Cancer Care Ontario

Management of Cancer Medication-Related Infusion Reactions: Drug Table

Ontario

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Drug Name/ Class	Characteristics	Mechanism	Symptoms	Prophylaxis	Acute Management	Re-challenge
Carboplatin [1–16]	**Incidence**:[2,9] • Varies from 1-44%. • Increases with repeated drug exposure, typically with the 7-10th exposure. **Onset**:[1] • Varies from minutes to hours. **Risk Factors**:[10,11] • Platinum-free interval more than 12 months. • History of other drug allergies.	Reactions to platinum compounds are typically consistent with IgE mediated **Type I** reactions.[12] Type I reactions include anaphylaxis (a severe, rapid onset and life-threatening reaction).[1] Type IV reactions have been described with cisplatin and carboplatin. Type IV reactions are delayed reactions which are mediated by T-cells. Examples of Type IV reactions include allergic contact dermatitis, erythema multiforme and toxic epidermal necrolysis.[1,10] Type II reactions have been implicated with oxaliplatin.[9] Type II reactions are mediated by antibodies, such as IgG and IgM. Examples of Type II reactions include hemolytic anemia and thrombocytopenia.[1]	Rash, itching, erythema on palms and soles, abdominal cramps, facial edema, flushing, hypotension, bronchospasm, chest pain, tachycardia, systemic anaphylaxis	**Pre-medications:** • There is insufficient evidence that routine prophylaxis with pre-medications reduce infusion reaction (IR) rates.[13–16] • Corticosteroids and H1-receptor antagonists ± H2-receptor antagonists **may** reduce IR rates for some patients (e.g. gynecological patients with a PFI >12 months or a history of drug allergy who are receiving carboplatin starting from the 7th cycle) but no optimal pre-medication regimen has been established.[1,11,13–16] **Extended Infusion:**[13–16] • There is insufficient evidence that routine prophylaxis with extended infusion reduces IR rates.	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate. **Grade 3-4**: • Stop treatment. • Aggressively manage symptoms.	**Grade 1-2:** • There is evidence that re-challenging with **cisplatin** after carboplatin IR may be a viable option.[6,7] • **However**: exact cross reactivity between platinum agents is not known, and can be as high as 25%.[9] • Consider pre-medications and infusing at a reduced infusion rate prior to re-challenge[17–23] • May consider adding montelukast ± acetylsalicylic acid[24] *Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist).[8] **Grade 3-4:**[2,6,7,12,18–22,25–28] • Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.
Cisplatin [6–10,12,29–32]	**Incidence:** • Low rates of reaction reported (1-5%), but have also been reported up to 20%.[9,29] • Reactions usually occur after cycle 6 and are mostly mild.[30] **Onset:**[9,30,31] • Varies from minutes to days. **Risk Factors:**[32] • Concomitant radiation.					
Oxaliplatin [1,8,9,12,17,29–31,33–36]	**Incidence:** • Varies from 10-19% of cases.[9,30] • IRs can occur with any cycle but incidence increases as cycle number increases (generally after 6 cycles).[9,29,30,35] **Onset:**[1] • Usually within 60 minutes after the start of the infusion. **Risk Factors:**[9,31,36] • Younger age. • Female gender. • Prior exposure to platinum salts. • Platinum-free intervals ≥ 3 years.		Sweating, rash, pruritus, back or chest pain, dyspnea, laryngospasm, urticaria, bronchospasm, hypotension	**Pre-medications:** • There is insufficient evidence that routine prophylaxis with pre-medications reduces IR rates.[17,33,36] • Consider corticosteroids and H1-receptor antagonists ± H2-receptor antagonists in high-risk patients.[17,33,36]		

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Paclitaxel [1,8,12,27,37–56]	**Incidence:** • Incidence of reaction without pre-medication is as high as 30%.[1,51] • Incidence of IR despite pre-medication varies from 10% (all grades) to 2-4% (severe reactions).[1,12,52] **Onset:**[1,51,52] • Usually occurs during the 1st or 2nd dose. • Within the first 10 minutes of infusion. **Risk Factors:**[1,53] • Incomplete mixing of excipient and drug (e.g. Cremophor EL with paclitaxel and Polysorbate 80 with docetaxel).	Anaphylactoid, likely due to the direct release of mast cell mediators such as histamine and tryptase.[1,12] *Excipients Cremophor EL and Polysorbate 80 are also capable of complement activation in vitro.[1,52]	Dyspnea, flushing, skin reactions, hypotension, tachycardia, angioedema, urticaria, bronchospasm, back pain[49,50]	**Pre-Medications for Q3W paclitaxel:**[27,37–39,51,52,54–56] • Dexamethasone 20 mg PO 12-and 6-hours **OR** Dexamethasone 20 mg IV 30 minutes pre-infusion* • Diphenhydramine 25-50 mg IV/PO 30-60 minutes pre-infusion • Ranitidine 50 mg IV **OR** Famotidine 20 mg IV 30-60 minutes pre-infusion *Oral and IV dexamethasone are both effective at reducing overall IR rates. Some evidence suggests that oral dexamethasone may be more effective for reducing severe reactions; however, adverse effects and compliance remain a concern.[37,39–41,51] **Pre-Medications for weekly paclitaxel:**[27,37–39,42,43,51,52,54–56] To be given 30-60 minutes 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 for paclitaxel if there was no IR in the first 2 doses.[27,44–46] • Extended infusion of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.[8,44,45,55] • Gently rotate the IV bag prior to administering to ensure proper mixing. • There is insufficient evidence to recommend the addition of Hydrocortisone 100 mg IV to the existing standard pre-medication regimen.[56]	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± a reduced infusion rate. **Grade 3-4:** • Stop treatment. • Aggressively manage symptoms.	**Grade 1-2:** • Consider re-challenge with pre-medications and at a reduced infusion rate.[18,19,43] • After 2 subsequent IRs, consider replacing with a different taxane. Give intensified pre-medications and reduce the infusion rate.[29] • May consider adding oral montelukast ± oral acetylsalicylic acid.[24] **Grade 3-4:**[47,48] • Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary. • There is insufficient evidence to recommend substitution with another taxane at re-challenge. • High cross-reactivity rates have been reported.

