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Acute Infusion-Related Adverse Events to Chemotherapy and Monoclonal Antibodies

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Cancer Care Alberta

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Background

Many chemotherapy drugs and monoclonal antibodies are reported to cause acute infusion-related allergic and allergic-like reactions in cancer patients. These reactions range from mild cutaneous appearances (e.g. pruritus and hives) to life-threatening anaphylaxis with hypotension, oxygen desaturation and cardiovascular collapse, and death.[1] Acute infusion-related adverse events vary based on the type of drug used, as well as the duration, frequency of infusion and prior exposure to the drug.[2]

Understanding the pathophysiology of these acute infusion-related adverse events and the terminology used to describe them is confusing. The traditional classification relies on the clinical presentation of typical symptoms and their timing, and include:[3]

- type I (IgE mediated reactions)
- type II (antibody mediated cytotoxicity reactions)
- type III (immune complex-mediated reactions)
- type IV (delayed reactions)

The traditional classification, however, does not encompass the current spectrum of reactions and symptoms occurring in cancer patients.[1, 4, 5] Some of the reactions have no known underlying mechanism, others have a known mechanism which is not part of the traditional classification, while some drugs induce mixed reactions with two or more proposed mechanisms.[1]

Regardless of the underlying mechanism, acute infusion-related adverse events to chemotherapy drugs and monoclonal antibodies are unexpected, can be severe, and can prevent the use of first-line therapies which has the potential to negatively impact patient's survival and quality of life.[1] To facilitate prompt identification and management of these reactions, a shared understanding of the terminology, incidence, characteristics, and management approaches is required between healthcare professionals.

Guideline Questions

As it pertains to chemotherapy drugs and monoclonal antibodies:

1. How are acute infusion-related adverse events defined?
2. What are the risk factors for acute infusion-related adverse events?
3. What is the incidence of acute infusion-related adverse events?
4. What are the characteristics (signs, symptoms, timing, and grading) of acute infusion-related adverse events?
5. What is unique about acute infusion-related adverse events with the following drugs classes:
    a. Platinum derivatives?
    b. Anthracyclines?
    c. Taxanes?
    d. Monoclonal antibodies?

6. How should the various types of acute infusion-related adverse events be managed?
7. How should patients experiencing an acute infusion-related adverse events be followed-up?

Search Strategy

The PubMed and EMBASE database were searched for relevant studies, guidelines and consensus documents published up to May 2019. The specific search strategy, search terms, and search results, are presented in Appendix A, and evidence tables are available upon request. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: Cancer Care Ontario (CCO), The Comité de l'évoltion des pratiques en oncologie (CEPO), and the European Society for Medical Oncology (ESMO).

Target Population

The recommendations presented in this guideline apply to **adult patients over the age of 18** who are receiving chemotherapy and/or monoclonal antibodies. Different principles may apply to pediatric patients.

Guideline Development Notes

Acute infusion-related adverse events associated with chemotherapy drugs and monoclonal antibodies is difficult to evaluate through prospective randomized studies because of the unexpected nature of these reactions.[6] The available published data is largely drug-specific, and while reported as secondary outcomes or included in safety analysis from randomized controlled trials, the data is primarily derived from single-center cohort, retrospective, or case reports.

We chose to provide high-level recommendations about the identification and management of infusion-related adverse events in this guideline and refer clinicians to the drug table in Appendix B for specific details about individual chemotherapy drugs and monoclonal antibodies. The information presented in Appendix B was largely identified in Lexicomp (specific drug or drug class) using a combination of search terms, including infusion reaction, infusion-related reaction, anaphylaxis, cytokine release, and hypersensitivity. For some drugs, additional new information was added from Cancer Care Ontario's Cancer Medication Infusion Reactions Drug Table.[7] Acute infusion-related adverse associated with supportive drugs used during cancer treatment (e.g. sargramostim) are beyond the scope of this guideline.

For recommendations about the management of acute infusion-related adverse events following treatment with immune effectors cells, please refer to Alberta Health Services' Alberta Bone Marrow and Blood Cell Transplant Program: Standard Practice Manual.[8]

Recommendations

1. Acute Infusion-Related Adverse Events Terminology

Several terms are used to describe acute infusion-related adverse events to chemotherapy and monoclonal antibodies, including drug hypersensitivity reactions, infusion-related reactions, cytokine release syndrome and anaphylaxis. We recommend using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to help standardize the definitions of some of these terms.[9] The CTCAE is a commonly used system of nomenclature for classifying adverse events and their associated severity in cancer clinical trials.[10]

- Drug hypersensitivity reactions (HSR) are the adverse effects of pharmaceutical formulations (including active drugs and excipients) that clinically resemble allergic reactions.[11]
- Infusion-related reaction (IRR) is a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.[9] An IRR may occur during administration (intravenous/subcutaneous) or sometime after on the first day of drug administration.[12]
- Cytokine release syndrome (CRS) is a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.[9] CRS is a specific type of nonantibody-mediated infusion reaction (often referred to as anaphylactoid reactions) that is associated with monoclonal antibodies and T-cell-directed therapies.[13]
- Anaphylaxis is a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, anaphylaxis presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.[9]

2. Risk Factors for Acute Infusion-Related Adverse Events

There are no well-established risk factors to identify who may experience an acute infusion-related adverse events. Low-level evidence has identified some drug-related, treatment regimen-related, and patient-related risk factors, which are summarized in Table 1.[14-30]

Table 1. Risk factors for acute infusion-related adverse events

Patient-Related	Treatment Regimen-Related	Drug-Related
• Pre-existing allergies to foods, blood products or radiographic contrast material (IgE-mediated reaction) • Bee sting allergy (e.g. paclitaxel) • High number of circulating tumour cells (e.g. rituximab)	• Intravenous administration (e.g. L-asparaginase) • High drug concentration and rate of infusions (e.g. etoposide) • Lack of steroid premedication (e.g. rituximab) • First infusion (e.g. cetuximab, daratumumab, rituximab, trastuzumab)	• Drugs supplied in the solvents polyoxyl 35/polyoxyethylated castor oil (cremophor EL) and polysorbate 80 (Tweens) (e.g. docetaxel, etoposide, paclitaxel, pembrolizumab, rituximab)

Patient-Related	Treatment Regimen-Related	Drug-Related
• B-cell chronic lymphocytic leukemia and high lymphocyte counts (e.g. rituximab) • History of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose (alpha-gal) (e.g. cetuximab)	• Prior exposure or multiple cycles (e.g. platinum drugs) • Prior infusion reaction to a drug of the same chemical class (e.g. paclitaxel and docetaxel) • Monoclonal antibody in combination with chemotherapy (e.g. bevacizumab)	

3. Incidence of Acute Infusion-Related Adverse Events

Capturing the incidence of acute infusion-related adverse events, drugs involved, management, treatment, and outcomes has been possible only through volunteer registries.[31, 32] Thus, it can be expected that the incidence of acute infusion-related adverse events with chemotherapy drugs and monoclonal antibodies is often different depending on the source of evidence. To assist healthcare professionals with risk recognition we chose Lexicomp as our source of evidence and allocated individual chemotherapy drugs and monoclonal antibodies into one of three categories based on arbitrarily selected ranges:[26-30, 33-60]

- High potential (≥30%): blinatumomab, daratumumab, obinutuzumab (1st infusion), paclitaxel (conventional), rituximab (decreases with subsequent infusions)
- Moderate potential (<30% to ≥10%): asparaginase (*E. coli*), carboplatin, cetuximab, cisplatin, daunorubicin (liposomal), docetaxel, nivolumab, obinutuzumab (2nd infusion), pertuzumab, ramucirumab, trastuzumab
- Low potential (<10%): alemtuzumab, atezolizumab, bevacizumab, bleomycin, brentuimab vedotin, cabazitaxel, daunorubicin (conventional), doxorubicin (conventional), doxorubicin (liposomal), epirubicin, etoposide, idarubicin, inotuzumab ozogamicin, ipilimumab, obitutuzumab (≥ 3rd infusion), oxaliplatin, paclitaxel (protein bound), panitumumab, pembrolizumab,

While most chemotherapy drugs and monoclonal antibodies have an anaphylactic incidence rate of less than 1%, they are reported as the third leading cause of fatal drug-induced anaphylaxis.[61]

4. Characteristics of Acute Infusion-Related Adverse Events

Signs and symptoms. Common signs and symptoms of acute infusion-related adverse events include:

- Cutaneous e.g. rash, flushing, urticaria, pruritus
- Respiratory e.g. dyspnea, bronchospasm
- Circulatory e.g. hypotension, lightheaded, dizzy, weak
- Gastrointestinal e.g. abdominal pain nausea, vomiting, cramps, diarrhea
- Neuromuscular e.g. back pain

Anaphylaxis is the most serious of the acute infusion-related adverse events and can be fatal. Its diagnosis is frequently delayed, and misdiagnosis often occurs with asthma or urticarial.[62] Alberta Health Services' clinical criteria should be used to rapidly diagnose anaphylaxis.[63]

Table 2. Criteria for Suspected Anaphylaxis

Suspected anaphylaxis criteria	System	Symptoms may include
1. After unknown exposure – presenting with **acute onset of illness, with**: • skin and/or mucosa, plus • at **least one (1) symptom** from **either** of the listed respiratory-airway or cardiovascular **systems**.	Skin and/or mucosa	Flushed skin, generalized hives, itchiness, swollen face/lips/tongue and/or uvula.
	Respiratory-airway	Accessory muscle use, cough, decreased air entry, drooling/difficulty swallowing, grunting, hypoxemia, increased respiratory rate, increased work of breathing, nasal flaring, shortness of breath, sneezing, stridor, vocal changes, wheeze.
	Cardiovascular	Cyanosis/pale/grey, dizziness, headache, hypotension, loss of consciousness, poor capillary refill time, restlessness/irritability, sweating, tachycardia, throbbing or ringing ears, weakness.
2. After exposure to a likely or known allergen for that patient, with: • at **least one (1) symptom** from **two (2) or more** of the listed **symptoms.**	Skin and/or mucosa	Flushed skin, generalized hives, itchiness, swollen face/lips/tongue and/or uvula.
	Respiratory-airway	Accessory muscle use, cough, decreased air entry, drooling/difficulty swallowing, grunting, hypoxemia, increased respiratory rate, increased work of breathing, nasal flaring, shortness of breath, sneezing, stridor, vocal changes, wheeze.
	Cardiovascular	Cyanosis/pale/grey, dizziness, headache, hypotension, loss of consciousness, poor capillary refill time, restlessness/irritability, sweating, tachycardia, throbbing or ringing ears, weakness.
	Gastrointestinal	Cramping abdominal pain, diarrhea, incontinence, nausea, vomiting.
3. After exposure to a known allergen for that patient, with: • **only hypotension.** • this may occur in rare circumstances.	Cardiovascular	Hypotension.

