Management of Cancer Medication-Related Infusion Reactions

Ontario

ACKNOWLEDGEMENTS

Working Group Members

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BACKGROUND

Infusion reactions (IRs) commonly occur with several anticancer medications, ranging in severity from mild flushing to severe anaphylaxis-type symptoms. These reactions are not always predictable or associated with a drug's mechanism of action.[1,2] The incidence of IRs varies depending on the anticancer agent used. In some cases, the incidence of reactions may be low but the risk for potentially life-threatening reactions exists.[2,3] Most IRs occur within the first hour of either the first or second administration of an intravenous anticancer medication; therefore, careful monitoring during infusion initiation is necessary to detect potential IRs and manage accordingly.[3] In cases where IRs may be prevented, the administration of prophylactic medications is key.

Appropriate clinical assessment of IRs is necessary to ensure optimal management. Anticancer medications causing reactions should be discontinued in patients who are likely to experience a severe, potentially life-threatening reaction upon re-challenge.[2–5] In some cases, equally effective alternatives are available, and treatment can be switched. In other cases, it may be safe to re-challenge with the offending agent at reduced rates, with additional pre-medications, or if no other options exist, through desensitization.[2,3,5,6]

Patients who experience IRs may be irreversibly labeled with an allergy to the medication in question, restricting the use of first-line therapies.[1,7] It is, therefore, important to have protocols in place for the prevention and management of IRs to minimize their negative impact on treatment. Variability in the prevention and management of IRs across Ontario centres has been identified as a quality and safety gap. This clinical practice guideline, informed by best available evidence and expert consensus, was developed to help standardize the prevention and management of IRs across the province.

Definitions

The term IR is a broad classification; therefore, a standardized definition is needed to facilitate accurate documentation of reactions and provide guidance on treatment and re-challenge decision-making.

An **infusion reaction** (IR) is any adverse sign or symptom that occurs during the infusion of a medication or within the first day of administration.[8]

Hypersensitivity reactions (HSRs) are a subset of IRs that occur at doses normally tolerated by patients and are not consistent with a known toxicity of the drug.[2] **HSRs** can be divided into subtypes as defined by Gell and Coombs, depending on the mechanism of reaction.

- **Type I reactions** are those mediated by immunoglobulin E (IgE) antibodies, and include **anaphylaxis**, a type of systemic HSR that is severe, rapid in onset, and life-threatening.[2,9] As defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, symptoms can include breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness.[10]

- **Type II reactions** are mediated by antibodies, such as IgG and IgM. Examples of Type II reactions include hemolytic anemia and thrombocytopenia.[2]

- **Type III reactions** are mediated by immune complexes. Examples of Type III reactions include serum sickness and vasculitis.[2]

- **Type IV reactions** are delayed reactions which are mediated by T-cells. Examples of Type IV reactions include allergic contact dermatitis, erythema multiforme and Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS).[2]

Anaphylactoid reactions resemble anaphylaxis, but arise from non-immunological means.[2] An example of an anaphylactoid reaction is **cytokine release syndrome (CRS),** which results from widespread degranulation of mast cells, often after the initial infusion with a monoclonal antibody (MoAb).[11] As defined by NCI CTCAE version 5.0, symptoms can include fever, hypotension and/or hypoxia.[10]

Depending on the severity of the IR, treatment may be restarted and/ or re-challenged.

- **Restart** refers to the continuation of the infusion (usually at a reduced infusion rate) once symptoms of the IR have been managed**.**

- **Re-challenge** refers to the re-exposure of the treatment (usually with additional pre-medications and/or a reduced infusion rate) at a future date.

Standardization of the prevention and management of IR reaction types described above are the focus of this guideline. Reactions considered out-of-scope for this clinical practice guideline include irinotecan-related acute cholinergic reaction, delayed reactions, severe non-type 1 reactions (such as Stevens-Johnson syndrome), and extravasation. This guideline will not address funding, oral systemic therapy, or other side effects of systemic therapy, including local injection site reactions.

METHODS

This clinical practice guideline was developed by a multidisciplinary Working Group consisting of oncologists/hematologists, pharmacists, nurses and administrators who are knowledgeable in the management of cancer medication-related infusion reactions. The Working Group appraised available literature on prevention, management, grading and desensitization protocols. An iterative consensus-building process was used to develop a practical guideline. Final guideline content was validated by external experts. Complimentary patient information was created based on best practices and input from patient education experts, patients, and caregivers.

Literature Search Strategy

A systematic review was conducted using Medline, Embase and CINAHL on June 12, 2018. Search terms related to the appropriate methods for preventing and managing infusion reactions related to anticancer medications. Results were limited to English publications from January 1990 to current.

Search terms included hypersensitivity, chemotherapy, monoclonal antibodies (and specific names of chemotherapy and monoclonal antibodies), grading or severity, chemotherapy or oncology, risk factors, infusion rate or route of administration or formulation, common terminology criteria for adverse events and clinical severity scale.

A grey literature search was also conducted through focused and targeted internet databases and websites, such as TRIP database, NHS Evidence, University of York CRD, National Cancer Institute, National Comprehensive Cancer Network, Health Canada's Drug Products Database, and other Canadian and International Health Technology agencies. The keywords used were reflective of the Ovid Medline and Ovid Embase search strategies. In addition, the search limits placed on the literature database search were also applied to the grey literature search.

After preliminary review of the search results, additional searches were performed using PubMed, GoogleScholar, articles referenced within other studies, CCO drug formulary documents, manufacturer published product monographs and organization-specific management algorithms.

SUMMARY OF RECOMMENDATIONS

For quick reference to a section of the guideline or to clinical questions with the associated summary of evidence and discussion, please click on the relevant hyperlink in the document.

Refer to Appendix 1 (Drug Table) for a summary of IR characteristics, mechanism, symptoms, prophylaxis, acute management, and re-challenge recommendations for select anticancer medications associated with an increased risk of IRs.

Prophylaxis

1.1 General Prevention Strategies:

	General Recommendations
General Approach to Prophylaxis	- Assess risk factors - Optimize pre-medications - Administer treatments using graduated infusion rates
Risk Factors	- Anticancer medication - Concomitant medications - Route of administration - Drug formulation - Patient factors
Additional Considerations	Consider a non-sedating H1-receptor antagonist (e.g. cetirizine 10 mg) in patients with comorbidities where diphenhydramine may be contraindicated.[12,13]

Key prophylactic recommendations by medication

1.2 Taxanes:

Anticancer Medication	Prevention Strategy
Paclitaxel every 3 weeks[7,14–24] (Recommendation 1.1)	- Dexamethasone 20 mg PO 12- and 6- hours prior to paclitaxel **OR** Dexamethasone 20 mg IV 30-60 minutes prior to paclitaxel. - Diphenhydramine 25-50 mg IV/PO 30-60 minutes prior to paclitaxel. - Ranitidine 50 mg IV or Famotidine 20 mg IV 30-60 minutes prior to paclitaxel.

Anticancer Medication	Prevention Strategy
Weekly Paclitaxel[7,17,18,22,23,25,26] ([Recommendation 1.2](), [Recommendation 1.3]())	To be given 30-60 minutes prior to paclitaxel: • Dexamethasone 10 mg IV. • Diphenhydramine 25-50 mg IV/PO. • Ranitidine 50 mg IV or Famotidine 20 mg IV.
Paclitaxel - additional considerations ([Recommendation 1.4](), [Recommendation 1.5](), [Recommendation 1.6]())	• Consider discontinuing pre-medications for paclitaxel (single agent or combination) if there was no previous IR in the first 2 doses.[7,27–30] • Extended infusion (i.e. graduated rate) of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.[4,18,27,28] • There is currently insufficient evidence to recommend the addition of Hydrocortisone 100 mg IV to the existing standard pre-medication regimen.[19] • It is recommended to gently rotate the paclitaxel bag prior to administration to ensure proper mixing.[14] Incomplete mixing of the drug in the diluent may contribute to IRs due to uneven distribution of the excipient (Cremophor EL) and the drug (paclitaxel).
Docetaxel[18,31–33] ([Recommendation 1.7]())	• Dexamethasone 8 mg PO twice daily for 3 days, starting 1 day prior to the docetaxel infusion to decrease the incidence and severity of IRs and fluid retention. • Dexamethasone 10-20 mg IV can be given 30-60 minutes prior to the infusion if the patient forgot to take one or more oral dose(s). • This pre-medication regimen should be continued, even in the absence of an IR, due to the benefits of dexamethasone on other adverse effects, such as pain and edema.
Docetaxel – **alternative** for patients with prostate cancer concurrently being treated with prednisone[34–37] ([Recommendation 1.8]())	• Dexamethasone 8 mg PO 12 hours, 3 hours and 1 hour prior to the docetaxel infusion can be given as outlined in the product monograph (pattern of practice varies - see summary of evidence and discussion).
Docetaxel – additional considerations	• To minimize IRs, docetaxel should initially be infused at a slow rate, then incrementally increased to the planned rate.[38] • It is recommended to gently rotate the docetaxel bag prior to administration to ensure proper mixing.[36] Incomplete mixing of the drug in the diluent may

Anticancer Medication	Prevention Strategy
	contribute to IRs due to uneven distribution of the excipient (Polysorbate 80) and the drug (docetaxel).
Cabazitaxel[7,21,39–42] ([Recommendation 1.9](#))	To be given at least 30 minutes prior to cabazitaxel: • A corticosteroid (e.g. dexamethasone 8 mg) IV/PO. • An H1-receptor antagonist (e.g. diphenhydramine 25 mg) IV/PO. • An H2-receptor antagonist (e.g. ranitidine 50 mg) IV/PO.
Cabazitaxel – additional considerations	• It is recommended to gently rotate the cabazitaxel bag prior to administration to ensure proper mixing.[39]

1.3 Platinums:

Anticancer Medication	Prevention Strategy
Carboplatin ([Recommendation 2.1](#), [Recommendation 2.2](#))	• Pre-medications and extended infusion are not routinely recommended for patients receiving carboplatin.[2,43–48] • Consider pre-medications (e.g. corticosteroids, H1-receptor antagonists ± H2-receptor antagonists) in high-risk gynecological patients receiving carboplatin starting from the 7th cycle. High-risk factors include a platinum-free interval (PFI) >12 months and a history of drug allergy.[2,43–47] • Prophylactic skin testing to predict carboplatin IRs is not recommended.[43–47,49–51]
Oxaliplatin ([Recommendation 2.3](#), [Recommendation 2.4](#))	• Pre-medications are not routinely recommended for patients receiving oxaliplatin.[52–54] • Consider pre-medications (e.g. corticosteroids, H1-receptor antagonists ± H2-receptor antagonists) in high-risk patients. High-risk factors include female gender, younger age, and prior exposure to platinums, including the administration of oxaliplatin after the 6th cycle.[52–56] • Prophylactic skin testing to predict oxaliplatin IRs is not recommended.[52–54,57]
Cisplatin ([Recommendation 2.5](#))	• Pre-medications and extended infusion duration are not routinely recommended for patients receiving cisplatin.[35,58,59]

1.4 Monoclonal Antibodies:

Anticancer Medication	Prevention Strategy
Rituximab[60–67] (Recommendation 3.1)	To be given 30 minutes prior to rituximab: • Oral antipyretic (e.g. acetaminophen). • H1-receptor antagonist (e.g. diphenhydramine). • Corticosteroid (e.g. methylprednisolone 80 mg IV or equivalent) in patients with bulky disease or pulmonary involvement (if no corticosteroids are already being given as part of the chemotherapy regimen). *For subcutaneous rituximab, especially in patients who experienced adverse effects from pre-medications, the omission of pre-medications may be considered.[68]
Rituximab – additional considerations (Recommendation 3.2)	• Transient hypotension may occur during rituximab infusion. Consider holding anti-hypertensive medications 12 hours prior to and throughout the rituximab infusion.[69] • The first cycle of rituximab IV is recommended to be administered over a graduated rate. If no severe IR (grade 3 or 4) occurred with the first cycle, a rapid infusion of IV rituximab over a total of 90 minutes can be initiated with cycle 2. Alternatively, subcutaneous administration of rituximab can be considered starting with cycle 2.[6,64,69–72]
Rituximab – for patients with a high lymphocyte count (e.g. > 25-50 x 10^9/L)[11,60,69,73–75] (Recommendation 3.3)	It is recommended to consider patient-specific risk factors when prescribing strategies to prevent rituximab IRs. The following strategies can be considered: • Dose splitting over 2 days. • Reduced infusion rate. • Delay rituximab treatment until chemotherapy has reduced the lymphocyte count.
Cetuximab[3,6,76,77] (Recommendation 3.4)	• Pre-medication with an H1-receptor antagonist (e.g. diphenhydramine 50 mg IV) for cycle 1 of cetuximab is recommended. A corticosteroid for cycle 1 of cetuximab can be considered. • Pre-medications for subsequent cycles are based on clinical judgment, and the presence and severity of a prior IR.
Daratumumab – pre-medications[78–80] (Recommendation 3.5)	• Please refer to *Appendix 1* for a description of recommended pre- and post-infusion medications.

Anticancer Medication	Prevention Strategy
	• The addition of montelukast to the existing pre-medication regimen can be considered to reduce respiratory IRs.
Daratumumab – additional considerations (Recommendation 3.6)	• It is recommended to infuse daratumumab at a graduated rate as described by the product monograph.[81] • For the first dose of daratumumab, consideration can be given to split the dose over 2 days with pre-medications given on both days prior to the infusion.[78,82] • If no IR in the first 2 doses, consider administering as a rapid infusion starting with the 3rd dose (20% of the dose over 30 minutes at 200 mL/hour, then the remaining 80% of the dose over 60 minutes at 450 mL/hour).[83,84]
Alemtuzumab[65,85–88] (Recommendation 3.7)	To be given 30 minutes prior to alemtuzumab: • H1-receptor antagonist (e.g. diphenhydramine 50 mg IV). • Oral acetaminophen 650 mg. *May consider corticosteroids (methylprednisolone 1g) on the first 3 days.[2] **Subcutaneous administration of alemtuzumab can be considered to reduce IRs (except in patients with T-cell prolymphocytic leukemia, where the intravenous route is recommended).[89,90]
Bevacizumab – pre-medications[3,6,91,92]	• Pre-medications are not routinely recommended prior to bevacizumab administration for the purposes of preventing IR. • Pre-medications can be considered for patients who experienced an IR with a previous bevacizumab infusion.
Bevacizumab – additional considerations (Recommendation 3.8)	• Bevacizumab 5 mg/kg and 7.5 mg/kg doses can be safely administered as a rapid infusion (i.e. over 10 minutes).[93,94]

For all other medications, please refer to Appendix 1.

Acute Management of Infusion Reactions[2,10,35,95–101]

Prior to the infusion:[2]
- Assess history for risk factors
- Ensure appropriate pre-medications taken/given at the specified time periods
  - Patients with history of non-compliance to oral pre-medications should receive intravenous pre-medications[35]
- Updated IR protocol (including standing orders) and medical equipment/supplies needed for resuscitation must be available
- Educate patient and caregiver about signs and symptoms of IRs

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Prompt recognition of reaction and assessment of reaction severity

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Grade 1 or 2 Reactions:[2,35,95]
- Stop or slow infusion
- Have someone call for medical assistance
- Maintain IV line with normal saline or other appropriate solution
- Assess vitals and level of consciousness regularly
- Position patient appropriately
- Administer oxygen, if required
- Administer prn medications

Grade 3 or 4 Reactions:[2,35,95]
- Stop infusion and assess for anaphylaxis – follow local institutional anaphylaxis guidelines
- Have someone call for medical assistance
- Maintain IV line with normal saline or other appropriate solution
- Assess vitals and level of consciousness regularly
- Position patient appropriately
- Administer oxygen, if required
- Administer prn medications

SYMPTOM	TREATMENT
Flushing, rash, urticaria	- 1st generation H1-receptor antagonist (e.g. diphenhydramine 25-50 mg IV) x 1[2,95,96,98-101] - Ranitidine 50 mg IV[95,96,101] or Famotidine 20 mg IV x1[98] - Hydrocortisone 100 mg IV x 1[98-100]
Fever	- Antipyretic (e.g. acetaminophen 650 mg PO x 1[98-100])
Rigors/chills†	- Meperidine 25-50 mg IV x 1[97,98]
Nausea and/or vomiting	- Dimenhydrinate 25-50 mg IV x 1[99,100]
Hypotension	- Normal saline as per hospital policy
Wheezing/SOB	- Salbutamol 2.5-5 mg nebules inh q 20 min x 3 doses, then q1-4h PRN[96]

Symptom resolution

Grade 1 or 2 Reactions:[2]
- Consider restart and re-challenge at a reduced rate with pre-medications

Grade 3 or 4 Reactions:[2]
- Restart is discouraged‡
- If severe reaction occurred (e.g. anaphylaxis), re-challenge is strongly discouraged
- May consider re-challenge if no vital symptoms are affected (i.e. absence of respiratory distress, hypotension, etc)‡
- If no other suitable treatment options exist, desensitization may be considered to safely re-challenge

GRADE 1-2	GRADE 3-4
Any one of the following symptoms:	**Any one of the following symptoms:**
Transient flushing or rash (covering <30% BSA)	Severe rash (covering >30% BSA)
Dizziness (not interfering with activity)	Lightheadedness/ dizziness (interferes with activity)
Pruritus	Agitation
Fever 38ºC-40ºC	Fever >40ºC
Mild dyspnea (SOB with moderate to minimal exertion)	Bronchospasm with or without urticaria
Mild to moderate rigors/chills	Respiratory distress
Mild chest discomfort	Hypoxia
Mild abdominal discomfort	Chest tightness
Mild hypotension (less than 20mmHg drop from baseline)	Uncontrolled hypotension (more than 20 mmHg drop from baseline)
	Cyanosis
	Altered LOC
	Angioedema, periorbital/facial
	Severe nausea, vomiting, and/or diarrhea

Adapted from CTCAE (v. 5.0)[10]

*This is a general management approach, and may not be applicable to all medications, such as rituximab.

†Use with caution in elderly patients and patients with decreased renal function due to risk of confusion and hypotension.

‡May not be applicable to all anticancer medications. Please see Appendix 1 for further information.

Detailed documentation of the IR in the patient chart is imperative. Clear communication among healthcare providers is necessary to identify patients at risk for future IRs and to ensure patients are re-challenged safely. IRs should be reported through the appropriate channels for provincial tracking.

