Premedications for Cancer Therapies: A Primer for the Hematology/Oncology Provider

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Abstract

Chemotherapeutic agents and radiation therapy are associated with numerous potential adverse events (AEs). Many of these common AEs, namely chemotherapy- or radiation-induced nausea and vomiting, hypersensitivity reactions, and edema, can lead to deleterious outcomes (such as treatment nonadherence or cessation, or poor clinical outcomes) if not prevented appropriately. The occurrence and severity of these AEs can be prevented with the correct prescribing of prophylactic medications, often called "premedications." The advanced practitioner in hematology/oncology should have a good understanding of which chemotherapeutic agents are known to place patients at risk for these adverse events as well as be able to determine appropriate prophylactic medications to employ in the prevention of these adverse events. While several guidelines and literature exist regarding best practices for prophylaxis strategies, differences among guidelines and quality of data should be explored in order to accurately implement patient-specific recommendations. Herein, we review the existing literature for prophylaxis and summarize best practices.

Virtually all anticancer regimens have potential adverse events. Often, some of these adverse events, such as chemotherapy- and radiation-induced nausea and vomiting (CINV; RINV), infusion reactions (IRs), and edema, can be prevented or ameliorated by the administration of premedications. Therefore, it is highly recommended that all hematology/oncology practitioners be well versed in these potential adverse events and the premedications necessary to minimize their occurrence and severity (Roeland et al., 2020).

Chemotherapy-induced nausea and vomiting is one of the most distressing and frequent side effects of cancer treatment and can have a significant impact on a patient's quality

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of life. Unless adequately prevented and treated, CINV can lead to adverse outcomes such as metabolic derangements, nutritional depletion and anorexia, esophageal tears, premature withdrawal of antineoplastic treatment, and/or degeneration of self-care and functional ability (National Comprehensive Cancer Network [NCCN], 2021).

Infusion reactions (often referred to as "hypersensitivity reactions") are defined as unexpected reactions that cannot be explained by a drug's known toxicity profile. These are either allergic reactions to foreign proteins (generally immunoglobulin E [IgE]-mediated) or non–immune-mediated reactions (Chung, 2008). Infusion reactions can range from mild (e.g., flushing, itching, fever, and/or shaking chills) to severe and even fatal reactions (e.g., dyspnea, throat tightening, hypoxia, and/or seizures). Identifying and treating IRs is critical, as failure to do so can lead to potentially avoidable morbidities and mortalities, particularly upon reexposure.

Fluid retention is an adverse event associated with the taxoid group of drugs and can occasionally lead to discontinuation of treatment (Lagrue et al., 1979; Taylor, 1984; Vayssairat et al., 1993). Patients typically present with peripheral edema, which starts at the lower extremities (ankles) but can progress to generalized anasarca. Corticosteroid premedication has been effective for this particular adverse effect.

In this review, we present concise evidence-based recommendations for use of premedications aimed at assisting clinicians in their everyday decision-making for commonly used anticancer regimens.

PROPHYLAXIS FOR CINV

Intravenous Chemotherapy

Current management of CINV remains suboptimal despite the availability of effective antiemetics and existence of several guidelines (Hesketh et al., 2020; NCCN, 2021; Razvi et al., 2019; Roila et al., 2016). Reasons may include poor adherence to existing antiemetic guidelines, patient-specific characteristics and factors not included in current CINV guidelines, antiemetic regimen not tailored to individual risk for CINV, and others (Clemons, 2018; Roeland et al., 2020). A need exists for practitioners to compare recommendations among guidelines and evaluate their limitations in order to optimally tailor CINV prophylaxis for each patient. Herein, only recommendations for adult patients are discussed.

Guidelines divide anticancer therapies into four risk categories: highly emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), low emetogenic chemotherapy (LEC), and minimally emetogenic, which causes CINV in > 90%, 30% to 90%, 10% to 30%, and ≤ 10% of patients, respectively (NCCN, 2021). Guidelines also delineate recommended prophylaxis regimens needed in acute (within first 24 hours) vs. delayed (> 24 hours after chemotherapy) phases. Chemotherapy-induced nausea and vomiting can also be classified as anticipatory (conditioned response and occurs before chemotherapy begins), breakthrough (occurs within 5 days of prophylactic antiemetics and requires rescue therapy), refractory, and chronic (Grunberg et al., 2005; Hesketh, 2008; Kris et al., 2011). Chronic CINV in advanced cancer patients is associated with a variety of poorly understood potential etiologies (Schwartzberg et al., 2006).

Existing guidelines differ in their scope and frequency of updates (i.e., evidence-based vs. consensus-based). The NCCN (2021) produces consensus-based antiemetic guidelines with supporting evidence that are updated as frequently as panel members determine necessary, while American Society of Clinical Oncology (ASCO) antiemetic evidence-based guidelines were last updated and published in 2020 (Hesketh et al., 2020). The Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO) antiemetic guidelines are evidence based and were recently updated in July 2019 (slide deck version), although the most recent peer-reviewed publication is from 2016 (Roila et al., 2016). Within these guidelines, consensus exists on a few key principles, as shown in Table 1.

While these guidelines agree on key principles, numerous differences are worth noting; however, it is important to highlight that some of the variations reflect the information available at the time of guideline publication. Therefore, practitioners should consider this point when choosing a guideline recommendation to implement for

Table 1. Key Principles of Antiemetics for CINV

- First and foremost, CINV prophylaxis should be initiated prior to chemotherapy with > 10% risk of CINV (i.e., LEC, MEC, and HEC).
- Antiemetic(s) (either as monotherapy or in combination) should be continued for long enough to cover the duration of emetic risk.
- For combination chemotherapy regimens, the agent with the highest emetogenic potential should guide selection of antiemetic prophylaxis.
- For breakthrough CINV, general consensus is to reevaluate emetic risk, disease status, concurrent illnesses, and medications, and ascertain that the best regimen is being administered for the emetic risk. It is also a general consensus to add an antiemetic with a different mechanism of action than that of those used in the previous cycle of chemotherapy.
  - » Olanzapine is the first-line agent for management of breakthrough CINV.

Note. CINV = chemotherapy-induced nausea and vomiting; LEC = low emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy.

individual patients. Antiemetic recommendations for IV chemotherapy are summarized in Table 2, while specific dosing information is provided in Table 3.

Differences Among CINV Guidelines

Classification of Emetic Risk. Several differences exist among the guidelines. Namely, carboplatin (Paraplatin) AUC ≥ 4, doxorubicin (Adriamycin) ≥ 60 mg/m^2, ifosfamide (Ifex) ≥ 2 gm/m^2/dose, and epirubicin (Ellence) > 90 mg/m^2 are classified as HEC per NCCN, but as MEC per ASCO and MASCC/ESMO; carmustine (BiCNU) > 250 mg/m^2 is HEC per NCCN while ASCO and MASCC/ESMO classify it as HEC without any dose limit; thiotepa (Thioplex) and romidepsin (Istodax) are classified as LEC per NCCN, but MEC per ASCO and MASCC/ESMO; alemtuzumab (Campath) is minimal per NCCN, but MEC per ASCO and MASCC/ESMO. Further, as NCCN is updated more frequently, novel agents are incorporated that are not listed in previously published ASCO or MASCC/ESMO guidelines (Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016).

Choice of 5-HT3 Receptor Antagonist (RA). ASCO states no 5-HT3-RA is preferred while MASCC/ESMO does not comment; however, NCCN recommends either palonosetron (Aloxi) or subcutaneous (SC) granisetron extended-release injection (Sustol) as preferred 5-HT3-RA for MEC when used with dexamethasone (Decadron) two-drug antiemetic regimens (i.e., no neurokinin-1 [NK1] RA; Gralla et al., 2003; Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016).

Prophylaxis of HEC. NCCN and ASCO recommend a four-drug combination for acute CINV based on trial data (Chiu et al., 2016; Navari et al., 2016), while MASCC considers addition of olanzapine (Zyprexa) to NK1-RA–based triplet therapy as optional. The recommendation is based on a trial by Navari and colleagues (2016) which found olanzapine-based quadruplet therapy led to superior complete response (CR) rate (no emesis, no rescue) for acute (86% vs. 65%, $p < .001$), delayed (67% vs. 52%, $p = .007$), and overall time periods (64% vs. 41%, $p < .001$) when compared with NK1-RA–based triplet therapy.

