

BC Cancer Protocol for Cytokine Release Syndrome Management

Protocol Code

SCCRS

Tumour Group

Supportive Care

Physician Contact

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Cytokine Release Syndrome (CRS)

CRS is an acute systemic inflammatory syndrome associated with certain immune therapies including bispecific T-cell engaging antibodies and chimeric antigen receptor (CAR) T-cell therapy. Clinical symptoms indicative of CRS are **fever, rigors, hypotension and hypoxemia within the first weeks of initiation of a new bispecific antibody or CAR T-cell therapy**. Signs and symptoms may also include but are not limited to: tachycardia, tachypnea, dyspnea, nausea, vomiting, diarrhea, mental status changes, transaminitis, fatigue, malaise, myalgias, headache, and rash.

When starting immune therapies associated with a risk of CRS, patients must be closely monitored for early signs and symptoms indicative of CRS.

At initial presentation of fever, consider other differential diagnoses including infection/sepsis (blood and urine cultures, CXR, and/or other investigations directed at symptoms) and consider broad-spectrum antibiotics, particularly if neutropenic, **concurrently while treating CRS. Do not wait for infectious work up before starting treatment for CRS.***

***CRS only occurs within the first few weeks of initiation of a bispecific T-cell engager** (generally in cycles 1-2, during step-up dosing or with the first full dose). Onset of symptoms is within 48 hours of preceding bispecific dose. If a patient has had a full dose of the bispecific T-cell engager without CRS, then future presentations of fever should be considered unrelated to CRS and a full work up for infectious/other causes should be undertaken.

This protocol refers to management of CRS associated with bispecific T-cell engaging antibodies. Treatment of CRS associated with CAR T-cell therapy is managed through the Leukemia/BMT Program of BC.

Immune effector cell-associated neurotoxicity syndrome (ICANS) may occur concurrently with CRS during treatment with certain bispecific antibodies, such as epcoritamab and teclistamab. Patients on such treatments should be monitored closely for concurrent CRS and ICANS. **See the *Supportive Care Immune Effector Cell-Associated Neurotoxicity Syndrome (SCICANS) protocol for specific treatment recommendations for ICANS.***

TESTS:

- **For persistent Grade 1 or Grade 2 CRS and as required:** CBC & Diff, electrolyte panel, creatinine, ALT, alkaline phosphatase, LDH, total bilirubin, lactate, CRP, ferritin, INR, PTT, fibrinogen
 - Labs should be repeated serially if there are any abnormalities (q4h) and must be repeated again prior to discharge
- If clinically indicated: chest x-ray, urinalysis with culture, blood cultures

TREATMENT:

A physician must be notified at the first signs of CRS.

CRS Grading Criteria (ASTCT consensus criteria)¹

Grade	Fever	with Hypotension	and/or Hypoxia
1	≥ 38.0 °C	None	None
2	≥ 38.0 °C	Not requiring vasopressors (ie. responsive to IV fluids)	Requiring oxygen delivered by low-flow nasal cannula (≤ 6 L/min) or blow-by
3	≥ 38.0 °C	Requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula (> 6 L/min), facemask, nonrebreather mask, or Venturi mask
4	≥ 38.0 °C	Requiring multiple vasopressors (excluding vasopressin)	Requiring oxygen delivered by positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Immediate management:

If systolic blood pressure less than 100 mmHg or if greater than 20 mmHg drop from baseline, **notify** physician and start NaCl 0.9% IV fluid bolus.

Oxygen to maintain oxygen saturation above 92%.

