Cytokine Release Syndrome

Management Guidelines for BFCR4350A [cevostamab]

What is Cytokine Release Syndrome?

Cytokine Release Syndrome (CRS) is a condition that may occur during the use of this therapy, which is a type of cancer immunotherapy. It usually occurs within 24-48h after treatment. Per NCI CTCAE version in the study protocol, CRS is characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. In the case of this medication, it typically occurs with the first or second dose. Therefore, it is mandatory for patients to remain in the clinic for observation during this period.

Do not give next dose if:

- Prior CRS has not resolved
- Patient has had fever in the past 24 hours
- Patient has ongoing or new neurological symptoms
- Vital signs are unstable
- Clinically significant laboratory abnormalities have not been corrected or, in the case of liver and renal labs, have not returned to Grade 1 or baseline.

Lee Criteria (2019)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temp. ≥38°C	Temp. ≥38°C	Temp. ≥38°C	Temp. ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or †		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula‡, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE version in the study protocol but they do not influence CRS grading.

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* Fever is defined as temperature 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Supportive Care:

At any CRS grade, consider and provide if patient needs:

- Acetaminophen/paracetamol
- Antihistamines/analgesics
- Oxygen or other ventilation to maintain adequate oxygen saturation
- Treatment of neutropenia and other cytopenias
- Treatment of electrolyte abnormalities
- Treatment of fever; consider broad spectrum antibiotics if indicated
- IV fluids (as per guidelines for individual CRS grades)
- Monitoring of cardiac and other organ function closely
- Consider if patient needs tocilizumab

Treat CRS quickly and consider Tocilizumab early

Grade 1 CRS:

- If BFCR4350A infusion is still ongoing, interrupt infusion immediately.
- Call to have tocilizumab ready if needed.
- In the case of rapid decline; no response to supportive care; or significant signs, symptoms or co-morbidities:
  - consider corticosteroids*.
  - consider tocilizumab**.

Grade 2 CRS:

- If BFCR4350A infusion is still ongoing, interrupt immediately.
- Hospitalize until CRS resolves; ICU if appropriate.
- If hemodynamic support needed, give IV fluid bolus 250-500 cc, up to 2000 cc total (avoid fluid overload).
- Administer tocilizumab 8mg/kg IV**.
- Consider IV corticosteroids*, either:
  - Methylprednisolone 2 mg/kg/day OR
  - If neurological symptoms give dexamethasone 10 mg IV up to every 6 hours as needed
- Rule out other inflammatory conditions that can mimic CRS (e.g. sepsis).
- Work up for MAS/HLH (Macrophage Activation Syndrome and Hemophagocytic Lymphohistiocytosis) if no improvement in 24 hours or atypical presentation.
- Collect cytokine panel.
- Consider collecting data for ADA (anti-drug antibody).

Grade 3 CRS:

- Stop BFCR4350A infusion immediately.
- Hospitalize until CRS resolves; ICU recommended.
- If hemodynamic support needed, give IV fluid bolus 250-500 cc, up to 2000 cc total (avoid fluid overload); provide vasopressor support as required.

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* Administer IV corticosteroids, either Methylprednisolone 2 mg/kg/day OR Dexamethasone 10 mg IV up to every 6 hours as needed.

** Tocilizumab should be administered at dose of 8 mg/kg IV (8m g/kg for participants at or above 30 kg weight only; 12mg/kg for participants less than 30 kg weight; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (up to maximum of 4 doses).

- Administer tocilizumab 8mg/kg IV**.
- Administer IV corticosteroids*, either:
  - Methylprednisolone 2 mg/kg/day OR
  - If neurological symptoms give dexamethasone 10 mg IV up to every 6 hours as needed.
- Rule out other inflammatory conditions that can mimic CRS (e.g. sepsis).
- Work up for MAS/HLH (Macrophage Activation Syndrome and Hemophagocytic Lymphohistiocytosis) if no improvement in 24 hours or atypical presentation.
- Collect cytokine panel.
- Consider collecting data for ADA (anti-drug antibody).

Grade 4 CRS:

- Stop BFCR4350A infusion immediately.
- Hospitalize in ICU for hemodynamic monitoring and/or mechanical ventilation, and/or IV fluids and vasopressors as needed.
- Administer tocilizumab 8mg/kg IV**.
- Give IV corticosteroids*, either:
  - Methylprednisolone 2 mg/kg/day OR
  - Dexamethasone 10 mg IV up to every 6 hours as needed.
- For patients refractory to tocilizumab therapy, other therapies may be considered at discretion of investigator.
- Rule out other inflammatory conditions that can mimic CRS (e.g. sepsis).
- Work up for MAS/HLH (Macrophage Activation Syndrome and Hemophagocytic Lymphohistiocytosis) if no improvement in 24 hours or atypical presentation.
- Collect cytokine panel.
- Consider collecting data for ADA (anti-drug antibody).

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Restarting Infusion

If CRS was:

Grade 1: If infusion was interrupted, wait 30 minutes after event has been resolved and restart at 50% of original rate. If symptoms return, discontinue.

Grade 2: Wait 30 minutes after event has been resolved then restart at 25% of original rate. If symptoms return, discontinue.

Grade 3 & 4: Do not restart infusion.

Next Immediate Dose

Grade 1: Consider extending infusion times for subsequent doses. Pretreat with antihistamine/antipyretics, analgesics, and IV corticosteroids (methylprednisolone 80mg of dexamethasone 20mg)

Grade 2: May receive next dose of BFCR4350A infusion if symptoms resolved to ≤ grade 1 for 3 consecutive days. Reduce rate to 50% of previous rate. Consider hospitalization for next dose. Pretreat with antihistamine/antipyretics, analgesics, and IV corticosteroids (methylprednisolone 80mg of dexamethasone 20mg)

Grade 3: Discontinue BFCR4350A infusion if:

- This is a second occurrence of ≥ grade 3 IRR/CRS.
- Patient has ≥ grade 3 wheezing or bronchospasm.
- Patient has generalized urticarial.

If symptoms resolved to ≤ grade 1 for 3 consecutive days, BFCR4350A infusion may be given in next cycle as long as:

- Patient is hospitalized for minimum 24 hours.
- Premedication with antihistamines, antipyretics/NSAIDs and corticosteroids is given.
- Infused at a reduced rate of 50% of previous rate.

If the patient experienced Grade 3 CRS following the Cycle 1 Day 1 dose, the step-up dose must be repeated.

Grade 4: Permanently discontinue BFCR4350A infusion.

Any Subsequent Cycles After Grade 1-3 CRS

If there is an occurrence of IRR or CRS Grade ≥ 3 in any of the subsequent cycles, permanently discontinue BFCR4350A infusion regardless of recovery (see Grade 3 management guidelines).

If there is an occurrence of a Grade ≤ 2 CRS in subsequent cycles, manage symptoms per grade 1 or 2 management guidelines.

Notes