BC Cancer Protocol for Cytokine Release Syndrome Management

Protocol Code	*SCCRS*
Tumour Group	*Supportive Care*
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Cytokine Release Syndrome (CRS)

CRS is an acute systemic inflammatory syndrome associated with certain immune therapies including bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapy. Clinical symptoms indicative of CRS are **fever, rigors, hypotension and hypoxemia**. 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.**

All patients receiving treatments that have a risk of CRS must have two IVs inserted prior to treatment.

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

TESTS:

- **For Grade 2 CRS and as required:** CBC & differential, platelets, electrolyte panel, creatinine, ALT, alkaline phosphatase, LDH, bilirubin, lactate, CRP, INR, PTT, fibrinogen
    - Labs should be repeated serially if there are any abnormalities (q4h) and must be repeated again prior to discharge

TREATMENT:

A physician must be notified at the first signs of CRS. See SCCRS preprinted order for immediate management.

CRS Grading Criteria (ASTCT consensus criteria)[1]

Grade	Fever	with Hypotension	and/or Hypoxia
1	≥ 38.0 ºC	None	None
2	≥ 38.0 ºC	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 ºC	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 ºC	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, page physician and start NaCl 0.9% IV fluid bolus.

Oxygen to maintain oxygen saturation above 92%

CRS	Management
Grade 1 Symptoms are not life threatening and require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, malaise).	**Avoid treatment interruption – continue infusion and administer symptomatic treatment** Page the admitting or covering physician Administer the following as ordered: ▪ acetaminophen 650 mg or 975 mg PO every 4 hours PRN ▪ diphenhydrAMINE 50 mg IV every 4 hours PRN ▪ metoclopramide 10 mg PO/IV every 4 hours PRN ▪ ondansetron 8 mg PO/ IV every 8 hours PRN Consider IV fluids if required. Monitor for CRS symptoms including vital signs and pulse oximetry at least every hour for 12 hours or until resolution of symptoms, whichever is earlier. If febrile, initiate concurrent septic work up and consider empiric coverage with broad-spectrum antibiotics, particularly if immunocompromised and/or neutropenic.

CRS	Management
Grade 2 Symptoms require and respond to moderate intervention. Grade 1 CRS symptoms and: ▪ Hypotension not requiring vasopressors And/or ▪ Hypoxia requiring low-flow oxygen (≤ 6L/min) or blow-by If patients have extensive comorbidities or poor performance status, manage per grade 3 CRS guidance below	**Immediately interrupt/delay infusion until event improves to CRS grade ≤ 1** Page the admitting physician or covering physician if not already done. Administer the following as ordered: ▪ 500 mL to 1 L NaCl 0.9% IV fluid bolus or continuous infusion ▪ acetaminophen 650 mg or 975 mg PO every 4 hours PRN ▪ diphenhydrAMINE 50 mg IV every 4 hours PRN ▪ metoclopramide 10 mg PO/IV every 4 hours PRN ▪ ondansetron 8 mg PO/ IV every 8 hours PRN If blood pressure does not respond to IV fluids (i.e. after 2 fluid boluses), tocilizumab and/or steroids should be strongly considered. Early administration of tocilizumab decreases rates of progression to grade 3 or 4 CRS. If grade 2 CRS occurs, **administer tocilizumab first*,** reserving steroids if no response to tocilizumab within 1 to 2 hours**.** ***Note:** Melanoma patients are particularly responsive to steroids, therefore **for melanoma patients only, administer steroids first**, reserving tocilizumab if symptoms do not resolve post steroid administration within 1 to 2 hours. Tocilizumab dosing: ▪ 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). Steroid dosing: ▪ methylPREDNISolone 1 mg/kg IV every 12 hours or ▪ dexamethasone 10 mg IV every 6 hours Continue corticosteroids until event is Grade 1 or less, then taper over 3 days. If required: ▪ salbutamol 5 mg nebule for inhalation by nebulizer every 20 minutes (maximum 3 doses) Vital sign monitoring and pulse oximetry frequency should increase to at least every hour, and more frequently if necessary, until resolution of CRS symptoms.

CRS	Management
Grade 3 and 4 Symptoms require and respond to aggressive intervention. Transfer to ER/ ICU required. Grade 1 CRS symptoms and: ▪ Hypotension requiring one or more vasopressors (ie. not responding to IV fluids and medical management) And/or ▪ Hypoxia requiring high-flow oxygen (>6 L/min) or mask or positive pressure ventilation	**Immediately stop infusion.** 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. Page the admitting physician or covering physician if not already done. Arrange emergent transfer to higher level of care. Administer the following as ordered: ▪ acetaminophen 650 mg or 975 mg PO every 4 hours PRN ▪ diphenhydrAMINE 50 mg IV every 4 hours PRN ▪ 500 mL to 1L NaCl 0.9% IV fluid bolus or continuous infusion ▪ metoclopramide 10 mg PO/IV every 4 hours PRN ▪ ondansetron 8 mg PO/ IV every 8 hours PRN **All patients should receive BOTH steroids and tocilizumab:** Tocilizumab dosing: ▪ 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). Steroid dosing: ▪ methylPREDNISolone 1 mg/kg IV every 12 hours or ▪ dexamethasone 10 mg IV every 6 hours or ▪ methylprednisolone 1 gram IV qdaily x 3 days Continue corticosteroids until event is Grade 1 or less, then taper over 3 days. If required: ▪ epinephrine 1 mg/mL (1:1000) 0.5 mg IM every 5 minutes (maximum 3 doses) ▪ salbutamol 5 mg nebule for inhalation by nebulizer every 20 minutes (maximum 3 doses)

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.
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.