2.1 General Approach to Restarting:

	General Recommendations
General Approach to Restarting (Clinical Question 5.1)	• Consider restarting at a reduced infusion rate (i.e. at 50% of the rate at which the infusion reaction occurred) and titrate to tolerance for grade 1 or 2 reactions.[3,6,7,21] • Alternatively, local experience with a graduated infusion rate may be considered (e.g. re-challenge at 25% for 5 minutes, 50% for 5 minutes, 75% for 5 minutes then full rate if no reaction). • Restart is discouraged for grade 3 or 4 reactions.

Re-challenge

3.1 General Re-challenge Strategies:

	General Recommendations
General Approach to Re-challenge	• Careful consideration of the potential clinical benefit and risks of further treatment are required. • Concurrent consideration of patient factors, the severity and nature of the IR and availability of a suitable alternative treatment is recommended. • Patient education regarding the risks with this procedure is recommended.
Grade 1-2 Reactions	• **Reduced administration rate** (i.e. initiate at 50% of the previous administration rate at which the infusion reaction occurred and titrate to tolerance) and • **Additional pre-medications** (i.e. corticosteroids, H1-receptor antagonists, H2-receptor antagonists). May also consider adding montelukast 10 mg ± acetylsalicylic acid 325 mg).[102]
Grade 3-4 Reactions	• Re-challenge is discouraged. • May consider re-challenge if no vital symptoms affected during the IR (i.e. absence of respiratory distress, hypotension, etc.).

General Recommendations	
	• Consider re-challenge with intensified pre-medications and extended infusion duration if clinically necessary and no alternative treatment available. • A desensitization protocol may be required to safely re-administer the medication .[2,3,35]
Recurrent IRs	• Switch therapy. • Discontinue treatment. • Desensitization prior to each subsequent administration.
Additional Considerations – Montelukast and ASA (Recommendation 6.1)	• There is limited evidence to support the addition of oral montelukast ± oral acetylsalicylic acid as routine pre-medications in the secondary prophylaxis setting; however, based on expert consensus, it can be a reasonable approach.[102]

Key re-challenge recommendations by medication

3.2 Anticancer Medication Class:

Class of Medication	Recommendations
Taxanes (Recommendation 6.2, Recommendation 6.3)	• If a patient experiences an IR with a taxane (e.g. paclitaxel), there is insufficient evidence to recommend re-challenge with a different taxane (e.g. docetaxel) due to high rates of cross-reactivity.[7,35,103,104] • There is insufficient evidence to support a specific re-challenge protocol for taxanes. [26,105,106] • For grade 1-2 IRs, consider re-challenge at a reduced infusion rate with pre-medications.[26,105,106] • If a patient who experienced a grade 3-4 IR is to be re-challenged, consider desensitization.
Platinums (Recommendation 6.4, Recommendation 6.5)	• For patients who experienced a grade 1-2 IR previously, the addition of pre-medications and/or extending the duration of the infusion are potential strategies that may facilitate safe re-challenge.[54,105–110] • Re-challenge with cisplatin for patients who experienced a grade 3 or 4 IR with carboplatin requires careful consideration of the potential clinical

Class of Medication	Recommendations
	benefit and risks of further treatment. 2 deaths have been reported in literature.[111–116]
Monoclonal Antibodies - Rituximab[102,117] ([Recommendation 6.6](#))	• For patients who experienced a grade 1-2 IR with rituximab previously, the use of additional pre-medications and/or extending the duration of the infusion are potential strategies that may facilitate safe re-challenge. • Re-challenge with rituximab for patients who experienced a grade 3 or 4 IR previously requires careful consideration of the potential clinical benefit and risks of further treatment.

Re-Challenge using a desensitization protocol

4.1 General Desensitization Strategies:

	General Recommendations
Qualification[2] ([Recommendation 7.1](#))	• Patients who experienced a grade 3 or 4 IR <u>and</u> who have no clinically appropriate alternative available. • Patients who had repeated IRs during re-challenge.
Contraindications[118] ([Recommendation 7.2](#))	• Type II Reactions. • Type III Reactions. • Severe cutaneous adverse reactions (e.g. SJS, TEN, DRESS).
Skin Testing ([Recommendation 7.3](#))	• Skin testing may be used as a tool during patient assessments; however, other patient-specific clinical features should be taken into consideration concurrently.
Prophylaxis ([Recommendation 7.4](#))	A reasonable desensitization pre-medication regimen includes:[112,119–121] • H1-receptor antagonist (e.g. diphenhydramine or a non-sedating equivalent). • H2-receptor antagonist (e.g. ranitidine). • Corticosteroid (e.g. dexamethasone). • Montelukast 10 mg. • ASA (e.g. 500 mg, or the dose that is commercially available, such as 325 mg). Beta-blockers and ACE-inhibitors should be held for 24 hours before implementing the desensitization protocol, as they may interfere with the action of rescue medications if an IR occurs during the desensitization process.

General Recommendations	
Desensitization Protocol ([Recommendation 7.5](#))	- The protocol with the most evidence is a three-bag 12 step protocol developed by Castells et al.[112,119] - If a three-bag 12 step protocol is not feasible, a one-bag 12-step protocol developed by Chung et al. can be a reasonable alternative.[120,122–126] - For high-risk patients (e.g. patients who experienced severe anaphylaxis during the initial infusion, as well as patients with severe respiratory or cardiac disease and patients who are pregnant), a four-bag 16 step protocol can be used.[112,118,119,127]

RECOMMENDATIONS FOR INFUSION REACTION PROPHYLAXIS

▬▬▬▬ [[Return to Table 1.1](#)]

Risk Factors

Given the potential for life-threatening injury when an IR occurs, it is important to consider all the possible factors that may increase a patient's risk for experiencing a reaction. There are classes of agents that are more likely to cause an IR, including taxanes (paclitaxel, docetaxel, cabazitaxel), platinum compounds (carboplatin, oxaliplatin, cisplatin), monoclonal antibodies (rituximab, daratumumab and obinutuzumab), and epipodophyllotoxins (etoposide).[4] Concomitant medications may alter the risk for an IR, as seen with carboplatin. The incidence of IR was higher in patients receiving carboplatin-paclitaxel or carboplatin alone compared to carboplatin with pegylated liposomal doxorubicin.[128,129] Concomitant radiation may increase the risk for an IR, as seen with cisplatin.[55,56,130]

Other risk factors include route of administration, such as intravenous etoposide (which has a higher incidence of reaction compared to oral etoposide) or intravenous monoclonal antibodies such as rituximab (which has a higher incidence of reaction compared to subcutaneous rituximab) and rate of administration, with slower rates typically associated with less risk for reaction.[4] The interval between treatments can impact IR rates, as shown with carboplatin, which has a higher incidence of severe reactions if the interval between courses exceeds 24 months, compared with less than 12 months.[131] Previous exposure to a platinum may increase the risk for experiencing an IR. This occurs with carboplatin, which has an increased incidence of IR from <1% in 5 or fewer cycles to 19.5% after 8 cycles.[111] This is also seen with oxaliplatin, where IRs occur mostly after the 6th cycle.[55,56]

Drug formulation has been implicated in IRs, with certain excipients associated with a higher incidence of reaction as opposed to the drug itself (for example, Polysorbate 80 and Cremophor EL).[4] Incorrect reconstitution techniques may lead to increased risk for IR. This was observed when incorrect preparation of cyclosporin led to higher Cremophor EL concentrations infused in the first 10 minutes of administration than intended.[132]

Patient factors may also contribute to the risk of developing an IR. It has been suggested that patients experience an IR more often with taxanes if they have a history of atopy.[133] In addition, a higher incidence of IRs with paclitaxel was observed in ovarian cancer patients who have a history of mild dermal reactions in previous courses, respiratory dysfunction, obesity, and/or those who were postmenopausal at time of ovariectomy.[134] Patients with a history of drug allergies may be at increased risk of IR with carboplatin.[55,56,111] Female patients of younger age may be at increased risk of IR with oxaliplatin.[55,56] High tumor burden (e.g. lymphocyte count higher than 25-50 x 10^9/L) can increase the risk of CRS with rituximab.[6,69,135] Patients with head and neck

cancer are at increased risk of developing an IR with cetuximab than patients with other types of cancer.[136]

Prophylaxis

Due to the potential negative impact of IRs on patient safety and treatment, it is important to consider and implement strategies to minimize the risk of IRs. Some strategies that may be implemented include assessing patient risk factors for IRs, optimizing pre-medications and administering treatments using graduated infusion rates. Some commonly used cancer medications are associated with a high risk of IR. Certain prevention strategies used in clinical practice may differ from the product monograph. These will be discussed in further detail below. Refer to Appendix 1 for prevention strategies for all other medications.

During IRs, leukotrienes, prostaglandins, and histamines, amongst other factors, are released. Medications capable of preventing and mitigating IRs are those which target the mechanisms of the IRs.

- **Corticosteroids** cause immunosuppression, inhibiting the expression and action of cytokines, leukotrienes, and prostaglandins, amongst other actions.[102]

- **Histamine 1 and 2 (H1 and H2) antagonists** prevent histamine release from mast cells, with H2 blockers potentiating the effects of H1 blockers.[101,137]

- **Montelukast** inhibits the mast cell mediated release of leukotrienes and may be used to reduce inflammation and bronchoconstriction.[102,138]

Taxanes

IRs may occur due to complement activation by excipients (Cremophor EL with paclitaxel or Polysorbate 80 with docetaxel) and/or IgE-mediated mechanisms towards the taxanes or solvents. Incidence of any grade IR with paclitaxel is reported to be up to 30%.[2,17] Incidence of any grade IR with docetaxel is reported to be 5-20%.[3,36] The majority of IRs to taxanes occur during the first two cycles of therapy.[2,3,139] Symptoms can develop within the first 10 minutes of the infusion, and may cause dose interruptions, delays or discontinuations.[2,3,139] Prophylaxis with pre-medications prior to taxane infusion has become the standard of care.

PACLITAXEL

Clinical Question 1.1: **What is the recommended route of administration of dexamethasone for paclitaxel IR prevention?**

Recommendation 1.1: Both oral and IV dexamethasone are acceptable options. Both are effective at reducing the rate of IR. Results of a meta-analysis and retrospective studies suggest that oral dexamethasone may be slightly more effective when compared to IV; however, a RCT found no significant difference in IR rates. Patient compliance and adverse effects can be of concern with the oral route.[7,14–24]

Summary of Evidence & Discussion:

In clinical practice, some Ontario centres have substituted IV dexamethasone for the recommended oral route of administration.[3,4] Five studies comparing oral to IV dexamethasone were reviewed.

A meta-analysis analyzed 6 studies including patients (n = 1347) who received paclitaxel. The studies compared the standard oral dexamethasone pre-medication regimen to the experimental IV dexamethasone pre-medication regimen. The standard pre-medication consisted of oral dexamethasone 12- and 6-hours prior to paclitaxel administration with IV cimetidine and IV diphenhydramine 30 minutes prior to paclitaxel administration. The experimental IV dexamethasone pre-medication regimen consisted of a single dose of IV dexamethasone administered 30 minutes prior to paclitaxel administration. Doses of these pre-medications were not specified. Overall, the meta-analysis found a decreased incidence of severe IRs when comparing oral to IV dexamethasone regimens (2.5% vs 5%, OR 0.53, 95% CI 0.28-0.99, p = 0.05), suggesting that the oral route is more effective. No significant difference was seen in the overall paclitaxel-related IR rates between oral vs. IV dexamethasone (OR 0.76, 95% CI 0.55-1.06, p = 0.11).[23]

A double-blinded RCT evaluated gynecological patients (n = 281) who received their first cycle of combined carboplatin and paclitaxel. Patients in the PO-D group received oral dexamethasone 20 mg 12- and 6- hours prior to the paclitaxel infusion and IV 0.9% normal saline solution (i.e. placebo) 30 minutes prior to the paclitaxel infusion. Patients in the IV-D group received oral lactose tablets (i.e. placebo) at 12- and 6- hours prior to the paclitaxel infusion and IV dexamethasone 20 mg 30 minutes prior to the paclitaxel infusion. All patients also received IV ranitidine 50 mg and IV diphenhydramine 50 mg 30 minutes prior to the paclitaxel infusion. No significant difference in overall (18% vs 19%, p = 0.78) or severe (0.7% vs 0%, p = 0.498) IR rates were found when comparing oral to IV dexamethasone regimens. There was, however, an increased rate of side effects (i.e. acne, 10.6% vs 2.6%, p = 0.004) and a trend towards an increase in other side effects [i.e. stomach irritation (p = 0.338), increased appetite (p = 0.092), and insomnia (p = 0.258)] in patients given oral dexamethasone.[24]

One retrospective analysis reviewed gynecological patients (n = 148) who received paclitaxel every 3 weeks. Patients were given an oral pre-medication regimen (oral

dexamethasone 20 mg 12- and 6-hours prior to paclitaxel) or an IV pre-medication regimen (IV dexamethasone 20 mg 30 minutes prior to paclitaxel). Overall IR rates (14.5% vs 5.4% vs, p = 0.07) and grade 3 IR rates (5.4% vs 0%, p = 0.049) were higher with the IV dexamethasone regimen, suggesting that the oral dexamethasone regimen may be more effective.[15]

One retrospective cohort study reviewed patients with ovarian or primary peritoneal carcinoma (n = 217) who received paclitaxel. Patients received either the conventional prophylactic regimen (i.e. oral dexamethasone 20 mg 12- and 5-hours prior to paclitaxel, IV diphenhydramine 50 mg and IV ranitidine 50mg 30 minutes prior to paclitaxel) or the modified prophylactic regimen (i.e. IV dexamethasone 20 mg 30 minutes prior to paclitaxel, IV diphenhydramine 50 mg and IV ranitidine 50 mg 30 minutes prior to paclitaxel). 107 patients received the conventional prophylactic regimen, and 110 patients received the modified prophylactic regimen. Overall IR rates (7.5% vs 17.3%, p = 0.047) were lower in the conventional prophylactic regimen group. Similarly, severe IR rates (0.9% vs 7.3%, p = 0.026) were lower in the conventional prophylactic regimen group. All IRs except one occurred during the first cycle. This study suggests that the conventional prophylactic regimen with oral dexamethasone may be more effective.[16]

Another retrospective analysis reviewed non-small cell lung cancer patients (n = 107) who received paclitaxel with carboplatin every 3 weeks. Patients were given a conventional pre-medication regimen (IV dexamethasone 20 mg 12- and 6- hours prior to paclitaxel infusion, with oral diphenhydramine 50 mg and IV ranitidine 100 mg) or a short pre-medication regimen (single dose of IV dexamethasone 20 mg 30 minutes prior to paclitaxel infusion, with oral diphenhydramine 50 mg and IV ranitidine 100mg). The study found no significant difference in IR rates between conventional and short regimens (32.3% vs 45.2%, p = 0.177). Severe reactions were significantly higher in the short regimen (14.3% vs 1.5%, p = 0.027). The authors then looked at patients prospectively (n = 22) who were given a modified pre-medication regimen. The modified pre-medication regimen consisted of oral dexamethasone 8 mg the night prior to the paclitaxel, in addition to IV dexamethasone 20 mg, IV diphenhydramine 50 mg and IV ranitidine 100 mg to be given 30 minutes prior to paclitaxel infusion. An incidence of 63% in grade 1 IRs was found in this group of patients, with no incidence of IRs of higher severity. This study suggests that the conventional pre-medication regimen may be more effective at preventing severe IRs than the modified pre-medication regimen.[20]

Based on the majority of studies described, there appears to be a trend towards oral dexamethasone being more effective than IV dexamethasone; however, the well-designed RCT suggests no difference in IR rates between the two. Patient compliance and side effects may be an issue with the oral route.

Clinical Question 1.2: **What is the recommended dose of dexamethasone for patients receiving weekly paclitaxel?**

Recommendation 1.2: Dexamethasone 10 mg IV administered 30-60 minutes prior to weekly paclitaxel infusions.[17,18,22,25,26]

Summary of Evidence & Discussion:

Currently, there is no consensus for the recommended pre-medication schedule for weekly paclitaxel regimens. Given the risk of side effects associated with high doses of dexamethasone, a balance between the lowest effective dose to prevent IR while minimizing the risk of side effects is needed.[17] In clinical practice, some Ontario centres use IV dexamethasone 10 mg for weekly paclitaxel regimens. Three studies reviewing the doses of dexamethasone with weekly paclitaxel regimens were reviewed.

