BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Systemic Therapy Agents

Protocol Code	*SCDRUGRX*
Tumour Group	*Supportive Care*
Contact Physician	*Dr. Helen Anderson*
Contact Nurse	*Professional Practice Nursing*

Definition of Infusion-Related Reactions

An adverse sign or symptom occurring during drug infusion or within the first day of drug administration. Infusion-related reactions include hypersensitivity or allergic reactions such as anaphylaxis (antibody mediated), or anaphylactoid reactions (not antibody mediated) such as cytokine-release syndrome.[1-6] Reactions may include urticaria, dyspnea, bronchospasm, angioedema, hypotension, tachycardia, and back or abdominal discomfort/pain. Occasionally cardiorespiratory arrest may occur.

TREATMENT[7-15]

- A physician or nurse practitioner must be notified for any infusion-related reaction greater than a mild (grade 1) reaction (see table below) and re-start instructions will be written (where electronic order entry is not in place).
- For all reactions, a clinical description and rate of infusion at the time of reaction will be documented by nursing.
- For reactions grade 2 or higher, clinical description, time, and management of reaction will be documented in the clinical note section of the medical record by the physician or nurse practitioner.

Two preprinted physician orders are available for use:

A. Preprinted Order A **(PPO A) for immediate management**, including the infusion rate for resumption of infusion for selected drugs (PACLitaxel, DOCEtaxel, riTUXimab, daratumumab).
B. Preprinted Order B **(PPO B) for subsequent cycle management** after infusion-related reaction.

Immediate Management – use PPO A:

Follow the general management below or as directed by the physician or nurse practitioner.

A) Based on their clinical judgment nursing may choose to stop an infusion at any time for safety reasons. If an infusion is stopped then written orders are required to restart.

Table 1: Infusion-Related Reaction Grading and Immediate Management

Infusion-Related Reactions	Immediate Management
Mild (Grade 1) *Mild-transient reaction; infusion interruption not indicated; intervention not indicated*[24] **Any of the following symptoms may be observed:** • Mild flushing • Mild chills • Dizziness (not interfering with activity) • Pruritus (mild or localized) • Transient rash (covering less than 10% BSA with or without symptoms) • Mild allergic rhinitis	• Assess and monitor patient closely (see point A above) • Remain with patient until symptoms have resolved. • Ensure equipment and medication are readily available should the reaction progress. **If symptoms progress to Grade 2 proceed as outlined below.**

Infusion-Related Reactions	Immediate Management

Moderate (Grade 2)
Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); medications indicated for less than or equal to 24 h[24]
 	
Any of the following symptoms may be observed:
• Transient rash (covering 10 to 30% BSA with or without symptoms)
• Moderate flushing
• Dizziness (moderate unsteadiness or sensation of movement)
• Pruritus (intense or widespread; intermittent)
• Moderate allergic rhinitis
• Urticaria (lesions covering 10 to 30% BSA)
• Moderate dyspnea (shortness of breath with minimal exertion)
• Rigors (associated with administration of monoclonal antibodies)
• Mild to moderate chest discomfort
• Mild to moderate abdominal discomfort
• Mild to moderate back pain
• Mild hypotension (less than or equal to 20 mmHg drop from baseline)
• Mild to moderate nausea, vomiting, and/or diarrhea
• Fever 39 to 40 degrees Celsius
	Use Preprinted Order A
	• Stop infusion.
	• Notify that a reaction is taking place (Centre specific).
	• Check the chemotherapy protocol.
	• Give diphenhydrAMINE 50 mg IV and/or hydrocortisone sodium succinate 100 mg IV per physician orders and VCH Parenteral Drug Therapy Manual (PDTM).
	• After recovery of symptoms, resume infusion at a rate per protocol. If no direction in protocol, use the following increments (assuming no reaction after the assigned minutes, proceed to the next increment):
	  ○ 25% of the rate at time of reaction for 5 minutes
	  ○ 50% of the rate at time of reaction for 5 minutes
	  ○ 75% of the rate at time of reaction for 5 minutes
	  ○ 100% of the rate at time of reaction
	• Depending on the severity of reaction, may increase to full rate at physician or nurse practitioner's discretion.

