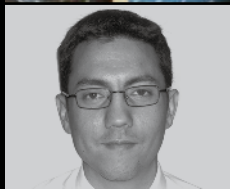




THEME

Nausea and vomiting



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Chemotherapy induced nausea and vomiting

Prevention and treatment

BACKGROUND

Chemotherapy induced nausea and vomiting are among the most feared consequences of cancer treatment. Recent developments in drug treatment make the goal of no nausea or vomiting during chemotherapy realistic.

OBJECTIVE

In this article we review the pathogenesis and management of chemotherapy induced nausea and vomiting.

DISCUSSION

Regimens to prevent chemotherapy induced nausea and vomiting are guided by the emetogenic potential of the chemotherapeutic agents used. Combined prophylactic therapy targets different pathways, improving the efficacy of prevention and treatment of chemotherapy induced nausea and vomiting. General practitioners have an important role in patients undergoing chemotherapy by reinforcing the importance of prophylactic treatment and administering rescue treatment for patients with breakthrough or prolonged nausea and vomiting postchemotherapy.

Chemotherapy induced nausea and vomiting (CINV) are two of the most distressing and feared toxicities of cancer treatment.¹ Recent developments in the understanding of the pathophysiology of CINV and the development of new drugs make the goal of no nausea or vomiting during chemotherapy realistic.²

Role of the GP

The general practitioner has an important role in prevention and management of CINV. Patients may see their oncologist only once per chemotherapy cycle, usually pretreatment. While antiemetics should be prescribed in this consultation, patients may require further explanation of dose and timing and reinforcement about the benefits of effective prophylaxis against CINV. The GP may also be required to 'rescue' patients experiencing CINV despite first line prophylaxis, or to assist with management of a longer than anticipated duration of CINV.

The importance of prevention

Prevention of CINV is important for a number of reasons besides patient comfort. Control of CINV improves the

tolerability of chemotherapy and the likelihood that patients will complete their regimen, which is particularly important for potentially curative treatment. Vomiting and nausea in cancer patients can also be detrimental to nutritional status, leading to a reduction in performance status and ability to tolerate further cycles of chemotherapy and diminishing the palliative benefits of treatment.³ Furthermore, once vomiting is established, it can be refractory to simple treatments.

Types of CINV

Chemotherapy induced nausea and vomiting can be divided into three major categories depending on the timing of symptoms in relation to chemotherapy (*Table 1*).³

Acute phase

Acute phase CINV generally peaks 5–6 hours after chemotherapy administration. Risk is related to the type of chemotherapy, as well as patient related factors. Risk is increased in younger patients, females, patients with a past history of low alcohol intake, and those who experienced emesis during pregnancy or motion sickness.³

Recent research also suggests patient expectations can be a strong predictor of CINV.⁴ General practitioners can help patients explore their expectations about CINV and educate them about the effectiveness of modern antiemetic regimens.

Delayed phase

Delayed CINV commonly occurs after the administration of cisplatin, carboplatin, doxorubicin and cyclophosphamide and may last up to 5 days. Prevention of acute CINV decreases the risk of delayed CINV.⁵

Anticipatory phase

Anticipatory CINV can occur any time after the first cycle of chemotherapy and is due to conditioning after experiencing vomiting secondary to chemotherapy. Prevention of CINV will also prevent anticipatory phase CINV.

Emetogenic potential of chemotherapy drugs

Chemotherapy drugs vary in their emetogenicity (ability to induce vomiting) (Table 2). Cisplatin is classically the most emetogenic drug. Other commonly used drugs with high emetogenic potential include cyclophosphamide, lomustine and dacarbazine. Emetogenicity can also be increased through the combination of different drugs with lesser potential individually to cause CINV, or higher doses of single agents. Understanding the emetogenic potential of a chemotherapy agent or combination is important in prescribing the appropriate prophylactic regimen. An adequate regimen should be put in place by the prescribing oncologist, and should also include 'rescue' medications. However, some patients may need escalation of their antiemetic regimen or further rescue medications prescribed by their GP.

Antiemetic agents

Emesis is generated through multiple pathways and hence the antiemetics used to prevent CINV act at different sites, with some acting at multiple sites. Combinations of antiemetics may improve control of CINV.