For prevention of delayed CINV, ASCO no longer recommends administration of dexamethasone on days 2 to 4 following doxorubicin and cyclophosphamide (Cytoxan) chemotherapy (AC regimen for breast cancer), whereas MASCC/ESMO and NCCN state that administration can continue (Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016). ASCO's recommendations are based on two randomized controlled trials, which evaluated the safety and efficacy of NK1-RA in patients on AC regimens in which dexamethasone was only administered on day 1 (Aapro et al., 2014; Warr et al., 2005).

Carboplatin Classification and Recommendations. NCCN classifies carboplatin when dosed at AUC ≥ 4 as HEC, while ASCO and MASCC/ESMO classify this as MEC. For these patients, ASCO and MASCC/ESMO recommend NK1-RA–based triplet therapy, while NCCN recommends quadruplet therapy (Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016; Yahata et al., 2016). NCCN changed the emetogenic classification for carboplatin when dosed at AUC ≥ 4 to HEC a few years ago because its emetogenicity is on the higher end within the

Table 2. CINV Prophylaxis Recommendations for IV Chemotherapy

		ASCO	MASCC/ESMO	NCCN
HEC	Acute phase	5-HT3-RA + dex + NK1-RA + olanzapine	5-HT3-RA + dex + NK1-RA +/- olanzapine	Option 1: 5-HT3-RA + dex + NK1-RA + olanzapine (preferred) Option 2: Any 5-HT3-RA + dex + NK1-RA Option 3: palonosetron + dex + olanzapine
	Delayed phase	Non-AC: dex days 2-4 + oral aprepitant (if used on day 1) days 2–3 + olanzapine days 2–4 AC: aprepitant (if given on day 1) + olanzapine	Non-AC: dex days 2–4 AC: aprepitant (if used on day 1) or dex days 2–3 +/- olanzapine. Note: no further prophylaxis if fosaprepitant (Emend for injection), netupitant (Akynzeo), or rolapitant used on day 1	Olanzapine days 2–4 + aprepitant po days 2–3 (if used on day 1) + dex days 2–4 Olanzapine days 2–4 Aprepitant po days 2–3 (if used on day 1) + dex days 2–4
Carboplatin	Acute phase	5-HT3-RA + dex + NK1-RA, when dosed at AUC ≥ 4	5-HT3-RA + dex + NK1-RA	Same as HEC above
	Delayed phase	No prophylaxis	Aprepitant days 2 and 3 if used on day 1	Same as HEC above
MEC	Acute phase	5-HT3-RA + dex	5-HT3-RA + dex	Option 1: 5-HT3-RA + NK1-RA + dex Option 2: 5-HT3-RA + dex Option 3: Olanzapine + palonosetron + dex
	Delayed phase	Dex *only* if patients receiving therapies with known potential for delayed CINV (i.e., oxaliplatin, anthracycline, cyclophosphamide)	Dex *only* if patients receiving therapies with known potential for delayed CINV (i.e., oxaliplatin, anthracycline, cyclophosphamide)	5-HT3-RA or dex or olanzapine (on days 2 and 3 only if given on day 1) Aprepitant (if given on day 1) +/- dex on days 2 and 3
LEC	Acute phase	5-HT3-RA or dex	Dex or 5-HT3-RA or dopamine RA	Dex or metoclopramide or prochlorperazine or 5-HT3-RA
	Delayed phase	None	None	None
Minimal	Acute phase	None	None	None
	Delayed	None	None	None

Note. ASCO = American Society of Clinical Oncology; MASCC = Multinational Association of Supportive Care in Cancer; ESMO = European Society for Medical Oncology; NCCN = National Comprehensive Cancer Network; RA = receptor antagonist; dex = dexamethasone; AUC = area under the curve; LEC = low emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy. Information from Hesketh et al. (2020); NCCN (2021); Roila et al. (2016).

MEC group (i.e., potential to cause CINV is closer to 90%). While NCCN classifies carboplatin AUC ≥ 4 as HEC, no trial data exists for the four-drug combination regimen for this specific population (NCCN, 2021).

Prophylaxis of MEC. ASCO, MASCC/ESMO, and NCCN recommend the 5-HT3-RA doublet. Only NCCN also recommends NK1-RA–based triplet or olanzapine-based triplet for select patients with additional risk factors. Notably, most evidence for olanzapine in CINV prophylaxis is for patients receiving HEC, and methodological flaws exist in the limited data available for MEC (Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016). In a meta-analysis by Chiu and colleagues (2016), none of the studies included trials

Table 3. Antiemetic Dosing for Prophylaxis With IV Chemotherapy Regimens[a]

Agent	Dosing
NK1-RA	
Aprepitant (po)	125 mg on day 1, 80 mg on days 2 and 3
Aprepitant emulsion (Cinvanti; IV)	130 mg on day 1
Fosaprepitant (IV)	150 mg on day 1
Rolapitant (Varubi; po)	180 mg on day 1
5-HT3-RA	
Ondansetron (po)	16–24 mg on day 1; 8 mg twice daily or 16 mg daily on subsequent days[b]
Ondansetron (IV)	8–16 mg on day 1 and subsequent days[c]
Palonosetron (IV)	0.25 mg on day 1
Granisetron SQ	10 mg on day 1
Granisetron po (Kytril)	2 mg on day 1
Granisetron IV (Kytril)	10 µg/kg (max 1 mg) on day 1
Granisetron patch (Sancuso)	3.1 mg/24-hour transdermal patch applied 24–48 hours prior to first dose of chemotherapy
Dolasetron (Anzemet; po)	100 mg on day 1
Combination products	
Netupitant palonosetron (NK1-RA/5-HT3-RA; po)	300 mg/0.5 mg
Fosnetupitant palonosetron (Akynzeo; NK1-RA/5-HT3-RA; IV)	235 mg/0.25 mg
Other agents	
Olanzapine (po)	5–10 mg on day 1 and subsequent days
Dexamethasone (po or IV)	12 mg on day 1[d]; 8 mg on subsequent days[e]
Lorazepam (Ativan; po/IV/SL)	0.5–2 mg every 6 hours
Prochlorperazine (oral/IV)	10 mg every 6 hours
Prochlorperazine (pr)	25 mg every 12 hours
Promethazine (Phenergan; po)	12.5–25 mg every 4 to 6 hr
Promethazine (pr)	25 mg every 12 hours
Metoclopramide (po, IV)	10–20 mg every 4 to 6 hr
Scopolamine (Transderm Scop; transdermal)	1.5 mg (1 patch) every 72 hr

Note. [a]Always consult up-to-date drug information resources when prescribing any antiemetic agent.
[b]ASCO includes 8 mg oral twice daily as an option for day 1.
[c]MASCC guideline does not distinguish dosing between day 1 and subsequent days. Recommendation is 8 mg or 0.15 mg/kg IV and 16 mg po. ASCO recommends ondansetron 0.15 mg/kg IV. Notably, FDA recommends a maximum of 16 mg for a single dose of IV ondansetron to prevent prolongation of the QT interval of the ECG.
[d]ASCO recommends dexamethasone 20 mg oral or IV if used concomitantly with rolapitant for CINV prophylaxis from MEC or HEC. MASCC/ESMO recommends dexamethasone 20 mg oral or IV for prevention of acute emesis from HEC except when used in combination with fosaprepitant or netupitant, in which case 12 mg oral or IV is recommended. In addition, MASCC/ESMO recommends 8 mg oral or IV on day 1, followed by 8 mg oral or IV daily on days 2–3.
[e]ASCO includes dexamethasone 8 mg oral or IV twice daily as an option for day 3 and 4. MASCC/ESMO recommends dexamethasone 8 mg oral or IV twice daily on days 3 and 4.

assessing only MEC. Results from another small trial that evaluated olanzapine, palonosetron, and dexamethasone in patients receiving MEC were limited in scope because only 50% of those classified as MEC received non-AC chemotherapy (Navari et al., 2007).