Infusion-Related Reactions	Immediate Management
Severe (Grade 3) *Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae*[24] **Any of the following symptoms may be observed:** • Severe rash (covering greater than 30% BSA with or without associated symptoms) • One or more symptoms of respiratory distress requiring treatment (e.g., repetitive cough, wheeze, throat tightness/change in voice) • Symptomatic bronchospasm with or without urticaria • Generalized urticaria (covering greater than 30% BSA) • Hypoxia: decreased oxygen saturation at rest (e.g., pulse oximeter less than 88%) • Edema/angioedema • Dizziness: severe unsteadiness or sensation of movement • Severe nausea, vomiting, and/or diarrhea • Uncontrolled hypotension (more than 20 mmHg drop from baseline) requiring therapy • Fever greater than 40 degrees Celsius **Severe (Grade 4)** *Life-threatening consequences; urgent intervention indicated*[24] **Any of the following symptoms may be observed:** • Hypoxia: Life-threatening airway compromise • Cyanosis • Altered level of consciousness • Severe angioedema (periorbital/facial)	**Use Preprinted Order A** • Stop infusion and do not restart. • Notify that a reaction is taking place (Centre specific). • Give diphenhydrAMINE 50 mg IV and/or hydrocortisone sodium succinate 100 mg IV per physician orders and VCH Parenteral Drug Therapy Manual (PDTM). • Normal saline if needed for hypotension per physician orders (see below). • Give epinephrine 0.5 mg* intramuscularly STAT. Repeat epinephrine at 5 minute intervals twice more as needed (i.e., if breathing becomes more laboured or level of consciousness decreases). Note: Administer a maximum of three doses of epinephrine. • Oxygen if needed for dyspnea (see below). • Bronchodilators if indicated (see below). • Either permanently discontinue the drug that caused the reaction or attempt to retreat on another occasion after premedication (see Prophylaxis section) and using a slower infusion rate. *Initiate Emergency Response System appropriate for facility if patient condition warrants.*

*Note: epinephrine 1:1,000 = 1 mg/mL and epinephrine 1:10,000 = 1 mg/10 mL

Other Immediate Management:

- **Hypotension:** Administer normal saline to maintain blood pressure per physician orders (e.g., 300 mL/h).

- **Dyspnea:** Administer oxygen to maintain oxygen saturations per physician orders and/or provide patient comfort.

- **Bronchospasm:**

Table 2: Drugs for Immediate Management of Bronchospasm

Drug	Dose	BC Cancer Administration Guideline (See Appendix I)
In Order of Preference:		
salbutamol (inhaler)*	200 mcg	2 puffs (100 mcg x 2) via aerosol chamber
salbutamol (nebules)	5 mg	by nebulizer per facility standard (must follow PPE requirements‡)
ipratropium / salbutamol§ (COMBIVENT RESPIMAT)	20 mcg / 100 mcg	1 puff via aerosol chamber
ipratropium (inhaler)† (ATROVENT)	40 mcg	2 puffs (20 mcg x 2) via aerosol chamber
ipratropium (nebules) (ATROVENT)	0.5 mg	by nebulizer per facility standard (must follow PPE requirements‡)
If severe bronchospasm:		
salbutamol AND ipratropium (ATROVENT)	Select one formulation of salbutamol AND one formulation of ipratropium listed above, and follow dosing and administration guidelines	
ipratropium / salbutamol§ (COMBIVENT RESPIMAT)	20 mcg / 100 mcg	1 puff via aerosol chamber

* Before administration, prime the device by shaking well and releasing 4 puffs into the air, away from the face.

§ Before administration, prime the device by releasing 1 puff into the air, away from the face, until a soft mist is visible. Then, repeat the process 3 more times. COMBIVENT RESPIMAT does not need to be shaken.

† Before administration, prime the device by shaking well and releasing 2 puffs into the air, away from the face.

‡ See Procedure: Application of COVID-19 Personal Protective Equipment (PPE) Framework for BC Cancer

Subsequent Management After An Infusion-Related Reaction – Use PPO B

- Assessment and differentiation of whether or not an infusion-related reaction represents anaphylaxis should take place. Any subsequent administration of an agent suspected of causing anaphylaxis or after a grade 4 infusion-related reaction should not take place unless medically indicated based on available evidence. [2]

- If you are making changes to the administration of a drug due to a prior infusion related reaction (e.g., addition of premedication, infusion rate adjustment), SCDRUGRX – PPO B is required.

- For the management of subsequent infusions consider the following actions:

    i. Substitution with an alternative agent may be considered at the provider's discretion based on the characteristics of the infusion-related reaction and other patient-specific factors.
    ii. If the drug or route is essential, premedicate prior to subsequent treatment/cycle(s) according to the prophylaxis guidelines for infusion-related reactions in the protocol by which the patient is being treated.
        a. If there are no specific protocol premedication guidelines, consider one or more of the options in Table 3 below.
    iii. Consider initiating and/or capping the infusion rate as outlined in the associated treatment protocol and as warranted by clinical judgement.
        a. If there are no specific protocol rate guidelines, use standardize rate options in PPO B.