A prospective study by Zidan et al. evaluated patients with various cancer types who received paclitaxel weekly (n = 100) and every 3 weeks (n = 80). Patients were given pre-medications with oral dexamethasone (10 mg for the 1st cycle, then at a tapering dose) 12- and 6-hours prior to paclitaxel, oral promethazine 25 mg 60 minutes prior to paclitaxel and IV cimetidine 300 mg 30 minutes prior to paclitaxel. The dexamethasone dose was tapered to 6 mg for the 2nd cycle, then 4 mg for the 3rd cycle, and 2 mg for the 4th cycle on. If IRs occurred with the first cycle of paclitaxel, dexamethasone was not tapered, and an additional dexamethasone dose of 10 mg IV was given 30 minutes prior to each subsequent paclitaxel infusion. Paclitaxel was infused over 60-90 minutes for weekly doses and over 3 hours for every 3-week doses. IRs occurred during the first cycle in 3 patients (4%) who received paclitaxel every 3 weeks. IRs occurred after the 4th cycle in 1 patient (1%) who received weekly paclitaxel. 2 of the 3 patients continued paclitaxel with no further IRs, and 1 of the 3 patients discontinued paclitaxel due to a second IR.   This study suggests that lower doses of dexamethasone may be effective in preventing IRs in patients receiving weekly paclitaxel.[25]

Another prospective study included patients with breast cancer (n = 122) who received weekly paclitaxel. Patients were given oral dexamethasone 20 mg 12- and 8-hours pre-infusion (with IV diphenhydramine 50 mg). If no IRs occurred, patients were given IV dexamethasone 20 mg prior to the 2nd cycle, and 10 mg IV prior to the 3rd and 4th cycle, after which it continued to be tapered by 2 mg with each cycle until discontinued. In addition, IV diphenhydramine 50 mg was changed to oral after 4 cycles if no IRs occurred. A total of 115 patients were given the tapering schedule, with most reaching no dexamethasone by the 9th cycle. Four IRs occurred in cycle 1 and one patient had an IR during the taper (on 10 mg of dexamethasone). This study suggests that reducing dexamethasone doses does not appear to have a significant impact on the risk of IRs.[26]

A retrospective comparison reviewed breast and gynecological patients (n = 358) who received at least 4 doses of paclitaxel. Patients were given one of two different pre-medication protocols. In the early termination protocol, all pre-medications were discontinued after the 2nd dose if no IR occurred. For patients who received weekly

paclitaxel, this protocol consisted of dexamethasone 8 mg, diphenhydramine 25 mg and famotidine 20 mg administered 30 minutes prior to paclitaxel infusion (routes of administration were not specified). For patients who received every 2- or 3-weeks paclitaxel, this protocol consisted of dexamethasone 20 mg 12- and 6-hours prior to infusion, in addition to diphenhydramine 25 mg and famotidine 20 mg administered 30 minutes prior to paclitaxel infusion (routes of administration were not specified). In the low-dose continuation protocol, only diphenhydramine and famotidine were discontinued after the 2nd dose if no IR occurred. This was used for patients who received weekly, every 2- or every 3-weeks paclitaxel infusions. This protocol consisted of dexamethasone 10 mg for the first 2 doses, then 8 mg starting with the third dose. Both were used in addition to diphenhydramine 25 mg and famotidine 20 mg (routes of administration were not specified). Data from 120 patients were analyzed (others were excluded due to non-compliance with the medication schedule). All IRs in this study occurred with the first infusion of paclitaxel. IR rates between the 2 protocols were not significantly different (7% vs 5%, p = 0.7). This study suggests that rates of IR were comparable between groups who used a higher versus lower dose of dexamethasone in the pre-medication regimen.[22]

Based on the results of the available studies, reducing the dose of dexamethasone with weekly paclitaxel regimens appears to be an effective and safe option, especially for patients experiencing (or at high risk of experiencing) side effects due to dexamethasone.[18]

Clinical Question 1.3: **What is the recommended route of administration of the H1-receptor antagonist (e.g. diphenhydramine) for paclitaxel IR prevention?**

Recommendation 1.3: Both oral and IV administration are acceptable options.[7,18,23,25,26]

Summary of Evidence & Discussion:
The product monograph of paclitaxel recommends using IV diphenhydramine 50 mg (or its equivalent) as part of the pre-medication regimen.[14] In clinical practice, some Ontario centres have substituted oral diphenhydramine for the recommended IV route of administration. Few studies specifically studied the use of oral diphenhydramine within the pre-medication regimen prior to paclitaxel infusions. According to 3 review articles, the FDA-approved package labeling for paclitaxel recommends the use of an IV or PO H1-receptor antagonist (e.g. diphenhydramine 25-50 mg) in addition to the other pre-medications, to be given 30-60 minutes prior to paclitaxel administration every 3 weeks.[7,18,23]

Braverman et al. used IV diphenhydramine initially as part of the pre-medication regimen prior to weekly paclitaxel administration in patients with breast cancer (n = 122). After 4 cycles of paclitaxel, diphenhydramine 50 mg was administered orally, instead of intravenously, if no IR occurred. The overall IR rate was 5.7% (4 patients during the 1st cycle, 2 patients during the 2nd cycle and 1 patient during the 4th cycle).

No IRs occurred after the 4th cycle, suggesting that oral diphenhydramine may be an effective alternative to prevent IRs.[18,26]

Zidan et al. evaluated patients who were given pre-medications with oral dexamethasone (10 mg for the 1st cycle, then at a tapering dose) 12- and 6-hours prior to paclitaxel, oral promethazine 25 mg 60 minutes prior to paclitaxel and IV cimetidine 300 mg 30 minutes prior to paclitaxel. The dexamethasone dose was tapered to 6 mg for the 2nd cycle, then 4 mg for the 3rd cycle, and 2 mg for the 4th cycle on. If IRs occurred with the first cycle of paclitaxel, dexamethasone was not tapered, and an additional dexamethasone dose of 10 mg IV was given 30 minutes prior to each subsequent paclitaxel infusion. Paclitaxel was infused over 60-90 minutes for weekly doses and over 3 hours for every 3-week doses. IRs occurred during the first cycle in 3 patients (4%) who received paclitaxel every 3 weeks. IRs occurred after the 4th cycle in 1 patient (1%) who received weekly paclitaxel. 2 of the 3 patients continued paclitaxel with no further IRs, and 1 of the 3 patients discontinued paclitaxel due to a second IR. This study suggests that administering an H1-receptor antagonist through the oral route may be an effective option to prevent IRs.[25]

Sasada et al. embedded both a retrospective and a prospective study design to sequentially review non-small cell lung cancer patients (n = 107) who received paclitaxel with carboplatin every 3 weeks. Patients were given a conventional pre-medication regimen (IV dexamethasone 20 mg 12- and 6- hours prior to paclitaxel infusion, with oral diphenhydramine 50 mg and IV ranitidine 100 mg) or a short pre-medication regimen (single dose of IV dexamethasone 20 mg 30 minutes prior to paclitaxel infusion, with oral diphenhydramine 50 mg and IV ranitidine 100mg). The study found no significant difference in IR rates between conventional and short regimens (32.3% vs 45.2%, p = 0.177).[17,20]

There is a paucity of literature comparing the efficacy of oral to IV administration of H1-receptor antagonists in the pre-medication regimen for paclitaxel. The limited data available together with clinician experience in the desensitization setting suggests that administering H1-receptor antagonists through the oral route may be a feasible and safe option.

Clinical Question 1.4: **Is there a role for discontinuing pre-medications after the 2nd dose of paclitaxel?**

Recommendation 1.4: Consider discontinuing pre-medications for paclitaxel (single agent or combination) if there was no previous IR in the first 2 doses.[7,27–30]

Summary of Evidence & Discussion:
Currently, there is no consensus for the discontinuation of pre-medications for paclitaxel regimens. Three studies and one poster presentation reviewing the impact of discontinuing pre-medications after dose 2 of paclitaxel were reviewed.

A prospective observational study by Berger et al. included patients with breast cancer (n = 55) who received either weekly or every 2 week paclitaxel, as a single agent or in combination (excluding cisplatin or carboplatin). Pre-medications used include IV dexamethasone 20 mg with IV diphenhydramine 50 mg and IV famotidine 20 mg given 30 minutes pre-infusion. If no IR occurred in the first 2 doses, pre-medications were discontinued. In this study, all patients had their pre-medications discontinued after 2 doses and none required rescue medications for IRs in subsequent doses, suggesting that this may be a safe course of action.[27]

A retrospective analysis subsequently published by Berger et al. reviewed patients with early breast cancer (n = 234) who received paclitaxel as a single agent or in combination with other agents (excluding cisplatin or carboplatin). The standard pre-medications included IV dexamethasone 20 mg, IV diphenhydramine 50 mg and IV famotidine 20 mg administered at least 30 minutes prior to paclitaxel infusion). These were discontinued prior to the 3rd paclitaxel infusion (and for subsequent infusions) if patients did not experience an IR during the first 2 doses of paclitaxel. The incidence of rescue medications used to treat an IR with dose 3-6 for patients who had their pre-medications discontinued was estimated. Of the 234 patients analyzed, only 2 of these patients required rescue medications to treat an IR with subsequent paclitaxel doses (0.85%; 95% CI 0.10-3.05%). The results suggest that pre-medications may not be required if no IR occurred during the first 2 doses of paclitaxel.[28]

A second retrospective analysis reviewed patients with breast cancer (n = 81) who received single agent paclitaxel or in combination with trastuzumab in which standard pre-medications were discontinued after 2 doses. Standard pre-medications were defined as IV dexamethasone 5 mg, IV diphenhydramine 25 mg and IV ranitidine 50 mg. The rate of IR in patients whose pre-medications were stopped in this study was 6.25% (with 5 patients experiencing an IR) occurring with the 3rd-6th doses.[30] This is comparable to the 10% rate of IR seen in patients who continued to receive pre-medications. The results suggest that the absence of pre-medications after 2 doses may not negatively impact the risk of IRs.[7]

A poster presentation of a retrospective chart review assessed patients with various cancers (n = 187) who received every 3 week or weekly paclitaxel with a platinum regimen (n = 111) and every 3 week, every 2 week or weekly paclitaxel +/- trastuzumab (n = 76). Patients had pre-medications discontinued starting from dose 3 if there was no history of IR. For patients who had pre-medications discontinued and who received paclitaxel + platinum, the incidence of non-severe IR was 1.80% (95% CI 0.22-6.36). Similarly, for patients who had pre-medications discontinued and who received paclitaxel +/- trastuzumab, the incidence of non-severe IR was 2.63% (95% CI 0.32-9.18). It was noted by the authors that the rates of IR in their study was comparable to that in existing literature. This suggests that even without pre-medications after 2 doses, the rates of IR were not significantly different than other studies in which pre-medications were continued.[29]

Local prescribing practices at two large Ontario cancer centres are congruent with that which was suggested by the literature presented above. Based on the current available evidence and expert consensus, the discontinuation of pre-medications may be a safe and feasible option for patients who did not experience an IR with their first two doses of paclitaxel.

[Clinical Question 1.5](#)*: Is there a role for extended infusion of paclitaxel in patients who have not experienced an IR?

Recommendation 1.5: Extended infusion of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.[4,18,27,28]

Summary of Evidence & Discussion:
Available literature suggests that changing the infusion rate is not an effective strategy for primary prevention of IRs.[4,27,28] Paclitaxel infusion duration has changed from 3-24 hours to 1-3 hours. It is suggested that many severe IRs associated with paclitaxel may be prevented using pre-medications alone.[18] IR rates appear to be similar when comparing duration of administration of paclitaxel over 24 hours and over 3 hours; however, administering paclitaxel over 24 hours has generally fallen out of favour due to the higher risk of febrile neutropenia.[7] Current recommendations are to administer paclitaxel over 3 hours, except for weekly dosing, where paclitaxel may be infused over 1 hour.[14,21,140]

It is not recommended to extend paclitaxel infusions as a strategy for primary prophylaxis of IRs due to the lack of evidence available to demonstrate benefit.

[Clinical Question 1.6](#): Is there a role for the addition of hydrocortisone 100 mg IV to the existing pre-medication regimen?

Recommendation 1.6: There is insufficient evidence to recommend the addition of hydrocortisone 100mg IV to the existing standard pre-medication regimen for paclitaxel.[19]

Summary of Evidence & Discussion:
Hydrocortisone is often used to treat symptoms of IR, with a quick onset of action. It is postulated that adding hydrocortisone to the pre-medication regimen may be effective in additionally reducing the rate of IRs.[19] This is not recommended and therefore, not commonly used in clinical practice. One study that added hydrocortisone to the standard pre-medications administered prior to paclitaxel infusion was reviewed.

One RCT including gynecological, paclitaxel naïve patients (n = 90) scheduled for 6 cycles of paclitaxel + platinum compared the addition of IV hydrocortisone 100 mg to the existing pre-medication schedule (IV dexamethasone 20 mg, IV chlorpheniramine 10 mg, oral diphenhydramine 25 mg and IV ranitidine 50 mg) to the existing pre-medication schedule alone. There was a significantly decreased rate of IR in the group of patients

who received hydrocortisone in addition to the existing pre-medication schedule in comparison to the group of patients who did not (2.4% vs 18%, p = 0.030). All IRs occurred in cycles 1-3, within 10 to 40 minutes after initiation of the infusion. IRs peaked in cycle 3 for patients who were given hydrocortisone in addition to the existing pre-medication schedule, compared to cycle 2 for patients who were given the existing pre-medication schedule with no hydrocortisone.[19]

Due to the sparse amount of evidence surrounding the use of hydrocortisone as part of the pre-medication regimen for prophylaxis of IRs, there is insufficient evidence currently to recommend using hydrocortisone routinely for this indication. Further studies are required.

DOCETAXEL

Clinical Question 1.7: **What is the recommended dexamethasone pre-medication regimen for IR prevention in patients receiving docetaxel?**

Recommendation 1.7: Dexamethasone 8 mg orally twice daily for 3 days starting the day prior to docetaxel is recommended. Dexamethasone 10-20 mg IV can be given 30-60 minutes prior to the infusion if the patient forgot to take one or more oral dose(s). This pre-medication regimen should be continued, even in the absence of an IR, due to the benefits of dexamethasone on adverse effects, such as pain and edema.[18,31–33]

Summary of Evidence & Discussion:
Like paclitaxel, a balance between the lowest effective dose to prevent IR while minimizing the risk of side effects with dexamethasone is needed. Currently, there is no consensus for reducing the dose of dexamethasone, the route of administration of dexamethasone or the optimal time (if any) for discontinuing dexamethasone in clinical practice. Five strategies for changing the dexamethasone pre-medication regimen administered prior to docetaxel administration have been suggested.

One strategy was outlined in a review of 3 RCTs including advanced lung or breast cancer patients (n > 400) who received every 3 week compared to weekly docetaxel. Patients who received the every 3 week docetaxel dose were given the standard 3-day dexamethasone pre-medication schedule. Patients who received weekly docetaxel were given oral dexamethasone 8 mg every 12 hours for 3 doses, starting 12 hours prior to the docetaxel infusion. Rates of IR reported in these trials were similar between the two groups.[18]

A second strategy was described by Sparano et al. in an RCT including operable breast cancer patients (n = 4950) who received every 3 week or weekly paclitaxel or docetaxel. Patients who received docetaxel every 3 weeks were given oral dexamethasone 8 mg twice daily for 3 days beginning one day prior to docetaxel infusion. Patients who received weekly docetaxel were originally scheduled to receive a pre-medication regimen comparable to that of the weekly paclitaxel regimen (e.g. single IV dose of dexamethasone). However, it was noted in the supplementary appendix that due to the

unexpectedly higher proportion of IRs with the first dose in the weekly docetaxel group, the regimen was changed to oral dexamethasone 8 mg twice daily for 2 days, beginning 24 hours prior to the docetaxel infusion. If these patients did not experience an IR after 2 docetaxel doses, dexamethasone was changed to a single dose of 10 mg IV given 30 minutes prior to the docetaxel infusion. There was a 5% incidence of IR in the group who received docetaxel every 3 weeks, compared to a 4% incidence of IR in the weekly docetaxel group. The rate of IRs with the single IV dose of dexamethasone pre-medication regimen was not reported. The change in pre-medication regimen partway through the study suggests that a single dose of dexamethasone IV may not be sufficient to prevent IRs with docetaxel, especially in patients at higher risk of IR. However, it may be reasonable to consider dexamethasone IV in some cases (e.g. patients who missed one or more doses of oral dexamethasone).[18,31]

A third strategy was outlined in a retrospective review of patients with various cancers (n = 206) who received weekly docetaxel. Patients in the control group (n = 109) were given both IV and oral dexamethasone. IV dexamethasone 10 mg was followed by oral dexamethasone 4 mg twice daily for 2 doses, starting 1 hour prior to the docetaxel infusion. Patients in the experimental group (n = 97) were given only dexamethasone 10 mg IV 1 hour prior to docetaxel infusion. The incidence of IR was similar between the control and experimental group (8.3% vs 8.2%, p = 0.998), suggesting that a single IV dose of dexamethasone may be comparable to the IV and oral dexamethasone pre-medication regimen in preventing IRs. However, this study is retrospective in nature and requires prospective studies to confirm the results.[32]

A fourth strategy was described in a retrospective review of patients with various cancers (n = 90) who received every 3 week or weekly docetaxel. Patients were given a single dose of IV dexamethasone 20 mg prior to the first two cycles of docetaxel. The incidence of IRs requiring treatment was noted to be 7.8% in this study. This is lower than the rate reported by the manufacturer (15.2%), who used the standard recommended oral dexamethasone regimen prior to docetaxel infusion. This suggests that a single dexamethasone IV dose prior to docetaxel therapy may be effective at preventing IRs; however, similar to the above study, it is retrospective in nature.[33]

A fifth strategy was suggested in an unpublished phase II study of metastatic breast cancer patients (n = 120) who received weekly docetaxel. This study compared IV dexamethasone 8 mg once prior to docetaxel or no dexamethasone. Although no IRs were reported within the 2 groups in this study, the group who did not receive pre-medication reported higher rates of non-hematologic toxicities (e.g. fluid retention, 12% vs 3%, p = 0.017). This study suggests that dexamethasone may be effective in not only preventing IRs, but also other adverse effects of docetaxel therapy, such as fluid retention.[18]

There are conflicting strategies regarding dexamethasone in the pre-medication regimen for docetaxel, with differences in the doses, route of administration and duration. In the absence of a clear superior regimen, the dexamethasone regimen recommended was drawn from manufacturer recommendations, expert consensus and

local experience. Consideration can be given to dexamethasone 10-20 mg IV if patient has forgotten to take the oral dexamethasone dose.

Clinical Question 1.8: **What dexamethasone regimen should be used for patients receiving docetaxel in addition to prednisone (i.e. prostate cancer)?**

Recommendation 1.8: Dexamethasone 8 mg PO twice daily for 3 days, starting the day prior to the docetaxel infusion. Alternatively, dexamethasone 8 mg PO at 12 hours, 3 hours and 1 hour prior to the docetaxel infusion may be given as outlined in the docetaxel product monograph.[34–37]

Summary of Evidence & Discussion:

Docetaxel is used in combination with oral prednisone for the treatment of hormone-resistant metastatic prostate cancer.[36] With a corticosteroid already being given as part of the treatment regimen, the dexamethasone dose as part of the pre-medication regimen to prevent IRs may be unclear. Current practice in some Ontario oncology centres is to give oral dexamethasone 8 mg twice daily for 3 days, starting the day prior to docetaxel for this patient population.

There is sparse literature available around the optimal dexamethasone dose in the pre-medication regimen for docetaxel in combination with oral prednisone in this specific patient population. The current ESMO Clinical Practice Guidelines for the management of infusion reactions in systemic anticancer therapy suggests oral dexamethasone 8 mg at 12 hours, 3 hours and 1 hour prior to the docetaxel infusion.[2] This is in concordance with the regimen suggested by the manufacturer.[36]

A large Phase III trial including patients with metastatic castrate-resistant prostate cancer (mCRPC, n = 662) who received every 3 week or weekly docetaxel in combination with oral prednisone 5 mg twice daily reported no IRs. Patients who received docetaxel every 3 weeks were given oral dexamethasone 8 mg 12 hours, 3 hours and 1 hour prior to the docetaxel infusion. Patients who received weekly docetaxel were given dexamethasone 8 mg 1 hour prior to the docetaxel infusion. Route of administration for dexamethasone was not specified. No IRs were reported in this trial.[37]

Based on expert consensus, it is reasonable to consider using the dexamethasone regimen described above for these patients as an alternative.