Duration of Dexamethasone for MEC. NCCN recommends dexamethasone continue through the entire risk period, which is 2 days after the last dose of MEC, whereas ASCO does not endorse routine use beyond day 1 due to absence of high-quality evidence for dexamethasone in delayed emesis prophylaxis for all MEC agents (Hesketh et al., 2020; NCCN, 2021). Adult patients who are treated with cyclophosphamide, doxorubicin, oxaliplatin (Eloxatin), and other MECs known to cause delayed nausea and vomiting may be offered dexamethasone on days 2 and 3. Similarly, MASCC/ESMO recommends continuing dexamethasone for delayed CINV prevention only if patients are receiving therapies with known potential for delayed CINV (oxaliplatin, anthracycline, and cyclophosphamide; Roila et al., 2016).

Prophylaxis for Multiday Chemotherapy. Multiday chemotherapy presents a uniquely complicated scenario since overlap of acute and delayed CINV exists after the first day of chemotherapy. Guidelines offer general recommendations to tailor therapy based on practical issues, such as inpatient vs. outpatient setting, preferred route of administration, tolerability of daily antiemetics, adherence/compliance issues, and individual patient risk factors. Further, ASCO and NCCN recommend offering antiemetics that are appropriate for the emetic risk of the anticancer agent administered on each day of the treatment and for 2 days after the completion of the anticancer therapy (Hesketh et al., 2020; NCCN, 2021). MASCC/ESMO makes a specific recommendation for metastatic germ cell tumor patients receiving multiday cisplatin (Platinol) to receive aprepitant (Emend), 5-HT3-RA, and dexamethasone for prevention of acute CINV with aprepitant and dexamethasone for prevention of delayed CINV (Roila et al., 2016).

Olanzapine Dose. Both NCCN and MASCC/ESMO guidelines acknowledge sedation as a concern related to 10-mg doses and suggest a lower dose in certain populations (i.e., elderly or oversedated) based on a phase II trial (Roila et al., 2016; Zhou et al., 2020). The option for a lower dose (5 mg) is included in the updated ASCO guideline dosing table (Hesketh et al., 2020). A phase III trial found efficacy with 5 mg olanzapine added to standard NK1-based triplet regimen (Hashimoto et al., 2020). In the 2020 update, NCCN added a caveat that olanzapine 2.5 mg may be considered in patients who have excessive sedation with a 5-mg dose, although no clinical trial data were cited.

Prophylaxis for Hematopoietic Cell Transplantation (HCT). ASCO and MASCC/ESMO support the use of a three-drug combination (NK1-RA, 5-HT3-RA, dexamethasone) in patients receiving high-dose chemotherapy for HCT (Hesketh et al., 2020; Roila et al., 2016). This recommendation is based on three randomized, placebo-controlled trials finding that the addition of aprepitant to 5-HT3-RA and dexamethasone resulted in significantly improved nausea control (Schmitt et al., 2014; Stiff et al., 2013; Svanberg & Birgegård, 2015). NCCN does not provide specific recommendations for this population; however, it cites a study of four-drug combination therapy (NK1-RA, 5-HT3-RA, dexamethasone, olanzapine) in patients receiving HEC for HCT (NCCN, 2021). In this phase III randomized trial, CR rate for those receiving the four-drug olanzapine regimen vs. those receiving the three-drug regimen was 55% vs. 26% in the overall phase (p = .003) and 60.8% vs. 30% (p = .001) in the delayed phase, respectively (Clemmons et al., 2018). Additionally, based off this same study, ASCO now includes the option of adding olanzapine to the three-drug combination for the adult HCT population (Hesketh et al., 2020).

Breakthrough CINV. Both ASCO and NCCN recommend adding olanzapine to standard antiemetic therapy if patients experience breakthrough CINV despite optimal prophylaxis if prophylaxis did not originally include olanzapine (Hesketh et al., 2020; Navari et al., 2013; NCCN, 2021). MASCC/ESMO does not comment on preferred breakthrough antiemetic (Roila et al., 2016).

Adjunctive Agents. Only NCCN specifically recommends considering histamine-2 receptor antagonists (H2RAs) or proton pump inhibitors in patients with dyspepsia, as this may mimic nausea (NCCN, 2021).

Oral Chemotherapy

Recommendations are severely limited for CINV prevention in patients receiving oral chemotherapy. Nearly all clinical trials for CINV prophylaxis focus on patients who are receiving IV chemo-

therapy or radiation. Neither NCCN, ASCO, nor MASCC/ESMO guidelines provide primary reference citations for prophylaxis of oral chemotherapeutics (Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016). Cancer Care Ontario (CCO) provides antiemetic guidelines from a working group (Salama et al., 2019). These authors state a paucity of data exists, citing only three small studies assessing antiemetic regimens for oral chemotherapy, specifically temozolomide (Temodar). These studies are limited by phase II nonrandomized design with fewer than forty participants each and concomitant radiation exposure, which can also be emetogenic (Affronti et al., 2016; Matsuda et al., 2016; Rozzi et al., 2011). Further, the primary outcome measure in these studies did not include nausea assessment, which is the gold standard for contemporary CINV studies. High-quality studies are needed to elucidate optimal CINV prophylaxis for patients receiving oral chemotherapeutic agents.

Based on the paucity of data available, existing antiemesis guidelines provide limited details on recommendations for oral chemotherapy CINV prophylaxis. NCCN divides oral chemotherapeutics into two categories: moderate to high risk vs. minimal to low risk, providing consensus-based antiemetic recommendations for each (Table 4; NCCN, 2021). Comparatively, both ASCO and MASCC/ESMO evidence-based guidelines divide oral chemotherapeutics into high, moderate, low, and minimal emetogenicity categories; however, these guidelines do not provide prophylaxis recommendations by these risk levels due to a lack of high-quality data (Hesketh et al., 2020; Roila et al., 2016).

In addition to the lack of available studies, several other challenges exist with determining optimal prophylaxis regimens in practice. First, many oral chemotherapeutics are administered over several days, falling into the "multiday" regimen category where there may be overlap of acute and delayed nausea. However, multiday dosing of oral chemotherapeutics may have lower emetic risk over time; therefore, some advocate for the use of antiemetics on an "as needed" (prn) basis instead of routine scheduled prophylaxis (MD Anderson Cancer Center, 2020). Second, oral chemotherapeutics are often given in conjunction with IV chemotherapy and/or radiation; therefore, overlap of toxicities can confound assessment. Lastly, practical issues must be taken into consideration when choosing a CINV prophylaxis regimen: inpatient vs. outpatient setting, route of administration, duration of risk period, and antiemetic duration of efficacy, adherence, tolerability of prolonged antiemetic use, etc.

Radiation Treatment

Guideline recommendations for prevention of RINV are based on emetogenic risk (high, moderate, low, and minimal), which is dependent on the anatomic site of radiation therapy (RT; Table 5). No other patient-, tumor-, or treatment-related factors (i.e., radiation dose, fractionation, technique, and field size) are accounted for in the risk classification (Hesketh et al., 2020; Roila et al., 2016).

While all guidelines recommend 5-HT3-RAs as the preferred agent for preventing RINV from

Table 4. CINV Prophylaxis Recommendations for Oral Chemotherapy

Moderate to high emetic risk	Recommendation: Start 5-HT3 receptor antagonist before chemotherapy and continue daily Prophylaxis options: • Dolasetron 100 mg po daily • Granisetron 1–2 mg po daily • Granisetron 3.1 mg/24-hr transdermal patch every 7 days • Ondansetron 8–16 mg po daily
Minimal to low emetic risk	Recommendation: Provide patient with an as needed (prn) antiemetic agent; if CINV occurs, begin scheduled antiemetic before chemotherapy and continue daily. Prophylaxis options: • Metoclopramide 10–20 mg po and then every 6 hr prn (maximum 40 mg/day) • One of the 5-HT3 receptor antagonists: » Dolasetron 100 mg po daily prn » Granisetron 1–2 mg po daily prn » Ondansetron 8–16 mg po daily prn

high and moderate emetic risk RT, the guidelines differ in recommendations regarding dexamethasone due to inconsistent trial data (Table 6). Further, while NCCN does not provide recommendations regarding antiemetic prophylaxis for low and minimal emetic risk RT, ASCO and MASCC/ESMO provide recommendations primarily based on expert consensus (Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016).