Table 3: Drugs for Preventing Infusion-Related Reactions in Subsequent Treatment

Drug	Dose	BC Cancer Administration Guideline
dexamethasone	20 mg given 12 h and 6 h pre-chemo	PO
hydrocortisone sodium succinate	100 mg given 30 min pre-chemo	IV in 50 to 100 mL NS over 20 min
diphenhydrAMINE	50 mg given 30 min pre-chemo	IV in 50 mL NS over 15 min
famotidine	20 mg given 30 min pre-chemo	IV in 100 mL NS over 15 min (diphenhydrAMINE and famotidine are Y-site compatible)

Related Documents:

- Provincial Systemic Program Policies:
  - III-10 Systemic Therapy Treatment Delivery Process
  - III-60 Drug Reaction Management - Physician Coverage During Delivery Of Selected Systemic Therapy Drugs
- R-40 Registered Nurse Initiated Activities

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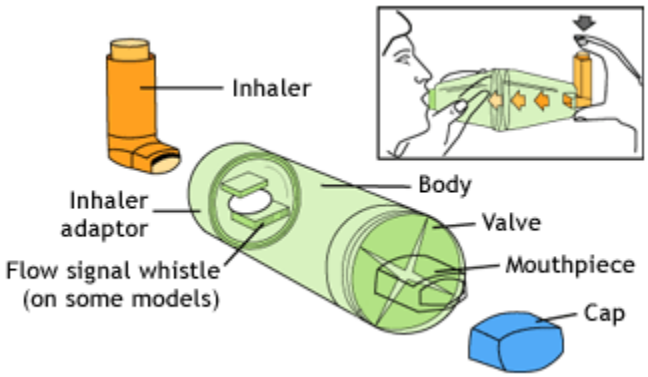
Appendix I: Instructions for administration of inhaler in combination with aerosol chamber

(Adapted from Asthma Canada – How to Use Your Inhaler)

1. Shake the inhaler well before use (as per footnotes in Dosing and Administration table).
2. Remove the cap from the inhaler.
3. Insert the inhaler into the aerosol chamber.
4. Instruct patient to breathe out, away from the aerosol chamber.
5. Bring the aerosol chamber to patient's mouth, and instruct the patient to put the mouthpiece between their teeth and close their lips around the mouthpience.
6. Press the top of the inhaler once.
7. Instruct patient to breathe in slowly, if possible, until a full breath is taken. If a whistle sound is heard, the patient is breathing in too fast.
8. Instruct the patient to hold their breath for several seconds, if possible, then breathe out slowly.



Appendix II: Common Terminology Criteria for Adverse Events (4.03) Table
This table is an aggregate of adverse events commonly related to infusion reactions to assist with assessment and documentation.

	Grade 1	Grade 2	Grade 3	Grade 4
Infusion Related Reaction[24]	Mild-transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); medications indicated for less than or equal to 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Any one of the following symptoms may be observed during an infusion reaction:				
	Grade 1	Grade 2	Grade 3	Grade 4
Abdominal Pain[24]	-	Moderate pain	Severe pain	-
Allergic Rhinitis[24]	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-
Anaphylaxis[24]	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated
Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death. Additional signs and symptoms include urticaria, repetitive cough, wheeze, and throat tightness or change in voice.[23]				
Back pain[24]	-	Moderate pain	Severe pain	-
Chills[24], Rigors[21]	Mild sensation of cold; shivering	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-
Dizziness[24]	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self-care ADL	-
Dyspnea[24]	-	Shortness of breath with minimal exertion	Shortness of breath at rest	Life-threatening consequences; urgent intervention indicated

	Grade 1	Grade 2	Grade 3	Grade 4
Hypoxia[24]	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter less than 88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter less than 88%)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Fever[24]	38.0 to 39.0 degrees C (100.4 to 102.2 degrees F)	39.1 to 40.0 degrees C (102.3 to 104.0 degrees F)	Greater than 40.0 degrees C (greater than 104.0 degrees F) for less than or equal to 24 h	Greater than 40.0 degrees C (greater than 104.0 degrees F) for greater than 24 hours
Flushing[24]	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension, and/or tachycardia; limiting self-care ADL	-
Hypotension[24]	Asymptomatic; intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
	Mild hypotension (less than or equal to 20 mmHg drop from baseline)[21]		Uncontrolled hypotension (more than 20 mmHg drop from baseline)[21]	
Non-cardiac chest pain[24]	-	Moderate pain	Severe pain	-
Pruritus[24]	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-
Rash (maculo-papular)[24]	Macules/papules covering less than 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 to 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering greater than 30% BSA with or without associated symptoms; limiting self-care ADL	-
Urticaria[24]	-	Urticarial lesions covering 10 to 30% BSA; oral intervention indicated	Urticarial lesions covering greater than 30% BSA; IV intervention indicated	-