CABAZITAXEL

Clinical Question 1.9: **What pre-medications are recommended for IR prevention in patients receiving cabazitaxel?**

Recommendation 1.9: The recommended pre-medications are a corticosteroid (e.g. dexamethasone 8 mg), an H1-receptor antagonist (e.g. diphenhydramine 25 mg) and an H2-receptor antagonist (e.g. ranitidine 50 mg). Pre-medications can be given intravenously or orally.[7,21,39–42]

Summary of Evidence & Discussion:

In two open-label studies (one prospective, single-arm, open label and one randomized Phase III), mCRPC patients (total n = 656) treated with cabazitaxel in combination with oral prednisone 10 mg daily reported no IRs. Patients were given pre-medications as follows: an H1-receptor antagonist, corticosteroid (i.e. dexamethasone 8 mg or equivalent) and H2-receptor antagonist. Route of administration for pre-medications were not specified.[40,41]

In contrast, a Phase II study including patients with taxane-resistant metastatic breast cancer (n = 71) treated with cabazitaxel reported a rate of mostly mild IRs of 4% after pre-treatment with an IV H1-receptor antagonist (medication and dose not specified) 30 minutes prior to cabazitaxel infusion.[42]

Based on the available studies, the pre-medications used are consistent with the manufacturer recommendations. Although studies used the IV route for pre-medications, in clinical practice, some Ontario centres have used the oral route with no concerns.

Platinums

IRs to platinum compounds are typically thought to be associated with IgE-mediated Type 1 reactions.[3,56] IRs rarely occur with the first cycle of treatment but tend to increase with repeated drug exposure, commonly during the 7th-10th cycle.[55,111]

Strategies postulated to reduce the incidence of IR include extended infusion duration, use of pre-medications before the infusion or skin testing to predict patients at risk of experiencing an IR. Routine prophylaxis with pre-medication is not recommended to prevent IRs with platinums due to insufficient evidence available demonstrating efficacy. Attempts have been made to predict and decrease the risk of IRs and its consequences.[43–46]

CARBOPLATIN

The overall incidence of IRs with carboplatin can range between 1% (for patients who recently started treatment) and 44% (for patients who received several lines of treatment).[112,114] Onset of symptoms can vary from minutes to hours. The risk of IRs with carboplatin can be increased with a history of drug allergies and a long platinum-free interval (>12 months).[55,56,111]

[Clinical Question 2.1](#): Do pre-medications and/or extended infusion duration reduce the incidence of IRs with Carboplatin?

Recommendation 2.1: There is insufficient evidence to conclude that routine primary prophylaxis with extended infusion and/or pre-medications reduce IR rates. Current evidence suggests that pre-medications may reduce IR rates; however, the optimal pre-medication regimen has yet to be established. It may be reasonable to consider pre-medications (e.g. corticosteroids, H1-receptor antagonists ± H2-receptor antagonists) routinely in gynecological patients receiving carboplatin starting from the 7th cycle, especially in patients at high risk of developing an IR. High risk factors include a platinum-free interval (PFI) >12 months and a history of drug allergy.[2,43–48]

Summary of Evidence & Discussion:

Five studies with gynecological patients were reviewed. These studies evaluated the use of pre-medications and extension of carboplatin infusions to 3 hours as primary prophylaxis to reduce IRs.

A retrospective study including patients with recurrent gynecological cancer (n = 707) who received second-line or greater carboplatin (single or combination) treatment reported a lower incidence of IR (3.4% vs 21%, p = 0.001) when comparing the group who received the extended infusion of carboplatin (i.e. over 3 hours, n = 174) to the group who received the standard infusion (over 30 minutes). 83% of the patients who received the extended infusion of carboplatin were given pre-medications as follows: oral dexamethasone 20 mg the night before and morning of carboplatin, in addition to IV diphenhydramine 50 mg and IV ranitidine 50 mg immediately prior to the carboplatin infusion. All patients who developed an IR had been given dexamethasone immediately prior to the carboplatin infusion. 54% of these patients were also given diphenhydramine. It is unclear if the lower incidence of IR was due to the extended infusion of carboplatin or due to the pre-medications.[43]

A prospective, single-arm study included patients with recurrent gynecological cancer (n = 99) who were previously treated with one or more lines of chemotherapy received carboplatin either as monotherapy every 3 weeks or in combination with paclitaxel (every 3 weeks), liposomal doxorubicin (every 4 weeks), or gemcitabine (day 1 and 8, every 3 weeks). All patients were given the following pre-medications: oral betamethasone 16 mg on the evening before carboplatin, IV betamethasone 16 mg with

IV clemastine 2 mg, IV ranitidine 50 mg and IV ondansetron 8 mg 30 minutes before carboplatin. Carboplatin was administered over 3 hours (1% of the full dose over the 1st hour, 9% of the full dose over the 2nd hour and the remaining dose over the 3rd hour). An overall IR rate of 11.1% was reported in this study. The low overall rate of IR in this study may be due to either pre-medications, extending the infusion duration, or a combination of the two strategies.[44]

An unblinded RCT evaluated IR rates in recurrent ovarian cancer patients (n = 114) who received carboplatin alone or in combination with pegylated liposomal doxorubicin, paclitaxel, bevacizumab or gemcitabine +/- bevacizumab. Carboplatin was infused over 3 hours at a graduated rate in one group and compared to a standard 30-minute infusion in the other group. Rates of IRs (11% vs 16%, p = 0.582) were similar between the two groups. All patients in both groups were given the same pre-medication regimens: oral montelukast 10 mg daily for 3 days prior to carboplatin, oral dexamethasone 20 mg the night before and the day of the infusion, IV diphenhydramine 50 mg prior to the infusion, and either IV ranitidine 50 mg or IV famotidine 20 mg prior to the infusion. The results of this study suggest that there may be no benefit of extended duration carboplatin infusion for prevention of IRs; however, the overall low rate of IRs appear to suggest that pre-medications may be a more effective strategy at reducing the rate of IRs.[45]

A retrospective study evaluated IR rates in gynecological patients (n = 326) who received at least 8 cumulative cycles of carboplatin. One group received carboplatin over 30-60 minutes (standard infusion group) and the other group received carboplatin over 3 hours (extended infusion group). The rate of IR was higher (39.8% vs 24.2%, p = 0.004) in the standard infusion group compared to the extended infusion group. More patients in the group who received carboplatin as an extended infusion were given pre-medications (consisting of a corticosteroid, H1-receptor antagonist and H2-receptor antagonist, or another pre-medication regimens). It is postulated that pre-medications contributed to the reduction of IRs (OR 0.59, 95% CI 0.36-0.97, p = 0.038).[46]

A retrospective study of women with epithelial ovarian cancer (n = 449) who received 6 or more cycles of carboplatin-based chemotherapy reviewed the rates of IR for patients given IV diphenhydramine 50 mg for prophylaxis compared to those who did not receive prophylaxis. The rate of IRs was similar (8% vs 11%, OR 1.50, 95% CI 0.78-2.87, p = 0.2) between the patients who received diphenhydramine prophylaxis and those who did not. When the subgroup of patients who had a platinum-free interval of over 12 months (n = 64) was analyzed, there appeared to be a trend towards a reduced rate of IR (20% vs 56%, OR 0.2, 95% CI 0.046-0.83, p = 0.04) in patients who received prophylaxis with diphenhydramine compared to those who did not.[47]

Current evidence surrounding extended infusion of carboplatin may be confounded due to the use of pre-medications within the protocols. Pre-medications may be effective at reducing the rate of IRs; however, due to the small number of patients, the lack of double-blinded RCTs, and the lack of standardization of pre-medication regimens used

in the studies, it was concluded that there is insufficient evidence at this time to make a definitive recommendation.

Clinical Question 2.2: What is the role of prophylactic skin testing for predicting carboplatin IRs?

Recommendation 2.2: Currently, there is insufficient evidence to recommend prophylactic skin testing to predict IRs in patients receiving carboplatin.[43–47,49–51]

Summary of Evidence & Discussion:

Three prospective studies evaluating the use of prophylactic skin testing to predict patients at risk of IRs with carboplatin were reviewed.

One prospective study included recurrent ovarian or primary peritoneal cancer patients (n = 47) treated with more than 7 cycles of carboplatin who received a skin test 1 hour before each carboplatin infusion starting at cycle 7. 13 patients (28%) had a positive skin test after a median of 9 cycles of carboplatin (8-17). Of the 13 patients who had a positive skin test, 4 received carboplatin. Of those, 3 patients experienced an IR and 1 did not. Of the other 9 patients with a positive skin test, 5 patients were administered a desensitization protocol prior to the planned carboplatin infusion. 3 patients experienced an IR (mild to moderate severity) despite pre-medication with a high-dose steroid. A negative skin test accurately predicted the absence of IR in 166 of 168 courses of chemotherapy. With the addition of a skin test, administering carboplatin in patients with a negative skin test may be associated with a lower incidence of allergic reaction compared to the historical control group (4% vs 27%, p = 0.002).[49]

Another study reviewed women with gynecologic cancers (n = 126) who had previously received more than 6 cycles of platinum-based chemotherapy. Patients had a skin test 30 minutes before each subsequent cycle of carboplatin. Of the 717 total skin tests completed (median 4 per patient), 5.7% were positive (41 tests in 39 patients). 7 of these patients were treated with carboplatin, of whom 6 experienced a non-severe IR upon initiation of the carboplatin infusion. Of the remaining 32 patients whose skin tests were positive, 7 received carboplatin or cisplatin using a desensitization program, of which 6 were successful. A false negative rate of 1.5% (95% CI 0.6-2.4) was cited by the authors (i.e. 7 of 87 patients experienced mild symptoms of IR during their treatment with carboplatin). 8 skin tests were interpreted as borderline positive. In these cases, patients received the carboplatin infusion with no IR. These results suggest that skin tests may not be able to accurately predict if a patient is at risk of experiencing an IR with carboplatin.[50]

A cohort study reviewed patients with recurrent ovarian cancer (n = 54) who received carboplatin reinduction chemotherapy. All patients received a skin test before each cycle of carboplatin chemotherapy. If the skin test was negative, patients were given pre-medications as follows: IV dexamethasone 8 mg (if patients received carboplatin-paclitaxel, pre-medications included IV dexamethasone 20 mg, IV ranitidine 50 mg and

IV clemastine 2 mg), IV granisetron 1 mg and oral dexamethasone 8 mg in the evening. 7 patients (13%) had a positive skin test, occurring after a median of 10 cycles of carboplatin (4-17 cycles). Of the 7 patients who had a positive skin test, 5 patients received desensitization with success (1 of whom developed IR after the 3rd carboplatin desensitization treatment and was subsequently switched to cisplatin). A false negative rate of 8.5% was cited by the authors (i.e. 4 of 47 patients who had a negative skin test experienced an IR). In this study, the skin test accurately predicted IR in 64% of the patients, suggesting that further study to improve the accuracy of skin tests to predict patients at risk of IRs is needed.[51]

Overall, the studies available had small sample sizes. It may be impractical to use skin tests routinely to screen patients in clinical practice. The accuracy of skin tests to predict patients at risk of IR requires more evaluation, as reflected in the variability in the rate of false positives and false negatives being reported. More studies are required prior to recommending this as routine practice.

OXALIPLATIN

The overall incidence of IRs with oxaliplatin can range between 10-19%, and generally occur after 6 cycles. The onset of symptoms can vary from minutes to days from the start of the infusion. Risk of IRs with oxaliplatin may be increased for females of younger age and with prior exposure to platinums.[55,56]

Clinical Question 2.3: Do pre-medications prevent oxaliplatin IRs?

Recommendation 2.3: There is insufficient evidence to conclude that routine prophylaxis with pre-medications reduces IR rates. It may be reasonable to consider the use of corticosteroids and H1-receptor antagonists ± H2-receptor antagonists in high-risk patients (e.g. female gender, younger age, prior exposure to platinums, including the administration of oxaliplatin after the 6th cycle).[52–56]

Summary of Evidence & Discussion:

Three retrospective studies that evaluated the use of prophylactic pre-medications to prevent IRs in patients receiving oxaliplatin were reviewed.

The first is a retrospective cohort study of patients with advanced colorectal cancer (n = 181) who received modified FOLFOX6 (mFOLFOX6) therapy. Patients received routine pre-medication with IV dexamethasone 8 mg and granisetron 3 mg for the first 5 cycles of mFOLFOX6. From cycle 6 onward, one group of patients received the same, standard pre-medications (n = 81) and the other group of patients received a modified pre-medication regimen, including oral diphenhydramine 50 mg given 30 minutes before oxaliplatin, followed by IV dexamethasone 20 mg, IV granisetron 3 mg and IV famotidine 20 mg given 15 minutes before oxaliplatin (n = 100). The rate of IRs was higher in the standard pre-medication group compared to the modified pre-medication group (20% vs 7%, p = 0.0153). The median number of cycles increased from 9 to 12

cycles when the pre-medications were modified, suggesting that the change in pre-medications may prevent IRs and allow patients to receive more cycles of treatment.[52]

The second is a retrospective cohort study of patients with various cancers (n = 191) who received oxaliplatin-containing regimens. Patients received routine pre-medications before oxaliplatin infusions consisting of IV methylprednisolone 120 mg and antiemetic prophylaxis (details not specified). The rate of IRs in this study population was 8.9%. IRs occurred after a median of 3 cycles (1-13 cycles) of oxaliplatin. The authors noted that the incidence of IRs and the number of previous cycles in this study appear to differ from other reports. This difference may be associated with the fact that 94% of patients in this study were female.[53]

The third is a retrospective cohort study that evaluated patients with advanced colorectal cancer (n = 272) who received FOLFOX4. All patients received the primary prevention regimen, consisting of IV dexamethasone 8 mg and oral famotidine 40 mg 30 minutes before oxaliplatin infusions in all patients starting with cycle 1 of therapy. Starting after cycle 4, oral diphenhydramine 50 mg 30 minutes before oxaliplatin infusions was added to the primary prevention regimen. The rate of IRs in this study population was 17.6% (48 patients; higher rate than other studies). IRs occurred after a median of 9 cycles (4-16 cycles) of oxaliplatin. The results of this study suggest that pre-medications may not be useful for primary prophylaxis of IRs in patients receiving oxaliplatin.[54]

Overall, the studies available that evaluated oxaliplatin IR prophylaxis were limited by size. Dexamethasone would likely already be given as part of the anti-emetic regimen for oxaliplatin. Based on the limited evidence, corticosteroids and H1-receptor antagonists (e.g. oral diphenhydramine 50 mg) ± H2-receptor antagonists (e.g. famotidine 20 mg) may be considered for high-risk patients.

Clinical Question 2.4: What is the role of prophylactic skin testing for predicting oxaliplatin IRs?

Recommendation 2.4: There is insufficient evidence to support routine prophylactic skin testing to predict infusion reactions with oxaliplatin.[52–54,57]

Summary of Evidence & Discussion:
One prospective study that evaluated the use of prophylactic skin testing to predict patients at risk of IRs with oxaliplatin was reviewed.

The prospective study evaluated patients with gastrointestinal cancers (n = 101) being treated with oxaliplatin (with 5-fluorouracil and bevacizumab, with capecitabine or with gemcitabine). 836 skin tests (average 8 per patient) were administered to patients 1 hour before each course of oxaliplatin, starting from the 2nd cycle of oxaliplatin. 2% of patients had a positive test (at 6-7th cycle). 5 patients developed an IR after a negative skin test. A false negative rate of 5.05% was cited by the authors (i.e. 5 of 99 patients experienced symptoms of IR during their treatment with oxaliplatin). IRs occurred in this

group of patients after an average of 7 cycles (5-8 cycles). The authors recommend that skin tests may be useful to predict IRs to oxaliplatin and they suggest screening patients starting from the 5th cycle.[57]

This study had an insufficient sample size to support any recommendation. In addition, it is impractical to use skin tests routinely to screen patients in clinical practice and this remains a controversial issue. More studies are required prior to recommending this as routine practice.

CISPLATIN

The overall incidence of IRs with cisplatin can range between 5-20%, and generally they occur after 6 cycles (between cycle 4-8). The onset of symptoms can vary from minutes to days from the start of the infusion. Symptoms are generally mild in nature. Risk of IRs with cisplatin can also be increased with concomitant radiation.[55,56,130]

Recommendation 2.5: Specific pre-medications to prevent IRs are not routinely recommended; however, dexamethasone is often used as part of the antiemetic regimen given the high emetogenic potential of cisplatin.[35,58,59]

For all other medications, please refer to Appendix 1.

Monoclonal Antibodies

The exact mechanism of IRs with monoclonal antibodies is not clear. Some theories include: antibody-antigen interactions (leading to cytokine release), activation of mast cells or basophils, or human anti-chimeric, human antihuman or human anti-mouse antibodies. The incidence of IRs varies among MoAbs. The highest rates of IRs are associated with rituximab, alemtuzumab, trastuzumab, cetuximab, daratumumab and obinutuzumab. Rates of severe IRs are typically low; however, anaphylaxis is still possible. It is important to differentiate symptoms of anaphylaxis from those of infusion reactions because, although there is some overlap in clinical presentation, the treatment of each is different. Most IRs happen during the first infusion, with the probability of IRs decreasing with each subsequent cycle.[3,6,135]

In general, strategies used to prevent the incidence and severity of IRs with MoAbs are empiric, with little supporting evidence. Strategies include:[3,6,135]

- Pre-medication with acetaminophen and an H1-receptor antagonist (e.g. diphenhydramine) with or without a corticosteroid and

- Reducing the rate of infusion to a slower, graduated rate.

In the absence of other supporting data, recommendations from the manufacturer should be followed.