Timing. Acute infusion-related adverse events can be classified as immediate or delayed. Immediate reactions are often caused by direct mast cell activation or IgE-mediated hypersensitivity and occur within 1 hour after the last drug administration.[64] Delayed reactions occur from 1 hour after drug administration and may result from antigen-specific IgG production, complement activation or a T-cell mediated response.[64]

Acute infusion-related adverse events to taxanes and monoclonal antibodies usually occur during the first or second infusion[65-68] versus platinum compounds where they typically occur after multiple cycles.[24, 69-71] For example, in retrospective reviews, reactions to oxaliplatin occurred at a median of 7 to 9 cycles as reported in Lexicomp (see Appendix B).

Grading. The CTCAE differentiates Grades 1 through 5 for acute infusion-related adverse events with unique clinical descriptions of severity for each (see Table 3).[9] These grades should be used to guide diagnosis and management decisions associated with acute infusion-related adverse events caused by chemotherapy drugs and monoclonal antibodies.

Table 3. Common terminology criteria for adverse events (CTCAE), version 5.0

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)	Grade 5 (Death)
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., antihistamines, NSAIDS, narcotics*, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	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
Cytokine release syndrome§	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia to <40% O_2‡	Hypotension managed with one pressor; hypoxia requiring ≥40% O_2‡	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/ angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

*Restricted use.

§Most of the current CRS data comes from CAR T cell and blinatumomab studies in hematologic malignancies where CRS has been reported in frequencies of up to 100% in CD19-targeted CAR T cell trials, sometimes with fatal outcome.[72]

[t] Provide oxygen as clinically indicated to prevent hypoxemia to maintain 0_2 saturations >90%.

5. Unique Characteristics of Acute Infusion-Related Adverse Events by Main Drug Class

Anthracyclines (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Valrubicin)[73]

- Reactions usually occur immediately.
- Reactions appear to be immunologically mediated. However, in the case of liposomal formulations, complement activation may be an important factor.
- Systemic hypersensitivity and anaphylaxis are rarely reported.

Platinum derivatives (Carboplatin, Cisplatin, Oxaliplatin)[74]

- Reactions are thought to be mainly caused by type I IgE-mediated or type IV T-cell-mediated hypersensitivity although nonimmune mechanisms may also play a role.
- Most reactions to platinum derivatives occur after multiple infusions.
- Reactions usually occur during or shortly after the infusion.
- The chance of hypersensitivity reactions is increased when platinum derivatives are given in combination with other chemotherapy.
- Cross-sensitivity may occur between the platinum derivatives.
- There is insufficient evidence that routine premedication with antihistamines, H2 blockers, and corticosteroids are effective in preventing hypersensitivity reactions to platinum salts.[75]
- Special considerations:
    - Corticosteroids and H1-receptor antagonists ± H2-receptor antagonists may reduce infusion-related reaction rates for some patients receiving carboplatin (e.g. gynecological patients with a platinum-free interval >12 months or a history of drug allergy who are receiving carboplatin starting from the 7th cycle) but no optimal premedication regimen has been established.[7]

Taxanes (Cabazitaxel, Docetaxel, Paclitaxel)[76]

- Hypersensitivity reactions are similar in nature between the taxanes and may include shortness of breath, itching, hypotension, back pain and erythematous rashes. Rarely, bronchospasm and death have occurred.
- Most hypersensitivity reactions are understood to be non-IgE-mediated. It is likely that allergic reactions can be attributed, at least in some instances to the vehicle (e.g. Cremophor EL, polysorbate 80)
- Most hypersensitivity reactions occur with the first or second dose.
- Cross-reactivity may exist between the taxanes.
- Special considerations:
    - Evidence indicates that premedications can be discontinued in patients who have completed two cycles of paclitaxel without a documented infusion-related reaction.[72]

- If the patient has reacted, or subsequently reacts, premedications should be given on every cycle

Monoclonal Antibodies[77]

- Most reactions are mild and non-life-threatening.
- Anaphylaxis is uncommon but has been reported with rituximab trastuzumab and cetuximab.
- Infusion-related reaction are typically immediate and occur during the initial few minutes of the first or second infusion.
- Reactions may occur after the first exposure or after many exposures, but in general, the risk of an infusion-related reaction decreases following each treatment.
- Most reactions appear to be due to antibody-antigen reactions prompting cytokine release.
- Information about cross-reactivity is lacking.

Biosimilars

- Biosimilars are currently available for bevacizumab, trastuzumab, and rituximab.
- For a drug to be called a biosimilar, the manufacturer must provide Health Canada with information to show that the biosimilar is highly similar to the reference biologic drug, and that there are no clinically meaningful differences in terms of safety and efficacy.[78] Therefore, clinicians should expect to see the same rate of acute infusion-related adverse events in biosimilars that they would expect to see in the biologic drug.
- Despite reported safety profiles and similar rates of adverse events, clinicians should be vigilant when switching patients who have already been treated with an originator drug.

6. Management of Acute Infusion-Related Adverse Events

Preparation

- All healthcare professionals should be trained to understand the risk and recognize the signs and symptoms of an acute infusion-related adverse events.
- Before chemotherapy drugs and monoclonal antibodies are administered, all patients should be asked about their medical history and history of acute infusion-related adverse events.[6]
- An updated organizational protocol for the management of acute infusion-related adverse events should be accessible.
- Emergency equipment and medications should be available for immediate use in case of serious, life threatening infusion-related adverse events.

Use of Premedication

- Premedication can be used to help prevent and/or reduce the severity of acute infusion-related adverse events, although it is less effective in preventing anaphylaxis.[79]

- For certain drugs that are associated with a high incidence of acute infusion-related adverse events, prophylaxis with one or more of the following is reported in the literature:
    - H1 antihistamine (diphenhydramine)
    - Glucocorticoid (dexamethasone, hydrocortisone, methylprednisolone)
    - H2 antihistamine (ranitidine, cimetidine, famotidine)
    - Antipyretic (acetaminophen)
    - Leukotriene receptor antagonist (montelukast)
- Specific prophylactic regimens that are recommended for individual drugs can be found in Appendix B. Note that these regimens are derived using empirical evidence rather than through randomized trials.[79]

Observation[6]

- Premedication does not exclude the possibility of an acute infusion-related adverse events.
- Patients should be observed closely during and after their infusion for acute infusion-related adverse events.
- Patients should be educated on a drug's potential to cause an acute infusion-related adverse event and notify healthcare providers promptly about any signs and symptoms.
- Recommended observation periods for certain drugs that are associated with a high incidence of acute infusion-related adverse events can be found in Appendix B.

General Treatment Recommendations (for more retailed recommendations see Appendix B)

Acute infusion-related adverse events require a rapid response from healthcare professionals. Management of the event is based on the severity of presenting symptoms, but also symptoms as the reaction is monitored and progresses (worsens/resolves). Because acute infusion reactions often unfold and change quickly, grading using CTCAE to document the severity of the reaction, should be reserved until after the reaction has resolved and all of the required treatment for the reaction has been administered. We recommend differentiating treatment as follows:

Mild to moderate reactions (no features suggestive of anaphylaxis). If the reaction is mild or moderate without features suggestive of anaphylaxis, interrupt or slow the rate of infusion (generally by 50%) and manage symptoms as appropriate. Upon symptom resolution, restart at reduced rate or slowly increase infusion from 50% as tolerated by the patient. Assess vitals, body systems for symptoms of further reaction, and level of consciousness often.

Severe reactions: If the reaction is severe, interrupt therapy and assess for features of anaphylaxis. If the patient fulfills any of the criteria for anaphylaxis (Table 2) refer to Alberta Health Services' policy

for Anaphylaxis Management: Administration of Intramuscular Epinephrine.[63] If vital symptoms were affected, permanently discontinue therapy.

If anaphylaxis criteria are not met (i.e. vital signs were not affected), manage symptoms as appropriate. Upon symptom resolution, the infusion may be reinitiated at no more than 50% of the rate at which the reaction occurred. If no further infusion-related symptoms occur, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Assess vitals and level of consciousness often.

Note: Some drugs should be discontinued immediately if a severe infusion-related adverse event, including:

- Alemtuzumab
- Atezolizumab
- Cetuximab
- Pembrolizumab
- Ramucirumab

Diagnostic tools. Serum, plasma, and urine obtained during or shortly after an acute infusion-related adverse events can support the clinical diagnosis of anaphylaxis. While assays for mediators released during anaphylaxis such as tryptase (serum/plasma) and histamine (plasma, urine) are commercially available, they are not routinely recommended in practice because these tests are not universally available, not performed in real time (i.e. emergency situations), and normal levels do not exclude the possibility of anaphylaxis.[6, 80, 81]

Re-start/Re-challenge:[6] No re-start/rechallenge should be undertaken for patients with suspected or confirmed anaphylaxis. The severity and nature of the acute infusion-related adverse event will determine the decision to restart the treatment once symptoms have been managed (usually at a reduced infusion rate), or to re-challenge (re-expose the patient to the treatment) at a later date (usually with a reduced infusion rate and additional premedications).

Desensitization: Desensitization protocols are potentially dangerous procedures and should only be performed by experienced individuals in an area with immediate access to emergency drugs and equipment[79, 82] Successful desensitization has been reported using the following drugs:

- Carboplatin[66, 69, 71, 83-87]
- Etoposide[88, 89]
- Oxaliplatin[90-93]
- Pegaspargase[94]

- Trastuzumab[83, 95]
- Infliximab[96]
- Rituximab[71]

We discourage the use of desensitization protocols unless performed by allergists, or oncologists who have experience with desensitization protocols.[79]

7. Acute Infusion-Related Adverse Event Follow-up[6]

Following an acute infusion-related adverse event, healthcare professionals should attempt to establish, based on the suspect drug and the characteristics of the event, the steps that could be taken to prevent future episodes. This information, including confirmation that a reaction occurred, should be communicated to patients and family members once any medication affecting cognitive function has worn off.