CRS	Management
<p>Grade 1</p> <p>Symptoms are not life threatening and require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, malaise).</p>	<p>Hold infusion until CRS symptoms resolve. Once resolved, may restart infusion as per specific drug protocol.</p> <p>Notify the admitting or most responsible physician</p> <p>If Patient is at Home:</p> <ul style="list-style-type: none"> • acetaminophen 650 mg to 1000 mg PO for fever ≥ 38.0 °C, can repeat every 4-6 hours PRN if clinically stable • Recommend aggressive oral hydration (2L orally daily, equivalent to 8-10 glasses of water) • Patient to continue to check temperature every 1 hour (and blood pressure, heart rate, oxygen saturation if able), until symptoms resolve • If persistent fever ≥ 3 hours after acetaminophen or recurrent fever in ≤ 6 hours, consider dexamethasone 10 mg orally once (if prescribed) and advise patient to present to health-care facility for evaluation • Advise patient to contact clinic for urgent evaluation and/or present directly to ER if: <ul style="list-style-type: none"> ○ New orthostatic symptoms, weakness, confusion, dizziness, shortness of breath ○ If systolic BP goes < 10 mmHg below baseline AND < 100 mmHg, if able to check at home ○ Patient may take dexamethasone 10 mg orally once, while enroute to health-care facility (if prescribed) • Consider in-person evaluation if extensive comorbidities or poor performance status <p>If Patient at Health-Care Facility:</p> <ul style="list-style-type: none"> • Administer acetaminophen 650 mg or 975 mg PO every 4 hours PRN for fever <p>Additional Symptom Management:</p> <ul style="list-style-type: none"> • diphenhydramine 50 mg IV every 4 hours PRN for rash, pruritis • metoclopramide 10 mg PO/IV every 4 hours PRN for nausea • ondansetron 8 mg PO/ IV every 8 hours PRN for nausea • Consider IV fluids if required <p>Monitor for CRS symptoms including vital signs and pulse oximetry every 1 hour until resolution of symptoms.</p> <p>If febrile, initiate concurrent septic work up and consider empiric coverage with broad-spectrum antibiotics, particularly if immunocompromised and/or neutropenic.</p> <p>For bispecific T-cell engagers where outpatient management is permitted: If CRS symptoms resolve and patient is afebrile with normal vital signs for at least 4 hours, contact the MRP to determine if the patient may be discharged home with a plan for ongoing home monitoring.</p> <p>If patients have persistent grade 1 CRS not responding to above measures, proceed to treat as grade 2 CRS.</p>

Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/terms-of-use

CRS	Management
<p>Grade 2</p> <p>Symptoms require and respond to moderate intervention.</p> <p>Grade 1 CRS symptoms and:</p> <ul style="list-style-type: none"> ▪ Hypotension not requiring vasopressors <p>And/or</p> <ul style="list-style-type: none"> ▪ Hypoxia requiring low-flow oxygen (\leq 6L/min) or blow-by <p>If patients have extensive comorbidities or poor performance status, manage per grade 3 CRS guidance below</p>	<p>Immediately discontinue current treatment and do not restart. Notify the most responsible physician if not already done.</p> <p>If Patient is at Home:</p> <ul style="list-style-type: none"> • Instruct patient to present urgently to health-care facility for evaluation and management. • Advise patient to take acetaminophen 650 mg to 1000 mg PO and consider dexamethasone 10 mg orally once (if prescribed) en route to health-care facility for evaluation. <p>If Patient at Health-Care Facility:</p> <ul style="list-style-type: none"> • Administer the following as ordered: 500 mL to 1 L NaCl 0.9% IV fluid bolus or continuous infusion for hypotension • acetaminophen 650 mg or 975 mg PO every 4 hours PRN for fever \geq 38.0 °C <p>If blood pressure does not respond to IV fluids (i.e. after 2 fluid boluses), tocilizumab and/or steroids should be administered.</p> <p>Early administration of tocilizumab decreases rates of progression to grade 3 or 4 CRS. If grade 2 CRS occurs, administer tocilizumab first*, reserving dexamethasone if no response to tocilizumab within 1 to 2 hours.</p> <p>*Note: Melanoma patients receiving tebentafusp are particularly responsive to steroids, therefore for melanoma patients only, administer methylPREDNISolone first, reserving tocilizumab if symptoms do not resolve post steroid administration within 1 to 2 hours.</p> <p>Tocilizumab dosing:</p> <ul style="list-style-type: none"> • tocilizumab 8 mg/kg (maximum 800 mg) IV in 100 mL NS over 1 hour. Repeat every 8 hours as needed if not responding to IV fluids or supplemental oxygen (limit 3 doses in 24 hours, 4 doses total). <p>Steroid dosing:</p> <ul style="list-style-type: none"> • dexamethasone 10 mg IV every 6 hours or • methylPREDNISolone 125 mg IV once (preferred steroid for melanoma patients treated with tebentafusp) <p>Continue corticosteroids until event is Grade 1 or less, then taper over 3 days.</p> <p>Additional Symptom Management:</p> <ul style="list-style-type: none"> • diphenhydramine 50 mg IV every 4 hours PRN for rash, pruritis • metoclopramide 10 mg PO/IV every 4 hours PRN for nausea • ondansetron 8 mg PO/ IV every 8 hours PRN for nausea • salbutamol 5 mg nebulizer for inhalation by nebulizer every 20 minutes PRN (maximum 3 doses) for shortness of breath, hypoxia <p>Vital sign monitoring and pulse oximetry frequency should increase to at least every hour, and more frequently if necessary, until resolution of CRS symptoms.</p>