Serotonin receptor antagonists

These are the most effective agents to prevent acute nausea and vomiting. Serotonin receptors are thought to be major neuroreceptors in the initiation of emesis, particularly in the acute phase of CINV.⁶

There are a number of agents available (ondansetron, granisetron, tropisetron and dolasetron). They are all highly effective at recommended doses and increasing beyond this dose is unnecessary due to receptor saturation (Table 3).² They are given just before highly or moderately

Table 1. Categories and treatment of chemotherapy induced nausea and vomiting

Category	Onset	Treatment
Acute	Within 24 hours of receiving chemotherapy	Serotonin receptor antagonists, dexamethasone, aprepitant
Delayed	1–5 days after chemotherapy	Dexamethasone, aprepitant
Anticipatory	Subsequent to first experience of chemotherapy Precipitated by chemotherapy associated sights/smells/visual cues/ thoughts/anxiety	Prevention of CINV during previous cycles Behavioural therapy Benzodiazepines

Table 2. Emetogenic potential of commonly used chemotherapeutic drugs^{2,3}

Emetogenic risk of chemotherapeutic agents	Common examples
High (>90% risk without antiemetics)	Cisplatin, dacarbazine, lomustine Doxorubicin or epirubicin combined with cyclophosphamide (in breast cancer patients)
Moderate (30–90% risk without antiemetics)	Irinotecan, oxaliplatin, doxorubicin, carboplatin, temozolomide
Low (10–30% risk without antiemetics)	Capecitabine, cetuximab, gemcitabine, fluorouracil, etoposide, pemetrexed
Minimal (<10% risk without antiemetics)	Bevacizumab, bleomycin, vinorelbine, vincristine, trastuzumab, gefitinib

Table 3. Serotonin receptor antagonists (usual dose)

Odansetron	4–8 mg/day
Granisetron	2 mg/day
Tropisetron	5 mg/day
Dolasetron	200 mg/day

emetogenic chemotherapy and continued for a few days to prevent further CINV. Common side effects include constipation and headache.

Neurokinin-1-receptor antagonists

Aprepitant (Emend™) is the only drug in this class currently available. It has a unique mechanism of action, blocking the neurokinin-1 receptor (NK-1). The NK-1 receptor is found in the vomiting and vestibular centres of the brain.⁷ Aprepitant has a clinically significant additional effect when combined with a serotonin receptor antagonist and dexamethasone therapy for both acute and particularly delayed CINV.⁶ It is used for 3 days with high risk emetogenic regimens (125 mg day 1, 80 mg day 2 and 3).⁷ As aprepitant induces cytochrome p450, it interacts with orally administered

dexamethasone (requiring approximately 50% dose reduction), warfarin (decreases INR) and the oral contraceptive pill.

Corticosteroids

Dexamethasone is the most commonly used antiemetic corticosteroid. Methylprednisolone has also been demonstrated to be effective in preventing CINV. Corticosteroids are synergistic with other agents and are particularly important in prevention of delayed CINV.⁵ The most common side effects with short term use for CINV prophylaxis include insomnia, indigestion and hyperglycaemia. Giving the entire dose by midday, either as single or divided doses, can reduce insomnia without reducing efficacy. Adrenal insufficiency does not seem to be a problem with short dose therapy for 3–4 days and high doses can be stopped without a tail off period.⁷

Dopamine receptor antagonists

Agents in this class include metoclopramide, prochlorperazine, promethazine and haloperidol. The efficacy of these agents in isolation for CINV is low.² They are sometimes used in low risk regimens or as add on therapy for breakthrough emesis. Prochlorperazine is particularly useful as an additional or rescue antiemetic when given as suppositories by the per rectum route, with the advantage that the vomiting patient does not have to take it orally.

Benzodiazepines

Benzodiazepines are useful agents in various settings during chemotherapy. They can reduce anxiety that some patients experience before receiving chemotherapy. They are useful in the treatment of anticipatory CINV and can be used as a short term add on therapy to other drugs for prevention and treatment of CINV where drowsiness and amnesia are acceptable. They are not efficacious as single agents. Lorazepam can be given sublingually, which can be useful in the vomiting patient.

Treatment guidelines

International published guidelines are available to guide the prevention and treatment of CINV.^{2,8} Table 4 summarises the major principles of these guidelines as they apply within the framework of the Pharmaceutical Benefits Scheme (PBS) listing in Australia, assuming the patient has chemotherapy on day 1 (D1) of the regimen only. Multiple day dosing regimens require an antiemetic regimen to be prescribed by the treating oncologist, usually guided by the most emetogenic drug/s within the regimen. Schedules

that cover the different periods of acute and delayed nausea prophylaxis for multiday regimens are beyond the scope of this article.

Anticipatory nausea and vomiting is best prevented through aggressive prophylaxis of nausea and vomiting during each cycle of chemotherapy. If it does develop, patients can be managed through behavioural modification therapy and/or use of oral benzodiazepines before chemotherapy.