Evidence-based recommendations for RINV prevention are limited due to the paucity of randomized clinical trials investigating optimal medication, dosing, and duration of prophylaxis regimens. While some studies address RINV prophylaxis in high and moderate emetic risk, limited data exist regarding low and minimal emetic risk. A systematic review of nine trials found 5-HT3-RAs to be superior to placebo or other antiemetics (metoclopramide [Reglan], prochlorperazine [Compazine], chlorpromazine [Thorazine]) in the prevention of emesis from RT (Salvo et al., 2012). The optimal dose, duration, and specific 5-HT3-RA is unclear due to significant heterogeneity among studies (Dennis et al., 2013; Roila et al., 2016; Salvo et al., 2012). Further, few studies have assessed dexamethasone for prevention of RINV.

Table 5. Emetic Risk by Site of Radiation

Emetic risk level	Site
High (> 90%)	Total body irradiation
Moderate (30%–90%)	Upper abdomen Craniospinal irradiation[a] Localized sites[b]
Low (10%–30%)	Brain/Cranium[c] Head and neck, thorax, pelvis
Minimal (< 10%)	Extremities, breast

Note. [a]Per ASCO and MASCC/ESMO only (Hesketh et al., 2020; Roila et al., 2016).
[b]Per NCCN only (NCCN, 2021).
[c]Per MASCC/ESMO only (Roila et al., 2016).

Table 6. RINV Prophylaxis Recommendations

	ASCO	MASCC/ESMO	NCCN
High emetic risk (TBI)	5-HT3-RA[a] (IV or po) + dex (IV or po) Before each fraction and on the day after each fraction if RT is not planned for that day	5-HT3-RA + dex Route of administration and timing not specified.	5-HT3-RA (po)[a] +/- dex po Start pretreatment for each day of RT treatment.
Moderate emetic risk	Upper abdomen and craniospinal: 5-HT3-RA[b] (IV or po) before each fraction +/- dex (IV or po) before the first 5 fractions	Upper abdomen and craniospinal: 5-HT3-RA + dex (optimal short course) Route of administration and timing not specified.	Upper abdomen/localized sites: 5-HT3-RA (po)[a] +/- dex po Start pretreatment for each day of RT treatment.
Low emetic risk	Brain (previously cranium): Dex rescue (IV or po) Head and neck, thorax, pelvis: Rescue therapy with a 5-HT3-RA[a], dex, or a dopamine receptor antagonist[c] (IV or po)	Cranium: Prophylaxis or rescue with dex Head and neck, thorax, pelvis: Prophylaxis or rescue with a 5-HT3-RA, dex, or a dopamine receptor antagonist[c] Route of administration not specified.	–
Minimal emetic risk (extremities, breast)	Rescue therapy with a 5-HT3-RA[a], dex, or a dopamine receptor antagonist[c] (IV or PO)	Rescue therapy with a 5-HT3-RA, dex, or a dopamine receptor antagonist[c] Route of administration not specified.	–

Note. RINV = radiation-induced nausea and vomiting; TBI = total body irradiation; dex = dexamethasone. Information from Hesketh et al. (2020); NCCN (2021); Roila et al. (2016).
[a]5-HT3-RAs: granisetron *OR* ondansetron.
[b]Granisetron *OR* ondansetron preferred; alternative is tropisetron (not available in US).
[c]Dopamine receptor antagonists: metoclopramide *OR* chlorpromazine.

A study evaluating dexamethasone vs. placebo reported significant improvement in emesis for patients receiving moderate-risk RT (Kirkbride et al., 2000). One study comparing ondansetron (Zofran) monotherapy with dexamethasone plus chlorpromazine in patients receiving lower hemibody RT concluded that ondansetron was significantly better at controlling emesis and nausea on day 1 of RT (Sykes et al., 1997). In a placebo-controlled study, the addition of dexamethasone to 5-HT3-RA for patients receiving moderate emetic risk RT significantly improved complete control of emesis and lowered average nausea scores (Wong et al., 2006). The overall paucity of data demonstates the need for further studies to determine ideal evidence-based regimens for prophylaxis of RINV.

Regarding those receiving concomitant radiation and chemotherapy, guidelines recommend antiemetic prophylaxis be determined based on the emetogenic risk of the chemotherapy regimen, unless the emetogenic risk level of RT is higher (Hesketh et al., 2020; NCCN, 2021; Roila et al., 2016). Additionally, if a patient continues RT after CINV prophylaxis for chemotherapy is discontinued, ASCO guidelines recommend antiemetic prophylaxis appropriate for the emetic risk of RT be used until the next period of chemotherapy (Hesketh et al., 2020). All patients receiving RT alone or in combination with chemotherapy should be prescribed prn antiemetics for breakthrough nausea and vomiting.

PROPHYLAXIS FOR HYPERSENSITIVITY REACTIONS

An IR is an adverse reaction to IV- or SC-administered medications, including chemotherapy and monoclonal antibodies (MoAbs). Reactions usually occur during infusion or within a day of administration. Symptoms range from mild (flushing, chills, pruritus) to severe (anaphylaxis, cardiac arrest). Incidence of IR varies by agent and reported rates may vary over time due to improvements in administration and premedication practices. While severe IRs are rare with an overall incidence of < 5%, they can greatly impact patient outcomes. Appropriate prophylactic medications can reduce the need for prolonged infusion times, dose reductions, delays, and discontinuations, and hospitalizations. Knowledge of IR risk and appropriate prevention strategies are therefore key to optimizing patient care (McBride et al., 2010). Herein we describe common strategies to prevent IRs; acute management of IRs and desensitization strategies is beyond the scope of this article and is discussed elsewhere (Crespo et al., 2019; Roselló et al., 2017).

Classification of Infusion Reactions

The nomenclature of IRs is not standardized and may vary based on the resource, with "hypersensitivity reaction" (HSR) sometimes used interchangeably with "infusion reaction." Hypersensitivity reactions are a subset of IRs that are immune mediated (true allergic responses) and can be further divided into Types I to IV based on the Gell and Coombs classification (Table 7). Nonimmune (nonallergic) IRs include pseudoallergic reactions such as anaphylactoid-appearing cytokine release syndrome (CRS), idiosyncratic reactions, and intolerances. Cytokine release syndrome is characterized by fever, tachycardia, hypotension, or hypoxia caused by the release of cytokines and is frequently seen after treatment with MoAbs and T-cell engaging agents. Symptoms of immune-mediated and nonimmune-mediated IRs greatly overlap and may be identical, making clinical differentiation difficult (Joerger, 2012; Roselló et al.,

Table 7. Gell and Coombs Classification of Hypersensitivity Reactions

Type I	Immunoglobulin E (IgE) antibody-mediated reactions; onset typically within 1 to 6 hours after administration (anaphylaxis)
Type II	Antibody-mediated cytotoxic reactions (hemolytic anemia, thrombocytopenia, blood transfusion reactions)
Type III	Immune complex-mediated hypersensitivity (serum sickness, vasculitis)
Type IV	Delayed T cell-mediated responses; onset from 1 hour to days after administration (allergic contact dermatitis, psoriasis, maculopapular exanthema, erythema multiforme, toxic epidermal necrolysis)

Note. Information from Roselló et al. (2017).

2017). The Common Terminology Criteria for Adverse Events (CTCAE) system for classifying adverse events distinguishes between infusion-related reactions, CRS, and anaphylaxis (Table 8), but the similarity in these presentations limits its usefulness (National Institutes of Health, 2017). When reviewing drug monographs and primary literature for IR data, determining how IRs were defined aids with analysis. For example, in the blinatumomab (Blincyto) monograph, incidence of any-grade IR is reported as 30% and any-grade CRS as 14%, but notably, their definition of IR included CRS and therefore are not additive (Amgen Inc., 2018).