Drug Name/ Class	Characteristics	Mechanism	Symptoms	Prophylaxis	Acute Management	Re-challenge
Docetaxel [1,29,55,57–62]			Dyspnea, bronchospasm, urticaria, rash, hypotension, flushing, chest or back pain, tachycardia	**Pre-Medications:**[29,55,57–62] • Dexamethasone 8 mg PO BID for 3 days, starting 1-day pre-infusion* *Dexamethasone 10-20 mg IV can be given if patient forgot to take oral doses. An alternative for patients with **prostate cancer** being treated with prednisone: • Dexamethasone 8 mg PO 12 hours, 3 hours, and 1 hour pre-infusion.[57] **Other considerations:** [29,55,57–63] • Do **not** discontinue dexamethasone, even in the absence of an IR, due to the benefits on other adverse effects (e.g. pain and edema).[60] • Gently rotate the IV bag prior to administering to ensure proper mixing. • Start infusion at a slow rate, then gradually increase to planned rate.	As above	As above
Cabazitaxel [27,64–68]	**Incidence:** • Overall incidence is unclear. • In a phase I study of cabazitaxel (where no patients received premedication), 2 of 25 patients experienced grade 1 IR.[66] • In a phase II study of 71 patients receiving premedication with diphenhydramine, 4 patients (6%) had an IR, 3 of which were grade 3/4.[67] • The phase III TROPIC trial used premedication (dexamethasone 8mg, H1-receptor antagonist, and H2-receptor antagonist) and no IRs were observed.[68] **Onset:**[64] • More common during the 1st and 2nd dose. • May occur within a few minutes of the start of the infusion.	Reactions may be caused by the drug or its vehicle (Polysorbate 80).[64] *Avoid cabazitaxel if documented reaction to other drugs containing polysorbate 80 (e.g. docetaxel and etoposide).[64]	Generalized rash/erythema, hypotension, bronchospasm[65]	**Pre-medications:**[27,64] At least 30 minutes prior to each administration of cabazitaxel: • A corticosteroid IV/PO (e.g. Dexamethasone 8 mg) • An H1-receptor antagonist IV/PO (e.g. Diphenhydramine 25 mg) • An H2- receptor antagonist IV/PO (e.g. Ranitidine 50 mg) **Other considerations:** • Gently rotate the IV bag prior to administering to ensure proper mixing.		

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Anthracyclines[1,28–30,65,69]	**Incidence:** • Incidence higher with PEGylated liposomal doxorubicin and daunorubicin (7%-11%).[1] **Onset:** • Majority occurs during the first infusion.[1]	PEGylated liposomal doxorubicin may cause complement activation, leading to reaction.[1]	Chest pain, flushing, syncope, pruritus, fever, urticaria, angioedema, rash, tachycardia, hypotension, dyspnea, nausea, vomiting, headache, back pain	**Pre-medications:** • Routine pre-medication is not recommended.[1,65] • If a reaction occurs, recurrence can be reduced by pre-treatment with diphenhydramine and corticosteroids.[65] **Other Considerations:**[1,65] • Limit initial infusion rate to ≤1 mg/min.	**Grade 1-2**: • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time. **Grade 3-4**: • Stop treatment. • Aggressively manage symptoms.	**Grade 1-2:**[29] • Consider pre-medications and administering at a slower infusion rate. **Grade 3-4:**[28,30,65,69] • Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.
Asparaginase[1,8,29,61,69,70]	**Incidence:** • Ranges between 6% to 43% (risk per dose is 5% to 8%, with an increase to 33% after the fourth dose).[69] • Severe reactions: <10%.[69] **Onset:**[8,61] • Usually after 2 weeks of either daily or 3 times per week regimens. • Usually within 1 hour of infusion. **Risk Factors:**[61] • IV > IM administration. • Time intervals ≥ 1 week > daily administration. • Previous exposure to L-asparaginase • Doses >6000 IU/m^2/day.[29]	Type I HSR (mediated by IgE or related to complement activation).[61,69]	Pruritus, dyspnea, urticaria or angioedema, bronchospasm, hypotension[29,61]	**Pre-medications:** • No standard prophylaxis regimen exists.[8] • Can consider corticosteroids, H1- and H2-receptor antagonists.[8,29] **Route of administration:**[70] • Consider administering L-asparaginase via intramuscular or subcutaneous route.	**If IR occurs:**[70] • Stop the administration. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time.	• If available, consider a switch from *E. coli*-derived L-asparaginase to *Erwinia*-asparaginase or PEG-asparaginase.[61,69] • Pre-medications with corticosteroids and H1-receptor antagonists.[29] • Consider desensitization.[29,61]
Bleomycin[1,65]	**Incidence:**[1] • Incidence of reactions is 1%. **Onset:**[1] • Usually occurs after the first or second dose, either immediately or delayed by several hours. **Risk Factors:**[1] • Patients with lymphoma.	Related to the release of pyrogenic cytokines (unlikely to be IgE-mediated due to lack of histamine release, hypotension, and tachycardia).[65]	Hypotension, mental confusion, fever, chills, wheezing[1]	**Pre-medications:**[65] • Routine pre-medication is not recommended.	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time. **Grade 3-4:** • Stop treatment. • Aggressively manage symptoms.	**Grade 1-4:** • No specific recommendations can be made at this time.