RITUXIMAB

The overall incidence of IRs with rituximab can range between 25-85%. Severe IRs may clinically present like CRS. Patients with a high tumor burden (e.g. lymphocyte count > 25-50 x 10^9/L) may be at higher risk of severe IRs and CRS. Severe IRs leading to death within 24 hours of infusion has been reported at 0.04-0.07%, most of which have occurred with the first infusion (77%). The incidence of IRs decreases with subsequent infusions (30% with the 4th infusion and 14% with the 8th infusion).[3,6,135] Onset of symptoms of an infusion reaction often occur within the first 30 minutes to 2 hours of the first infusion of rituximab. Symptoms may include pulmonary events, fever, chills, rigors and hypotension.[3,6,69,141,142]

Clinical Question 3.1: **What is the role of pre-medications for subcutaneous and IV rituximab?**

Recommendation 3.1: Pre-medication with acetaminophen and an H1-receptor antagonist is recommended to be given 30-60 minutes prior to each dose of rituximab (both subcutaneous and IV). Consider pre-medication with corticosteroids if not already being given as part of the chemotherapy regimen.[60–67] For subcutaneous rituximab, especially in patients who experienced adverse effects with pre-medications, the omission of pre-medications may be considered.[68]

Summary of Evidence & Discussion:

Subcutaneous administration of rituximab, compared with IV administration, increases patient convenience due to the short administration time; however, it is important to note that administration-related adverse reactions can still occur with subcutaneous administration. Reactions can include injection site erythema, pruritus, rash, pain, in addition to systemic reactions.[62] Like IV infusions, these reactions commonly appear with the first injection (i.e. during the second cycle of rituximab). The incidence and severity decreases with subsequent injections.[63,64]

SABRINA is a randomized, open-label phase 3 trial of patients with follicular lymphoma (FL) who were randomly assigned to receive IV (n = 210) or subcutaneous (n = 197) rituximab with 6-8 cycles of CHOP or 8 cycles of CVP. This study did not state whether pre-medications were given. In the first stage of the SABRINA trial, administration-related reactions from subcutaneous administration of rituximab included non-injection site erythema (8%), pruritus (6%), chills (3%), and vomiting (3%).[67] Patients administered subcutaneous rituximab have also been reported to have experienced severe administration-related reactions, including hypersensitivity reactions (3%).[61] The presence of administration-related reactions with the subcutaneous injection of rituximab suggests that pre-medications (e.g. an antipyretic and an H1-receptor antagonist) may be beneficial.[64–66]

A retrospective review evaluated patients who received subcutaneous rituximab (n = 51), all of whom received rituximab as an IV infusion for the first dose. There were 13 IRs (25%) documented with the IV infusion, all of which were grade 1-2. A total of 343

doses of rituximab were given subcutaneously. 36 of these doses were given with pre-medications, with 1 adverse event recorded (a local skin reaction). 307 doses were given with no pre-medications, with 2 adverse events recorded (a local skin reaction and post-administration myalgia). The overall reaction rate for all subcutaneous rituximab injections was 0.87%.[68] The study suggests that omitting pre-medications does not appear to affect IR rates.

There is emerging evidence that omitting pre-medications with the administration of subcutaneous rituximab may be a reasonable option. Additional prospective evidence is required prior to making a formal recommendation. For subcutaneous rituximab, especially in patients who experienced adverse effects with pre-medications, the omission of pre-medications can be considered.

There is emerging evidence suggesting that the addition of montelukast 10 mg, 12 hours and 30 minutes prior to the infusion of rituximab, and rupatadine 10 mg, 12 hours prior to the infusion, reduces the severity and incidence of infusion reactions. In a study conducted by Kotchetkov et al. adult patients (n = 93) with lymphoproliferative disorders (LPD) received standard pre-medications (diphenhydramine, acetaminophen), which was compared to the addition of rupatadine, montelukast or both (montelukast and rupatadine). The study was limited to the initial rituximab infusion. Infusion reactions occurred in 92% of patients solely receiving standard pre-medications (n = 26), compared to 38% receiving additional montelukast (n =21), 45% receiving additional rupatadine (n = 20), and 31% receiving additional montelukast and rupatadine (n = 26). The median reaction grade for patients who only received standard pre-medications was 2, compared to a median reaction grade of 1 for patients receiving additional montelukast, and 0 for patients receiving additional rupatadine or the combination of montelukast and rupatadine. The positive effects on IR rates with this prophylactic regimen are promising; however, at this time there is insufficient data to make a formal recommendation to add montelukast and rupatadine for prophylaxis of rituximab induced infusion reactions.[143]

Clinical Question 3.2: **What is the recommended infusion rate for IV rituximab?**

Recommendation 3.2: The first cycle of rituximab is recommended to be administered over a graduated rate. If no severe (grade 3 or 4) IR occurred with the first cycle, rapid infusion of IV rituximab over a total of 90 minutes (20% of the dose in the first 30 minutes and then remaining 80% of the dose in the next 60 minutes) can be initiated with cycle 2. Alternatively, subcutaneous administration of rituximab can be considered starting with cycle 2.[6,64,69–72]

Summary of Evidence & Discussion:

To reduce the risk of IRs, the manufacturer recommends administering rituximab at a graduated rate. The first infusion of rituximab is recommended to be administered over a total of 4.25 hours (initial rate of 50 mg/hour, escalating by 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour if no IR occurs). Subsequent infusions are recommended to be administered over a total of 3.25 hours (initial rate of 100 mg/hour,

escalating by 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour if no IR occurs).[6,69] Due to the potential impact on patient convenience and quality of life, studies have been conducted to assess the feasibility and safety of a rapid infusion rate (i.e. administering rituximab over 90 minutes).[70,71] In clinical practice, many Ontario centres have adopted this rapid infusion rate.

Two prospective studies evaluating the safety of rapid infusion of rituximab were reviewed.

The study by Sehn et al. evaluated patients with non-Hodgkins lymphoma (NHL, n = 150) who received the rituximab infusion at the rate specified by the product monograph for the 1st cycle. Patients with a high lymphocyte count were excluded from this study. Starting from the 2nd cycle, patients received a rapid infusion of rituximab (90-minute infusion schedule, with 20% of the dose administered over the first 30 minutes and the remaining 80% of the dose administered over 60 minutes). Patients were given the following pre-medications: oral diphenhydramine 50 mg, oral acetaminophen 375 mg and the daily corticosteroid dose according to the chemotherapy protocol. Each patient received a median of 3 rituximab infusions (with a total of 473 rapid infusions included in the study). The rate of grade 3 or 4 IR was 0% (95% CI 0-0.019%). Of the 10 patients who experienced an adverse reaction during cycle 1, all tolerated a rapid infusion of rituximab during subsequent cycles with no IR. None of these patients had an elevated lymphocyte count at the time of rapid infusion of rituximab. The authors noted that over 1200 patients have since been administered rituximab through a rapid infusion schedule, with only 1 patient experiencing an IR (grade 3), suggesting that it is a safe option.[72]

A Phase III study by Dakhil et al. included patients (n = 363) with diffuse large B-cell lymphoma (DLBCL) or FL who received 6 or 8 cycles of rituximab with CHOP for DLBCL or rituximab with CVP for FL. 425 patients received the first rituximab infusion at the rate specified by the product monograph. Patients with a high lymphocyte count were excluded from this study. Of these patients, 363 patients (85.4%) were able to continue with rituximab therapy (i.e. did not experience gr 3 or 4 IR with the first infusion). These patients received rituximab via rapid infusion (over 90 minutes, with 20% of the total dose given in the first 30 minutes, and the remaining 80% of the dose given over the next 60 minutes) for future cycles of rituximab. Patients were given acetaminophen and an H1-receptor antagonist as pre-medication (doses and route of administration not specified). A corticosteroid was given as part of the chemotherapy regimen. 37.2% of patients who received a rapid infusion rituximab experienced a grade 1 or 2 IR in cycle 2. 1.1% of patients experienced a grade 3 IR in cycle 2. 63.4% of patients experienced IRs in cycle 2-8, of which 2.8% were grade 3-4. The authors noted that 87.5% of all patients who received rituximab were able to receive rituximab infusions over 90 minutes, starting from cycle 2. The results of this study suggests that rapid infusion of rituximab may be a safe option.[70]

These two studies suggest that rapid infusion of rituximab given over 90 minutes starting at cycle 2 is a safe option. This corresponds with the recommendation from a

review article that analyzed the safety of the rapid infusion of rituximab in 7 different studies, all of which suggest that this practice does not significantly affect the incidence of IRs.[71] However, the exclusion of patients with a high lymphocyte count in these studies and lack of experience in this population suggest that there is inadequate safety data to recommend the administration of rituximab as a rapid infusion for these patients at this time.

Clinical Question 3.3: What is the clinically accepted definition of high lymphocyte count and what strategies may be employed to minimize the risk of IRs in these patients?

Recommendation 3.3: Clinicians are recommended to consider unique patient risk factors in decision-making. The following strategies recommended by Ontario cancer centres based on local experience for preventing rituximab IRs in patients with a high lymphocyte count (e.g. higher than 25-50 x 10^9/L) can be considered:[11,60,69,73–75]

- Dose splitting over 2 days

- Reduced infusion rate (as per the product monograph)

- Delay rituximab treatment until chemotherapy has reduced the lymphocyte count

Summary of Evidence & Discussion:
The definition of a high lymphocyte count may differ amongst clinical practices. In patients with hematologic malignancies with a high lymphocyte count, administration of rituximab may increase the risk of severe IRs (i.e. pulmonary IRs).[73]

In the rituximab product monograph, the manufacturer defines high lymphocyte count as > 25 x 10^9/L in the context of identifying patients who may benefit from the addition of IV methylprednisolone given as a pre-medication due to their increased risk of rate and severity of IRs and/or CRS.[69] The National Comprehensive Cancer Network (NCCN) defines high tumor burden for chronic lymphocytic leukemia (CLL) as absolute lymphocyte count ≥ 25 x 10^9/L.[74]

In a retrospective study by Winkler et al., patients with B-cell CLL or NHL (n = 11) being treated with rituximab were evaluated. Acetaminophen 1000 mg was administered before the beginning of each rituximab infusion. The infusion was administered at a graduated rate. All patients with a lymphocyte count over 50 x 10^9/L experienced severe IRs (n = 6), 5 of whom required temporary interruption of rituximab therapy. In contrast, patients with a lower lymphocyte count experienced fewer IRs which were also milder in severity (p = 0.0017).[11]

A case report by Hagberg et al. studied patients with lymphoma (n = 37) who received rituximab therapy. 2 of the patients included had high lymphocyte counts (18 x 10^9/L and 185 x 10^9/L), both of whom experienced IRs. One patient experienced a WHO grade 2 toxicity (defined as fever, chills, nausea, headache, asthenia and muscle pain) and the other patient experienced a WHO grade 3 toxicity (defined as dyspnea, chest pain and confusion).[75]

There is no clear consensus on the definition of high lymphocyte count in literature to stratify a patient's risk of IRs and CRS with rituximab. Consider evaluating the patient's lymphocyte count within the context of unique patient risk factors in decision-making.

CETUXIMAB

The overall incidence of IRs with cetuximab can range between 1-20%.[6,76,126] Symptoms of the IR commonly occur within 3 hours of starting the infusion. 90% of IRs occur during the first cycle of cetuximab despite the use of H1-receptor antagonists prophylactically.[3,77,126,136] However, IRs can still occur hours after the infusion was administered and during subsequent infusions.[126,136] The risk for developing an IR is higher in patients with head and neck cancer (p < 0.001).[136]

[Clinical Question 3.4](#): **Are pre-medications recommended for preventing cetuximab IRs?**

Recommendation 3.4: Pre-medication with an H1-receptor antagonist (e.g. diphenhydramine 50 mg IV) for cycle 1 of cetuximab is recommended. A corticosteroid for cycle 1 of cetuximab can be considered. Pre-medications for subsequent cycles are based on clinical judgment, and the presence and severity of a prior IR.[3,6,76,77]

Summary of Evidence & Discussion:

A retrospective cohort study evaluated patients (n = 51) treated with cetuximab who received pre-medications 30 minutes prior to the infusion. Pre-medications included IV diphenhydramine 50 mg plus others that differed based on patient cohort assignment. Patients in cohort 1 (n = 27) received IV dexamethasone 20 mg. Patients in cohort 2 (n = 8) received IV hydrocortisone 100 mg. Patients in cohort 3 (n = 7) received IV dexamethasone 20 mg and IV ranitidine 50 mg. Patients in cohort 4 (n = 9) received IV dexamethasone 20 mg, IV ranitidine 50 mg and a test dose of IV cetuximab 100 mg administered over 30 minutes. If no IR occurred after a 30-minute observation period, the remainder of the cetuximab dose was infused over 2 hours. The intent of separating patients into different cohorts was to determine if changing these pre-medications modified the risk of IR. The overall incidence of grade 2-4 IRs was 27%, all of which occurred during the first infusion. There was no difference in the incidence or severity of IR (p = 0.34) between the different patient cohorts. There were no risk factors identified in this study that were predictive of a patient's risk of IR. The results of this study suggest that there may be no additional benefit to adding a corticosteroid to the H1-receptor antagonist used in the pre-medication regimen to prevent IRs with cetuximab. However, due to the small patient numbers in each group, there may be inadequate power to identify meaningful differences in outcomes between the groups.[76]

A post hoc analysis of the MABEL study evaluated the incidence of IRs in patients with metastatic colorectal cancer (mCRC, n = 1147) who received cetuximab with irinotecan. For the purposes of the analysis, the authors noted that the specific pre-medications, doses and route of administration were not specified, but were broadly classified into

"H1-receptor antagonist" or "corticosteroid".   The study found a lower incidence of any grade IRs (9.6%, 95% CI 7.5-12.0 vs 25.6%, 95% CI 21.5-30.0) and a lower incidence of grade 3 or 4 IRs (1.0%, 95% CI 0.4-2.1 vs 4.7%, 95% CI 2.9-7.2) in the group of patients who received an H1-receptor antagonist with a corticosteroid compared to those who only received an H1-receptor antagonist. It was noted that most of the patients who received a corticosteroid received IV dexamethasone, at a dose of 8 mg or higher. Oral dexamethasone (dose not specified) was used in approximately 15% of patients. This study suggests that both an H1-receptor antagonist and a corticosteroid can be used as pre-medications for preventing IRs with cetuximab.[77]

An abstract of a retrospective study conducted at Memorial Sloan-Kettering Cancer Center (MSKCC) suggests that pre-medications can be discontinued safely after the first 2 cetuximab infusions if no IR was observed. Patients (n = 453) in the study were given diphenhydramine 50 mg prior to the first dose of cetuximab, and then diphenhydramine 25 mg prior to the second dose of cetuximab. 1.5% of patients experienced a grade 3 IR and 4% of patients experienced a mild to moderate IR, all of which occurred during the first infusion. Of the 429 patients who did not experience IRs within the first 2 cycles of cetuximab, none experienced IRs with subsequent cycles. The abstract suggests that pre-medications after the first 2 cetuximab infusions may not provide added benefit in preventing IRs for patients who did not experience an IR with previous cycles of cetuximab.[3,6]

It is unclear if there is a role for adding corticosteroids to the pre-medication regimen prior to cetuximab infusion to prevent IRs. Due to the conflicting evidence, clinical judgment is recommended.

DARATUMUMAB

The incidence of grade 1 and 2 IRs with daratumumab (monotherapy or combination treatment) can range between 35-52%. Grade 3 IRs can occur in 3-6% of patients. The incidence of any grade IRs is 46-48%, with the majority occurring during the 1st cycle (92-98%). Symptoms of the IRs commonly occur within 1.5 hours of starting the infusion.[81] Without post-infusion medications, IRs can occur up to 48 hours after infusion. Like cetuximab, IRs can still occur during subsequent infusions at a decreased incidence (2% with the 2nd infusion and 4% with the 3rd infusion). Pre- and post-infusion medications are recommended to reduce the risk of acute and delayed IRs.[79,81,144]

Clinical Question 3.5: What is the role of montelukast in the pre-medication regimen?

Recommendation 3.5: The addition of montelukast to the existing pre-medication regimen can be considered to reduce respiratory IRs.[78–80]

Summary of Evidence & Discussion:
A retrospective study by Nooka et al. evaluated IRs in patients (n = 94) who received daratumumab. 53% of patients experienced a grade 1 or 2 IR, 98% of which occurred

during the 1st infusion of daratumumab. Patients who did not experience an IR with their first infusion did not experience an IR with subsequent infusions. IRs occurred in 40.7% of patients who received montelukast and in 57.1% of patients who did not (p = 0.09). Respiratory symptoms occurred in 45.8% of patients who received montelukast and 66.7% of patients who did not (p = 0.16). Due to the reduction (although not statistically significant) in respiratory symptoms seen in this study and the low risk of side effects, the addition of montelukast has become a part of pre-medication regimens for daratumumab at some institutions.[78,79]

An abstract describing an open-label early access treatment protocol was reviewed. Patients received daratumumab for relapsed or refractory multiple myeloma (n = 348). All patients were given recommended pre- and post-infusion medications. Inhaled bronchodilators and corticosteroids were given to patients with obstructive lung disorders. 50 patients received oral montelukast 10 mg 30 minutes prior to the first infusion (298 patients did not). IRs occurred in 56% of patients, 8% of whom experienced grade 3 or 4 IRs. The most common IRs during the first infusion included cough (14%) and dyspnea (8%). The IR rate was 38.0% in patients who received montelukast prior to the first infusion of daratumumab. 58.5% of patients who did not receive montelukast experienced an IR. Respiratory symptoms occurred in 20% of patients who received montelukast. In comparison, 32% of patients who did not receive montelukast experienced respiratory symptoms. Additionally, a lower rate of gastrointestinal symptoms (4% vs 11%) was reported in patients who received montelukast compared to patients who did not receive montelukast.[80]

The available literature suggests that montelukast may be an effective and safe addition to preventing IRs. Therefore, consideration can be given to adding montelukast as part of the pre-medication regimen to prevent daratumumab IRs.

Clinical Question 3.6: What is the recommended infusion rate for daratumumab?