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CRS	Management
<p>Grade 3 and 4</p> <p>Symptoms require and respond to aggressive intervention. Transfer to ER/ ICU required.</p> <p>Grade 1 CRS symptoms and:</p> <ul style="list-style-type: none"> ▪ Hypotension requiring one or more vasopressors (ie. not responding to IV fluids and medical management) <p>And/or</p> <ul style="list-style-type: none"> ▪ Hypoxia requiring high-flow oxygen (>6 L/min) or mask or positive pressure ventilation 	<p>Immediately stop treatment and do not restart.</p> <p>Vital signs every 15 minutes or more frequently as ordered by MD until resolution to Grade 2 or less, then every hour until complete resolution of CRS.</p> <p>Notify the most responsible physician if not already done.</p> <p>Arrange emergent transfer to higher level of care.</p> <p>Administer the following as ordered:</p> <ul style="list-style-type: none"> ▪ acetaminophen 650 mg or 975 mg PO every 4 hours PRN for fever ≥ 38.0 °C ▪ 500 mL to 1L NaCl 0.9% IV fluid bolus or continuous infusion for hypotension <p>Additional Symptom Management:</p> <ul style="list-style-type: none"> ▪ diphenhydramine 50 mg IV every 4 hours PRN for rash, pruritis ▪ metoclopramide 10 mg PO/IV every 4 hours PRN for nausea ▪ ondansetron 8 mg PO/ IV every 8 hours PRN for nausea ▪ epinephrine 1 mg/mL (1:1000) 0.5 mg IM every 5 minutes (maximum 3 doses) PRN for severe hypotension ▪ salbutamol 5 mg nebulizer for inhalation by nebulizer every 20 minutes PRN for shortness of breath, hypoxia <p>All patients should receive BOTH steroids and tocilizumab:</p> <p>Tocilizumab dosing:</p> <ul style="list-style-type: none"> ▪ tocilizumab 8 mg/kg (maximum 800 mg) IV in 100 mL NS over 1 hour. Repeat every 8 hours as needed if not responding to IV fluids or supplemental oxygen (limit 3 doses in 24 hours, 4 doses total). <p>Steroid dosing:</p> <ul style="list-style-type: none"> ▪ dexamethasone 10 to 20* mg IV every 6 hours * Start at 10 mg and escalate to 20mg if no improvement in hypoxia at 24 hours or abrupt increase in oxygen needs <p>OR</p> <ul style="list-style-type: none"> ▪ methylprednisolone 1 gram IV qdaily <p>Continue corticosteroids until event is Grade 1 or less, then taper over 2 to 7 days.</p>

References

1. Lee DW, Santomaso 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.
2. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188-195.
3. Leukemia/Bone Marrow Transplant Program of British Columbia. *Leukemia/BMT Manual. E-edition. Chapter 27 CAR T-cell Therapy and Associated Toxicities (undated).* Vancouver, British Columbia: Vancouver Hospital and health Sciences Centre. Accessed November 18, 2024.
4. [Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3xCD20 bispecific antibody therapy. *Blood* 2024;143\(16\):1565-1575.](#)
5. [Puttkammer JR, Barreto JN, Jensen CJ, et al. Outpatient management of bispecific related toxicities: an observational study of safety outcomes and resource utilization. *JCO Oncol Pract*, 2025 April 15. doi:10.1200/PO-24-00930.](#)

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