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Etoposide [1,8,29,61,65,71]	**Incidence:** • Incidence of IRs (combined with tenoposide) range between 6-41%.[8,61,71] • Incidence of anaphylaxis is 1% to 3%.[1,65] • Reactions to oral etoposide have not been documented.[8] **Onset:**[1] • Usually occurs after the first dose. • Onset ranges between seconds to days from infusion initiation. **Risk Factors:**[8] • Multiple cycles.	Mechanism unclear, but symptoms are consistent with anaphylaxis.[65] *Reaction is thought to be related to the drug's vehicle, polysorbate-80.[65]	Hypotension, fever, chills, bronchospasm, urticaria, angioedema, chest discomfort, dyspnea[1,8,65,71]	**Pre-medications:**[65] • Routine pre-medication is not recommended. **Infusion time:**[1,61] • Infuse over 30 to 60 minutes.	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time. **Grade 3-4:** • Stop treatment. • Aggressively manage symptoms.	• Consider switch to oral etoposide, if clinically appropriate.[8] **Grade 1-2:** • Pre-medications with corticosteroids and H1-receptor antagonists.[1,8,29,65,71] • Slow infusion rate (infuse over 60-120 minutes).[29,72] **Grade 3-4:**[8] • Cross-reactivity reported between etoposide and teniposide.[61] • Consider desensitization.

Monoclonal Antibodies:

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Alemtuzumab[1,12,26,29,73–78]	Humanized Anti-CD52[1,73,74]	**Incidence:** • Serious reaction in 3%.[1,73] • IRs with subcutaneous alemtuzumab are much milder (off-label route of administration).[74] **Onset:**[1,12,26,73,75] • Most common during the first week of therapy. **Mechanism:** • Cytokine Release Syndrome (CRS).[1]	Hypotension, rigors, fever, shortness of breath, bronchospasm, chills, vomiting, rash, headache, fatigue, flushing, chest discomfort, dizziness, insomnia, tachycardia, anaphylaxis (rare)[1,75]	**Pre-medications:**[76–78] Administer 30 minutes prior to IV/SC alemtuzumab: • H1-receptor antagonist (e.g. diphenhydramine 50 mg IV) • Acetaminophen 650 mg PO *Can consider corticosteroids (methylprednisolone 1g) on the first 3 days.[1] **Administration:** • Administer IV infusion in a fractionated way to avoid CRS.[1] • Consider subcutaneous administration (except in patients with T-PLL).[76–80] **Other considerations:**[73] • Observe the patient during and for at least 2 hours after the infusion has been completed. • Counsel patients to continue to check for symptoms of IR for at least the first 24 hours after each infusion.	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Grade 3-4:** • Stop treatment. • Aggressively manage symptoms. **Restart:**[1,29] • Once symptoms resolve, the infusion can be restarted at a slower rate with pre-medications, unless a serious reaction occurred.	**Grade 1-4:** • No specific recommendations can be made at this time. If reaction was with IV route, switch to SC if possible.
Atezolizumab[1,81]	Humanized Anti-PD-L1[1,81]	**Incidence:** • Incidence of IRs is 1.1-2%, mostly mild.[1,81]	Dyspnea, pyrexia, chills, hypotension, itching, flushing, swelling, dizziness[1,81]	**Pre-medications:**[81] • There is insufficient evidence that routine prophylaxis with premedications reduce infusion reaction (IR) rates. • Consider antipyretic and H1-receptor antagonist upon re-challenge. **Administration:**[81] • Administer the first dose over 60 minutes and subsequent doses over 30 minutes if first dose was tolerated.	**Grade 1-2:** [1,81] • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time. **Grade 3-4:**[1,81] • Stop treatment. • Aggressively manage symptoms.	**Grade 1-2:**[81] • Re-challenge with close monitoring. Consider pre-medication with antipyretic and H1-receptor antagonists. **Grade 3-4:**[81] • Permanently discontinue (do not re-challenge).

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Bevacizumab [1,12,26,82–85]	Humanized Anti-VEGF[1]	**Incidence:**[12,26,84,85] • IRs reported up to 5%. • Overall incidence of severe IRs is rare (<1%). **Onset:**[12,26,84,85] • Commonly occurs during the 1st cycle. **Risk Factors:**[12,26,84,85] • When given in combination with chemotherapy. **Mechanism:**[86] • Suspected to be IgE mediated.	Dyspnea, flushing, rash, blood pressure changes, chest pain, rigors, nausea, vomiting, anaphylaxis[85]	**Pre-medications:**[1,12,26,84,85] • Routine pre-medication is not recommended. **Administration:** • First dose infused over 90 minutes, with subsequent doses infused over 30-60 minutes[1] • Bevacizumab rapid infusion (over 10 minutes) has safely been administered with no significant increase in IRs (for 5mg/kg and 7.5mg/kg doses).[82,83]	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate, unless a serious reaction occurred. **Grade 3-4:** • Stop treatment. • Aggressively manage symptoms.	**Grade 1-4:** • No specific recommendations can be made at this time.
Blinatumomab[1, 87]	Bispecific T cell-engaging antibody Anti-CD19/CD3[1]	**Incidence:**[1] • IRs reported as 44-67%. • Incidence of serious reactions is 0.5%. **Onset:**[1] • A median time to onset of a CRS event is 2 days. • A signature of three cytokines can identify the patients that will develop severe CRS.	Pyrexia, asthenia, headache, hypotension, nausea, disseminated intravascular coagulation (DIC), capillary leak syndrome, tumour lysis syndrome	**Pre-medications:** • Dexamethasone 20mg IV given 1 hour before infusion is recommended.[1,87] • An antipyretic is recommended during the first 48 hours of each cycle.[1] **Other Considerations:**[87] • Patients receiving blinatumomab infusions are recommended to be hospitalized for the first 9 days of the first cycle and the first 2 days of the second cycle to monitor for IRs that are clinically indistinguishable from CRS.	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Grade 3:** • Stop treatment. • Aggressively manage symptoms. **Restart:**[87] • After resolution of all symptoms, treatment can be resumed. For Grade 3 symptoms, resume at 9 ug/day, with an escalation to 28 ug/day after 7 days if the IR does not recur (patients ≥ 45 kg). **Grade 4:** • Stop treatment. • Aggressively manage symptoms.	**Grade 1-3:** • See restart. **Grade 4:**[87] • Permanently discontinue (do not re-challenge).