Recommendation 3.6: Infuse daratumumab at a graduated rate as described by the product monograph. For the first dose of daratumumab, consideration can be given to split the dose over 2 days with pre-medications given on both days prior to the infusion. If the patient did not experience an IR with the first 2 doses of daratumumab, consider administering as a rapid infusion starting with the 3rd dose (20% of the dose over 30 minutes at 200 mL/hour, then the remaining 80% of the dose over 60 minutes at 450 mL/hour).[78,81–84]

Summary of Evidence & Discussion:
The current product monograph states that daratumumab should be infused at a graduated rate. Daratumumab infusions should be started at 50 mL/hour, escalating by 50 mL/hour to a maximum rate of 200 mL/hour if tolerated. This can be translated to an infusion time of approximately 6.5 hours for the initial infusion of daratumumab diluted in 1000 mL, 4 hours for the second infusion of daratumumab diluted in 500 mL and 3.25 hours for subsequent infusions of daratumumab diluted in 500 mL.[78,79,81,145] A modified rate starting at 100 mL/hour, escalating by 50 mL/hour to a maximum rate of

200 mL/hour can be considered if there were no IRs of any grade experienced by the patient during the first two infusions when administered at a rate of 100 mL/hour.[145]

To accommodate out-patient administration, some Ontario centres have implemented a split-dose strategy for the first daratumumab infusion (2 doses of 8 mg/kg given over 2 consecutive days). The same pre-medications are given prior to each dose.[78]

A retrospective review evaluated the safety of split-dose daratumumab (8 mg/kg each day for 2 days) in patients with relapsed/refractory multiple myeloma (n = 13). Patients received pre-medications including acetaminophen 650 mg, montelukast 10 mg, diphenhydramine 25-50 mg and dexamethasone 10 or 20 mg. The day 1 dose was infused over a mean of 4.72 hours (4.40-6.48 hours) and the day 2 dose over a mean of 4.19 hours (3.25-4.47 hours). Split dosing was continued on days 8 and 9 of therapy if an IR occurred with the first dose, after which standard infusion rates published in the product monograph were followed. If no IR occurred with the first dose, subsequent doses were administered as per the standard infusion rates published in the product monograph. 2 patients (15%) experienced an IR. One patient experienced a grade 3 IR on day 1 but did not experience an IR on day 2. One patient experienced a grade 1 IR with the dose on day 1 and successfully resumed the daratumumab upon IR resolution. No IRs were reported with subsequent daratumumab doses. Although this study was retrospective and had small sample sizes, the results suggest that administering daratumumab as a split-dose over 2 consecutive days may be safe and convenient, with no increase in IR rates.[82]

Recently, small studies evaluating the safety and feasibility of rapid infusion of daratumumab over 90 minutes from the 3rd dose onwards have been published. One study and one abstract evaluating the use of rapid infusion with daratumumab over 90 minutes were reviewed.[84]

A prospective, single-center, open-label safety study by Barr et al. evaluated the safety of administering daratumumab as a rapid infusion over 90 minutes (total volume 550 mL) in patients with multiple myeloma who had received 2 or more doses of daratumumab at standard infusion rates (n = 28). Patients with respiratory conditions were not excluded from receiving the rapid infusion in this study. The rapid infusion was designed to deliver 20% of the dose over 30 minutes (at 200 mL/hour) and the remaining 80% of the dose over 60 minutes (at 450 mL/hour). For the first rapid infusion, patients were observed for 30 minutes after the completion of the infusion to assess for delayed IRs. A variable combination of pre-medications was given in this study, with the most common regimen being acetaminophen, diphenhydramine, famotidine and dexamethasone. The rapid infusion was well tolerated amongst all patients, with no incidence of grade 3 or above IRs. The only toxicity reported in this study was a grade 2 hypertension event. 11 patients (39.3%) had a history of IR with their first dose and no recurrence with their second dose. The median number of prior daratumumab infusions before study enrollment was 5.[84]

The authors noted that rapid infusion is the new standard-of-care at their institution, with the standard pre-medications for the first dose of daratumumab being acetaminophen

650 mg PO, diphenhydramine 50 mg PO/IV, dexamethasone 20 mg IV, famotidine 20 mg IV and montelukast 10 mg. The pre-medications were changed to just dexamethasone IV and montelukast PO with the 3rd dose (i.e. first rapid infusion), and then dexamethasone IV only with subsequent infusions.[84] Based on this small prospective study, the results suggest that rapid infusion of daratumumab starting from the 3rd dose may be a safe option. Evidence regarding pre-medication de-escalation is evolving - no recommendation regarding de-escalation can be made at this time.

An abstract of a retrospective chart review conducted at the Levine Cancer Institute evaluated patients with relapsed/refractory multiple myeloma (n = 73) or amyloidosis (n = 6) who completed at least 1 cycle of daratumumab. Patients were divided into 1 of 2 cohorts - cohort 1 included patients who received daratumumab using the standard infusion rate recommended in the product monograph. Cohort 2 included patients who received the first 2 doses of cycle 1 at the standard infusion rate, followed by a rapid infusion daratumumab over 90 minutes starting from the 3rd dose. Patients received the following pre-medications for the first 2 doses of cycle 1: acetaminophen, diphenhydramine, dexamethasone and montelukast. No difference in the rates of IRs between cohort 1 and 2 were found (5.0% vs 2.6%, p = 0.6). All IRs reported in both cohorts were grade 1. The results of this study suggest rapid infusion of daratumumab starting from the 3rd dose may be a safe option.[83]

ALEMTUZUMAB

The incidence of severe IRs with alemtuzumab is 3%.[146] The incidence of mild/moderate IR symptoms includes hypotension (15%), rigors (89%), fever (83%), nausea and vomiting (13%).[3,88] IRs are most common during the first week of therapy.[2,3,6,88,146]

Clinical Question 3.7: What is the most effective way to prevent alemtuzumab IRs?

Recommendation 3.7: Pre-medication with an H1-receptor antagonist (e.g. diphenhydramine 50 mg IV) and oral acetaminophen 650 mg 30 minutes prior to alemtuzumab administration is recommended to prevent IRs. Corticosteroids (methylprednisolone 1g) may be considered on the first 3 days. Subcutaneous administration of alemtuzumab can also be considered to reduce IRs. The exception is for patients with T-cell prolymphocytic leukemia (T-PLL), where the intravenous infusion of alemtuzumab has demonstrated superiority over subcutaneous administration.[2,65,85–90]

Summary of Evidence & Discussion:
Subcutaneous administration is favoured over IV infusion due to the decreased incidence of IRs and improved patient convenience.[65,85,86] Three articles evaluating the safety of subcutaneous alemtuzumab were reviewed.

A prospective phase II study evaluated patients with CLL (n = 85) who received alemtuzumab. Patients in cohort 1 received IV alemtuzumab (n = 39) and patients in

cohort 2 received subcutaneous alemtuzumab (n = 20). The alemtuzumab dose was escalated during the first week of therapy (i.e. alemtuzumab 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3). All subsequent doses were administered as 30 mg. Diphenhydramine 50 mg IV and acetaminophen 650 mg PO were given as pre-medications for the first two doses, after which further pre-medications were based on physician clinical judgment. All patients in cohort 1 experienced IRs of grade 2 severity or less, including shaking, chills, fever and hypotension. This occurred commonly during the first 2 weeks of alemtuzumab. In comparison, no patients in cohort 2 experienced systemic administration-related reactions. This suggests that subcutaneous administration of alemtuzumab may be an effective strategy to minimize reactions.[65,85]

A prospective phase II study evaluated patients with fludarabine-refractory CLL (n = 103) who received alemtuzumab. Treatment was initiated as a dose escalation (i.e. alemtuzumab 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3). IV dose escalation was given for 46 patients (cohort 1) and subcutaneous dose escalation was given for 57 patients (cohort 2). After completion of the dose escalation, alemtuzumab maintenance doses of 30 mg were given subcutaneously 3 times per week for 4-12 weeks. H1-receptor antagonist and analgesic pre-medications were administered (medication and dosing regimen not specified). The subcutaneous route of administration was well-tolerated. The overall rate of administration-related reactions was similar in both cohorts during the dose escalation phase, with a lower rate of chills in the cohort who received subcutaneous escalation (14% vs 35%, p = 0.018).[65,86]

A prospective phase II study evaluated patients with B-cell CLL (n = 41) who received alemtuzumab. Treatment was given as a subcutaneous dose escalation (i.e. alemtuzumab 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3). After this dose escalation phase, most patients self-administered the alemtuzumab (30 mg given 3 times weekly for a maximum of 18 weeks). Pre-medications included oral acetaminophen 1000 mg and H1-receptor antagonists (i.e. IV clemastine 2 mg) 30 minutes prior to the alemtuzumab injections. These were gradually omitted once the "first dose" reactions disappeared. The "first dose" reactions usually associated with IV administration of alemtuzumab were noted to rarely occur in this study (e.g. grade I-II fever in 68% of patients that disappeared rapidly with continued treatment, transient rigor in 17% of patients). The results of this study suggest that subcutaneous injections of alemtuzumab may be a safe and more convenient method of administration for patients.[87]

Subcutaneous administration of alemtuzumab is associated with a lower rate of and milder initial systemic reactions compared to IV infusion. Pre-medications are still used in the studies, which include an antipyretic (e.g. acetaminophen 650-1000 mg) and an H1-receptor antagonist (e.g. diphenhydramine 50 mg IV).

The exception is for patients with T-cell prolymphocytic leukemia (T-PLL), where the delivery of intravenous alemtuzumab remains the treatment of choice. In the UKCLL05 pilot study, patients with T-PLL received intravenous alemtuzumab as initial therapy

(n = 32), with 29 patients responding to treatment (ORR = 91%). This was compared to 9 patients who received subcutaneous alemtuzumab as initial therapy, with only 3 patients responding to treatment (ORR = 33%, p = 0.001).[89] This finding was further supported by the retrospective analysis carried out by Damlaj et al. The overall survival was significantly higher for patients administered intravenous alemtuzumab (n = 13) compared to the subcutaneous delivery (n = 5), at 40.5 months compared to 13.7 months, respectively (p = 0.0014).[90] The superior efficacy of intravenous alemtuzumab supports its use over the subcutaneous route in patients with T-PLL.

BEVACIZUMAB

The incidence of IRs with bevacizumab is reported to be up to 5%. The overall incidence of severe IRs is rare (<1%). Symptoms most commonly occur during the first cycle of bevacizumab. IRs appear to be more common when bevacizumab is given in combination with chemotherapy.[3,6,91,92]

[Clinical Question 3.8](#): **Is there a role for rapid infusion of bevacizumab?**

Recommendation 3.8: For bevacizumab 5 mg/kg and 7.5 mg/kg doses, consider administering bevacizumab as a rapid infusion (i.e. administered over 10 minutes).[93,94]

Summary of Evidence & Discussion:
Bevacizumab has been safely given over 10 minutes in clinical trials and is routinely administered in this manner in some Ontario centres.

A retrospective study by Reidy et al. evaluated the incidence of IRs possibly related to bevacizumab patients with colorectal cancer (CRC, n = 1077). 202 patients with CRC were treated with bevacizumab 5 mg/kg as 90-minute, then 60-minute, then 30-minute infusion. No IRs occurred for this group of patients. The institution subsequently changed its practice to administering bevacizumab over 30 minutes for all doses (including the initial dose). 464 CRC patients were subsequently treated with bevacizumab (5 mg/kg) as a 30-minute infusion. No IRs occurred for this group of patients, after which the institution changed its practice further to an infusion rate of 0.5 mg/kg/min for all bevacizumab infusions (e.g. 5 mg/kg bevacizumab would be administered over 10 minutes for initial and subsequent doses). 370 patients received bevacizumab (5 mg/kg) over 10 minutes, of which 6 patients (1.6%) experienced non-serious events (e.g. facial flushing, itchy throat, shaking chills). All of these patients were given pre-medications with subsequent infusions administered over 10 minutes with no issue, suggesting that rapid infusions of bevacizumab may be a safe and feasible option.[93]

In a prospective study by Mahfoud et al., patients with MCRC (n = 81) were treated with bevacizumab at 5 mg/kg or 7.5 mg/kg over 2 different rates. Patients in group A (n = 38) were administered bevacizumab over 90-, 60- then 30-minutes. If no IRs occurred, subsequent doses were given over 30 minutes. Patients in group B (n = 43) were administered bevacizumab over 10 minutes. None of the patients in group A

experienced an IR. 2 of the patients in group B experienced an IR, classified as grade 2. The results of this study suggest that rapid infusions of bevacizumab (doses up to 7.5 mg/kg) may be a reasonable option for patients.[94]

Based on these two studies, administering bevacizumab over 10 minutes appears to be a safe option for doses up to 7.5 mg/kg.

For all other monoclonal antibodies, please refer to <u>Appendix 1.</u>

Additional Considerations

[Clinical Question 4.1](#): **Can non-sedating H1-receptor antagonists replace diphenhydramine in the pre-medication regimen?**

Recommendation 4.1: Consider a non-sedating H1-receptor antagonist in patients with comorbidities where diphenhydramine may be contraindicated.[12,13]

Summary of Evidence & Discussion:

Based on experience at some Ontario centres, it was noted that an anti-histamine causing sedation (i.e. diphenhydramine) may not be ideal when considering patient convenience (i.e. if they need to drive after their clinic visit, for the administration of subcutaneous rituximab). A non-drowsy H1-receptor antagonist (e.g. cetirizine) was suggested as an effective alternative to diphenhydramine. One study and one abstract evaluating the use of a non-sedating H1-receptor antagonist in place of diphenhydramine were reviewed.

A retrospective study evaluated IRs in patients who received paclitaxel, rituximab or cetuximab (n = 207). Patients were given oral or IV diphenhydramine 50 mg (n = 124) or oral cetirizine 10 mg (n = 83) as part of the pre-medication regimen 30-60 minutes prior to the first 3 cycles of paclitaxel, rituximab or cetuximab. Acetaminophen 650 mg PO was also given for patients who received rituximab. Famotidine 20 mg IV and dexamethasone 20 mg IV were also given to patients who received paclitaxel. Rituximab was infused using a graduated rate of administration for the first cycle, then a rapid infusion over 90 minutes starting cycle 2 if no IRs occurred during the first cycle and if the patient's lymphocyte count was less than 5×10^9/L. The authors reported an overall IR rate of 19.3% (95% CI 11.4-29.4) in the cetirizine group compared to 24.2% (95% CI 17.0-32.7, p = 0.40) in the diphenhydramine group. Of the patients in the cetirizine group who experienced an IR in the 1st cycle of treatment, 41.7% (95% CI 13.7–74.3) received paclitaxel, 50.0% (95% CI 19.4–80.6) received rituximab, and 8.3% (95% CI 0.1–43.6) received cetuximab. Of the patients in the diphenhydramine group who experienced an IR in the 1st cycle of treatment, 26.1% (95% CI 5.7–51.4) received paclitaxel, 73.9% (95% CI 48.6–94.3) received rituximab and none received cetuximab. The overall comparable incidences of IR between the two groups and the trend toward lower IR rate with cetirizine (which was not statistically significant) in this study suggests

that cetirizine may be a viable substitute for diphenhydramine when given as a pre-medication to prevent IRs with chemotherapy and monoclonal antibodies.[12]

A case report described 2 breast cancer patients with a history of closed-angle glaucoma who received fexofenadine (an oral H1-receptor antagonist) to replace diphenhydramine as a pre-medication prior to paclitaxel administration due to the risk of aggravating glaucoma with diphenhydramine. It was noted that no IRs nor acute glaucoma attacks were observed in these two patients.[13]

Overall, there is a paucity of literature available supporting the routine use of oral, non-sedating H1-receptor antagonists as part of the pre-medication regimen to prevent IRs with chemotherapy and monoclonal antibodies. Current available literature and clinical experience from some Ontario centres suggest that substituting a non-sedating H1-receptor antagonist into the pre-medication regimen may be an effective, safe and more convenient option for patients; however, there is insufficient evidence to recommend routine use of non-sedating H1-receptor antagonists over diphenhydramine at this time.

RECOMMENDATIONS FOR ACUTE MANAGEMENT OF INFUSION REACTIONS

[Return to Table 2.1]

It is important to ensure that patients are monitored for IRs during the administration of chemotherapy and monoclonal antibodies. Prompt recognition and assessment of reaction severity is required to ensure that IRs will be managed effectively to minimize the impact on patient safety. A general management approach is outlined below. Please note that this general management approach may not be applicable to all anticancer medications (e.g. rituximab). All IR episodes must be thoroughly documented in the patient chart. Documentation should include pre-infusion assessments, an appropriate description and grading of the IR (CTCAE), and how the IR was managed.[2]

Effective management of IRs starts with prevention. Prior to initiating chemotherapy and monoclonal antibodies, it is recommended to assess the patient for any potential risk factors that may increase the patient's risk for IRs. In addition, appropriate pre-medications specific to each chemotherapy and monoclonal antibody regimen are recommended (please refer to the section titled 'Prophylaxis' and to the Drug Table in Appendix 1). Attention should be given to patients with a history of non-compliance to ensure the appropriate pre-medications are given at the specified time periods prior to the administration of chemotherapy and monoclonal antibodies if needed. It is also important to provide education to patients and their caregivers about the signs and symptoms of IRs to assist in the prompt recognition of IRs.[35] The patient information sheet developed for this purpose can be used in this setting. Please refer to Appendix 2.

General considerations for supportive care when an IR occurs include:[2,5,35]

- have someone call for medical assistance
- maintain the IV line with normal saline (or other appropriate solution)
- assess patient vitals and level of consciousness regularly
- position the patient appropriately
- administer oxygen if required
- administer medications as needed to manage symptoms

Detailed documentation of the IR in the patient chart is imperative. Clear communication among healthcare providers is necessary to identify patients at risk for future IRs and to ensure patients are re-challenged safely. IRs should be reported through the appropriate channels for provincial tracking.

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 is generally used to assess the severity of infusion reactions (Table 1).[10]

Table 1 CTCAE (version 5.0) Grading of Infusion Related Reaction[10]

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. H1-receptor antagonists, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 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	Death

For the purposes of this guideline, symptoms of IR have been grouped into 2 categories based on the CTCAE version 5.0:[2,5,124]

- **Grade 1-2 reactions (mild-moderate symptoms)**
  - If this occurs, it is recommended to stop or slow the infusion.
- **Grade 3-4 reactions (moderate-severe symptoms)**

      o   If this occurs, it is recommended to stop the infusion and assess for anaphylaxis.

Symptoms of IR should be treated as they occur. It is important to recognize signs and symptoms of anaphylaxis (e.g. with platinum medications)[2] and differentiate them from symptoms of CRS (e.g. with monoclonal antibodies)[6], and initiate the appropriate procedure accordingly (which may be specific to each institution).

As defined by the CTCAE version 5.0, symptoms of anaphylaxis may include symptomatic bronchospasm with or without urticaria, hypotension and allergy-related edema or angioedema. In severe circumstances, anaphylaxis can lead to cyanosis, loss of consciousness and potentially death; therefore, urgent parenteral intervention is recommended.[10] It is recommended to follow the local institutional guidelines for the management of anaphylaxis.

Once symptoms of IR resolve, consideration can be given to re-start the chemotherapy or monoclonal antibody at a reduced rate with pre-medications for grade 1-2 reactions. Re-start is strongly discouraged if a severe reaction occurred (e.g. anaphylaxis).[2,3]

Consider serum tryptase collection (within 15 minutes to 3 hours of an infusion reaction). Elevated tryptase suggests mast cell degranulation has occurred, which supports the use of a desensitization protocol at re-challenge. However, normal levels of tryptase do not rule out the clinical diagnosis of anaphylaxis.[2]

Clinical Question 5.1: What is the recommended infusion rate for restarting an infusion once symptoms of IR resolve?