For drugs that are restarted/rechallenged, patients should be observation for lengths of time that are based on the severity of the reaction and proximity to an emergency facility, with prolonged observation times or hospital admission for patients with severe or refractory symptoms.

If an acute infusion-related adverse event causes significant anxiety and distress for patients who require further treatment, an open discussion about the potential benefits of continuing with the drug and the risk of recurring acute infusion-related adverse events is recommended. Psychological intervention should be provided to alleviate symptoms of anxiety and distress related to a potential infusion-related adverse event with chemotherapy drugs or monoclonal antibodies.

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Appendix A. Literature Search Strategies and Result

Database	Date	Search Strategy	Limits	Selected /Total Results
PubMed	May 16, 2019	((((((((((Drug Hypersensitivity[MeSH Terms]) OR hypersensitivity) OR "infusion-related reaction*") OR "infusion related reaction*") OR "infusion reaction*") OR "cytokine release syndrome") OR Anaphylaxis[MeSH Terms]) OR anaphyla*)) AND Infusions, Intravenous[MeSH Terms]) AND (((((Antineoplastic Agents[MeSH Terms]) OR Drug Therapy[MeSH Terms]) OR Antibodies, Monoclonal[MeSH Terms]) OR chemotherapy) OR "monoclonal antibod*")	Published in last 10 yrs.; Humans; English; Adult: 19+ yrs. Only included articles w 'infusion reaction', 'infusion-related reaction', 'hypersensitivity' or 'cytokine release syndrome' or 'anaphlya*" in title or abstract Further excluded duplicates, pediatric studies, case reports, desensitization studies and studies re. Car-T therapy	22/243
EMBASE	May 16, 2019	1. antineoplastic agent.mp. or exp antineoplastic agent/ 2. exp cancer chemotherapy/ or chemotherapy.mp. 3. monoclonal antibody.mp. or exp monoclonal antibody/ 4. infusion related reaction.mp. or exp infusion related reaction/ 5. drug hypersensitivity.mp. or exp drug hypersensitivity/ 6. cytokine release syndrome.mp. or exp cytokine release syndrome/ 7. rechallenge.mp. or exp drug rechallenge/ 8. desensitization.mp. or exp desensitization/ 9. 1 or 2 or 3 10. 4 or 5 or 6 or 7 or 8 11. 9 and 10 12. limit 11 to (human and english language and (adult <18 to 64 years> or aged <65+ years>) and intravenous and last 10 years)	Further excluded pediatric studies, case reports, desensitization studies and studies Also excluded studies if they reported on incidence alone.	3/96
PubMed	May 28, 2019	("desensitization, immunologic"[MeSH Terms] OR ("desensitization"[All Fields] AND "immunologic"[All Fields]) OR "immunologic desensitization"[All Fields] OR "desensitization"[All Fields]) AND chemotherapeutic [All Fields] AND agents [All Fields]	Last 10 years	6/40

Appendix B. Acute Infusion Related Adverse Event Drug Table

Information listed in the table below was updated as of the date noted in parentheses. AHS has chosen Lexicomp as its primary drug information resource and endorse it as a clinical reference tool for use at the point of care. **AHS recommend checking Lexicomp frequently because its team of pharmacists and editors regularly review and monitor information to update its content.** Cancer Care Ontario's Cancer Medication Infusion Reactions Drug Table was reviewed, and any additional, relevant information was added to this table.

Lexicomp Drug Name/Class	Concerns associated with acute infusion-related reactions as document in Lexicomp
CISplatin* (Updated 2/5/20)	***Incidence*** • Overall incidence of reactions: 5-20% • Anaphylaxis (some fatal): <1% (post-marketing, and/or case reports) ***Onset*** • Most reactions to platinum derivatives occur after multiple infusions (usually occur after cycle 6), although reactions may occur after initial infusion • Reactions usually occur during or shortly after infusion; however, some reports of delayed reactions occurring hrs. to days later • HSRs have occurred within mins. of administration (in patients with prior cisplatin exposure) ***Risk factors*** • Chance of HSR increased when platinum derivatives given in combination with other chemotherapy and with multiple infusions • Concomitant radiation ***Mechanism*** • Exact mechanism of platinum reactions unknown; reactions thought to be mainly caused by type I IgE-mediated or type IV T-cell-mediated hypersensitivity although nonimmune mechanisms may also play a role ***Symptoms*** • Facial edema, wheezing, tachycardia, and hypotension • Chance of HSR increased when platinum derivatives given in combination with other chemotherapy ***Cross-reactivity*** • Cross-sensitivity may occur between platinum derivatives. Substitution of one platinum derivative has been done successfully in some instances, but it has also been unsuccessful and fatal in others ***Pre-medication*** • Insufficient evidence that routine pre-medications reduce IRR rates • Based on low level evidence, corticosteroids and H1 antagonists ± H2 antagonists may reduce IRR rates for some patients (e.g. gynecological patients with platinum-free interval >12 months or history of drug allergy who are receiving carboplatin starting from 7th cycle) but no optimal pre-medication regimen established ***Extended Infusion*** • Insufficient evidence that routine prophylaxis with extended infusion reduces IRR rates ***Management*** • Mild to moderate HSRs: range of different treatment strategies have been used, including lowering infusion rate and use of pre-medication with

	corticosteroids and H2 antagonists • Severe HSRs: discontinue cisplatin immediately, and manage appropriately ***Re-challenge*** • Successful re-challenges to platinum derivatives have occurred using pre-medication with steroids, antihistamines and various desensitization techniques • May consider adding montelukast ± acetylsalicylic acid. Up to 50% of patients can experience recurrent reactions during re-challenge despite using pre-medications (e.g. corticosteroid and H1/H2 antagonist) • Do not re-challenge with cisplatin in patients with history of severe HSRs • Desensitization protocols reported; decision to continue therapy with platinum drug after reaction using desensitization or substitution of another platinum derivative should be done carefully and only if benefits outweigh risks. Possibility of serious event or fatality should be considered and discussed with patient • Patch testing has not been of predictive value and is not recommended
CARBOplatin* (Updated 1/31/20)	***Incidence*** (percentages reported with single-agent therapy) • Overall incidence of reactions: 1-44% • Anaphylaxis: <1% (post-marketing, and/or case reports) ***Onset*** • Most reactions to platinum derivatives occur after multiple infusions, typically with 7^{th}-10^{th} exposure, although reactions may occur after initial infusion • Reactions usually occur during or shortly after infusion; however, some reports of delayed reactions occurring hrs. later • Anaphylactic-like reactions may occur within mins. of administration ***Risk factors*** • Previous exposure to platinum therapy, platinum-free interval >12 months, history of other systemic reactions, cumulative carboplatin dose, past drug allergies, disease severity, histological type, and malignant ascites, patients sensitized to oxaliplatin • Chance of HSR increased when platinum derivatives given in combination with other chemotherapy and with multiple infusions ***Mechanism*** • Exact mechanism of platinum reactions unknown; reactions thought to be mainly caused by type I IgE-mediated or type IV T-cell-mediated hypersensitivity although nonimmune mechanisms may also play a role ***Symptoms*** • Mild to moderate reactions consisting of itching or erythema alone, on palms and soles, or facial flushing • Rash, abdominal cramps, facial edema, hypotension, bronchospasm, chest pain, tachycardia, systemic anaphylaxis ***Cross-reactivity*** • Cross-sensitivity may occur between platinum derivatives. Substitution of one platinum derivative has been done successfully in some instances, but it has also been unsuccessful and fatal in others ***Pre-medication*** • Insufficient evidence that routine pre-medications reduce IRR rates • Based on low level evidence, corticosteroids and H1 antagonists ± H2 antagonists may reduce IRR rates for some patients (e.g. gynecological patients with PFI >12 months or history of drug allergy who are receiving carboplatin starting from 7^{th} cycle) but no optimal pre-medication regimen

	established ***Extended infusion*** • Insufficient evidence that routine prophylaxis with extended infusion reduces IRR rates ***Management*** • Mild to moderate HSRs: range of different treatment strategies have been used, including lowering infusion rate and use of pre-medication with corticosteroids and H2 antagonists • Patients reacting to carboplatin may be able to tolerate oxaliplatin or cisplatin ***Re-challenge*** • Successful re-challenges to platinum derivatives have occurred using pre-medication with steroids, antihistamines and various desensitization techniques • May consider adding montelukast ± acetylsalicylic acid. Up to 50% of patients can experience recurrent reactions during re-challenge despite using pre-medications (e.g. corticosteroid and H1/H2 antagonist) • Following carboplatin reactions, a dose escalation desensitization technique has been used to successfully treat patients with either cisplatin or carboplatin • Decision to continue therapy with platinum drug after reaction using desensitization or substitution of another platinum derivative should be done carefully and only if benefits outweigh risks • Patch testing has not been of predictive value and is not recommended
Oxaliplatin* (Updated 2/3/20)	***Incidence*** • Overall incidence of reactions: 10-19% • HSR (percentages reported with monotherapy): 3% ○ Includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope (grade 3-4: 2-3%) • Anaphylaxis, anaphylactic shock, anaphylactoid reaction, IRR (extravasation [including necrosis]) (percentages reported with mono- and combination therapy): <1% (post-marketing, and/or case reports) ***Onset*** • Reactions typically occur after multiple cycles; at median of 7 to 9 cycles, with onset of 5 to 70 mins. • Reactions usually occur during or shortly after infusion; however, some reports of delayed reactions occurring hrs. later • Anaphylactic reactions may occur within mins. of administration • Allergic reactions similar to reactions reported with other platinum analogs and may occur with any cycle ***Risk factors*** • Younger age, female, prior exposure to oxaliplatin and longer oxaliplatin-free interval • Chance of HSR increased when platinum derivatives given in combination with other chemotherapy and with multiple infusions ***Mechanism*** • Exact mechanism of platinum reactions unknown; reactions thought to be mainly caused by type I IgE-mediated or type IV T-cell-mediated hypersensitivity although nonimmune mechanisms may also play a role ***Symptoms*** • Symptoms may include bronchospasm (rare), erythema, hypotension (rare), pruritus, rash, and/or urticaria; previously untreated patients have also experienced flushing, diaphoresis, diarrhea, shortness of breath, chest pain, hypotension, syncope, and disorientation • Fever and mild dyspnea reported a few hrs. after 9th oxaliplatin dose