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Brentuximab vedotin[1,88]	Chimeric Anti-CD30 Antibody-drug conjugate[88]	**Incidence:**[1] • Incidence of IRs is 11% to 15% and most are grade 1 or 2. **Onset:**[88] • Within 2 days of infusion. **Mechanism:**[86] • Potentially IgE mediated due to risk of anaphylaxis.	Headache, rash, back pain, vomiting, chills, nausea, dyspnea, pruritus, and cough, fever, wheezing or breathing problems, anaphylaxis, tumour lysis syndrome[1,88]	**Pre-medications:** • Routine pre-medication is not recommended.[1,88] • May consider pre-medication with acetaminophen, H1-receptor antagonist and corticosteroid if an IR has occurred in the past.[88]	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Grade 3:** • Stop treatment. • Aggressively manage symptoms. **Restart:**[1] • The infusion may be restarted at a slower rate once symptoms have resolved. **Grade 4:** • Stop treatment. • Aggressively manage symptoms.	**Grade 1-3:**[88] • Consider pre-medication with acetaminophen, H1-receptor antagonist and a corticosteroid for subsequent infusions. **Grade 4:**[88] • Permanently discontinue (do not re-challenge).
Cetuximab[1,12,26,29,89–92]	Chimeric Anti-EGFR[1,90]	**Incidence:**[1,26,89,90] • Incidence of IRs range between 1-20%. • Severe IRs occur in 2-5% of cases. **Onset:**[1,12,26,90–92] • 90% of IRs occur during the 1st cycle despite the use of prophylactic H1-receptor antagonists. • Onset usually within 3 hours of infusion. **Risk Factors:**[92] • Patients with head and neck cancer. **Mechanism:**[26,86] • IgE mediated.	Flushing, rash, fever, urticaria, chills, bronchospasm, dyspnea, nausea, vomiting, blood pressure changes, angina, myocardial infarction, anaphylaxis	**Pre-medications:**[1,12,26,90,91] • H1-receptor antagonist (e.g. diphenhydramine 50 mg IV) 30-60 minutes prior to the dose. • Corticosteroid IV 30-60 minutes prior to the dose. • Consider discontinuing pre-medications after the 2nd infusion based on clinical judgment and the presence/severity of IR. **Extended Infusion:**[90] • Slower initial infusion (120 minutes for initial infusion, 60 minutes for subsequent infusions).	**Grade 1-2:**[1,90] • Stop or slow the infusion rate. • Manage the symptoms. **Grade 3-4:**[1,90] • Stop treatment. • Aggressively manage the symptoms. **Restart:**[26] • Once symptoms resolve, the infusion can be restarted at a slower rate, unless a serious reaction occurred.	**Grade 1-2:**[29] • Re-challenge with a reduced infusion rate of 50% at which the IR occurred. **Grade 3-4:**[29] • Permanently discontinue (do not re-challenge).
Daratumumab[1, 93–99]	Human Anti-CD38[93,94]	**Incidence:**[93–95] • Incidence of any grade IRs is 39-48%. • Incidence of grade 1-2 IRs range between 35-52%.	Nasal congestion, chills, cough, allergic rhinitis, throat irritation, dyspnea, anaphylactic reaction	**Pre-medications:**[93–96] To be given at least 1 hour prior to infusion: • Corticosteroid IV (e.g. methylprednisolone 100 mg or equivalent)*† • Oral antipyretic (e.g. acetaminophen 650-1000 mg)	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms.	**Grade 1-2:**[93] • Re-challenge with pre-medications and infusion rate modification as outlined in the product monograph.