Recommendation 5.1: Consider restarting at a reduced infusion rate (i.e. at 50% of the rate at which the infusion reaction occurred) and titrate to tolerance. Alternatively, local experience with a graduated infusion rate may be considered (e.g. 25% for 5 minutes, 50% for 5 minutes, 75% for 5 minutes then full rate if no reaction).[3,6,7,21]

Summary of Evidence & Discussion:
Restarting the infusion that had resulted in an IR may be considered once symptoms of the initial grade 1-2 IR have resolved. However, there is a lack of published data available regarding the recommended rate of infusion upon restarting.

In two review articles, infusions of monoclonal antibodies are recommended to be restarted at a reduced infusion rate (i.e. at 50% of the rate at which the infusion reaction occurred).[3,6]

There is insufficient evidence to recommend a specific infusion rate protocol upon restarting the infusion after an IR. Local experience with infusion rates may be considered in the absence of published information.

Please refer to the general management algorithm.

RECOMMENDATIONS FOR RE-CHALLENGE AFTER A PREVIOUS INFUSION REACTION

When patients experience IRs, re-challenge with the same treatment or a different medication in the same class may be considered, under specific conditions. The treatment medication which caused the IR, severity and nature of the reaction (i.e. risk of serious recurrent reaction), potential clinical benefit of further treatment and availability of suitable alternative treatment all need to be assessed when considering re-challenge.

Clinical Question 6.1: Is there a role for montelukast and acetylsalicylic acid as pre-medications in the secondary prophylaxis setting?

Recommendation 6.1: There is limited evidence to support the addition of oral montelukast ± oral acetylsalicylic acid as pre-medications in the secondary prophylaxis setting. Based on expert consensus, use in the desensitization setting, and a favourable safety profile, this can be considered a reasonable approach.[102]

Summary of Evidence & Discussion:

Montelukast and acetylsalicylic acid have been used in the desensitization setting to prevent IRs. Acetylsalicylic acid blocks the effects of prostaglandins, and may offer an additional and complementary mechanism to montelukast to avert mast-cell mediated hypersensitivity reactions.[102] Literature was reviewed to evaluate whether montelukast and acetylsalicylic acid can be effective and safe additions to existing pre-medication regimens (e.g. steroids, H1-receptor antagonists, H2-receptor antagonists) in the secondary prophylaxis setting.

In a letter to the editor, the clinical experience at Grand River Regional Cancer Centre was described. 32 of the 373 chemotherapy treatments containing a taxane, platinum and rituximab resulted in an IR. For secondary prophylaxis, montelukast was used alone or in combination with acetylsalicylic acid, in addition to steroids, H1-receptor antagonists and H2-receptor antagonists. It was found that montelukast ± acetylsalicylic acid was effective at reducing IRs. No admission to hospital or dilution protocols were required. Moreover, no changes to chemotherapy regimen protocols were necessary and subsequent cycles were delivered using standard timeframes.[102]

This suggests that adding oral montelukast ± oral acetylsalicylic acid to prevent recurrent IRs in the secondary prophylaxis setting may be effective; however, there is insufficient evidence to make a formal recommendation at this time. Due to the favourable side effect profile of montelukast, this approach may be reasonable.

Taxanes

Re-challenge with taxanes requires careful consideration of the potential clinical benefit and risks of further treatment. Concurrent consideration of patient factors, the severity and nature of the IR and availability of a suitable alternative treatment is recommended. Patient education regarding the risks with this procedure is recommended.

Clinical Question 6.2: Can patients who experienced an IR with a taxane be re-challenged with another taxane?

Recommendation 6.2: There is insufficient evidence to recommend substitution with another taxane at re-challenge. High cross-reactivity rates have been reported. [7,35,103,104]

Summary of Evidence & Discussion:

Taxanes are used in many chemotherapy regimens to treat different types of cancer. Cross-reactivity between taxanes (e.g. paclitaxel and docetaxel) may limit treatment options and increase the risk of IRs in patients who experienced an IR with prior taxane therapy.[7] Studies were reviewed to determine the rates of cross-reactivity reported in literature.

A retrospective study by Dizon et al. evaluated patients with breast or gynecologic cancer who received paclitaxel (n = 718) or docetaxel (n = 93). IRs occurred in 16 patients (2.2%) who received paclitaxel and 9 patients (9.7%) who received docetaxel. Pre-medications given to these patients were variable. 10 patients who experienced an IR with paclitaxel were re-challenged with docetaxel, of whom 9 experienced a subsequent IR despite dexamethasone being given as pre-medication. The overall cross-reactivity rate cited in this study was 90% and no deaths were reported.[7,35,103]

A retrospective study by Sánchez-Muñoz et al. evaluated patients with breast cancer (n = 23) who received paclitaxel (n = 12) or docetaxel (n = 11) and experienced an IR. Pre-medications given to patients who received paclitaxel were IV dexamethasone 20 mg, IV ranitidine 50 mg and IV dexchlorpheniramine 10 mg. Pre-medications given to patients who received docetaxel included oral dexamethasone 8 mg every 12 hours starting the day before infusion and IV dexamethasone 20 mg prior to infusion. After experiencing a severe IR with the first taxane, patients (n = 17) were given IV dexamethasone 20 mg, IV ranitidine 50 mg and IV dexchlorpheniramine 10 mg prior to the infusion of the other taxane. Time of infusion was also increased. 8 patients experienced IR with paclitaxel initially, of whom 3 experienced an IR with docetaxel. 9 patients experienced an IR with docetaxel initially, of whom 4 experienced an IR with paclitaxel. Of the 17 patients who received both paclitaxel and docetaxel, 7 patients (41%) experienced an IR, all of which were grade 3-4. The overall cross-reactivity rate cited in this study was 41% and no deaths were reported.[7,104]

Due to the potentially high rates of cross-reactivity, substitution of another taxane at re-challenge is not recommended.

Clinical Question 6.3: Are there strategies to facilitate safe re-challenge of taxanes?

Recommendation 6.3: There is insufficient evidence to support a specific re-challenge protocol for taxanes. For grade 1-2 IRs, consider re-challenge at a reduced infusion rate with pre-medications. If a patient who experienced a grade 3-4 IR is to be re-challenged with a taxane, consider desensitization.[26,105,106]

Summary of Evidence & Discussion:

Four articles evaluated whether intensifying pre-medications and/or extending the infusion duration may facilitate safe re-challenge with paclitaxel and/or docetaxel.

The study by Braverman et al. evaluated patients with breast cancer who received weekly paclitaxel (n = 122). Despite pre-medications, 5.7% of patients experienced an IR. 4 patients experienced an IR during the 1st cycle, 2 patients during the 2nd cycle and 1 patient during the 4th cycle. Of the 7 patients who experienced an IR, 5 patients tolerated paclitaxel with no IR when the duration of infusion was prolonged to 2 hours. Only 1 patient had tapering of the dexamethasone dose (to 10 mg) when these IRs occurred. These patients went on to receive 3-6 additional paclitaxel treatments, with their dexamethasone dose tapered to as low as 6 mg. This study suggests that extending the infusion duration of paclitaxel may decrease the risk of recurrent IRs.[26]

In another study, the efficacy and safety of a standardized re-challenge protocol was evaluated in patients with various cancers who received paclitaxel re-challenge (n = 12) and who received docetaxel re-challenge (n = 15). Doses of paclitaxel and docetaxel were not specified. These patients had experienced symptoms consistent with a grade 1 or 2 IR. The re-challenge protocol used for paclitaxel include intensified pre-medications (e.g. oral dexamethasone 20 mg twice daily on the day prior to paclitaxel infusion, IV dexamethasone 20 mg given 45 minutes prior to paclitaxel, and IV chlorpheniramine 20 mg with IV ranitidine 50 mg given 30 minutes prior to paclitaxel) and extending the infusion duration to 5 hours (from 1 or 3 hours, depending on the protocol). In the same study, the re-challenge protocol used for docetaxel included intensified pre-medications (e.g. oral dexamethasone 8 mg twice daily for 5 days starting 2 days prior to docetaxel infusion, IV dexamethasone 20 mg given 45 minutes prior to docetaxel, and IV chlorpheniramine 20 mg with IV ranitidine 50 mg given 30 minutes prior to docetaxel) and extending the infusion duration to 2 hours (from 1 hour).[105] The success rate of the first re-challenge cycle for patients who received paclitaxel was 91.7% and docetaxel was 93.3%. A median of 3 additional cycles (1-9 cycles) were given to patients using the re-challenge protocol. 1 patient re-challenged with paclitaxel and 1 patient re-challenged with docetaxel experienced an IR in the first re-challenge cycle. No deaths were noted in this study. This study suggests that re-challenges with paclitaxel and docetaxel after a grade 1-2 IR may be feasible and safe using pre-medications and reducing the infusion rate.[105]

In another study, 136 patients were re-challenged with paclitaxel (135 mg/m^2 dose every 3 weeks) using a re-challenge protocol which included pre-medications and

infusing paclitaxel over a graduated rate. Pre-medications included oral dexamethasone 20 mg, IV diphenhydramine 50 mg and IV cimetidine 300 mg. The authors implemented a graduated rate as follows: 40 mL/hour for 15 minutes, 60 mL/hour for 30 minutes, 80 mL/hour for 30 minutes, 90 mL/hour for 30 minutes and 100 mL/hour until completed. There was a decrease in percentage of patients who experienced IRs with the implementation of the re-challenge protocol (5% vs 27%) when compared with the use of an older regimen (details not specified in the article).[106]

In a review article, a proposed protocol for restarting paclitaxel after grade 1 IRs (or grade 2, based on clinical judgment and patient acknowledgement of risks and benefits) was recommended. For paclitaxel 135-175 mg/m^2 infusion every 3 weeks, the infusion can be administered over 3 hours as follows: 2 mL/hour for 15 minutes, then 8 mL/hour for 15 minutes, then increase to 80 mL/hour to complete the rest of the infusion if tolerated. For paclitaxel 50-80 mg/m^2 infusion every week, the infusion can be administered over 1 hour as follows: 2.5 mL/hour for 15 minutes, then 25 mL/hour for 15 minutes, then increase to 250 mL/hour to complete the rest of the infusion if tolerated. Patients should receive the same pre-medications as the initial infusion. If the patient tolerates this graduated infusion rate, then the authors recommend resuming subsequent infusions at the regular rate. It was noted that severe IRs may still result despite pre-medications and the implementation of a reduced infusion rate protocol.[7,21]

The above studies had a small sample size and are retrospective in nature. There is insufficient evidence to support a specific re-challenge protocol for taxanes. Re-challenge can be considered for patients who experienced a grade 1 or 2 IR with pre-medications and reduced infusion rate. Consider a desensitization protocol for patients who experienced a grade 3 or 4 IR who are to be re-challenged with a taxane.

Platinums

Re-challenge with cisplatin for patients who experienced an IR with carboplatin requires careful consideration of the potential clinical benefit and risks of further treatment. Concurrent consideration of patient factors, the severity and nature of the IR and availability of a suitable alternative treatment is recommended. Patient education regarding the risks with this procedure is recommended.[111–113,115,116]

Studies evaluating re-challenge protocols are small and retrospective in nature. These protocols focus on intensifying (or adding) pre-medications and extending the length of infusion. There is insufficient evidence to recommend a specific protocol. Local experience may be a suitable alternative when evidence is not available.[3,6,7,21,105–109]

Clinical Question 6.4: Are there strategies to facilitate safe re-challenge with platinums?

Recommendation 6.4: Careful consideration of the potential clinical benefit and risks of further treatment are required. Concurrent consideration of patient factors, the severity and nature of the IR and availability of a suitable alternative treatment is recommended. Patient education regarding the risks with this procedure is recommended. The addition of pre-medications or extending the duration of infusion at re-challenge are potential strategies that may facilitate safe re-challenge with platinums for patients who experienced a grade 1-2 IR with a platinum previously.[54,105–110]

Summary of Evidence & Discussion:

Two small studies evaluated the efficacy and safety of intensified pre-medications and extending the duration of infusion to facilitate safe re-challenge with carboplatin.

In one study, the efficacy and safety of a standardized re-challenge protocol was evaluated in patients with various cancers who received carboplatin re-challenge (n = 5) and who received oxaliplatin re-challenge (n = 15). These patients had experienced symptoms consistent with a grade 1 or 2 IR. The re-challenge protocol used for carboplatin and oxaliplatin included the addition of pre-medications (e.g. IV dexamethasone 20 mg given 45 minutes prior to infusion and IV chlorpheniramine 20 mg with IV ranitidine 50 mg given 30 minutes prior to infusion) and increasing the duration of infusion. For carboplatin, the duration of infusion was increased to 2 hours (from 0.5-1 hour) and for oxaliplatin, the duration of infusion was increased to 6 hours (from 2 hours). The success rate of the first re-challenge cycle for patients who received carboplatin was 100%. The success rate of the first re-challenge cycle for patients who received oxaliplatin was 93.3%. A median of 3 additional cycles (1-9 cycles) were given to patients using the re-challenge protocol. 1 patient re-challenged with oxaliplatin experienced an IR in the first re-challenge cycle and no deaths were noted. This suggests that administering pre-medications and extending the duration of infusion for secondary prophylaxis of IRs may be a safe option.[105]

A chart review described 24 patients who were re-challenged with carboplatin using a protocol which included pre-medications and infusing carboplatin over a graduated rate. Symptoms of IR with carboplatin experienced by patients prior to re-challenge ranged in severity, and included itching, shortness of breath, chest pain, nausea, dizziness, flushing and hypotension. Pre-medications given included IV ondansetron 32 mg, oral dexamethasone 20 mg and IV diphenhydramine 50 mg. The authors implemented a graduated rate as follows: 75 mL/hour for 10 minutes, 150 mL/hour for 10 minutes, 225 mL/hour for 10 minutes and 300 mL/hour until completed. There was a decrease in percentage of patients who experienced IRs with the implementation of the re-challenge protocol (8% vs 21%) when compared to before initiating the protocol.[106]

Additionally, five small studies evaluated the efficacy and safety of intensified pre-medications ± extending the duration of infusion to facilitate safe re-challenge with oxaliplatin.

One retrospective study evaluated patients with advanced colorectal cancer who experienced an IR with oxaliplatin and were re-challenged with oxaliplatin (n = 6). Symptoms of IR prior to re-challenge included dyspnea, facial edema, itching and agitation. These patients received pre-medication with steroids and H1-receptor antagonists (medications, doses, route of administration not specified). Of the 6 patients, 5 experienced a recurrent IR (success rate 17%).[107]

One retrospective study evaluated patients with minor IRs to oxaliplatin (n = 24). 9 patients were re-challenged without modification to the administration protocol. Of these patients, 2 did not experience a recurrent IR (success rate 22.2%). 15 patients were re-challenged with a protocol consisting of extending the duration of infusion to 4 or 6 hours, and/or the addition of dexchlorpheniramine as a pre-medication. Of these patients, 8 did not experience a recurrent IR (success rate 53.3%).[108]

A retrospective study evaluated patients with metastatic colorectal cancer who experienced an IR with oxaliplatin (n = 6). Symptoms of IR ranged in severity and included fever, dizziness, tachycardia and hypotension. These patients were re-challenged with oxaliplatin and were given pre-medications including IV dexamethasone 20 mg, IV diphenhydramine 50 mg and oral ranitidine 150 mg. 2 patients received oxaliplatin given over 2 hours and 4 patients received oxaliplatin given over 6 hours. Of the 2 patients who received oxaliplatin over 2 hours, both experienced a recurrent IR (success rate 0%). Of the 4 patients who received oxaliplatin over 6 hours, none experienced a recurrent IR (success rate 100%). The results of this study suggests that extending the duration of infusion of oxaliplatin upon re-challenge may be an effective strategy as secondary prophylaxis of IRs.[109]

A similar re-challenge protocol for patients who experienced grade 1-2 IRs with oxaliplatin at a single institute was described. This re-challenge protocol included pre-medications (e.g. IV dexamethasone 20 mg given 45 minutes prior to oxaliplatin, IV diphenhydramine 50 mg given 30 minutes prior to oxaliplatin, and IV ranitidine 50 mg given 30 minutes prior to oxaliplatin) and extending the duration of oxaliplatin infusion to 6 hours. They further described 20 patients who were re-challenged with oxaliplatin using this protocol. 6 patients (30%) experienced a recurrent IR (success rate 70%).[110]

A retrospective cohort study evaluated patients with advanced colorectal cancer (n = 272) who received FOLFOX4. Patients who experienced grade 1/2 IR despite primary prevention received the secondary prevention regimen, consisting of IV dexamethasone 20 mg, oral famotidine 40 mg and oral diphenhydramine 50 mg 30 minutes before oxaliplatin infusion. In addition, the duration of oxaliplatin infusion was extended to 4 hours (from 2 hours). Patients who experienced grade 3/4 IR or who experienced IR despite the secondary prevention regimen discontinued their chemotherapy treatment. Of the 48 patients who experienced an IR, 30 patients were re-challenged with oxaliplatin using the secondary prevention regimen. IRs occurred in 11 patients (36.7%) within 2 cycles. 2 of these patients had worse reactions after receiving the secondary prevention regimen. 63.3% of these patients received at least 2 additional

cycles of oxaliplatin after receiving the secondary prevention regimen. The results of this study suggests that using pre-medications and extending the duration of oxaliplatin infusion may be beneficial in preventing IRs in the setting of secondary prophylaxis.[54]

The success rate of these small studies appears to vary considerably. Due to the variation in pre-medications, doses, and route of administration, further study is required to confirm the optimal pre-medication regimen to prevent recurrent IRs for patients being re-challenged with platinums. However, the studies available suggest benefit of extending the duration of oxaliplatin infusion to 6 hours to prevent recurrent IRs if re-challenge is appropriate.

Clinical Question 6.5: Can cisplatin be substituted for patients who experienced an IR with carboplatin at re-challenge?

Recommendation 6.5: Re-challenge with cisplatin for patients who experienced an IR with carboplatin requires careful consideration of the potential clinical benefit and risks of further treatment. 2 deaths have been reported in literature.[111–116]

Summary of Evidence & Discussion:

Cross-reactivity between cisplatin and carboplatin, due to the similar chemical structures, may limit treatment options for patients. There is some evidence to suggest that re-challenging with cisplatin after a patient experiences IR with carboplatin may be a viable option; however, severe anaphylaxis reactions and death has been reported in 2 patients after re-challenge.[111–114]

A recently published retrospective study by Pasteur et al. evaluated patients who were referred for a dermato-allergology consultation after experiencing an IR with platinums (n = 155). Cross-reactivity to carboplatin in oxaliplatin-allergic patients was 45% (23 of 51 patients; 95% CI 36-66%). Cross-reactivity to oxaliplatin in carboplatin-allergic patients was 37% (16 of 43 patients; 95% CI 23-53%). It was noted in this study that the cross-reactivity to cisplatin was low in comparison. Cross-reactivity to cisplatin in carboplatin-allergic patients was 7% (3 of 43; 95% CI 2-17%) and in oxaliplatin-allergic patients was 0% (0 of 51, 95% CI 0-7%).