Table 4. Guidelines for the prevention of chemotherapy induced nausea and vomiting^{2,8}

Emetogenic potential of regimen	Recommended therapy	Comments
High	Aprepitant 125 mg D1, 80 mg D2+3 Dexamethasone 12 mg D1 and 8 mg D2–4 Serotonin receptor antagonist D1 Other drugs (eg. lorazepam, metoclopramide) as needed	Duration of cover 4 days with steroid
Moderate	Dexamethasone 12 mg D1 and 8 mg D2–3 Serotonin receptor antagonist D1	Duration of cover for 3 days with steroid
Low	Dexamethasone (day 1 only) or metoclopramide/prochlorperazine or lorazepam as needed	Can add further prophylactic therapy for subsequent cycles if nausea or vomiting experienced
Minimal	No routine prophylaxis	Can add prophylactic therapy if nausea or vomiting experienced

Table 5. Differential diagnosis of nausea and vomiting in cancer patients

Treatment related complications	Cancer specific complications	Other common causes
Radiation induced nausea and vomiting	Gastroparesis (from tumour infiltration)	Gastrointestinal infections
Vestibular dysfunction	Brain metastasis and increased intracranial pressure	Small bowel obstruction
Other drugs (eg. opiates)	Ascites and peritoneal metastasis	Anxiety
Gastroparesis (chemotherapy induced)	Hypercalcaemia, hyponatremia	Constipation
Gastritis secondary to NSAIDs or corticosteroids	Bowel obstruction due to mechanical compression	Primary gastrointestinal disorder

Table 6. Possible drugs for breakthrough CINV

Serotonin antagonist or dexamethasone if not already used, increase dose of dexamethasone
Oral metoclopropamide (10–20 mg 4 hourly as required) or prochlorperazine (10 mg 6 hourly as required)
Sublingual lorazepam 0.5–2 mg every 4–6 hours
Prochlorperazine (Stemetil™ suppositories) 25 mg up to 3 times per day
Oral promethazine 12.5–25 mg 6 hourly as required
Oral or subcutaneous cyclizine 50 mg three times per day

What if the patient is vomiting?

Diagnosis

A problem arises in the setting of outpatient treatment of the vomiting patient receiving chemotherapy. Although chemotherapy is a common cause of nausea and vomiting, it is important to consider other possible causes in cancer patients, particularly if vomiting has not occurred in previous cycles or if the emetogenic potential of the chemotherapy regimen is low. *Table 5* summarises some other causes to consider when reviewing these patients.

Rescue treatment for breakthrough CINV

If CINV is the diagnosis, it is important to consider the most appropriate setting for patient treatment. If the episode of CINV is severe, including if the patient is dehydrated or not responding to breakthrough therapy, then referral to the treating oncologist or nearest hospital for further assessment and parental therapy is recommended.

If it is felt that the nausea and vomiting are due to chemotherapy and nonparental therapy is adequate, then a number of breakthrough treatment options are available. These are summarised in *Table 6*. The general principle of breakthrough treatment is to add in a drug from a different class to that used during the routine prophylactic schedule. If optimal prophylactic therapy was given upfront, then sedative medications (eg. benzodiazepines and neuroleptic agents) or dopamine receptor antagonists may be useful.²

Oral therapy is often as effective as parenteral therapy if the patient can retain oral medication. However, if the patient is unable to tolerate oral therapy, consider nonoral routes of drug administration (sublingual and rectal for outpatients, intravenous for inpatients). Typical drugs used in this situation for outpatients include prochlorperazine suppositories and sublingual lorazepam or ondansetron. Prochlorperazine (Stemetil™) suppositories can be a particularly useful rescue medication if taken regularly 30 minutes before oral medications, allowing the oral medications to be retained. It is also important to ensure the patient has adequate fluid

intake during this period by monitoring fluid and electrolyte balance through clinical assessment and blood electrolytes.

Once a patient develops breakthrough CINV after a cycle of chemotherapy, and other causes of nausea or vomiting have been excluded (*Table 5*), then consideration needs to be given to changing the baseline prophylactic regimen to be used during the next cycle.

Conclusion

Recent progress in the prevention and treatment of CINV has improved the treatment of patients receiving chemotherapy. By prescribing appropriate prophylactic medication for the emetogenic potential of the chemotherapy regimen, most cases of CINV can be prevented. General practitioners have an important role in patients undergoing chemotherapy by reinforcing the importance of prophylactic treatment and administering rescue treatment for patients with breakthrough or prolonged nausea and vomiting postchemotherapy.

Conflict of interest: none declared.

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