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Daratumumab (Continued)		• Grade 3 IRs can occur in 3-6% of patients. **Onset:**[93] • 92-98% of IRs occur during the 1st cycle. • Onset usually within 1.5 hours of infusion. • Without post-infusion medications, IRs can occur up to 48 hours after infusion.	Less frequent: bronchospasm, hypertension, hypoxia,	• H1-receptor antagonist IV/PO (e.g. diphenhydramine 25-50 mg or equivalent) • Famotidine 20 mg IV (or equivalent) • Montelukast 10 mg PO** *This dose may be reduced following the second infusion (i.e. IV methylprednisolone 60 mg or equivalent).[93] †For daratumumab combination therapy, corticosteroid IV/PO (e.g. dexamethasone 20 mg) is recommended.[93,94,96] **The addition of montelukast given prior to the first infusion numerically reduced the incidence of respiratory IRs in the study by Nooka et al.[94] **Post-medications**:[93] • Oral corticosteroid (e.g. methylprednisolone 20 mg or equivalent) for 2 days post-infusion‡ • Consider bronchodilators (e.g. short and long acting) and inhaled corticosteroids if chronic obstructive pulmonary disorder&*** ‡For daratumumab combination therapy, corticosteroid PO (e.g. dexamethasone 20 mg) on the day after infusion is recommended. &For daratumumab combination therapy, consider adding an H1-receptor antagonist if the patient is at higher risk of respiratory complications. ***These may be discontinued after the 4th infusion if no major IRs occurred.[93,95] **Other Considerations:**[93] • It is recommended to 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 infusion.[97,100] • If the patient did not experience an IR in the first 2 infusions of daratumumab, consideration can be given to administer daratumumab 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).[98,99]	**Grade 3:** • Stop treatment. • Aggressively manage symptoms. **Restart:**[93] • Once symptoms have resolved, the infusion may be restarted at a rate of no more than 50% of the rate at which the reaction occurred. • If no reaction occurs, escalate the rate at no more than 50 mL/hour every hour. **Grade 4:**[1,93] • Stop treatment. • Aggressively manage symptoms.	**Grade 3:**[93] • Re-challenge with pre-medications and infusion rate modification as outlined in the product monograph. • If a grade 3 IR recurs for the 3rd time, discontinue permanently (do not re-challenge). **Grade 4:**[93] • Discontinue permanently (do not re-challenge).

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Elotuzumab[94,101]	Humanized Anti-SLAMF7[101]	**Incidence:**[94,101] • IRs occur in 10% of pre-medicated patients, most commonly after the first infusion. • In a phase I clinical trial, 58% of patients experienced a mild to moderate IR in the absence of premedication.	Fever, chills, fatigue, cough, headache, anemia, nausea, back pain, hypertension[94,101]	**Pre-medications:**[94,101] To be administered 45-90 minutes prior to infusion (except dexamethasone PO*): • Acetaminophen 650-1000 mg PO • H1-receptor antagonists (e.g. Diphenhydramine 25-50 mg IV/PO or equivalent) • H2-receptor antagonists (e.g. Ranitidine 50 mg IV or equivalent) • Dexamethasone IV† • Dexamethasone PO*(to be administered between 3 and 24 hours prior to infusion) †Dosing schedule of dexamethasone as follows: • For cycle 1-2, give 8 mg IV with PO dexamethasone • For cycle 3 onwards, give 8 mg IV on day 1 and 15 of the cycle with PO dexamethasone *Dosing schedule of dexamethasone as follows: • For cycle 1-2, give 28 mg PO with IV dexamethasone • For cycle 3 onwards, give 28 mg PO on day 1 and 15 of the cycle with IV dexamethasone • For cycle 3 onwards, give 40 mg PO on day 8 and 22 of the cycle	If IR occurs, monitor vital signs every 30 minutes for 2 hours after the infusion has ended.[101] **Grade 1:** [101] • Stop or slow the infusion rate. • Manage the symptoms. **Restart:**[101] • Restart the infusion at 0.5mL/min, and increase by 0.5mL/min every 30 minutes. **Grade ≥2:**[101] • Stop treatment. • Manage symptoms.	**Grade 1-2:**[101] • Re-challenge with a reduced infusion rate and close monitoring. **Grade 3-4:**[101] • If severe IRs occur, discontinue permanently (do not re-challenge).
Inotuzumab	Humanized Anti-CD22	**Incidence:** • IRs occur in 2% of pre-medicated patients, are generally Grade 2 or lower and usually occur just after cycle 1 infusions.	Fever, chills, rash, breathing problems	**Pre-medications:** • Corticosteroid, antipyretic, and antihistamine are recommended prior to each dose. .	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a reduced infusion rate (ie. 50% at which IR occurred). **Grade 3-4:** • Stop treatment and aggressively manage symptoms.	**Grade 1-2:** • Re-challenge with pre-medications and at a reduced infusion rate of 50% at which the IR occurred. • Consider adding montelukast ± acetylsalicylic acid. **Grade 3-4:** • Discontinue permanently (do not re-challenge).
Ipilimumab[1,29,102–104]	Human Anti-CTLA-4[1,102]	**Incidence:** • Incidence of IRs is 2% to 5% (majority of IRs are grade 2).[1]	Pruritus, maculopapular rash, cough, shortness of breath, chills, rigors, facial	**Pre-medications:**[1] • Consider an antipyretic and H1-receptor antagonist.	**Grade 1-2:** • Stop or slow the infusion rate. • Manage the symptoms.	**Grade 1-2:**[29] • Re-challenge with a reduced infusion rate of 50% at which the IR occurred.