Prevention

Due to possible negative consequences of IRs on patient safety and treatment continuation, it is important to implement strategies to minimize IR risk. Strategies may include assessing patient-specific risk factors, individual anticancer agent IR risk, drug formulation, concomitant medications, route and rate of administration, and optimization of prophylactic medications (Crespo et al., 2019). Patient-specific risk factors for severe and fatal immune-related IRs include older age, use of β-adrenergic blockers or angiotensin-converting enzyme inhibitors, and certain comorbidities (e.g., respiratory or cardiovascular disease, allergic rhinitis, mastocytosis; Simons et al., 2011). Tumor burden is an important patient risk factor for pseudoallergic IRs, such as CRS; therefore, pseudoallergic IRs are often most severe and frequent with the first dose as commonly seen with MoAbs and T cell–engaging agents (Asselin, 2016; Maude et al., 2014; Winkler et al., 1999). While any IV or SC anticancer agent has the potential for IRs, certain agents are associated with higher rates, as detailed in the following pages. Additionally, excipients rather than the drug itself can cause IRs.

Table 8. CTCAE Grading for Infusion-Related Reactions, Cytokine Release Syndrome, and Anaphylaxis

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction[a]	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 hr	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[b]	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O_2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis[c]	–	–	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

Note. CTCAE = Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug. Information from National Institutes of Health (2017).
[a]Infusion-related reaction is a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.
[b]Cytokine release syndrome is characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.
[c]Anaphylaxis is 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, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness, and may lead to death.

Modifiable risk factors for IRs include route and rate of administration, with SC administration and slower infusion rates being associated with lower reaction rates for some agents.

Commonly used agents to prevent IRs include acetaminophen, corticosteroids, and histamine-1 (H1) and H2RAs. These agents are used in various combinations, doses, routes, and administration times as directed by drug monographs. For some anticancer agents, current premedication practices may differ from the monograph recommendations based on subsequently published data. How strictly practitioners need to follow monograph recommendations regarding route (i.e., IV vs. oral) and timing (i.e., 30 vs. 60 minutes) is controversial, with practice frequently differing by institution based on experience and subsequent literature (Crespo et al., 2019). Table 9 describes premedication strategies and considerations for prophylaxis of agents commonly associated with IRs.

Taxanes

Despite premedication, incidence of IRs associated with taxanes has been reported as 10% for paclitaxel (Taxol) and 5% for docetaxel (Taxotere; Picard & Castells, 2014). Taxane IRs may be due to IgE-mediated reactions to the drug or excipient, or due to complement activation by the excipients: Cremophor EL in paclitaxel and polysorbate 80 in cabazitaxel (Jevtana) and docetaxel (Crespo et al., 2019). Cross-reactivity rates between paclitaxel and docetaxel are as high as 41% to 90%, suggesting IRs are frequently related to drug rather than excipient (Sánchez-Muñoz et al., 2011; Dizon et al., 2006). Albumin-bound paclitaxel (Abraxane) does not contain Cremophor EL and has an IR rate of < 2% with no premedication required (Abraxis BioScience LLC., 2019). Case reports exist describing successful treatment with albumin-bound paclitaxel after experiencing severe IRs with docetaxel or paclitaxel; however, such a switch should be carefully considered as efficacy data may not be available, so caution should be exercised and the switch should be guided based on clinical data as these agents are not necessarily therapeutically equivalent (de Leon et al., 2013; Fader & Rose, 2009; Pellegrino et al., 2017; Picard & Castells, 2014).

Taxane IRs most commonly occur during the first or second dose within 10 minutes from the start of infusion. With paclitaxel, the compounded product needs to be thoroughly mixed, as incomplete mixing can lead to excessive complement activation and IRs. No benefit from extended duration (3-hour vs. 24-hour) or lower dose (175 vs. 135 mg/m^2) has been identified (Picard & Castells, 2014). For patients on weekly paclitaxel, some institutions choose to reduce the steroid dose or omit it and other premedications entirely if a patient does not experience a reaction to the first two doses, with safety demonstrated in a few retrospective studies of breast cancer patients (Berger et al., 2015; de Castro Baccarin et al., 2019; Parinyanitikul et al., 2018; Picard & Castells, 2014).

Platinum Agents

Infusion reactions associated with the platinum agents (cisplatin, carboplatin, and oxaliplatin) are typically consistent with IgE-mediated Type 1 reactions, resulting in increasing IR risk with subsequent cycles. Incidence of IR peaks around cycles seven through ten for carboplatin and oxaliplatin and around cycles four through eight for cisplatin, with cisplatin-induced IRs typically milder than those seen with carboplatin and oxaliplatin (Makrilia et al., 2010). Routine premedication is not recommended since it has not been effective. In select cases, such as high-risk gynecologic malignancy patients receiving a seventh cycle of carboplatin, premedication with corticosteroids and H1RAs without or without H2RAs may be considered (Crespo et al., 2019; O'Cearbhaill et al., 2010).

Monoclonal Antibodies

Incidence of MoAb-induced IRs is variable, and the mechanism is not fully elucidated. Infusion reactions may be related to mast cell or basophil activation, antibody-antigen interactions, or immunogenicity of each specific agent based on its ability to induce human antichimeric, human antihuman, or human antimouse antibodies. Monoclonal antibody–related IRs are most frequently attributed to the direct activity of the MoAb on the target cell (antibody-antigen interaction), leading to CRS; therefore, the highest risk of MoAb-related IRs is seen with the first one to two doses.

To reduce the incidence and severity of these IRs, common practice is to start the first infusion at a slower rate and titrate up for subsequent doses

Table 9. Summary of Guideline and Manufacturer Recommendations and Considerations for Prophylaxis of Infusion Reactions in Chemotherapeutics and Monoclonal Antibodies

Drug	Prophylaxis	Comment
Anthracyclines, liposomal	• No routine premedication • Infusion rate: limit initial infusion rate to ≤ 1 mg/min	–
Asparaginase (erwinia chrysanthemi asparaginase, pegaspargase, calaspargase)	• No routine premedication per manufacturer recommendations	• MASCC/ESMO guidelines recommend and CCO guidelines recommend considering: » Antihistamines » Corticosteroids • Universal premedication can be considered due to availability of therapeutic drug monitoring to assess for drug-inactivating antibodies • Agents (see references for specific regimens): » +/- acetaminophen 650 mg po » +/- diphenhydramine (Benadryl) 50 mg IV/po » +/- famotidine (Pepcid) 20 mg IV/po » +/- hydrocortisone (Solu-Cortef) 100 mg IV • Onset of IR usually after several doses • Consider administering asparaginase via intramuscular or SC route to reduce rate of IRs • Pegylated formulations are least immunogenic
Carfilzomib (Kyprolis)	For cycle 1 of carfilzomib monotherapy • Timing: 30 minutes to 4 hours prior • Agents: » Dex 4 mg IV/po when carfilzomib given over 10 minutes » Dex 8 mg IV/po when carfilzomib given over 30 minutes	• Combination regimens incorporate dexamethasone; therefore, premedication is unnecessary
Platinum agents (carboplatin, cisplatin, oxaliplatin)	• No routine premedication	• Caution in carboplatin patients approaching 7th cycle of treatment or a retreatment interval of > 2 years and with oxaliplatin patients approaching 7th cycle
Taxane: Cabazitaxel	• Timing: 30 minutes prior • Agents: » Diphenhydramine 25 mg IV » H2RA IV » Dex 8 mg IV	–

Note. Some drug monographs do not recommend a specific agent within a class or a specific dose). IR = infusion reaction; dex = dexamethasone. MRD = minimal residual disease; ALL = acute lymphoblastic lymphoma. Information from Amgen, Inc. (2017, 2018); Barr et al. (2018); Berger et al. (2015); Biogen and Genentech USA, Inc. (2020a, 2020b); Bristol-Myers Squibb Company (2018); Chouhan & Herrington (2011); Cooper et al. (2019); Crespo et al. (2019); Daiichi Sankyo, Inc. (2019); de Castro Baccarin et al. (2019); Eli Lilly and Company, 2020); EMD Serono, Inc. and Pfizer, Inc. (2019); Genentech, Inc. (2018, 2019a, 2019b, 2020a, 2020b, 2020c); Genzyme Corporation (2019); Hamadeh et al. (2020); Hofmeister & Lonial (2016); Hospira, Inc. (2018, 2019); ImClone LLC (2019); Janssen Biotech, Inc. (2019, 2020); Jazz Pharmaceuticals, Inc. (2019); Lenz (2007); Marini et al. (2019); Markman et al. (1999); Montoya et al. (2007); Nooka et al. (2018); Novartis Pharmaceuticals Corporation (2016); Onyx Pharmaceuticals, Inc. (2019); Parinyanitikul et al. (2018); Roselló et al. (2017); Sanofi-Aventis U.S. LLC (2020); Servier Pharmaceuticals LLC (2019a, 2019b); Shah et al. (2013); Siena et al. (2007); Stock et al. (2011); Wyeth Pharmaceuticals LLC (2018, 2020); Yanaranop & Chaithongwongwatthana (2016).