	Cross-reactivity • Cross-sensitivity may occur between platinum derivatives. Substitution of one platinum derivative has been done successfully in some instances, but it has also been unsuccessful and fatal in others ***Pre-medication*** • Insufficient evidence that routine prophylaxis with pre-medications reduces IRR rates. Consider corticosteroids and H1 antagonists ± H2 antagonists in high-risk patients ***Management*** • Mild to moderate HSRs: range of different treatment strategies have been used, including lowering infusion rate and use of pre-medication with corticosteroids and H2 antagonists • Anaphylactic reactions: symptoms may be managed with epinephrine, corticosteroids, antihistamines, and discontinuation; oxygen and bronchodilators have also been used ***Re-challenge*** • According to manufacturer, re-challenge contraindicated (deaths due to anaphylaxis associated with platinum derivatives) • In patients re-challenged after mild hypersensitivity, reaction recurred at higher level of severity • For patients with severe hypersensitivity, re-challenge with 2-3 days of antihistamine and corticosteroid pre-medication, plus prolongation of infusion time, allowed for 2-4 additional oxaliplatin cycles. However, re-challenge not feasible in nearly two-thirds of patients due to severity of initial reaction • Patients sensitized to oxaliplatin may be at higher risk of developing a reaction to carboplatin and cisplatin • Desensitization protocols reported; decision to continue therapy with platinum drug after reaction using desensitization or substitution of another platinum derivative should be done carefully and only if benefits outweigh risks • Patch testing has not been of predictive value and is not recommended

Anthracycline Allergy[l]
 	
(Updated 4/12/2019)
	Associated drugs
	• Daunorubicin (Conventional); Daunorubicin (Liposomal); Daunorubicin and Cytarabine (Liposomal); Doxorubicin (Conventional); Doxorubicin (Liposomal); Epiruicin; Idarubicin; Valrubicin
	
	Incidence
	• Daunorubicin (conventional)
	  ○ Anaphylactoid reaction, HSR (systemic; includes angioedema, dysphagia, dyspnea, pruritus, urticaria): <1% (post-marketing, and/or case reports)
	• Daunorubicin (liposomal)
	  ○ IRR: 14% (includes back pain, flushing, chest tightness)
	  ○ HSR: 24%
	• Doxorubicin (liposomal)
	  ○ HSR: 1-5%
	  ○ Acute IRRs: 11% of patients with solid tumours
	• Doxorubicin (conventional)
	  ○ Anaphylaxis, HSR (systemic; including angioedema, dysphagia, and dyspnea, pruritus, urticaria): <1% (post-marketing, and/or case reports)
	• Epirubicin
	  ○ HSR frequency not defined
	  ○ Anaphylaxis: <1% (post-marketing, case reports)
	• Idarubicin
	  ○ Incidence not reported for IRRs, HSRs or anaphylaxis

- Valrubicin
    - Incidence not reported for IRRs, HSRs or anaphylaxis

Onset

- Non-immunologic anaphylaxis (non-immunologically mediated hypersensitivity) reactions more likely associated with 1st or 2nd dose of anthracyclines
- Anaphylaxis (immunologically mediated reactions) usually occurs after initial drug exposure

Mechanism

- Mechanism of these reactions is unknown. Histamine release appears to be significant contributor to these reactions. However, in the case of liposomal formulations, complement activation may be an important factor. Indirect evidence suggests that at least some reactions may be mediated by mechanisms other than histamine release
- Some reactions may not be related to drug itself, but to component of formulation:
    - Polyoxyethyleneglycol (Cremophor EL) in valrubicin
    - Liposomal component in liposomal formulations of doxorubicin and daunorubicin
    - Evaluation of reactions to these agents should explore these possibilities (e.g. by specific testing for sensitivity to excipient through intradermal testing)

Symptoms

- Rare systemic hypersensitivity, including urticaria, pruritus, angioedema, dysphagia, and dyspnea, generally from post-marketing reports
- Chest pain, flushing, syncope, fever, tachycardia, hypotension, nausea, vomiting, headache, back pain
- Anaphylaxis reported rarely but has been, in case of epirubicin, linked to shock and death
- Rash and urticaria may occur in a significant number of patients (up to 11% with idarubicin)
- Urticaria following IV doxorubicin administration noted in early clinical experience

Cross-reactivity

- Cross-reactivity may be possible with structurally related anthracenediones (mitoxantrone) and with other anthracyclines
- In absence of clear data about cross-reactivity, not possible to make recommendation concerning likelihood of cross-reaction. However, reactions which may be nonimmunologic anaphylaxis (histamine release), rather than immunologically mediated, should be carefully evaluated since non-immunologically mediated reactions would not contraindicate use of related compound
- Cross-reaction between anthracyclines and other drug classes not well documented

Pre-medication

- Routine pre-medication not recommended
- Doxorubicin (liposomal) has potential for HSRs and patients should be prescribed diphenhydramine as pre-medication

Management

- Some acute reactions have responded to antihistamines or corticosteroids; these would not be considered anaphylactic but non-immunologic anaphylaxis in nature
- Withhold doxorubicin (liposomal) for infusion-related reactions and resume at a reduced rate. Discontinue doxorubicin (liposomal) for serious or life-threatening infusion-related reactions
- For infusion reactions with daunorubicin (liposomal) (usually within first 5 mins. of infusion): temporarily interrupt infusion; may resume at a slower rate

Re-challenge

- In patients with reactions that have responded to antihistamines (diphenhydramine) or corticosteroids, prophylaxis with these therapies may be considered upon re-exposure
- Successful desensitization to liposomal doxorubicin and doxorubicin has been described

DOCEtaxel[§]
 	
(Updated 2/6/20)
	Incidence *(Percentages reported for docetaxel monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and pre-medication)*
	• HSR: 6-21%
	• Anaphylactic shock: <1% (post-marketing, and/or case reports)
	
	Onset
	• Most HSRs occur with 1st or 2nd dose
	
	Mechanism
	• Most HSRs thought to be non-IgE-mediated
	
	Symptoms
	• Minor reactions including flushing or localized skin reactions may occur
	• Severe HSRs, characterized by generalized rash/erythema, hypotension, bronchospasms, or rare anaphylaxis may occur (may be fatal; has occurred in patients receiving 3-day corticosteroid pre-medication)
	• Dyspnea, urticaria, chest or back pain, tachycardia
	
	Cross-reactivity
	• Cross-reactivity may exist between taxanes
	• Nab-paclitaxel has been well-tolerated in patients with previous histories of taxane HSRs
	
	Pre-medication
	• Pre-medication with oral corticosteroids recommended to decrease incidence and severity of HSRs
	  ○ Dexamethasone 16 mg/day (8 mg twice daily) orally for 3 days, starting day before docetaxel administration. Dexamethasone 10-20 mg IV can be given if patient forgot to take oral doses
	  ○ For prostate cancer, when prednisone part of antineoplastic regimen, dexamethasone 8 mg orally administered at 12 hrs., 3 hrs., and 1 hr. prior to docetaxel
	  ○ Do not discontinue dexamethasone, even in absence of IRR, due to benefits on other adverse effects (e.g. pain and edema)
	
	Management
	• Do not administer to patients with severe hypersensitivity to docetaxel or polysorbate 80
	• Observe for hypersensitivity, especially with first 2 infusions
	• HSRs require immediate discontinuation and administration of appropriate therapy
	• Patients with history of HSR to paclitaxel may develop hypersensitivity to docetaxel; may be severe or fatal (including anaphylaxis); monitor patients with paclitaxel hypersensitivity closely during initiation of docetaxel
	• Discontinue for severe reactions
	
	Re-challenge
	• Consider re-challenge with pre-medications and at reduced infusion rate
	• Severe hypersensitivity reactions have been reported despite dexamethasone pre-medication
	• After 2 subsequent IRRs, consider replacing with different taxane. Give intensified pre-medications and reduce infusion rate
	• May consider adding oral Montelukast ± oral acetylsalicylic acid

	• Patients may be able to undergo rapid drug desensitization to remain on first-line therapy • Do not re-challenge if hypersensitivity severe ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80[β]

PACLitaxel[§]
 	
(Updated 2/3/20)
	Incidence *(reported with single-agent therapy)*
	• HSR: 31-45%
	• Incidence of reaction without pre-medication as high as 30%; despite pre-medication varies from 10% (all grades) to 2-4% (severe reactions)
	• Anaphylaxis and severe HSRs (dyspnea requiring bronchodilators, hypotension requiring treatment, angioedema, and/or generalized urticaria) have occurred in 2-4% of patients in clinical studies
	
	Onset
	• Most HSRs occur with 1st or 2nd dose, within 1st 10 mins. of infusion, although reports of reactions occurring after 3rd dose have been reported
	
	Risk factors
	• Incomplete mixing of excipient and drug (e.g. Cremophor EL with paclitaxel and polysorbate 80 with docetaxel
	
	Mechanism
	• Anaphylactoid, likely due to direct release of mast cell mediators such as histamine and tryptase
	*Excipients Cremophor EL and Polysorbate 80 capable of complement activation in vitro
	
	Symptoms
	• Shortness of breath, itching, hypotension, and erythematous rashes; rarely, more serious incidents of bronchospasm and death have occurred
	• Dyspnea, flushing, skin reactions, tachycardia, angioedema, urticaria, back pain
	
	Cross-reactivity
	• Cross-reactivity may exist between taxanes
	• Nab-paclitaxel has been well-tolerated in patients with previous histories of taxane HSRs
	
	Pre-medication
	• Pre-medicate with:
	  ○ Dexamethasone (20 mg orally at 12 and 6 hrs. prior to dose [reduce dexamethasone dose to 10 mg orally with advanced HIV disease])
	  ○ Diphenhydramine (50 mg IV 30-60 mins. prior to dose)
	  ○ Famotidine, or ranitidine (IV 30-60 mins. prior to dose) recommended
	• Some reactions fatal despite pre-medication
	
	Pre-medication for Q3W paclitaxel
	• Dexamethasone 20 mg PO 12-and 6-hrs **OR** dexamethasone 20 mg IV 30 mins. pre-infusion*
	• Diphenhydramine 25-50 mg IV/PO 30-60 mins. pre-infusion
	• Ranitidine 50 mg IV **OR** famotidine 20 mg IV 30-60 mins. pre-infusion
	
