD prior to administration.
Grade 2 Temp ≥ 100.4°F AND Hypotension NOT requiring vasopressors AND/OR Hypoxia requiring low flow nasal cannula or blow by	Must be evaluated urgently in clinic or emergency department (ED). • Acetaminophen 1000 mg by mouth Q8H for elevated temperature • Normal saline 1000 ml over 30-60 minutes (may bolus as needed for blood pressure) • Monitor neurologic status • O_2 to maintain O_2 Sats	Dexamethasone 16 mg (take at home before coming to clinic or ED). • If hypotension continues despite tocilizumab and fluids, administer 10 mg IV every 12 hours.	Administer tocilizumab 8 mg/kg (max 800 mg) IV. • May repeat every 8 hours for a maximum of 3 doses in 24 hours; 4 doses total if not responsive to IV fluids or increasing supplemental oxygen.

Grade 3 Temp ≥ 100.4°F AND Hypotension requiring a vasopressor with or without vasopressin AND/OR Hypoxia requiring high-flow nasal cannula (Oxygen delivered at > 6 L/minute), facemask, nonrebreather mask, or Venturi mask	**Hospital admission (Consider intensive care unit (ICU))** • Management per grade 2 hemodynamic monitoring, intravenous fluids, O_2 support, vasopressor support.	Dexamethasone 10 to 20 mg every 6 hours (or equivalent) and continue until event is grade 1 or less. Taper over 3 days once patient is grade 1.	As per grade 2 recommendations.
Grade 4 Temp ≥ 100.4°F AND Hypotension requiring multiple vasopressors (excluding vasopressin) AND/OR Hypoxia requiring positive pressure (e.g.,	**Hospital admission (ICU)** • Manage per grade 3. • Mechanical ventilation may be required.	Dexamethasone 10 to 20 mg every 6 hours (or equivalent) and continue until event is grade 1 or less. Taper over 3 days once patient is grade 1. • Alternatively, administer methylprednisolone 1000 mg IV daily X 3 days.	As per grade 2 recommendations.

CPAP (continuous positive airway pressure), BiPAP (bilevel positive airway pressure), intubation and mechanical ventilation)			

Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ICU, intensive care unit

- Atypical CRS presentations:
  - Persistent CRS-like symptoms for >1 week despite appropriate supportive measures
  - Febrile illness outside of the normal CRS timeframes
  - Accompanying significant organ dysfunction
- Consider diagnostic work up to rule out alternative diagnoses, such as infections or hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)

6. References

1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758.

7. Revision History

Version #	Date	Description of Changes	Reviewed / Approved By