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Table 9. Summary of Guideline and Manufacturer Recommendations and Considerations for Prophylaxis of Infusion Reactions in Chemotherapeutics and Monoclonal Antibodies (cont.)

Drug	Prophylaxis	Comment
Taxane: Docetaxel	• Timing: 1 day prior • Agents: » Dex 8 mg po bid × 3 days starting 1 day before dose » For metastatic castration-resistant prostate cancer on concurrent prednisone, dex 8 mg po at 12, 3, and 1 hour prior to dose	• If adherence to po regimen is questionable, consider administering dex 10–20 mg IV 30 min prior to dose
Taxane: Paclitaxel	• Timing: 30 minutes prior (see below for dex po timing) • Agents: » Diphenhydramine 50 mg IV/po » H2RA IV » Dex 20 mg po 12 and 6 hours prior *OR* dex 20 mg (10 mg if weekly regimen) IV	• If no IR with the first 2 doses, consider decreasing or omitting premedications
Alemtuzumab (Campath, Lemtrada)	• Dose: escalate per drug monograph • Timing: 30 min prior • Agents: » Acetaminophen 650 mg po » Diphenhydramine 50 mg IV » +/- methylprednisolone (Solu-Medrol) 1,000 mg IV × 3 days (use for Lemtrada formulation; consider for Campath formulation)	• Consider SC administration of Campath formulation to reduce risk of IRs
Atezolizumab (Tecentriq)	• No routine premedication • Infusion rate: » First dose: over 60 minutes » Subsequent doses: over 30 minutes if first dose well-tolerated	–
Avelumab (Bavencio)	First 4 doses • Timing: Not specified • Agents: » Acetaminophen » Antihistamine	–
Bevacizumab (Avastin)	• No routine premedication • Infusion rate: » First dose: over 90 minutes » Second dose: over 60 minutes » Subsequent doses: over 30 minutes » All longer infusions tolerated: consider rapid infusion over 10 to 15 minutes (0.5 mg/kg/minute) for doses up to 7.5 mg/kg	–

Note. Some drug monographs do not recommend a specific agent within a class or a specific dose). IR = infusion reaction; dex = dexamethasone. MRD = minimal residual disease; ALL = acute lymphoblastic lymphoma. Information from Amgen, Inc. (2017, 2018); Barr et al. (2018); Berger et al. (2015); Biogen and Genentech USA, Inc. (2020a, 2020b); Bristol-Myers Squibb Company (2018); Chouhan & Herrington (2011); Cooper et al. (2019); Crespo et al. (2019); Daiichi Sankyo, Inc. (2019); de Castro Baccarin et al. (2019); Eli Lilly and Company, 2020); EMD Serono, Inc. and Pfizer, Inc. (2019); Genentech, Inc. (2018, 2019a, 2019b, 2020a, 2020b, 2020c); Genzyme Corporation (2019); Hamadeh et al. (2020); Hofmeister & Lonial (2016); Hospira, Inc. (2018, 2019); ImClone LLC (2019); Janssen Biotech, Inc. (2019, 2020); Jazz Pharmaceuticals, Inc. (2019); Lenz (2007); Marini et al. (2019); Markman et al. (1999); Montoya et al. (2007); Nooka et al. (2018); Novartis Pharmaceuticals Corporation (2016); Onyx Pharmaceuticals, Inc. (2019); Parinyanitikul et al. (2018); Roselló et al. (2017); Sanofi-Aventis U.S. LLC (2020); Servier Pharmaceuticals LLC (2019a, 2019b); Shah et al. (2013); Siena et al. (2007); Stock et al. (2011); Wyeth Pharmaceuticals LLC (2018, 2020); Yanaranop & Chaithongwongwatthana (2016).

Table 9. Summary of Guideline and Manufacturer Recommendations and Considerations for Prophylaxis of Infusion Reactions in Chemotherapeutics and Monoclonal Antibodies (cont.)

Drug	Prophylaxis	Comment
Blinatumomab (Blincyto)	MRD ALL indication • Timing: 1 hour prior • Agents: » Dex 16 mg IV *OR* prednisone 100 mg po Relapsed/refractory ALL indication • Timing: 1 hour prior to infusion start, dose increase, and restart after interruption ≥ 4 hours • Agent: » Dex 20 mg IV	• Median time to onset of CRS of 2 days, with IRs occurring in 44%–67% of patients
Cetuximab (Erbitux)	• Infusion rate: » First dose: over 2 hours » Subsequent doses: over 1 hour First 2 doses • Timing: 30–60 min prior • Agents: » Diphenhydramine 50 mg IV » +/- corticosteroid IV	• MASCC/ESMO and CCO guidelines recommend addition of IV corticosteroid premedication to reduce IR rate • Consider discontinuing premedication after 2nd infusion based on clinical judgment if no IR experienced
Daratumumab (Darzalex) Daratumumab/ hyaluronidase (Darzalex Faspro)	• Timing: 1 to 3 hours prior • Agents: » Acetaminophen 650–1,000 mg po » Diphenhydramine 25–50 mg IV/po » Corticosteroid - Monotherapy: Methylprednisolone 100 mg IV or equivalent. Third dose onward: methylprednisolone 60 mg IV/po or equivalent - Combination therapy: Dex 20 mg IV. Second dose onward: Dex 20 mg IV/po. If dex is part of regimen, it will serve as premedication » Montelukast (Singulair) 10 mg po (first 1 to 3 doses; only data with IV daratumumab) » Famotidine 20 mg IV (first 1 to 3 doses; only data with IV daratumumab) • Post-medications: » Corticosteroid starting day after infusion - Monotherapy: Methylprednisolone 20 mg or equivalent po daily × 2 days - Combination therapy: Methylprednisolone ≤ 20 mg or equivalent daily × 1 day. - If dex or prednisone is part of regimen, additional post-medication may not be necessary » Consider bronchodilators in patients with chronic obstructive pulmonary disorder	• Consider administering premedications 30 min prior based on expert opinion and retrospective chart reviews of rapid infusion daratumumab with premedications administered 30 min prior to infusion • Consider splitting first daratumumab dose over 2 days in clinics with limited hours, with premedications given on both days • Consider rapid infusion if no IRs seen with first 2 doses at standard infusion rates

Note. Some drug monographs do not recommend a specific agent within a class or a specific dose). IR = infusion reaction; dex = dexamethasone. MRD = minimal residual disease; ALL = acute lymphoblastic lymphoma. Information from Amgen, Inc. (2017, 2018); Barr et al. (2018); Berger et al. (2015); Biogen and Genentech USA, Inc. (2020a, 2020b); Bristol-Myers Squibb Company (2018); Chouhan & Herrington (2011); Cooper et al. (2019); Crespo et al. (2019); Daiichi Sankyo, Inc. (2019); de Castro Baccarin et al. (2019); Eli Lilly and Company, 2020); EMD Serono, Inc. and Pfizer, Inc. (2019); Genentech, Inc. (2018, 2019a, 2019b, 2020a, 2020b, 2020c); Genzyme Corporation (2019); Hamadeh et al. (2020); Hofmeister & Lonial (2016); Hospira, Inc. (2018, 2019); ImClone LLC (2019); Janssen Biotech, Inc. (2019, 2020); Jazz Pharmaceuticals, Inc. (2019); Lenz (2007); Marini et al. (2019); Markman et al. (1999); Montoya et al. (2007); Nooka et al. (2018); Novartis Pharmaceuticals Corporation (2016); Onyx Pharmaceuticals, Inc. (2019); Parinyanitikul et al. (2018); Roselló et al. (2017); Sanofi-Aventis U.S. LLC (2020); Servier Pharmaceuticals LLC (2019a, 2019b); Shah et al. (2013); Siena et al. (2007); Stock et al. (2011); Wyeth Pharmaceuticals LLC (2018, 2020); Yanaranop & Chaithongwongwatthana (2016).