After skin tests were conducted, platinums were re-challenged in 58 patients (30 patients with positive tests and 28 patients with negative tests). Of the 30 patients with positive tests who were re-challenged with platinums, all were exposed to another platinum (carboplatin = 2, oxaliplatin = 4, cisplatin = 24). No IRs were noted. Of the 28 patients with negative tests, 16 patients were re-exposed to the same platinum (carboplatin = 6, oxaliplatin = 10). 12 patients were exposed to another platinum (carboplatin = 1, oxaliplatin = 2, cisplatin = 9). No IRs were noted.[115]

In addition, a review of published case reports by Callahan et al. looked at patients with epithelial ovarian cancer and primary peritoneal cancer (n = 24) who experienced a documented IR to carboplatin, and who were subsequently re-challenged with cisplatin. 12 of these patients had a mild IR to carboplatin, and 12 of these patients had a severe

IR to carboplatin. All patients received cisplatin over 1.5 hours with standard pre-medications (ondansetron 16 mg and dexamethasone 20 mg; route of administration was not specified). 75% of patients tolerated cisplatin with no IR. 6 patients (25%) eventually developed a reaction to cisplatin (none of which were life threatening, 1 requiring hospitalization). 1 patient (4%) experienced an IR to cisplatin with the first infusion of cisplatin. The other 5 patients who experienced an IR to cisplatin received a median number of 3.4 cycles (1-4 cycles). 96% of patients tolerated at least 1 cycle of cisplatin. The authors noted that there were previous small case series and case studies including a total of 35 patients who experienced IRs with carboplatin. These studies documented successful re-challenges with cisplatin in 30 of these patients. 5 of these patients experienced IRs, of which 2 experienced fatal anaphylactic reactions.[113] This review of case reports suggests that IRs of variable severity with cisplatin are possible.

A retrospective review of patients with recurrent ovarian cancer (n = 183) who were retreated with carboplatin showed that 26.8% experienced an IR with carboplatin. The mean number of cycles before IR occurred was 8 (3-17 cycles), and most IRs were grade 2 (83%). Of the 49 patients who experienced an IR, 37 patients (77%) were re-challenged with cisplatin in combination with paclitaxel or gemcitabine. In addition to routine anti-emetics, pre-medication consisted of the following, starting 3 days before cisplatin therapy: oral ranitidine 150 mg twice daily, oral betamethasone 1 mg twice daily and oral promethazine 25 mg. Additional pre-medication given 30 minutes prior to cisplatin infusion included IV dexamethasone 20 mg, IV ranitidine 50 mg and IM promethazine 50 mg. 5 patients (13.1%) experienced an IR to cisplatin (3 after two cycles and 2 after six cycles). In all cases, IRs were mild to moderate in nature, and occurred during or at the end of cisplatin infusion.[116] The results of this study suggests that IRs (albeit mild to moderate in severity) can occur with cisplatin if the patient had experienced an IR with carboplatin previously.

Thus far, the available evidence regarding the safety of switching carboplatin to cisplatin after an IR to carboplatin is comprised of small studies. Current practice differs across different Ontario centres. Desensitization or administration of an alternative therapy can be considered if clinicians determine the risk of cross-reactivity for the patient who experienced an IR with carboplatin in the past outweighs the benefits of cisplatin therapy.

Monoclonal Antibodies

Clinical Question 6.6: **What is the recommended approach to re-challenge for rituximab after a patient experiences an IR?**

Recommendation 6.6: The addition of pre-medications or extending the duration of infusion are potential strategies to facilitate safe re-challenge with rituximab for patients who experienced a grade 1-2 IR previously. Re-challenge with rituximab for patients who experienced a grade 3 or 4 IR requires careful consideration of the potential clinical benefit and the risks of further treatment.[102,117]

Summary of Evidence & Discussion:

The incidence of IRs with rituximab can be high, especially with the initial infusion. Despite this, there is limited information available on the safety of re-challenge protocols for patients who experienced an IR with rituximab.

One retrospective study evaluated patients who experienced an IR with the initial infusion of rituximab (n = 67). 11 patients who experienced a grade 1 IR and 31 patients who experienced a grade 2 IR with the initial infusion subsequently received rituximab again within 4 months of the initial reaction. A slowed infusion rate was used, and 5 patients were pre-medicated with acetaminophen, diphenhydramine, and hydrocortisone. Pre-medication details were not available for the remaining 7 patients. Of the 11 patients, 1 patient did not have a recorded outcome, 1 patient experienced a recurrent IR and 9 tolerated the re-challenge. Of the 31 patients who experienced a grade 2 IR, 16 tolerated the re-challenge, 13 did not have a recorded outcome, 1 had a grade 2 IR, and 1 had a grade 3 IR. Pre-medications and infusion rates were not sepcified.[117] This study suggests that if patients experienced a grade 1 or 2 IR with the initial infusion, it may be safe for re-challenge at future cycles.

Based on the above study, and recommendation 6.1, the addition of pre-medications such as montelukast ± acetylsalicylic acid and extending the infusion time may facilitate safe re-challenge for patients who experienced a grade 1 or 2 IR with rituximab previously.[102] Subcutaneous administration may be also be considered.

If the patient experienced a grade 3 or 4 IR with the initial infusion and if there is no alternative treatment option, consider a desensitization protocol. Further studies are required to evaluate the safety of re-challenging patients who experienced a grade 3-4 IR with rituximab.

RECOMMENDATIONS FOR RE-CHALLENGE USING A DESENSITIZATION PROTOCOL

Drug desensitization protocols are designed to induce temporary immune tolerance to an offending medication. Temporary immune tolerance can be achieved by increasing the dose of medication in a stepwise manner, such that the exposure to the medication is continuous. Exposure begins at very low doses and increases slowly in a graduated manner.[118,147] The maintenance of the desensitized state requires continuous drug exposure, and the protocol needs to be repeated if several half-lives of the medication have elapsed since the previous time of administration.[112,118,119] As cancer treatments are rarely administered continuously, patients who had a successful desensitization will require a desensitization protocol to be implemented for all future treatment cycles. Patients should be informed that they are still at risk of IRs despite past desensitization.

Patients should be desensitized in an intensive care unit or closely monitored outpatient setting, with trained clinicians and one-to-one nursing, provided that resuscitative equipment and medications necessary to treat IRs are available. Nurses must be trained to monitor desensitization protocols as well as recognize and treat IRs. It is suggested that you establish a protocol for desensitization with a multidisciplinary team and plan for the resources necessary to support the process. Consultation with an allergist, if available, can be helpful to both develop the protocol and evaluate patients.[148,149]

Clinical Question 7.1: **Which patients may be considered for desensitization?**

Recommendation 7.1: Due to the time-consuming nature of desensitization procedures, it should be reserved for patients who experienced a grade 3 or 4 IR <u>and</u> who have no clinically effective alternative available.[2] Desensitization should also be considered for patients who had repeated IRs during re-challenge.

Clinical Question 7.2: **In which patients is desensitization contraindicated?**

Recommendation 7.2: Desensitization is **contraindicated** in patients who experienced type II reactions (e.g. immune-cytotoxic reactions), type III reactions (e.g. serum sickness-like reactions) or severe cutaneous adverse reactions (e.g. SJS, TEN, DRESS).[118] For these patients, exposure to even small amounts of the offending medication can induce irreversible and potentially fatal reactions.

Clinical Question 7.3: What is the role of skin testing for desensitization protocols?

Recommendation 7.3: Skin testing may be used as a tool during patient assessments; however, other patient-specific clinical features should be taken into consideration concurrently.

Summary of Evidence & Discussion:

Most protocols described in the literature include routine skin testing before the desensitization procedures are carried out. However, there is inconsistent utility of skin testing before the implementation of a desensitization protocol described in the literature. Skin testing appears to be more accurate for platinum agents than taxanes; however, even carboplatin skin tests cannot reliably predict a patient's risk of experiencing an IR.[51,55,124] In addition, the positive and negative predictive value of skin testing for many new agents are not known.

A positive skin test may be useful in identifying the cause of a grade 3 or grade 4 reaction when several drugs have been given concurrently or in rapid succession before the allergic reaction. However, a recent anaphylaxis episode within the previous month can lead to temporary skin non-reactivity and thus may yield false negative results. Skin testing should also be performed by an allergist, due to the small risk of inducing an allergic reaction. The value and access of skin testing should therefore be considered before desensitization protocols.[150]

Clinical Question 7.4: What prophylaxis strategies should be implemented with desensitization protocols?

Recommendation 7.4: A reasonable desensitization pre-medication regimen includes[112,119–121]:
- H1-receptor antagonist (e.g. diphenhydramine or a non-sedating equivalent)
- H2-receptor antagonist (e.g. ranitidine)
- Corticosteroid (e.g. dexamethasone)
- Montelukast 10 mg
- ASA (e.g. 500 mg, or the dose that is commercially available, such as 325 mg)

Beta-blockers and ACE-inhibitors should be held for 24 hours before initiating the desensitization protocol, as they may interfere with the action of rescue medications if an IR occurs during the desensitization process.

Summary of Evidence & Discussion:

Desensitization procedures can be risky for patients, as severe reactions can still occur during the procedure. When patients undergo the desensitization procedure, there is a risk of IRs (of similar or greater severity) recurring with repeated exposure to the offending agent. Therefore, pre-medications are recommended and necessary.

Most published desensitization protocols used H1-receptor antagonists, corticosteroids and H2-receptor antagonists before the procedure.[112,119–121,123,124,127,151] Dexamethasone is commonly used with taxane desensitization protocols.[112,122,123] There is a growing body of evidence supporting the use of ASA (500 mg or at a dose that is commercially available, such as 325 mg) and montelukast 10 mg as pre-medications for desensitization; however, the optimal dosing regimen is not established.[120–124]

[Clinical Question 7.5](): Which desensitization protocol(s) are recommended?

Recommendation 7.5: The protocol with the most evidence is a three-bag 12 step protocol developed by Castells et al. If a three-bag 12 step protocol is not feasible, a one-bag 12-step protocol developed by Chung et al. can be a reasonable alternative. For high-risk patients, a four-bag 16 step protocol can be used.[112,118–120,122–127]

Summary of Evidence & Discussion:

The protocol with the most evidence is a three-bag 12 step protocol developed by Castells et al.[112,119] In this protocol, three solutions (each 250 mL) are administered in consecutive steps at increasing infusion rates.[112,119] An example protocol for carboplatin with detailed calculations is shown in [Appendix 3](). Solution A (step 1-4) is a 100-fold dilution of the final target concentration, solution B (step 5-8) is a 10-fold dilution of the final target concentration, and the concentration of solution C (step 9-12) was calculated by subtracting the cumulative dose administered in steps 1-8 from the total target dose.[112,119] Steps 1 to 11 are 15 minutes each and step 12 is prolonged until the entirety of the target dose is infused.[112,119] The dose is increased by 2 to 2.5 fold at each step prior to the final step. For paclitaxel, the volume of solution C may be adjusted to keep the concentration below the saturation point of the drug (1.2 mg/mL).[112,119] Solution A and B will have leftover volume that is to be discarded.[118] IRs during desensitization should be treated immediately by stopping the infusion and managing the symptoms.[112,119] Once the symptoms of IR resolve, the desensitization protocol can be restarted from the step at which it had been stopped.[112,119]

Recently, various one-bag desensitization protocols have been published.[122–124] While the results of these studies are promising, one-bag protocols have less supporting evidence when compared to three-bag protocols, especially in patients who experienced severe IRs in the past. In addition, published one-bag protocol studies used different infusion rates and steps for different drugs and different doses.[122–124] In situations where the implementation of three-bag protocols are not feasible, a one-bag 12 step protocol similar to the one developed by Chung et al. can be a reasonable alternative, especially for platinum agents.[124] Chung et al. reported that their one-bag 12 step protocol is non-inferior to the three-bag 12 step standard protocol for patients receiving platinum desensitization.[124] In addition, for medications which cannot be diluted (such as cetuximab), one-bag desensitization protocols can be used.[120,125,126] The principle behind the one-bag protocol is similar to the others, in which the dose is increased by 2 to 2.5 fold with every step.

For high-risk patients, a four-bag 16 step protocol can be used, in which four 15-minute steps using a 1000-fold diluted solution can be added before the standard three-bag 12 step protocol.[112,119] An example of the four-bag 16 step protocol has been described by Sloane et al.[119] Examples of high-risk patients include patients who experienced severe anaphylaxis during the initial infusion, as well as patients with severe respiratory or cardiac disease and patients who are pregnant.[118] A modified, 10 step version of the three-bag protocol has been reported as well.[120,121] This modified protocol aims to address the small amount of primer fluid that is in the IV line in the beginning, and the total duration of infusion is shorter in comparison.[120,121] The total duration of infusion for the three-bag 12 step protocol is just under 6 hours while the four-bag 16 step protocol takes 6 hours and 40 minutes.[118,119,127] In contrast, the three-bag 10 step protocol can be infused in 4 hours and 15 minutes.[120,121]

Please refer to <u>Appendices 3 & 4</u> for examples of desensitization protocols.
Please refer to <u>Appendix 5</u> (Exel) for a three-bag 12-step protocol calculation tool.

Conclusion

This guideline was developed to support clinicians in the prevention and management of cancer medication related IRs. A standardized approach can help to reduce the impact of IRs on patient safety and treatment quality. Prevention of IRs (e.g. using pre-medications and/or infusing the anticancer medication at a graduated rate) is a key factor in the reduction of the incidence and severity of IRs. When IRs occur, prompt management of symptoms is imperative. Based on the proposed algorithm, the symptoms of IR can be classified into two categories which can assist to inform clinicians in the setting of acute management and re-challenge. An example of a desensitization protocol was included as a potential approach to re-challenge after a grade 3-4 IR has occurred and no suitable alternative treatment options exist. There is an overall paucity of high-quality evidence and lack of standardization of recommended strategies to prevent and manage IRs. Expert consensus and local experience were applied in areas where the evidence is lacking.

APPENDIX 1: DRUG TABLE

Refer to the drug table for IR characteristics, mechanism, symptoms, prophylaxis, acute management, and re-challenge for specific anticancer medications.

APPENDIX 2: PATIENT INFORMATION SHEET

Refer to the patient information sheet for patient-friendly information on infusion reactions.

APPENDIX 3: SAMPLE THREE-BAG 12 STEP PROTOCOL FOR CARBOPLATIN 470 MG, ADAPTED FROM CASTELLS ET AL[112]

Pre-medications recommended 20 minutes prior to implementing this protocol:[112]
- Diphenhydramine 25 mg or Hydroxyzine 25 mg PO/IV
- Famotidine 20 mg or Ranitidine 50 mg IV

Note: For paclitaxel desensitization protocols, dexamethasone 20 mg PO is recommended the night before and the morning of paclitaxel desensitization.

Sample three-bag 12 step protocol for carboplatin 470 mg, adapted from Castells et al[112]

	Volume (mL)	Solution Concentration (mg/mL)	Dose in solution (mg)
Solution A	250	0.0188	4.7
Solution B	250	0.188	47
Solution C	250	1.865	466.3

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	A	2	15	0.5	0.0094	0.0094
2	A	5	15	1.25	0.0235	0.0329
3	A	10	15	2.5	0.047	0.0799
4	A	20	15	5	0.094	0.1739
5	B	5	15	1.25	0.235	0.4089
6	B	10	15	2.5	0.470	0.8789
7	B	20	15	5	0.940	1.8189
8	B	40	15	10	1.880	3.6989
9	C	10	15	2.5	4.663	8.3619
10	C	20	15	5	9.326	17.6879
11	C	40	15	10	18.652	36.3399
12	C	75	186	232.5	433.660	470

1. Typical concentration in 250 mL bag is calculated as 470 mg/250 mL = 1.88 mg/mL.
2. Solution A and B concentrations are 1/100 and 1/10 dilutions of typical concentration.
3. The total dose across three bags is 518 mg but only 470 mg will be infused, as solution A and B will not be infused fully.
4. Infusion rate is always set up as shown in the Castells' protocol.[112] The established infusion rate shown here will not need to be changed for different drugs or doses.
5. Dose administered with each step and cumulative dose is calculated for step 1-8 (infusion time x infusion rate x solution concentration).

6. Dose in Solution C is calculated as: target dose (470 mg) - cumulative dose by the end of step 8 (3.6989 mg) = 466.3011 mg
7. Concentration of Solution C is calculated as 466.3011 mg / 250 mL = 1.8652 mg/mL.
8. Dose administered for step 9-12 is calculated based on the calculated concentration of solution C.
9. Total infusion for protocol is approximately 5.85 hours for most drugs.
10. **Due to the small volumes infused for solution A and B, the IV lines should be primed with the drug solutions instead of saline or D5W. In addition, for every solution change, new IV lines should be used and re-primed.**

APPENDIX 4: SAMPLE ONE-BAG 12 STEP PROTOCOL FOR CARBOPLATIN 470 MG, ADAPTED FROM CHUNG ET AL[124]

Sample one-bag 12 step protocol for carboplatin 470 mg, adapted from Chung et al[124]

	Volume (mL)	Solution Concentration (mg/mL)	Dose in solution (mg)
Solution A	250	1.88	470

Step	Rate (mL/h)	Time (min)	Step Volume (mL)	Step dose (mg)	Cumulative Dose (mg)
1	0.1	15	0.025	0.047	0.0470
2	0.2	15	0.05	0.094	0.1410
3	0.5	15	0.125	0.235	0.3760
4	1.2	15	0.3	0.564	0.9400
5	2.5	15	0.625	1.175	2.1150
6	5	15	1.25	2.35	4.4650
7	10	15	2.5	4.7	9.1650
8	20	15	5	9.4	18.5650
9	40	15	10	18.8	37.3650
10	60	15	15	28.2	65.5650
11	80	15	20	37.6	103.1650
12	150	78	195.13	366.835	470
For cisplatin, a 13th step at 450 mL/h should be added.					

APPENDIX 5: THREE-BAG 12-STEP PROTOCOL: CALCULATION TOOL

Use the calculation tool to help calculate a three-bag 12-step desensitization.

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