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Ipilimumab (Continued)		**Onset:** • Usually occurs during (and up to 30 minutes after) the second infusion.[103]	flushing, chest, abdominal or back pain, dizziness, fainting, hives, anaphylactic reaction (<0.01%), tumour lysis syndrome (<1%)[1,102,103]	**Other Considerations:** • Consider post-infusion monitoring for a short time after the infusion, as IRs have occurred up to 30 minutes after the infusion.[1,102,103] • Consider infusing 3 mg/kg dose over 30 minutes.[103,104]	**Restart:**[1,102,103] • Once symptoms have resolved, the infusion may be restarted with pre-medications and close monitoring. **Grade 3-4:** • Stop treatment. • Aggressively manage symptoms.	**Grade 3-4:**[29] • Discontinue permanently (do not re-challenge).
Nivolumab[1,105]	Human Anti-PD-1[1,105]	**Incidence:** • 5%, including grade 3-4 IRs.[1]	Chills or shaking, itching, rash, flushing, difficulty breathing, dizziness, fever, hives, angioedema, anaphylactic reaction (<1%)[1,105]	**Pre-medications:**[1] • Routine pre-medication is not recommended. • May consider pre-medication with antipyretics and H1-receptor antagonists if an IR has occurred in the past.	**Grade 1-2:** • Stop or slow the infusion rate. • Manage symptoms. **Restart:**[105] • Once symptoms have resolved, the infusion may be restarted with close monitoring. **Grade 3-4:** • Stop treatment. • Aggressively manage symptoms.	**Grade 1-2:**[105] • Re-challenge with close monitoring and pre-medications. **Grade 3-4:**[105] • Discontinue permanently (do not re-challenge).
Obinutuzumab[106]	Humanized Anti-CD20[106]	**Incidence:**[106] • Incidence with the 1st 1000 mg of the infusion was 65% in patients with CLL (20% were grade 3-4 IRs). • Incidence with 1st infusion was 55%-72% in patients with NHL (Up to 12% were grade 3-4 IRs). • Incidence decreased with subsequent doses. **Risk Factors:**[106] • Severe reactions in patients with higher tumour burden (e.g. high circulating lymphocyte count in CLL, > 25 x 10^9/L).	Nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, constipation, rash, hypertension, hypotension, flushing, headache, pyrexia, chills[106] Less commonly: anaphylactoid/anaphylactic reactions, bronchospasm, larynx/throat irritation, wheezing, laryngeal edema, and cardiac symptoms (e.g.	**Pre-medications:**[106] For CLL patients, Cycle 1, Days 1 and 2 and for FL patients, Cycle 1, Day 1 only: • Corticosteroid IV*† (e.g. Methylprednisolone 80 mg or Dexamethasone 20 mg) at least 60 minutes prior to infusion • Antipyretic PO (e.g. acetaminophen 1000 mg) at least 30 minutes prior to infusion • H1-receptor antagonist (e.g. Diphenhydramine 50 mg) at least 30 minutes prior to infusion *If a corticosteroid-containing chemotherapy regimen is administered on the same day as obinutuzumab, the corticosteroid can be administered as PO if given at least 1 hour prior to obinutuzumab, in which case additional IV corticosteroid as pre-medication is not required †Hydrocortisone is not recommended as it has not been effective in reducing rates of IR	**Grade 1-2:**[106] • Slow the infusion rate. • Manage the symptoms. **Restart:**[106] • Once symptoms have resolved, continue infusion. • If IR does not recur, may escalate the dose at increments appropriate for the treatment dose (see product monograph). For CLL patients receiving the cycle 1, day 1 dose split over 2 days, day 1 infusion rate may be increased to 25mg/hr after 1 hour (but should not exceed this rate).	**Grade 1-3:**[106] For CLL patients: • For Cycle 1 Day 1 or 2, re-challenge with a reduced administration rate (start at 25 mg/hour). The rate of infusion can be escalated in increments of up to 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. • For Cycle 1 Day 8 or 15, or Cycle 2-6 Day 1, re-challenge with a reduced administration rate (start at 50 mg/hour). The rate of infusion can be escalated

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Obinutuzumab (Continued)		**Mechanism:**[86] • CRS.	atrial fibrillation)[106]	For CLL and FL patients, subsequent infusions: *If no IR during previous infusion:* • Antipyretic PO at least 30 minutes prior to infusion *If grade 1 or 2 IR with previous infusion:* • Antipyretic PO at least 30 minutes prior to infusion • H1-receptor antagonist at least 30 minutes prior to infusion *If grade 3 with previous infusion OR patients with lymphocyte counts > 25 x 10^9/L prior to next treatment:* • Corticosteroid IV at least 60 minutes prior to infusion • Antipyretic PO at least 30 minutes prior to infusion • H1-receptor antagonist at least 30 minutes prior to infusion **Administration:**[106] • Consider splitting first treatment over 2 days • Graduated rate of infusion as per product monograph **Other Considerations:**[106] • Consider holding antihypertensive medications for 12 hours prior to, during, and for the first hour after obinutuzumab infusion.	**Grade 3:**[106] • Stop the infusion. • Aggressively manage symptoms. **Restart:**[106] • Once symptoms have resolved, restart the infusion at no more than half the previous rate (at which the IR occurred). • If IR does not recur, may escalate the dose as outlined above for grade 1-2 IRs. **Grade 4:**[106] • Stop the infusion. • Aggressively manage symptoms.	in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. For FL patients: • If the patient experienced a grade 1 infusion reaction, where the final infusion rate was ≥100 mg/hour, re-challenge with a rate starting at 100 mg/hour. . The rate of infusion can be escalated in increments of 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. • If the patient experienced a Grade 2 or 3 infusion reaction, re-challenge with a rate starting at 50 mg/hour. The rate of infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. *If a grade 3 IR recurs for the 2nd time, discontinue permanently (do not re-challenge). **Grade 4:**[106] • Discontinue permanently (do not re-challenge).