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Table 9. Summary of Guideline and Manufacturer Recommendations and Considerations for Prophylaxis of Infusion Reactions in Chemotherapeutics and Monoclonal Antibodies (cont.)

Drug	Prophylaxis	Comment
Elotuzumab (Empliciti)	• Timing: 45–90 min prior • Agents: » Acetaminophen 650–1,000 mg po » Diphenhydramine 25–50 mg IV/po » Famotidine 20 mg IV » Dexamethasone 8 mg IV • Timing: 3–24 hours prior • Agents: » Dex 28 mg po for patients ≤ 75 years on pomalidomide-based regimen or all patients on lenalidomide-based regimen » Dex 8 mg po for patients > 75 on pomalidomide-based regimen	• Most IRs (70%) occur with first dose
Gemtuzumab ozogamicin (Mylotarg)	• Timing: 1 hr prior • Agents: » Acetaminophen 650 mg po » Diphenhydramine 50 mg IV/po • Timing: 30 min prior • Agents: » Methylprednisolone 1 mg/kg or equivalent	• In patients with high disease burden, consider cytoreduction to reduce the incidence of IRs
Inotuzumab ozogamicin (Besponsa)	• Timing: Not specified • Agents: » Acetaminophen » Antihistamine » Corticosteroid	• IRs generally occur during cycle 1 shortly after the end of infusion • In patients with high disease burden, consider cytoreduction to reduce the incidence of IRs
Obinutuzumab (Gazyva)	• Timing: 1 hour prior • Agents: » Dex 20 mg IV or methylprednisolone 80 mg IV. First dose AND any subsequent dose if grade 3 IR with prior dose or lymphocyte > 25,000/mm^3 • Timing: 30 min prior • Agents: » Acetaminophen 650-1000 mg po. All doses. » Diphenhydramine 50 mg IV/po. First dose AND any subsequent dose if had any-grade IR with prior dose or lymphocyte > 25,000/mm^3	• IRs reported in 65% of CLL patients with first 1,000 mg and in 37%–60% of non-Hodgkin lymphoma patients with first dose, with > 10% of IRs being grade 3–4 • Consider holding antihypertensives on day of infusion due to risk of hypotension

Note. Some drug monographs do not recommend a specific agent within a class or a specific dose). IR = infusion reaction; dex = dexamethasone. MRD = minimal residual disease; ALL = acute lymphoblastic lymphoma. Information from Amgen, Inc. (2017, 2018); Barr et al. (2018); Berger et al. (2015); Biogen and Genentech USA, Inc. (2020a, 2020b); Bristol-Myers Squibb Company (2018); Chouhan & Herrington (2011); Cooper et al. (2019); Crespo et al. (2019); Daiichi Sankyo, Inc. (2019); de Castro Baccarin et al. (2019); Eli Lilly and Company, 2020); EMD Serono, Inc. and Pfizer, Inc. (2019); Genentech, Inc. (2018, 2019a, 2019b, 2020a, 2020b, 2020c); Genzyme Corporation (2019); Hamadeh et al. (2020); Hofmeister & Lonial (2016); Hospira, Inc. (2018, 2019); ImClone LLC (2019); Janssen Biotech, Inc. (2019, 2020); Jazz Pharmaceuticals, Inc. (2019); Lenz (2007); Marini et al. (2019); Markman et al. (1999); Montoya et al. (2007); Nooka et al. (2018); Novartis Pharmaceuticals Corporation (2016); Onyx Pharmaceuticals, Inc. (2019); Parinyanitikul et al. (2018); Roselló et al. (2017); Sanofi-Aventis U.S. LLC (2020); Servier Pharmaceuticals LLC (2019a, 2019b); Shah et al. (2013); Siena et al. (2007); Stock et al. (2011); Wyeth Pharmaceuticals LLC (2018, 2020); Yanaranop & Chaithongwongwatthana (2016).

Table 9. Summary of Guideline and Manufacturer Recommendations and Considerations for Prophylaxis of Infusion Reactions in Chemotherapeutics and Monoclonal Antibodies (cont.)

Drug	Prophylaxis	Comment
Ofatumumab (Arzerra, Kesimpta)	• Timing: 30 minutes to 2 hours prior • Agents: » Acetaminophen 1000 mg po » Diphenhydramine 50 mg po/IV or cetirizine 10 mg po or equivalent » Prednisolone IV or equivalent - Previously untreated CLL: doses 1–2: 50 mg IV; doses ≥ 3: consider reducing or omitting after 2nd dose if no grade 3 or 4 IR - Refractory CLL: use full corticosteroid dose for doses 1, 2, and 9. Doses 1, 2, and 9: 100 mg IV. Doses 3-8: may reduce dose or omit. Doses 10-12: may reduce dose to 50% if no grade 3 or 4 IR with dose 9	• IRs most common with first 2 doses
Panitumumab (Vectibix)	• No routine premedication • Infusion rate: » First dose: over 1 hour if ≤ 1000 mg » Subsequent doses: over 30 min if tolerated » Doses > 1000 mg: infuse over 90 min	–
Polatuzumab vedotin (Polivy)	• Infusion rate: » First dose: over 90 min » Subsequent doses: over 30 min • Timing: 30–60 min prior if not already premedicated for other drugs • Agents: » Acetaminophen » Antihistamine	• Approved for use in combination with bendamustine and rituximab, so patients should already be premedicated for rituximab regardless of polatuzumab administration
Ramucirumab (Cyramza)	• Timing: Not specified • Agents: » Diphenhydramine IV » If grade 1 or 2 IR with prior dose, dex/ equivalent or acetaminophen	• Most IRs reported during or following first or second dose

Note. Some drug monographs do not recommend a specific agent within a class or a specific dose). IR = infusion reaction; dex = dexamethasone. MRD = minimal residual disease; ALL = acute lymphoblastic lymphoma. Information from Amgen, Inc. (2017, 2018); Barr et al. (2018); Berger et al. (2015); Biogen and Genentech USA, Inc. (2020a, 2020b); Bristol-Myers Squibb Company (2018); Chouhan & Herrington (2011); Cooper et al. (2019); Crespo et al. (2019); Daiichi Sankyo, Inc. (2019); de Castro Baccarin et al. (2019); Eli Lilly and Company, 2020); EMD Serono, Inc. and Pfizer, Inc. (2019); Genentech, Inc. (2018, 2019a, 2019b, 2020a, 2020b, 2020c); Genzyme Corporation (2019); Hamadeh et al. (2020); Hofmeister & Lonial (2016); Hospira, Inc. (2018, 2019); ImClone LLC (2019); Janssen Biotech, Inc. (2019, 2020); Jazz Pharmaceuticals, Inc. (2019); Lenz (2007); Marini et al. (2019); Markman et al. (1999); Montoya et al. (2007); Nooka et al. (2018); Novartis Pharmaceuticals Corporation (2016); Onyx Pharmaceuticals, Inc. (2019); Parinyanitikul et al. (2018); Roselló et al. (2017); Sanofi-Aventis U.S. LLC (2020); Servier Pharmaceuticals LLC (2019a, 2019b); Shah et al. (2013); Siena et al. (2007); Stock et al. (2011); Wyeth Pharmaceuticals LLC (2018, 2020); Yanaranop & Chaithongwongwatthana (2016).

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Table 9. Summary of Guideline and Manufacturer Recommendations and Considerations for Prophylaxis of Infusion Reactions in Chemotherapeutics and Monoclonal Antibodies (cont.)

