

Managing chemotherapy-induced nausea and vomiting

Prescriber's Corner describes situations encountered by pharmacist prescribers and invites you to consider clinical decisions about the patient. In this case, you are working in the chemotherapy unit of a hospital, prescribing supportive therapy to a patient on her first course of chemotherapy.

You are a newly qualified independent prescriber working in the chemotherapy unit of a hospital. You are prescribing supportive therapy for a patient with cancer.

The case

Mrs SB is 50 years old. She is 152cm tall and weighs 60kg. She has invasive, node-positive cancer of the right breast and has recently undergone a lumpectomy. She has been prescribed the FEC-T (5-fluorouracil, epirubicin, cyclophosphamide, docetaxel) regimen. Administration is as follows:

- NaCl 0.9% 500ml rapidly infused
- Dexamethasone 20mg IV over a minimum of two minutes
- Ondansetron 8mg IV bolus
- Epirubicin 100mg/m² infused with fast running NaCl 0.9%
- Cyclophosphamide 500mg/m² infused with fast running NaCl 0.9%
- 5-fluorouracil 500mg/m² infused with fast running NaCl 0.9%

This regimen (FEC-100) is administered every 21 days for three cycles. It is then followed by three cycles of the following, administered every 21 days:

- Day 0–2
- Dexamethasone PO 8mg BD
- Day 1
- Ondansetron 8mg IV bolus
 - Docetaxel 100mg/m² IV in 0.9% NaCl over 60 minutes

The patient will be routinely sent home after each cycle with the following anti-emetic therapy:

- Ondansetron PO 8mg BD for 2–3 days post chemotherapy
- Dexamethasone PO 4mg BD for 1–3 days post chemotherapy



- Metoclopramide PO 10mg–20mg three to four times daily

Points to consider

1. What is the emetogenic potential of the chemotherapy prescribed for Mrs SB?
2. What are the risk factors associated with the development of chemotherapy-induced nausea and vomiting (CINV)?

Emetic potential Not all chemotherapeutic agents have the same potential to cause nausea and vomiting. For the purpose of managing CINV, expert groups have allocated a level of risk to the different drugs used. This is shown in Table 1 (p47). The emetic potential of these drugs multiplies when given in combination.

CINV risk factors Not all patients demonstrate the same response to chemotherapy in terms of nausea and vomiting. Risk factors associated with more severe CINV are:

- Being female
- Previous nausea and vomiting during pregnancy

- Previous motion sickness
- Younger age (<50 years)
- Previous uncontrolled CINV
- High pre-treatment expectation

A chronic high consumption of alcohol appears to protect against CINV, as does a history of drug misuse and smoking.

Of all risk factors associated with CINV, the emetogenic potential of the administered drug is the most important and should direct the type of prophylaxis offered to the patient.

Mrs SB has two teenage children (aged 18 and 15). During both pregnancies she suffered with sickness for the whole gestation period. Around the sixth month of her second pregnancy Mrs SB was admitted to hospital in an attempt to control her nausea and vomiting. Her notes suggest that this was severe and was classified as hyperemesis gravidarum.

This is Mrs SB's first cycle of chemotherapy. She was not particularly anxious about CINV; her experiences during pregnancy appear to have made her less concerned than might be expected.

Point to consider

3. What is the rationale for the anti-emetic therapy prescribed in this case, and why are these drugs prescribed in combination?

As described in the panel on p46, CINV is mediated by numerous neurotransmitter pathways and CINV prophylaxis should be prescribed based on the emetogenic potential of the drug regimen.

Mrs SB is being given epirubicin and cyclophosphamide, both of which have a moderate (level 3) CINV risk, and 5-fluorouracil which has a low (level 2) CINV risk. The dose of epirubicin used in this case (100mg/m²) is likely to increase the

Mechanism and classification of chemotherapy-induced nausea and vomiting (CINV)

The mechanism of emesis in response to administration of chemotherapy is complex. The process involves release of 5-hydroxytryptamine (5-HT) from enterochromaffin cells located in the mucosa of the proximal end of the small intestine. This release is thought to occur in response to free radical generation following administration of the chemotherapeutic agent. These free radicals induce the exocytotic release of serotonin, which can then stimulate receptors on vagal afferents located in the bowel wall, to create a signal that terminates at the nucleus tractus solitarius (NTS). This, and the area postrema (often referred to as the chemoreceptor trigger zone) are collectively known as the dorsal vagal complex and are located in the dorsal brain stem. The NTS then initiates further signals that stimulate the central pattern generator (sometimes referred to as the vomiting centre), and the vomiting reflex is initiated.