	*Oral and IV dexamethasone both effective at reducing overall IRR rates. Some evidence suggests that oral dexamethasone may be more effective for reducing severe reactions; however, adverse effects and compliance remain a concern
	
	Pre-medication for weekly paclitaxel
	To be given 30-60 mins. prior to paclitaxel infusion:

	• Dexamethasone 10 mg IV, starting in cycle 1 • Diphenhydramine 25-50 mg IV/PO • Ranitidine 50 mg IV **OR** famotidine 20 mg IV ***Other considerations*** • Consider discontinuing pre-medications if there was no IRR in 1st 2 doses • Extended infusion not recommended as primary prophylaxis to reduce IRRs • Insufficient evidence to recommend addition of hydrocortisone 100 mg IV to existing standard pre-medication regimen ***Management*** • IRR hypotension, bradycardia, and/or hypertension may occur; frequent monitoring of vital signs recommended, especially during 1st hr. of infusion • Minor HSRs (flushing, skin reactions, dyspnea, hypotension, or tachycardia) do not require interruption of treatment • If severe hypersensitivity occurs, stop infusion and do not re-challenge ***Re-challenge*** • Patients may be able to undergo rapid drug desensitization to remain on first-line therapy ***Dosage form specific issues*** • Conventional paclitaxel formulations contain polyoxyl 35/polyoxyethylated castor oil (Cremophor EL), which is associated with HSRs

Cabazitaxel§
 	
(Updated 1/29/20)
	Incidence
	• Adverse reactions reported for combination therapy with prednisone
	• HSR: <1% (post-marketing, and/or case reports)
	
	Onset
	• Observe closely during infusion, especially during 1st and 2nd infusions; reaction may occur within mins.
	
	Mechanism
	• Most HSRs thought to be non-IgE-mediated
	• Avoid cabazitaxel if documented reaction to other medications containing polysorbate 80. Reactions may be caused by drug or its vehicle (polysorbate 80)
	
	Symptoms
	• Shortness of breath, itching, hypotension, and erythematous rashes; rarely, more serious incidents of bronchospasm and death have occurred
	
	Cross-reactivity
	• Cross-reactivity may exist between taxanes
	
	Pre-medication
	• Pre-medicate at least 30 mins. prior to each administration with:
	  ○ Antihistamine (e.g. diphenhydramine IV 25 mg or equivalent)
	  ○ Corticosteroid (e.g. dexamethasone 8 mg IV or equivalent)
	  ○ H2 antagonist (e.g. ranitidine 50 mg IV or equivalent)
	
	Management
	• Immediate discontinuation required if hypersensitivity severe; administer appropriate supportive medications
	
	Re-challenge

	• Patients may be able to undergo rapid drug desensitization to remain on first-line therapy • Do not re-challenge after severe HSRs ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80[β]

Asparaginase[α]
 	
(*Erwinia*, Updated 1/16/20)
 	
(*E. coli*, Updated 1/29/20)
 	
(Pegasparagase, Updated 2/3/20)
	Associated drugs
	• Asparaginase *(E. coli)*, asparaginase *(Erwinia)*, pegasparagase
	
	Incidence
	• Asparaginase *(E. coli)*
	  ○ HSRs: 15-35%
	  ○ Frequency not defined: Anaphylactic shock, anaphylaxis, hypersensitivity reaction, type I hypersensitivity reaction
	• Asparaginase (*Erwinia*)
	  ○ HSR: 25%; serious HSRs (grade 3 and 4), including anaphylaxis, have occurred in 5% of patients in clinical trials
	  ○ Local HSR: 1-10%
	  ○ Anaphylaxis: <1%
	• Pegasparagase
	  ○ HSR: 1-10%; (grades 3/4: 1%, includes anaphylaxis, bronchospasm, erythema, hives, hypotension, laryngeal edema, skin rash, swelling, urticaria; relapsed ALL with no prior asparaginase hypersensitivity: 10%; relapsed ALL with prior asparaginase hypersensitivity: 32%)
	  ○ Incidence of reactions increases to about 32% in patients who have had prior sensitivity to asparaginase *(E. coli)*
	  ○ Hypersensitivity to L-asparaginase (grades 3/4: 2%): <1%
	
	Onset
	• Reactions to IV asparaginase *(E. coli)* and asparaginase (*Erwinia*) described as increasing from 8% with 1st dose to 32% with 5th and subsequent doses
	• Asparaginase *(E. coli)*
	  ○ Reactions generally occur 30 to 60 mins. following administration; however, delayed reactions have occurred hrs. after IM administration
	  ○ Number of doses for patients to react range from 1 to 12 with the average occurring after 7th dose in one study
	
	Symptoms
	• Hypersensitivity reactions to asparaginase products include anaphylaxis, chills, dyspnea, edema, fever, flushing, hyperthermia, hypotension, skin rash, and urticaria
	• Pegasparagase
	  ○ Angioedema, lip swelling, eye swelling, hypotension, bronchospasm, dyspnea, erythema, pruritus, and rash
	
	Risk factors
	• Asparaginase *(E. coli)*
	  ○ Prior exposure to asparaginase is a risk factor for allergic reactions; IV administration (compared to IM or SubQ administration) and younger age also may be associated with HSRs
	  ○ Patients who have an allergic reaction to asparaginase (*E. coli)* may also react to asparaginase (*Erwinia*) or to pegaspargase
	• Pegasparagase
	  ○ Risk of serious hypersensitivity reactions is increased in patients with known hypersensitivity to *E. coli* derived L-asparaginase products
	
	Mechanism
	• Most allergic reactions are likely IgE-mediated or related to complement activation
	
	Cross-Reactivity

	• Some patients reacting to asparaginase *(E. coli)* have tolerated asparaginase *(Erwinia)* or asparaginase *(E. coli)* bound to polyethylene glycol. Reactions to both asparaginase *(E. coli)* and asparaginase *(Erwinia)* occurred in 19% in one study and 22% in another • Reactions to asparaginase *(E. coli)* and pegasparagase have been estimated to occur in 32% of individuals by manufacturer ***Assessment*** • General precautions for anaphylaxis should apply. Probability of anaphylaxis decreases in patients who are also receiving prednisone and vincristine and increases when there is break in therapy • Manufacturer recommends test dose, only for asparaginase (*E. coli)*, be given prior to initial doses of asparaginase and subsequent doses when the interval between doses is greater than 1 week. However, false-positive and false-negative results have been documented. The possibility of a reaction still should be considered, even following a negative test dose ***Pre-medications*** • No standard pre-medication for asparaginase *(Erwinia)* or pegasparagase • Asparaginase *(E. coli)* o May administer corticosteroids 1-2 days prior to initiating reinduction therapy (to prevent HSR) ***Management*** • Asparaginase *(E. coli),* asparaginase *(Erwinia),* pegasparagase o May continue dosing for urticaria without bronchospasm, hypotension, edema, or need for parenteral intervention o If wheezing or other symptomatic bronchospasm with or without urticaria, angioedema, hypotension, and/or life-threatening hypersensitivity reactions occur, discontinue for serious HSRs and administer appropriate treatment • Pegasparagase o Mild: Reduce the infusion rate by 50% o Moderate: Interrupt infusion and manage symptoms; when symptoms resolve, resume the infusion with the infusion rate decreased by 50% o Severe: Permanently discontinue **Re-challenge** • In patients in whom the benefits of therapy continuation outweigh risks, or in patients experiencing milder but intolerable symptoms, desensitization or switching to another product may be viable alternatives • In Canada and Europe, asparaginase *(Erwinia)* is available and can be used in patients with allergic reactions to other asparaginase products • Pegaspargase considered least immunogenic and can be used in patients with history of allergic reactions • In case of mild reaction, continued therapy of same agent may be considered. Pre-medication with diphenhydramine, famotidine, and hydrocortisone (for patients re-challenged to pegasparagase after previous reaction) has been used to reduce IRRs • Other strategies for decreasing reactions when asparaginase is administered IV include reducing infusion rate and prolonging infusion duration • Changing route of administration has also been described as method to continue therapy, although results have not been consistent
Bleomycin (Updated 2/5/20)	***Incidence*** • Hypersensitivity: Anaphylactoid reaction (including chills, confusion, fever, hypotension, wheezing; onset may be immediate or delayed for several hrs.; includes idiosyncratic reaction in 1% of lymphoma patients): 1-10% ***Onset*** • Reactions usually occur after 1st or 2nd dose; careful monitoring essential after these doses • Reaction either immediate or delayed by several hrs. ***Risk factors*** • Lymphoma patients

	Mechanism • Related to release of pyrogenic cytokines (unlikely to be IgE-mediated due to lack of histamine release, hypotension, and tachycardia) ***Symptoms*** • Severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing (similar to anaphylaxis) has been reported in 1% of lymphoma patients treated with bleomycin ***Pre-medication*** • Routine pre-medication not recommended

Etoposide
 	
(Updated 1/28/20)
	Incidence (Note: hypotension (IRR) may occur with higher doses used in stem cell transplantation)
	• Hypersensitivity: Anaphylactoid reaction (IV: 1-2%; oral capsules: <1%; including bronchospasm, chills, dyspnea, fever, tachycardia)
	• HSR, apnea (hypersensitivity-associated): <1% (post-marketing, and/or case reports)
	• Anaphylaxis: 1-3%
	
	Onset
	• IRRs usually occur after 1st dose; ranges between seconds to days from infusion initiation
	
	Risk factors
	• IV administration (incidence up to 2%) compared to oral administration (<1%)
	• Multiple cycles
	
	Symptoms
	• May cause anaphylactic-like reactions manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension
	• Facial/tongue swelling, coughing, chest tightness, cyanosis, laryngospasm, diaphoresis, hypertension, back pain, loss of consciousness and flushing reported, but less common
	
	Pre-medication
	• Routine pre-medication not recommended
	
	Other considerations
	• High drug concentration and rate of infusion, as well as presence of polysorbate 80 and benzyl alcohol in IV etoposide formulation, suggested as contributing factors to development of HSRs
	  ○ IV etoposide formulations may contain polysorbate 80 and/or benzyl alcohol, while IV etoposide phosphate (water-soluble prodrug of etoposide) formulation does not contain either vehicle
	  ○ Etoposide phosphate has been used successfully in patients with previous HSRs to etoposide
	
	Management
	• Mild to moderate: Stop or slow infusion rate. Manage symptoms. No specific recommendations can be made to restart
	• Severe: Stop treatment. Aggressively manage symptoms
	