Drug	Prophylaxis	Comment
Rituximab (Rituxan) Rituximab/ hyaluronidase (Rituxan Hycela)	• Infusion rate: titrate per package insert • Timing: 30 min prior • Agents: » Acetaminophen » Antihistamine » +/- corticosteroid if high-bulk disease, non-Hodgkin lymphoma, or CLL (consider for IV rituximab only)	• Consider addition of corticosteroid to premedication for IV rituximab if high-bulk disease, non-Hodgkin lymphoma, or CLL • For previously untreated follicular lymphoma and diffuse large B-cell lymphoma patients, if no grade 3 or 4 IR occurred with first cycle, 90-min infusion (rapid) can be considered with a glucocorticoid-containing regimen; not recommended for patients with clinically significant cardiovascular disease or with circulating lymphocyte count ≥ 5000/mm^3 • Rapid administration is also frequently used off-label for other indications • For patients with bulky disease or high lymphocyte count > 25–50 × 10^9/L, consider using reduced infusion rate, splitting dose over two days, or deferring rituximab until chemotherapy has debulked disease • Before use of rituximab/hyaluronidase SC formulation, patient must tolerate IV rituximab without IRs
Trastuzumab (Herceptin) Trastuzumab emtansine (Kadcyla) Trastuzumab deruxtecan (Enhertu)	• No routine premedication • Infusion rate: » First dose: over 90 min » Subsequent doses: over 30 min	–

Note. Some drug monographs do not recommend a specific agent within a class or a specific dose). IR = infusion reaction; dex = dexamethasone. MRD = minimal residual disease; ALL = acute lymphoblastic lymphoma. Information from Amgen, Inc. (2017, 2018); Barr et al. (2018); Berger et al. (2015); Biogen and Genentech USA, Inc. (2020a, 2020b); Bristol-Myers Squibb Company (2018); Chouhan & Herrington (2011); Cooper et al. (2019); Crespo et al. (2019); Daiichi Sankyo, Inc. (2019); de Castro Baccarin et al. (2019); Eli Lilly and Company, 2020); EMD Serono, Inc. and Pfizer, Inc. (2019); Genentech, Inc. (2018, 2019a, 2019b, 2020a, 2020b, 2020c); Genzyme Corporation (2019); Hamadeh et al. (2020); Hofmeister & Lonial (2016); Hospira, Inc. (2018, 2019); ImClone LLC (2019); Janssen Biotech, Inc. (2019, 2020); Jazz Pharmaceuticals, Inc. (2019); Lenz (2007); Marini et al. (2019); Markman et al. (1999); Montoya et al. (2007); Nooka et al. (2018); Novartis Pharmaceuticals Corporation (2016); Onyx Pharmaceuticals, Inc. (2019); Parinyanitikul et al. (2018); Roselló et al. (2017); Sanofi-Aventis U.S. LLC (2020); Servier Pharmaceuticals LLC (2019a, 2019b); Shah et al. (2013); Siena et al. (2007); Stock et al. (2011); Wyeth Pharmaceuticals LLC (2018, 2020); Yanaranop & Chaithongwongwatthana (2016).

as tolerated (Crespo et al., 2019). To facilitate administration, the first dose of daratumumab (Darzalex) can be split over 2 days as the initial infusion duration is frequently prolonged due to high IR rates (Janssen Biotech, Inc., 2019). Split-day administration and slower infusion rate of rituximab (Rituxan) can also be considered for patients with high lymphocyte counts greater than 25 to 50 $\times 10^9$/L (Crespo et al., 2019).

Subcutaneous formulations of rituximab (Rituxan Hycela) and daratumumab (Darzalex Faspro) in combination with hyaluronidase have recently been approved, but notably only for some indications (Biogen and Genentech USA, Inc., 2020a, 2020b; Janssen Biotech, Inc., 2019, 2020). Before use of rituximab/hyaluronidase SC, a full dose of IV rituximab must be tolerated without severe adverse reaction (Biogen and Genentech USA, Inc. 2020b). Daratumumab/hyaluronidase SC can be used in daratumumab-naive patients. The SC formulation is associated with lower rates of IR on first dose with 10% vs. 37% for SC and IV formulations, respectively. Time to onset of IR with the first dose is slower with SC, with median 3.7 hours (range: 9 minutes–3.5 days) vs. 1.5 hours (range: 0 to 3 days) for IV, so observation time with the first dose of the SC formulation should be carefully considered (Janssen Biotech, Inc., 2019, 2020).

Prevalence of IRs with cetuximab (Erbitux), a chimeric human/mouse MoAb, has a strong geographical association. While the drug monograph reports severe IR rates of approximately 3%, higher rates of up to 22% have been reported in the middle southeastern United States (Chung et al., 2008; ImClone LLC, 2019). This has been deemed to be due to IgE-mediated anaphylaxis, with the majority of patients who experienced severe reactions having preexisting antibodies to galactose-α-1,3-galactose, a component of cetuximab (Chung et al., 2008). Evidence suggests that this antibody may develop as a result of tick bites, as the cetuximab reaction distribution mimics the distribution of the Lone Star tick species (Steinke et al., 2015).

Many MoAbs do not require prophylaxis due to the low incidence of IRs, while some MoAbs only require extended infusion times with initial doses. In general, MoAbs that target the CD20 antigen (rituximab, ofatumumab [Arzerra, Kesimpta], obinutuzumab [Gazyva]) require extensive premedication with acetaminophen, antihistamines, and corticosteroids; similarly, daratumumab also requires extensive premedication (Table 9). In the absence of additional data supporting alternative premedication strategies, manufacturer recommendations should be followed (Crespo et al., 2019).

PROPHYLAXIS FOR EDEMA

Fluid retention is a common side effect following infusion with taxoid agents, docetaxel, and paclitaxel. The exact mechanism by which fluid retention occurs is unknown; however, it has been proposed that docetaxel increases the permeability of capillaries leading to capillary leak syndrome (Ho & Mackey, 2014). This leakage can lead to pleural or pericardial effusions, ascites, and peripheral edema (Baker et al., 2009). Severity of fluid retention is directly related to cumulative dose administered; therefore, even if the first doses of docetaxel are well tolerated, prophylaxis against fluid retention should be continued (Ho & Mackey, 2014). To reduce the incidence and severity of fluid retention reactions, the manufacturer of docetaxel recommends premedication with oral corticosteroids such as dexamethasone 16 mg daily in split dosing for 3 days starting one day prior to docetaxel administration. For patients with prostate cancer who are receiving concomitant prednisone, the recommended dexamethasone dosing is 8 mg given 12 hours, 3 hours, and 1 hour prior to chemotherapy (Hospira, Inc., 2019).

Although effective as prophylaxis, dexamethasone is associated with various side effects and the potential for nonadherence. Therefore, some studies have evaluated the effectiveness of single-dose dexamethasone vs. the standard 3-day regimen. These studies found a lower incidence of fluid retention with single-dose dexamethasone 20 mg po/IV premedication compared to previously published data with the standard 3-day dexamethasone (Chouhan & Herrington, 2011; Montoya et al., 2007). As these studies were retrospective in nature and used historical data as a comparator, the results should ideally be confirmed by prospective studies. A preferred regimen is not yet established, but single-dose dexamethasone premedication should be considered if a patient has been nonadherent to the 3-day regimen.

CONCLUSION

This article summarizes available evidence-based recommendations on premedications and is designed to serve as a quick guide to clinicians in the field of hematology/oncology. Variations in adherence by clinicians to guidelines in the use of recommended prophylaxis against CINV, hypersensitivity, and fluid retention could lead to avoidable toxicity-related morbidities and mortalities. Practitioners should periodically review the literature for updates and consider the differences among existing guidelines when making patient-specific decisions. Further studies are warranted for optimal prophylaxis of these adverse events, particularly for oral chemotherapy, radiation therapy, and multiday chemotherapy, as well as for optimal prophylaxis of certain anticancer agents associated with hypersensitivity and edema.

Disclosure

The authors have no conflicts of interest to disclose.

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