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Ofatumumab[1, 107]	Human Anti-CD20[1,107]	**Incidence:**[1,107] • IRs occurred in 69% of patients receiving one or more doses of ofatumumab. Majority of these IRs were grade 1-2. • Grade 3 or 4 IRs occurred in 10% of patients. **Onset:**[1,107] • Commonly occurred with the first two treatments. **Mechanism:**[86,107] CRS.	Anaphylactoid/anaphylactic reactions, bronchospasm, cardiac events (e.g. myocardial ischemia, bradycardia), chills, rigours, cough, diarrhea, dyspnea, fatigue, flushing, hypotension, nausea, pain, pulmonary edema, pruritus, pyrexia, rash, hypertension, urticaria, tumour lysis syndrome[1,107]	**Pre-medications:**[1,107] Administer pre-medications 30 minutes to 2 hours prior to each infusion. • Acetaminophen 1000 mg PO (or equivalent) • Diphenhydramine 50 mg IV/PO or cetirizine 10 mg PO (or equivalent) • Prednisolone IV 50 mg* In previously untreated CLL: • If the patient does not experience a grade 3 or 4 IR in the 1st and 2nd infusion, the corticosteroid may be reduced or omitted. In refractory CLL: • *Dose of prednisolone is 100 mg or equivalent for these patients • Do not reduce corticosteroid dose for doses 1, 2 and 9. • For doses 3-8, based on clinical judgment, corticosteroid dose may be gradually reduced with successive infusions if a grade 3 or 4 IR did not occur with a preceding dose. For doses 10-12, based on clinical judgment, prednisolone 50-100 mg or equivalent may be given if a grade 3 or 4 IR did not occur with dose 9.	**Grade 1-2:**[1,107] • Stop the infusion. • Manage the symptoms. **Restart:**[1,107] • Restart the infusion at 50% of the rate at which the IR occurred (at least 12mL/hr). • Infusion rate may be increased according to standard procedure. **Grade 3:**[1,107] • Stop the infusion. • Aggressively manage symptoms. **Restart:**[1,107] • Restart the infusion at 12mL/hour and increase according to standard procedure. **Grade 4:** • Stop the infusion. • Aggressively manage symptoms.	**Grade 1-3:**[107] • No specific recommendations can be made at this time. • Discontinue permanently if vital signs affected (e.g. anaphylaxis). **Grade 4:**[29,107] • Discontinue permanently (do not re-challenge).
Panitumumab[1,26,29,108]	Human Anti-EGFR[1,108]	**Incidence:**[26] • Overall incidence is 4% (approximately 1% incidence of severe reactions).	Chills, dyspnea, flushing, blood pressure changes, pyrexia, tachycardia, vomiting, anaphylaxis, angioedema, bronchospasm[1]	**Pre-medications:**[1] • Routine pre-medication is not recommended. **Administration:**[1] • Administer the first dose over 60 to 90 minutes.* • Subsequent doses may be infused over 30 minutes. *If the patient's actual body weight requires doses higher than 1000 mg, administer infusions over approximately 90 minutes.	**Grade 1-2:** • Stop the infusion. • Manage the symptoms. **Restart:** • Restart the infusion at 50% of the rate at which the IR occurred. **Grade 3-4:** • Stop the infusion. • Aggressively manage symptoms.	**Grade 1-2:**[29] • Re-challenge at 50% of the rate at which the IR occurred. **Grade 3-4:**[29] • Discontinue permanently (do not re-challenge).
Pembrolizumab[1,109]	Humanized Anti-PD-1[1,109]	**Incidence:**[1] • Overall incidence of 3% (<1% incidence of grade 3 or 4 IRs).	Pyrexia, chills, risk of anaphylaxis (0.2%)[1,109]	**Pre-medications:** • Routine pre-medication is not recommended.[1] • May consider antipyretic and H1-receptor antagonist in patients who experienced a grade 1-2 IR.[109]	**Grade 1-2:** • Stop or slow the infusion. • Manage the symptoms.	**Grade 1-2:**[109] • Consider re-challenge with close monitoring and pre-medications (antipyretic and

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Pembrolizumab (Continued)					**Restart:** • No specific recommendations can be made at this time. **Grade 3-4:** • Stop the infusion. • Aggressively manage symptoms.	H1-receptor antagonist). **Grade 3-4:**[109] • Discontinue permanently (do not re-challenge).
Pertuzumab[110]	Humanized Anti-HER2[110]	**Incidence:** • Incidence of IR is 9.8%-13.2% (approximately 1% incidence of severe IRs), on the first day of infusion.[110] **Mechanism:**[86] IgE mediated.	Pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, vomiting, dysgeusia, myalgia, risk of anaphylaxis[110]	**Pre-medications:**[110] • Routine pre-medication is not recommended. **Other Considerations:**[110] • Monitor patients for the first 60 minutes after the first infusion, and for the first 30 minutes after subsequent infusions.[110]	**Grade 1-2:**[110] • Stop or slow the infusion. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time. **Grade 3-4:**[110] • Stop the infusion. • Aggressively manage symptoms.	**Grade 1-2:** • No specific recommendation can be made at this time. **Grade 3-4:**[110] • Discontinue permanently (do not re-challenge).
Ramucirumab[111]	Human Anti-VEGF[111]	**Incidence:**[111] • Overall incidence of 0.4%. **Onset:**[111] • Most IRs occurred during or after the 1st and 2nd infusions.	Rigours, tremors, back pain, back spasms, chest pain or tightness, chills, flushing, dyspnea, wheezing, hypoxia, paresthesia[111] Severe symptoms: bronchospasm, supraventricular tachycardia, hypotension[111]	**Pre-medications:**[111] • H1-receptor antagonist IV (e.g. diphenhydramine) For patients who experienced a grade 1 or 2 IR: • H1-receptor antagonist IV (e.g. diphenhydramine) • Dexamethasone IV (or equivalent) • Acetaminophen	**Grade 1-2:**[111] • Stop or slow the infusion. • Manage the symptoms. **Restart:**[111] • Slow the rate to 50% of the original rate at which the IR occurred for the remainder of the infusion. **Grade 3-4:**[111] • Stop the infusion. • Aggressively manage symptoms.	**Grade 1-2:**[111] • Consider re-challenge pre-medications (H1-receptor antagonist, dexamethasone and acetaminophen) and reduce administration rate by 50% at which the IR occurred. **Grade 3-4:**[111] • Discontinue permanently (do not re-challenge).