It should be noted that the vomiting centre is not a discreet anatomical site in the CNS but more of a loosely related set of cells involved in a highly co-ordinated physical response to stimuli.

The area postrema is located in the floor of the fourth ventricle of the brain and is exposed to potential emetic stimuli from both blood and cerebrospinal fluid. It may therefore be involved in the signal to the central pattern generator as a result of direct interaction with the chemotherapeutic drug in the same way as it would from ingestion of any other noxious substance.

The dorsal vagal complex contains receptors for dopamine, serotonin and neurokinin-1, as do the terminal ends of the vagal afferents in the bowel wall. The influence of these receptors in CINV is becoming increasingly clear. In particular, the effect of substance P at neurokinin-1 receptors in mediating both acute and delayed emesis, is directing trends in current pharmaceutical development.

CINV is classified as acute, delayed or anticipatory.

Acute CINV CINV that occurs within 24 hours of chemotherapy is defined as acute CINV.

Delayed CINV CINV occurring more than 24 hours after chemotherapy is defined as delayed CINV. It may continue for up to seven days. It then gradually dissipates. Delayed CINV is most closely associated with cisplatin, carboplatin and cyclophosphamide, and anthracycline antibiotics such as epirubicin and bleomycin.

Anticipatory CINV Anticipatory CINV is a conditioned response to previous poor experiences. It can be triggered by sights or smells that the patient has psychologically associated with previous chemotherapy cycles. Anticipatory CINV is becoming less of a problem as CINV treatments become more advanced.

emetogenic potential of the drug towards the higher end of level 3, and possibly into level 4.

There are a number of factors that indicate that Mrs SB may have problems with CINV, including the fact that she has had a significant history of nausea and vomiting in pregnancy.

Ondansetron The choice of ondansetron, a selective 5-HT₃ receptor antagonist, as first-line anti-emetic therapy is appropriate when considering the emetogenic potential of the drugs in the FEC-T regimen and, in particular, the dose of epirubicin being used. 5-HT₃ receptor antagonists have revolutionised prevention of CINV. The initial drugs launched (granisetron, dolasetron, ondansetron and tropisetron) are of equal efficacy in preventing acute CINV but show demonstrably poorer activity in treating delayed CINV.² This is likely to be because delayed emesis is mediated by neurotransmitters other than serotonin. This is why treatment with 5-HT₃ antagonists is restricted to the initial few days following administration.

With the exception of granisetron, all 5-HT₃ antagonists are metabolised by microsomal enzyme CYP2D6. This isoenzyme has been shown to demonstrate variable activity depending on patients'

genotype. Patients who have high CYP2D6 activity are likely to have a less than optimal response to 5-HT₃ antagonists, and vice versa. The question of routine pharmacogenomic screening for patients' inherent ability to clear a drug is a topic of much debate, and needs to be clarified.

Dexamethasone Mrs SB has been prescribed dexamethasone prior to her chemotherapy and as discharge medication. Dexamethasone is thought to have an effect on both acute and delayed emesis. The site of action is not entirely clear although there is a suggestion that the anti-inflammatory action of the drug may play a part. In addition, dexamethasone may alter the activation of 5-HT₃ receptors on the vagal afferents. Dexamethasone has been shown to work better when given in combination with other antiemetics.³

Metoclopramide Metoclopramide, the third drug in Mrs SB's discharge medication, works directly on dopamine D₂ receptors in the periphery and central nervous system. At higher dosage (>40mg/day) metoclopramide also has a weak antagonist action at 5-HT₃ receptors. Metoclopramide given together with corticosteroids is a useful combination for managing delayed CINV.

The potential for adverse effects with metoclopramide, including extrapyramidal symptoms as a result of dopamine antagonism in the substantia nigra, limit its use at higher dosage.

In this case Mrs SB was advised to use as low a dose as possible of metoclopramide but, if necessary, she should increase towards the maximum prescribed dose of 20mg four times daily (this is an unlicensed dose).

Mrs SB has her first cycle of FEC-100. The following day she begins to vomit uncontrollably despite having taken her discharge medication as prescribed. The vomiting eventually subsides over a number of days.

Clinical decision

What are the options for CINV prophylaxis for Mrs SB's next cycle of chemotherapy?