	Re-challenge
	• Consider switch to oral etoposide, if clinically appropriate
	• Mild to moderate: Pre-medications with corticosteroids and H1 antagonists. Slow infusion rate (infuse over 60-120 mins.)
	• Severe: Cross-reactivity between etoposide and teniposide. Consider desensitization

	Dosage form specific issues • Some dosage forms may contain polysorbate 80[β]
Alemtuzumab (Updated 1/29/20)	***Incidence*** *(in B-cell chronic lymphocytic leukemia)* • Anaphylactic shock, anaphylaxis: <1% (post-marketing, and/or case reports) • Serious reaction: 3% ***Onset*** • Incidence of IRR highest during first week of B-CLL treatment ***Mechanism*** • CRS ***Symptoms*** • In patients treated for B-CLL, IRR symptoms may include acute respiratory distress syndrome, anaphylactic/ anaphylactoid shock, angioedema, bronchospasm, cardiac arrest, cardiac arrhythmias, chills, dyspnea, fever, hypotension, myocardial infarction, pulmonary infiltrates, rash, rigors, syncope, or urticarial ***Pre-medication*** • Pre-medication with acetaminophen 500 to 1,000 mg and diphenhydramine 50 mg recommended 30 mins. prior to first dose, with dose escalations, and as clinically indicated; IV glucocorticoids may be used for severe IRRs • Pre-medication with corticosteroids for initial 3 days of each treatment course recommended. Antihistamines and/or antipyretics may also be considered ***Management*** • Use caution and carefully monitor blood pressure in patients with ischemic heart disease and patients on antihypertensive therapy • For B-CLL, gradual escalation to recommended maintenance dose required at initiation and with treatment interruptions (for ≥7 days) to minimize IRRs • Withhold treatment for serious or life-threatening IRRs • Consider additional monitoring in patients with existing cardiovascular or respiratory compromise • Advise patients to monitor for signs/symptoms of IRR, particularly during 48 hrs. following infusion ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80[β]
Atezolizumab (Updated 2/5/20)	***Incidence*** • IRR: 1%; severe or life-threatening IRRs reported • Frequency and severity of IRRs similar whether administered as single agent or in combination with other antineoplastic agents, and similar across various approved dose ranges (840 mg q 2 wks., 1200 mg q 3 wks., or 1680 mg q 4 wks.) ***Symptoms*** • IRRs mostly mild • Dyspnea, pyrexia, chills, hypotension, itching, flushing, swelling, dizziness ***Pre-medication*** • Consider antipyretic and H1 antagonist

	Management • Interrupt or slow infusion rate in patients with mild or moderate IRRs; consider pre-medication with subsequent doses • Permanently discontinue for severe or life-threatening IRRs
Bevacizumab (**Note:** Mvasi and Zirabev have been approved as biosimilars to Bevacizumab) (Updated 2/12/20)	***Incidence*** *(% reported as monotherapy and as part of combination chemotherapy regimens. Some studies only reported hematologic toxicities grades ≥4 and nonhematologic toxicities grades ≥3)* • IRR: <3%; severe reactions rare ***Risk factors*** • Given in combination chemotherapy ***Mechanism*** • IgE mediated suspected ***Symptoms and onset*** • Hypertension, hypertensive crisis (associated with neurologic signs/symptoms), wheezing, oxygen desaturation, hypersensitivity (grade 3), chest pain, rigors, headache, and diaphoresis) may occur with 1st infusion (uncommon) ***Pre-medication*** • Routine pre-medication not recommended ***Management*** • Clinically insignificant (mild): Decrease infusion rate • Clinically significant: Interrupt infusion; after symptoms resolve, resume at decreased rate • Severe: Discontinue
Blinatumomab (Updated 8/24/20)	***Incidence*** • IRR: 30-77% • HSR: CRS 7-15% • HSR: anaphylaxis frequency not defined ***Onset*** • Median time to onset and resolution of CRS was 2 days (following the start of infusion) and 5 days (among cases that resolved), respectively ***Symptoms*** • CRS manifestations may include chills, dizziness, loss of strength and energy, fever, headache, passing out, rash, swelling in your throat, trouble breathing, nausea, vomiting, or wheezing • Symptoms of infusion reactions, capillary leak syndrome, and hemophagocytic histiocytosis/macrophage activation syndrome may overlap with CRS symptoms ***Pre-medication*** • For ALL (B-cell precursor), minimal residual disease (MRD)-positive (≥0.1%) premedicate with the IV equivalent to prednisone 100 mg or dexamethasone 16 mg IV one hr. prior to the first dose of each cycle • For ALL (B-cell precursor), relapsed/refractory premedicate with dexamethasone 20 mg one hr. prior to the first dose of each cycle, prior to a step dose (e.g. Cycle 1 day 8), and when restarting therapy after an interruption of ≥4 hrs. ***CRS Management***

	• Severe: Interrupt blinatumomab therapy. Administer dexamethasone 8 mg (or 5 mg/m^2 if <45 kg; max.: 8 mg) IV or orally every 8 hrs. for up to 3 days, then taper over 4 days. Upon resolution, resume blinatumomab dosing at 9 mcg daily (or 5 mcg/m^2/day if <45 kg). Increase dose to 28 mcg daily (or 15 mcg/m^2/day if <45 kg) after 7 days if adverse reaction does not recur • Life-threatening: Discontinue blinatumomab permanently. Administer dexamethasone 8 mg (or 5 mg/m^2 if <45 kg; maximum: 8 mg) IV or orally every 8 hrs. for up to 3 days, then taper over 4 days • Tocilizumab may be considered in the management of severe or life-threatening CRS associated with bi-specific T-cell engaging therapy ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80[β]

Brentuximab vedotin
 	
(Updated 1/3/20)
	Incidence
	• IRRs: 11-15%; most grade 1-2
	• IRR:
	  ○ Pruritus 2-5%
	  ○ Nausea 3-4%
	  ○ Cough 2%
	  ○ Dyspnea 2-3%
	  ○ Fever 2%
	  ○ Chills 4%
	• Anaphylaxis: <1% (post-marketing, and/or case reports)
	
	Onset
	• Onset within 2 days of infusion
	
	Mechanism
	• Potentially IgE mediated due to risk of anaphylaxis
	
	Pre-medication
	• Routine pre-medication not recommended
	
	Management
	• Mild to moderate: interrupt infusion and manage symptoms
	• Severe: stop treatment and aggressively manage symptoms; may restart at slower rate once symptoms have resolved
	• Life-threatening: stop treatment and aggressively manage symptoms; discontinue use
	
	Re-challenge
	• Mild, moderate or severe IRR: consider pre-medication with acetaminophen, antihistamine, and/or corticosteroid for subsequent infusions
	• Life-threatening: do not rechallenge
	
	Dosage form specific issues
	• Some dosage forms may contain polysorbate 80[β]

Cetuximab (Updated 1/20/20)	***Incidence*** • IRR: 8-18%; serious ad fatal IRRs reported • Severe IRRs: 2-5% ***Onset***

	• Approx. 90% of reactions occur with 1st infusion despite use of prophylactic antihistamines • IRRs may occur during or several hrs. after infusion (usually within 3 hrs. of infusion) ***Risk factors*** • Risk for anaphylactic reactions may increase in patients with history of tick bites, allergies to red meat, or when IgE antibodies against galactose-α-1,3-galactose (alpha-gal) present • Severe HSR reported more frequently in patients living in middle south area of the United States, including North Carolina and Tennessee • Head and neck cancer patients ***Mechanism*** • IgE mediated ***Symptoms*** • Reactions have included airway obstruction (bronchospasm, stridor, hoarseness), hypotension, loss of consciousness, shock, myocardial infarction, and/or cardiac arrest ***Pre-medication*** • Pre-medicate with IV H1 antagonist 30-60 mins. prior to 1st dose. Pre-medication with IV corticosteroid prior to 1st dose may be used • Pre-medication for subsequent doses based on clinical judgment and with consideration of prior reaction to initial infusion • Use of nebulized albuterol-based pre-medication to prevent IRR reported ***Management*** • Monitor patients for at least 1 hr. following completion of infusion, or longer (until resolution) if reaction occurs • Mild to moderate IRRs (chills, fever, and dyspnea): managed by slowing infusion rate by 50% • Severe IRRs: Immediately and permanently discontinue
Daratumumab (Updated 1/29/20)	***Incidence*** • IRR: 48%; grade 1-2 IRRs 35-52%; grade 3 IRRs 3-6% ***Onset*** • Most IRRs occur during 1st infusion (92-98%) • May also be seen during subsequent infusions • Generally, occur during infusion or within 4 hrs. of completion (onset usually within 1.5 hrs. of infusions); without post-infusion medications some reactions reported up to 48 hrs. after infusion ***Symptoms*** • Severe and/or serious IRRs may occur (less frequent), including anaphylactic reactions, bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema, and pulmonary edema • Signs and symptoms include cough, throat irritation, and nasal congestion, chills, vomiting, and nausea • Wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension less commonly reported ***Pre-medication*** • Administer 1-3 hrs. prior to each infusion. If dexamethasone is the background regimen-specific corticosteroid, the dexamethasone treatment dose will serve as the corticosteroid pre-medication on daratumumab infusion days. Additional background regimen-specific corticosteroids (e.g. prednisone) should NOT be administered on daratumumab infusion days when patients receive dexamethasone (or equivalent) as a pre-medication. • Corticosteroid:

	○ Monotherapy: Methylprednisolone 100 mg IV or equivalent intermediate- or long-acting corticosteroid; following the second infusion, the dose may be decreased (e.g. methylprednisolone 60 mg [IV or oral] or equivalent) ○ Combination therapy: Dexamethasone 20 mg (or equivalent) prior to each daratumumab infusion; administer IV prior to the first infusion; oral administration may be considered prior to subsequent infusions **plus** • Antipyretic: Oral: Acetaminophen 650 to 1,000 mg **plus** • Antihistamine: IV or Oral: Diphenhydramine 25 to 50 mg or equivalent • The following pre-medication regimen has also been reported: ○ First infusion: Acetaminophen 325 mg orally, diphenhydramine 25 mg orally or IV, dexamethasone 20 mg IV, montelukast 10 mg orally, and famotidine 20 mg IV. ○ Subsequent infusions: Acetaminophen 325 mg orally, diphenhydramine 25 mg IV, and dexamethasone 20 mg IV ***Post-medication*** • Monotherapy: ○ Administer oral intermediate- or long-acting corticosteroid (e.g. methylprednisolone 20 mg or equivalent) on the first and second day after all daratumumab infusions • Combination therapy: ○ Consider administering oral methylprednisolone (≤20 mg) or equivalent intermediate- or long-acting corticosteroid on the first day after the daratumumab infusion. If dexamethasone or prednisone is administered the day after the daratumumab infusion as part of background combination chemotherapy regimen, additional post-infusion corticosteroid therapy may not be necessary • In patients with a history of chronic obstructive pulmonary disease: ○ Also consider short- and long-acting bronchodilators and inhaled corticosteroids post-infusion. If no major infusion reactions occur during first 4 daratumumab infusions, these additional inhaled post-infusion medications may be discontinued ***Other considerations*** • Infuse at graduated rate as described by product monograph • For 1st dose, consider splitting dose over 2 days with pre-medications given on both days prior to infusion. • If patient did not experience IRR in 1st 2 infusions, consider administering as rapid infusion starting with 3rd dose (20% of dose over 30 mins. at 200 mL/hr., then remaining 80% of dose over 60 mins. at 450 mL/hr.) ***Management*** • Immediately interrupt infusion for reaction of any severity and manage symptoms as clinically appropriate. • Mild to moderate: Once symptoms resolve, resume infusion at no more than 50% of rate at which reaction occurred. If no further reactions observed, may escalate infusion rate as appropriate up to max rate of 200 mL/hr. • Severe: Once symptoms resolve, consider resuming infusion at no more than 50% of rate at which reaction occurred. If no further reactions observed, may escalate infusion rate as appropriate. If grade 3 reaction recurs, repeat steps above. Permanently discontinue if grade 3 IRR occurs for 3rd time • Anaphylactic reaction or life-threatening: Permanently discontinue
Durvalumab (Updated 1/3/20)	***Incidence*** • IRR: 2% (including severe or life-threatening) ***Management*** • Mild to moderate: Interrupt or slow infusion. Consider pre-medications with subsequent doses • Severe or life-threatening: Discontinue permanently
Inotuzumab ozogamicin	***Incidence*** • IRR: 2%; grade 2: 2%; includes hypersensitivity

(Update 8/3/20)	***Onset*** • Infusion reactions usually occurred in cycle 1 shortly after the end of the infusion and resolved spontaneously or with medical management ***Symptoms*** • Fever, chills, rash, dyspnea ***Pre-medication*** • Corticosteroid, an antipyretic, and an antihistamine recommended prior to dosing. Observe for symptoms of IRR during and for at least 1 hr. after end of the infusion. ***Management*** • If an IRR occurs, interrupt infusion and manage appropriately. Depending on severity, consider discontinuing infusion or administering corticosteroids and antihistamines • Permanently discontinue if severe or life-threatening infusion reaction occurs ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80$^{\beta}$
Ipilimumab (Updated 2/3/20)	***Incidence*** • IRR: <1% (post-marketing, and/or case reports) • Have occurred when used in combination with nivolumab; may be severe ***Onset*** • Usually occurs during (and up to 30 mins. after) 2nd infusion ***Symptoms*** • Pruritus, maculopapular rash, cough, shortness of breath, chills, rigors, facial flushing, chest, abdominal or back pain, dizziness, fainting, hives, and anaphylactic reaction (<0.01%), tumour lysis syndrome (<1%) ***Pre-medication*** • Consider antipyretic and H1 antagonist ***Management*** • Mild or moderate reaction: Interrupt or decrease infusion rate • Severe or life-threatening reaction: Discontinue ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80$^{\beta}$
Nivolumab (Updated 12/23/19)	***Incidence*** *(includes unapproved dosing regimens)* • IRRs: 5% (including grade 3-4) • IRRs have occurred with both single-agent and in combination with ipilimumab • Severe reactions, although rare, observed when given as single agent • Anaphylactic reaction: <1% ***Onset*** • Small percentages of patients receiving 60-min., or 30-min. infusion reported to experience reactions within 48 hrs. of infusion, which resulted in

	dose delay, permanent discontinuation, or withholding of nivolumab (0.5% and 1.4%, respectively) ***Symptoms*** • Chills or shaking, itching, rash, flushing, difficulty breathing, dizziness, fever, hives, angioedema ***Pre-medication*** • Routine pre-medication not recommended • May consider pre-medication with antipyretics and H1 antagonists if IRR has occurred in past ***Management*** • Mild or moderate: interrupt or decrease infusion rate • Severe or life-threatening: Discontinue ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80[β]

Obinutuzumab
 	
(Updated 1/9/20)
	Incidence
	• Incidence with 1st 1000 mg of infusion 65% in patients with CLL (20% grade 3-4 IRRs)
	• Incidence with 1st infusion 55-72 in patients with NHL (up to 12% grade 3-4 IRRs)
	• Incidence decreased with subsequent doses
	
	Mechanism
	• CRS
	
	Risk factors
	• Severe reactions in patients with higher tumour burden (e.g. high circulating lymphocyte count in CLL, > 25 x 109/L)
	
	Symptoms
	• Less common: anaphylactoid/anaphylactic reactions, bronchospasm, larynx/throat irritation, wheezing, laryngeal edema, and cardiac symptoms (e.g. atrial fibrillation
	
	Onset
	• IRRs occur more frequently with 1st 1000 mg infused or on day 1 of infusion
	• Delayed reactions (up to 24 hrs. later) and reactions with subsequent infusions have occurred
	
	Symptoms
	• May cause severe and life-threatening IRRs; reactions may include bronchospasm, dyspnea, chest discomfort, tachycardia, larynx and throat irritation, wheezing, laryngeal edema, flushing, rash, hypertension, hypotension, fever, dizziness, nausea, vomiting, diarrhea, headache, fatigue, and/or chills
	
	Pre-medication to prevent infusion reactions (CLL and FL)
	• CLL (cycle 1 [days 1 and 2]) and FL (day 1)
	  ○ Acetaminophen (650-1000 mg) at least 30 mins. prior to infusion
	  ○ Antihistamine (e.g. diphenhydramine 50 mg) at least 30 mins. prior to infusion
	  ○ IV glucocorticoid (dexamethasone 20 mg or methylprednisolone 80 mg) at least 60 mins. prior to infusion
	  ▪ If glucocorticoid-containing chemotherapy regimen administered on same day as obinutuzumab, glucocorticoid may be administered as oral medication if administered at least 1 hr. prior to obinutuzumab (IV glucocorticoid therefore not required)
	  ▪ Hydrocortisone not effective in reducing rate of IRRs and not recommended

	• For subsequent infusions:
	  ○ All patients should receive acetaminophen 650-1000 mg at least 30 mins. prior to infusion
	  ○ If grade 1-2 IRR with previous infusion:
	  ▪ Antihistamine (e.g. diphenhydramine 50 mg) in addition to acetaminophen at least 30 mins. prior to infusion
	  ○ If grade 3 IRR with previous infusion or lymphocyte count >25,000 cells/mm^3 prior to next treatment:
	  ▪ IV glucocorticoid (dexamethasone 20 mg or methylprednisolone 80 mg) at least 60 mins. prior to infusion, in addition to acetaminophen and antihistamine at least 30 mins. prior to infusion
	• Monitor patients with preexisting cardiac or pulmonary conditions closely
	• Consider temporarily withholding antihypertensive therapies for 12 hrs. prior to, during, and for 1 hr. after administration
	
	Management
	• Mild to moderate: Reduce infusion rate or interrupt infusion and manage symptoms. Upon symptom resolve, continue or resume infusion. If no further IRR symptoms occur, may resume infusion rate escalation as appropriate for treatment cycle dose
	  ○ For CLL only, day 1 (cycle 1) infusion rate may be increased up to max of 25 mg/hr. after 1 hr.
	• Severe: Interrupt therapy; manage symptoms. Upon symptom resolution, may reinitiate infusion at no more than 50% of rate at which reaction occurred. If no further IRR symptoms occur, may resume infusion rate escalation as appropriate for treatment cycle dose. Permanently discontinue if ≥ grade 3 IRR symptoms occur upon re-challenge
	  ○ For CLL only, day 1 (cycle 1) infusion rate may be increased back up to max of 25 mg/hr. after 1 hr.
	• Life-threatening: Discontinue infusion immediately; permanently discontinue therapy
	
	Other considerations
	• HSRs may be difficult to clinically differentiate from IRRs. However, hypersensitivity very rarely occurs with initial infusion and generally occurs after prior exposure
	• Signs of immediate-onset hypersensitivity include dyspnea, bronchospasm, hypotension, urticaria, and tachycardia
	• Late-onset hypersensitivity (diagnosed as serum sickness) reported; symptoms include chest pain, diffuse arthralgia, and fever
	• If HSR suspected during or after infusion, stop infusion and permanently discontinue treatment
	• Do not retreat with obinutuzumab in patients with known HSRs, including serum sickness

Panitumumab **(Updated 1/17/20)**	***Incidence*** • Overall IRR incidence: 3% • Severe IRRs: ~1%; fatal IRRs reported with post-marketing surveillance. ***Symptoms*** • Severe IRRs: bronchospasm, dyspnea, fever, chills, and hypotension ***Pre-medication*** • Routine pre-medication not recommended ***Management*** • Mild to moderate: Reduce infusion rate by 50% for duration of infusion • Severe: Stop infusion and consider permanent discontinuation (depending on severity or persistence of reaction)
Pembrolizumab **(Updated 1/29/20)**	***Incidence*** *(includes unapproved dosing regimens)* • IRR: ≤9% • Anaphylaxis, HSR: <1% (post-marketing, and/or case reports) ***Symptoms***

	• Rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, fever, pyrexia ***Pre-medication*** • Routine pre-medication not recommended • May consider antipyretic and H1 antagonist in patients who experienced grade 1-2 IRR ***Management*** • Mild to moderate: Interrupt infusion or slow the infusion rate. • Severe: Permanently discontinue pembrolizumab. **Dosage form specific issues** • Some dosage forms may contain polysorbate 80[β]
Pertuzumab (Updated 2/5/20)	***Incidence*** *(reported in combination therapy with trastuzumab and docetaxel)* • Hypersensitivity: 1-11% • IRRs: 13% (Grade 3 or 4 infusion reactions occur rarely) • Overall incidence of hypersensitivity/anaphylaxis slightly higher in group receiving pertuzumab (compared to placebo) in combination with trastuzumab and docetaxel ***Onset*** • During or on day of infusion ***Mechanism*** • IgE mediated ***Symptoms*** • Fever, chills, fatigue, headache, weakness, myalgia, abnormal taste, vomiting, anaphylaxis, angioedema, pyrexia, asthenia, dysgeusia, myalgia ***Pre-medication*** • Routine pre-medication not recommended ***Management*** • Monitor for 1 hr. after 1st infusion and for 30 mins. after subsequent infusions • For significant IRRs: interrupt or slow infusion rate and administer appropriate supportive management • For severe IRRs: consider permanently discontinuing
Ramucirumab (Updated 2/3/20)	***Incidence*** *(as reported with monotherapy)* • IRR: ≤9%; reactions minimized with pre-medications ***Onset*** • Generally, occur with 1st or 2nd dose ***Symptoms*** • Chills, flushing, hypotension, bronchospasm, dyspnea, hypoxia, wheezing, chest pain/tightness, supraventricular tachycardia, back pain/spasms, rigors/tremors, and/or paresthesia ***Pre-medication*** • Pre-medicate prior to infusion with IV H1 antagonist (e.g. diphenhydramine)

	• For patients who experienced grade 1-2 IRR with prior infusion, also pre-medicate with dexamethasone (or equivalent) and acetaminophen ***Management*** • Mild to moderate: Reduce infusion rate by 50% • Severe or life-threatening: Discontinue immediately and permanently **Dosage form specific issues** • Some dosage forms may contain polysorbate 80[β]
RiTUXimab (**Note:** Truximan has been approved as a biosimilar to Rituimab) (Updated 2/6/20)	***Incidence*** *(Most reported adverse reactions from studies in which rituximab given concomitantly with chemotherapeutic agents, glucocorticoid steroids, or methotrexate)* • IRR: 1st dose 12-77% (decreases with subsequent infusions) • Severe IRRs leading to death within 24 hrs. of infusion reported at 0.04-0.07% mostly with 1st infusion • With SC injection, administration-related reactions reported in up to 50% of patient and more common with first administration • With SC injection, grade 3+ reactions reported in 3% of patients • Hypersensitivity, angioedema: 11% • Anaphylactoid shock, anaphylaxis: <1% (post-marketing and/or case reports) ***Onset*** • Serious (including fatal) IRRs reported, usually with 1st infusion; fatalities reported within 24 hrs. of infusion • Reactions usually occur within 30-120 mins. ***Risk factors*** • Allergies to other drugs, young age, female gender, high lymphocyte count, history of IRR during first infusion, patients with intravascular large B cell lymphoma or CLL ***Mechanism*** • CRS, IgE mediated ***Symptoms*** • Hypotension, angioedema, bronchospasm, hypoxia, urticaria, and, in more severe cases, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events • May be associated with features of tumour lysis syndrome ***Pre-medication*** • Pre-medicate with acetaminophen and antihistamine prior to infusion • Corticosteroid (e.g. methylprednisolone 80 mg IV) recommended in patients with high bulk disease or pulmonary involvement if no corticosteroids already being given as part of chemotherapy regimen • For SC rituximab, in patients who experienced adverse effects with pre-medications, omission of pre -medications can be considered ***Additional considerations*** • Consider holding antihypertensive medications for 12 hrs. prior to and throughout rituximab infusion • Initial infusion: Start infusion rate of 50 mg/hr.; if no IRR, increase rate by 50 mg/hr. increments q 30 mins. to max rate of 400 mg/hr. • Subsequent infusions: Standard infusion rate: If patient tolerated initial infusion, start at 100 mg/hr.; if no IRR, increase rate by 100 mg/hr. increments q 30 mins. to max rate of 400 mg/hr. • Accelerated infusion rate (90 mins.). For patients with previously untreated follicular NHL and diffuse large B-cell NHL receiving corticosteroid as part of combination chemotherapy regimen, circulating lymphocyte count <5,000/mm^3, or no significant cardiovascular disease. After tolerance established (no grade 3-4 IRR event) at recommended infusion rate in cycle 1, rapid infusion rate may be used beginning with cycle 2. Daily

	corticosteroid, acetaminophen, and diphenhydramine administered prior to treatment, then rituximab dose administered over 90 mins., with 20% of dose administered over first 30 mins. and remaining 80% given over 60 mins. If 90-min. infusion in cycle 2 tolerated, same rate may be used for remainder of treatment regimen (through cycles 6 or 8) • SC rituximab should not be administered until patient has received rituximab IV (i.e. for 1st cycle) without IRR ***For patients with high lymphocyte count (>25-50 x 10^9/L)*** • Monitor and consider patient-specific risk factors when prescribing strategies to prevent IRRs • Consider splitting dose over 2 days • Consider reduced infusion rate • Consider delaying rituximab treatment until chemotherapy has reduced lymphocyte count ***Management*** • Medications for treatment of HSRs (e.g. bronchodilators, epinephrine, corticosteroids, and oxygen) should be available for immediate use; treatment symptomatic • Carefully monitor patients with history of prior cardiopulmonary reactions or with preexisting cardiac or pulmonary conditions and patients with high numbers of circulating malignant cells (≥25,000/mm^3) • If IRR occurs, temporarily or permanently discontinue infusion (depending on severity of reaction and required interventions) • After symptoms resolve, infusion may resume with at least 50% infusion rate reduction • Discontinue for severe reactions and provide medical intervention for severe or life-threatening IRRs ***Dosage form specific issues*** • Some dosage forms may contain polysorbate 80^{β} ***Contraindications*** • No contraindications listed in manufacturer's US labeling; known Type 1 hypersensitivity or anaphylactic reaction to murine proteins listed in manufacturer's Canadian labeling

Trastuzumab
 	
(**Note:** Kanjinti and Ogivri have been approved as biosimilars to Trastuzumab)
 	
(Updated 1/27/20)
 	
and
 	
Ado-trastuzumab emastine
 	
(Updated 2/5/20)
	Incidence *(% reported with single-agent therapy)*
	• Trastuzumab
	  ○ HSR: 3%
	  ○ IRR: 21-40% (chills and fever most common; severe: 1%)
	  ○ Anaphylactic shock, anaphylactoid reaction, anaphylaxis: <1% (post-marketing, and/or case reports as a single-agent or with combination chemotherapy)
	  ○ 20-40% on 1st infusion
	• Ado-trastuzumab emastine
	  ○ HSR: 2-3%
	  ○ IRR: 1-2%
	  ○ Nonimmune anaphylaxis: <1%
	  ○ Serious allergic/anaphylactic reaction has been observed (rare).
	
	Onset
	• Trastuzumab
	  ○ Most reactions occur during or within 24 hrs. of 1st infusion
	  ○ Risk of late onset symptoms or pulmonary symptoms (>6 hrs. after start of infusion)
	• Ado-trastuzumab emastine
	  ○ Monitor closely for IRRs, especially during initial infusion (monitor during infusion and for 90 mins. after initial infusion, and then for 30 mins. after subsequent infusions)

	Mechanism
	• CRS, IgE mediated
	
	Symptoms
	• Trastuzumab
	  ○ Fever and chills, nausea, vomiting, pain, headache, dizziness, dyspnea, hypotension, rash, weakness
	• Ado-trastuzumab emastine
	  ○ Flushing, chills, fever, bronchospasm, dyspnea, wheezing, hypotension, and/or tachycardia
	
	Pre-medication
	• Routine pre-medication not recommended for either drug
	
	Other considerations
	• Administer over 90 mins. Observe during infusion and for at least 90 mins. following initial dose
	• If no previous IRR, administer over 30 mins. Observe patients during infusions and for at least 30 mins. after infusions
	• Consider administering as SC infusion
	• Ado-trastuzumab emastine not recommended in patients who had trastuzumab permanently discontinued due to infusion reaction or hypersensitivity (has not been evaluated)
	
	Management
	• Trastuzumab
	  ○ Mild-moderate IRRs: Decrease infusion rate
	  ○ Dyspnea or clinically significant hypotension: Interrupt infusion
	  ○ Anaphylaxis or angioedema: Discontinue
	  ○ Treatment with acetaminophen, diphenhydramine, and/or meperidine usually effective for managing IRRs
	• Ado-trastuzumab emastine
	  ○ Slow infusion rate or interrupt infusion
	  ○ Permanently discontinue if life-threatening infusion reactions occur
	  ○ After termination of infusion, reactions generally resolve within several hrs. to a day
	
	Re-challenge
	• Trastuzumab
	  ○ Re-treatment of patients who experienced severe HSRs has been attempted (with pre-medication). Some patients tolerated re-treatment, while others experienced second severe reaction

ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; FL, follicular lymphoma; HSR, hypersensitivity reaction; IRR, infusion-related reaction; IV, intravenous; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung carcinoma; PFI, platinum free interval; SC, subcutaneous	

*Supplemented with information from Lexicomp topic, 'Platinum Derivative Allergy (Drug Allergy and Idiosyncratic Reactions) (updated 6/28/2018)
ǂSupplemented with information from Lexicomp topic 'Daunorubicin Conventional' (updated 2/6/20), 'Daunorubicin Liposomal' (updated 1/30/20), 'Doxorubicin Conventional' (updated 2/10/20), 'Doxorubicin Liposomal' (updated 1/24/20), 'Epirubicin' (12/31/19), 'Idarubicin' (2/7/20), Valrubicin (Updated 10/31/19)
§Supplemented with information from Lexicomp topic 'Taxane Allergy" (updated 7/30/18)
αSupplemented with information from Lexicomp topic, 'Asparaginase Allergy (Drug Allergy and Idiosyncratic Reactions) (updated (7/12/19)
βHSRs, usually delayed reaction, reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals

Development and Revision History

This guideline was reviewed and endorsed by members of the Alberta Provincial Tumour Teams. Members include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2020.

Maintenance

A formal review of the guideline will be conducted in 2024. If critical new evidence is brought forward before that time the guideline working group members will revise and update the document accordingly. The accompanying drug table will be updated annually to account for new drugs and updated information in Lexicomp.

Abbreviations

CCO, Cancer Care Ontario, CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; IRR, infusion-related reaction; NCI, National Cancer Institute;

Disclaimer

The recommendations contained in this guideline are a consensus of members of the Alberta Provincial Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Krista Rawson (Nurse Practitioner) has nothing to disclose.
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