Rituximab 1,12,26,76,112–130	Chimeric Anti-CD20 1,74,125,129	**Incidence:**[1,12,26,125–127] • Overall incidence of IRs can range between 25-85%. • Incidence decreases with subsequent infusions (77% with the 1st infusion, 30% with the 4th infusion, and 14% with the 8th infusion). • Severe IRs leading to death within 24 hours of infusion has been reported at 0.04%-0.07%, mostly with the first infusion (77%). • With subcutaneous (SC) injection, administration-related reactions occurred in up to 50% of patients and were more common with the first administration.[114, 129] • With the SC injection, grade 3+ reactions were reported in 3% of patients. **Onset:**[12,26,125,127,128] • Within 30 minutes to 2 hours of the first infusion. **Risk Factors:**[127] • Allergies to other drugs. • Young age. • Female gender. • High lymphocyte count. • History of IR during first	Fever, chills, rash, dyspnea, hypotension, nausea, rhinitis, urticaria, pruritus, asthenia, angioedema, bronchospasm, rigours, fatigue, headache, flushing, anaphylaxis[12,26,125,127,128] May be associated with features of tumour lysis syndrome[1,125,129]	**Pre-medications:**[76,112–117,125,129] Administer 30 minutes prior to IV/SC rituximab: • Oral antipyretic (e.g. acetaminophen) • H1-receptor antagonist (e.g. diphenhydramine) • Corticosteroid (e.g. methylprednisolone 80 mg IV) in patients with high bulk disease or pulmonary involvement if no corticosteroids are already being given as part of the chemotherapy regimen. For SC rituximab, in patients who experienced adverse effects with pre-medications, the omission of pre-medications can be considered.[130] **Additional Considerations:** • Consider holding antihypertensive medications for 12 hours prior to and throughout rituximab infusion.[112] • The first cycle of rituximab IV is recommended to be administered over a graduated rate (as outlined in the product monograph). • If no severe IR occurred with the first cycle, a rapid infusion of IV rituximab over a total of 90 minutes (20% of the dose over 30 minutes, and remaining 80% of the dose administered over 60 minutes) can be initiated with cycle 2.[26,117–119,125] • SC rituximab should not be administered until the patient has received rituximab IV (i.e. for the first cycle) without IR.[115] **For patients with a high lymphocyte count (>25-50 x 10^9/L):**[112,120–123,125] • Monitor and consider patient-specific risk factors when prescribing strategies to prevent IRs. • Consider splitting the dose over 2 days. • Consider a reduced infusion rate as per the product monograph. • Consider delaying rituximab treatment until chemotherapy has reduced the lymphocyte count.	**Grade 1-2:**[1,124,125] • Stop or slow the infusion. • Manage symptoms. **Restart:**[1,124,125] • Once symptoms have resolved, restart at 50% of the rate at which the IR occurred. **Grade 3-4:**[1,124,125] • Stop the infusion. • Aggressively manage symptoms.	**Grade 1-2:**[24,26,86,131] • Re-challenge at 50% of the administration rate at which the IR occurred and with pre-medications. • Consider adding montelukast ± acetylsalicylic acid. **Grade 3-4:**[124,125] • Consider clinical benefit and risks of further treatment. Consider patient factors, severity and nature of the IR and availability of suitable alternative treatment. • Consider desensitization for patients with recurrent reactions despite pre-medications and a slower infusion rate.[86]

Drug Name	Type of Antibody	Characteristics	Symptoms[1]	Prophylaxis	Management[1]	Re-challenge
Rituximab (Continued)		infusion of rituximab. • Patients with intravascular large B cell lymphoma or CLL than with other lymphomas. **Mechanism:**[86] • CRS. • IgE mediated.				
Trastuzumab [1,29,132–134]	Humanized Anti-HER2[1,132,133]	**Incidence:**[1] • Incidence of IR is 20-40% on the first infusion (<1% incidence of severe reactions). • Incidence of IR with trastuzumab emtansine is 1.4%, mainly grade 1-2. Symptoms resolved over the course of several hours to a day after the infusion was terminated.[132] **Onset:**[133] • Symptoms occurred within 24 hours of trastuzumab infusion, usually with the first infusion. • Risk of late onset infusion symptoms or pulmonary symptoms (>6 hours after start of infusion). **Mechanism:**[86] • CRS. • IgE mediated.	Chills, fever, blood pressure changes, bronchospasm, itching, dyspnea, wheezing, arrhythmia, angioedema, urticaria, risk of anaphylaxis/anaphylactoid reaction[1,132]	**Pre-medications:**[1,132,133] • Routine pre-medication is not recommended. **Other Considerations:**[1,132,133] • Administer over 90 minutes. Observe during the infusion and for at least 90 minutes following the initial dose. • If no previous IR, administer over 30 minutes. Observe patients during the infusions and for at least 30 minutes after the infusions. • Consider administering as a subcutaneous infusion.[134]	**Grade 1-2:**[1,132,133] • Stop or slow the infusion. • Manage the symptoms. **Restart:**[1,132,133] • Once symptoms have resolved, if IR was not severe, consider resuming the infusion at a slower rate. **Grade 3-4:**[1,132,133] • Stop the infusion. • Aggressively manage symptoms.	**Grade 1-2:**[29,86] • Re-challenge with pre-medications (e.g. H1-receptor antagonist and corticosteroid). **Grade 3-4:**[29] • Discontinue permanently (do not re-challenge).

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