Since Mrs SB has experienced severe CINV after her first cycle of FEC-100 she is likely to be anxious about her second cycle, which in turn would be likely to make the problem worse. Considering her risk of developing severe CINV there are a number of options available.

Level 1 (minimal risk, <10%*)	Level 2 (low risk, 10–30%*)	Level 3 (moderate risk, 31–90%*)	Level 4 (high risk, >90%*)
Bevacizumab Bleomycin Busulfan Cladribine Fludarabine Vinblastine Vincristine Vinorelbine	Bortezomib Cetuximab Cytarabine (<100mg/m ²) Docetaxel Etoposide Fluorouracil Gemcitabine Ixabepilone Lapatinib Methotrexate Mitomycin Paclitaxel Pemetrexed Temsirrolimus Topotecan Trastuzumab	Carboplatin Cyclophosphamide (<1.5g/m ²) Cytarabine (>1g/m ²) Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin	Carmustine Cisplatin Cyclophosphamide (>1.5g/m ²) Dacarbazine Mechlorethamine

Table 1: The emetogenic risk of chemotherapy agents.¹ *The percentage figures indicate the risk of vomiting in the absence of anti-emetic prophylaxis.

Palonosetron Palonosetron (Aloxi; Cambridge) is a newer 5-HT₃ antagonist with a much higher binding affinity for the 5-HT₃ receptor and a significantly longer half-life than other drugs in the class. Palonosetron has been shown to demonstrate a significantly improved response over ondansetron and dolasetron.⁴ This response is maintained through both the acute and delayed phase of CINV following a single intravenous dose given before the chemotherapy cycle. Further research is required before this drug could be considered first line, but it is an option for Mrs SB.

Aprepitant Aprepitant (Emend; MSD) is an antagonist of the neurokinin-1 receptor and blocks the ligand substance P from exerting an effect both peripherally and centrally. Aprepitant has been shown to improve

control of CINV and reduce the need for rescue therapy following breakthrough emesis. The drug has demonstrated superiority over combinations of ondansetron and dexamethasone or dexamethasone alone in both the initial and delayed phase of CINV.

Aprepitant is an inhibitor of microsomal enzyme CYP3A4 and a weak inducer of CYP2C9. Since dexamethasone is metabolised by CYP3A4 aprepitant can potentially increase the plasma concentration of dexamethasone when co-administered. This should be considered when prescribing both drugs (the dose of dexamethasone may be decreased accordingly). Doses of 12mg of dexamethasone IV prior to chemotherapy are considered normal. The effect of dexamethasone on CYP2C9 means it interacts with warfarin, possibly decreasing the INR as a result of increased warfarin metabolism. This may be a consideration in some cases.

Since Mrs SB is considered to be at high risk of CINV, you decided to add palonosetron and aprepitant to her therapy. She was administered the following regimen for her next cycle of FEC-100:

- NaCl 0.9% 500ml rapidly infused
- Dexamethasone 12mg IV over a minimum of 2 minutes
- Palonosetron 250µg 30 minutes prior to chemotherapy
- Aprepitant 125mg one hour before chemotherapy
- Epirubicin 100mg/m² infused with fast running NaCl 0.9%

- Cyclophosphamide 500mg/m² infused with fast running NaCl 0.9%
- 5-fluorouracil 500mg/m² infused with fast running NaCl 0.9%

She was given the following medicines on discharge:

- Aprepitant PO 80mg OD for two days
- Dexamethasone PO 8mg OD for two days

The decision to use both aprepitant and palonosetron would not necessarily be the choice made in all centres. Some may choose to add aprepitant to ondansetron and see if the patient responded with the next cycle. This is clearly a cost-based decision.

In this case the decision was taken to ensure that Mrs SB did not experience uncontrolled CINV, which may have had significant consequences as the cycles of treatment continued. This prescribing decision has to be made carefully because it not only affects the immediate cycle of chemotherapy, but the development of severe CINV is likely to make her more susceptible to CINV in future chemotherapy cycles.

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Key principles

This case study has been designed to encourage readers to think about the following overarching principles:

1. Complex prescribing decisions require a fundamental understanding of the therapeutics of individual drugs and how they can act synergistically.
2. Risk-profiling for adverse effects associated with prescribed drugs is important and should be something pharmacists always monitor.
3. Prescribing decisions cannot always be made purely on cost-benefit analysis. Long-term consequences must be considered for each clinical situation.