1. Antiemetic Guidelines for Chemotherapy and Radiation Therapy

1.1 Introduction

Nausea and vomiting are common problems associated with chemotherapy and radiation therapy. The goal of anti-emetic therapy is to completely prevent nausea and vomiting. With the current range of anti-emetics available it is possible to control the majority of treatment induced emesis with the selection of appropriate anti-emetics.

The aim of these guidelines is to minimise and where possible prevent nausea and vomiting. The correct use of antiemetics ***prior to and during*** cytotoxic therapy is crucial in meeting this aim

1.2 Scope

All medical and nursing and radiation therapy staff caring for patients undertaking chemotherapy and/or radiation therapy

1.3 Mechanism of Vomiting

Vomiting is mediated through a complex series of multi-afferent neural pathways involving the neuro-transmitters - 5HT3, serotonin, dopamine, histamine and acetylcholine. Drugs that block these receptors have useful anti-emetic properties. Antagonists of histamine and acetylcholine are more useful in controlling vomiting associated with motion sickness, whereas serotonin receptor antagonists (ondansetron) and dopamine receptor antagonists (metoclopramide) are more useful in controlling chemotherapy induced emesis.
Ondansetron prevents acute nausea and vomiting in 60% of patients. Corticosteroids (i.e. dexamethasone), whose mode of action is uncertain; improve success by a further 15-25%.

1.4 Associated Documents

Anti-emetic Summary Sheet
Table of emetogenicity
Patient antiemetic information sheets

1.5 Definitions

Acute emesis: Occurs within first 24 hours after administration of chemotherapy
Delayed emesis: Begins after 24 hours, may last for several days.
Anticipatory emesis: Learned or conditioned response from poorly controlled nausea and vomiting associated with previous chemotherapy.
CINV: Chemotherapy induced nausea and vomiting

1.6 General Statements

Risk Factors for CINV

- Female sex
- < 30yrs
- History of sickness: travel, pregnancy, surgery
- Anxiety
- Vomiting with prior chemo
- Past history of low alcohol consumption

Consider increasing the anti-emetic regimen in patients with more than 1 risk factor for nausea and vomiting. Prevention of cycle 1 CINV is critical. Seventy percent of patients who vomit after their first cycle of chemotherapy will do so again in at least one subsequent cycle.

Risk Factors for Radiation

The treatment field is one of the major determinants of emetic risk and patients receiving irradiation to the abdomen are at high risk of emesis. Another important consideration for risk is the dose of radiotherapy administered per fraction and the pattern of fractionation. Patients receiving total body irradiation are one of the highest risk groups.

General Principles

Consider fortifying the anti-emetic regimen in patients with more than 1 risk factor for nausea and vomiting. Consult risk factors above.

Anti-emetics are preferentially given orally; as they work as well as IV formulations provided they are given sufficient time to be absorbed prior to chemotherapy delivery. Highly emetogenic chemotherapy e.g. cisplatin has a rapid onset of emetogenicity (1.5 hours), so it is important that if pre-chemotherapy agents are given orally, they have sufficient time to be absorbed. Intravenous anti-emetics should only be given if the patient is unable to take oral anti-emetics and should be 30 minutes before treatment, and only for the dose immediately before highly and moderate to highly emetogenic chemotherapy.

Optimal emetic control in the acute phase is essential to prevent delayed phase emesis. Seventy percent of patients who vomit after their first cycle of chemotherapy will do so again in at least one subsequent cycle.

Prescribing anti-emetics

- Pre and post chemotherapy anti-emetics will be printed on all chemotherapy prescriptions; medical staff will alter these on the chemo prescription if appropriate.
- Ensure patients **fill their prescriptions and bring the anti-emetics with them** for their first dose of chemotherapy, so the nursing staff can go over the tablets with the patient if necessary.
- Prescribe sufficient quantities of anti-emetics to ensure that patients do not have to pay unnecessary prescription fees. E.g. prescribe 60-100 domperidone at a time (or 50 and 1 repeat) in moderate to severely emetogenic regimens.

Emetogenicity Chart for Cytotoxic Agents

RISK	INTRAVENOUS AGENTS		ORAL AGENTS
High (>90%)	Cisplatin ≥ 50mg/m2 Streptozotocin Cyclophosphamide > 1500 mg/m2 Dacarbazine Carmustine Dactinomycin		
Moderate (30-90%)	Cisplatin < 50mg/m2 Oxaliplatin Cytarabine > 1 gm/m2 Carboplatin Ifosfamide Cyclophosphamide < 1500 mg/m2	Doxorubicin Daunorubicin Epirubicin Idarubicin Irinotecan	
Low (10-30%)	Paclitaxel Docetaxel Mitoxantrone Topotecan Etoposide Pemetrexed Methotrexate Liposomal Doxorubicin	Mitomycin Gemcitabine Cytarabine ≤ 100 mg/m2 5-Fluorouracil Bortezomib Cetuximab Trastuzumab	Procarbazine Cyclophosphamide Etoposide Temozolomide Vinorelbine
Minimal (<10%)	Bleomycin Busulfan Fludarabine Vinblastine Vincristine Vinorelbine Bevacizumab		Chlorambucil Hydroxyurea Methotrexate Imatinib Gefitinib Capecitabine
Combination regimens have greater emetogenic potential than any single agent. Identify the most emetogenic agent in the combination then assess the relative contribution of other agents: Minimally emetogenic agents do not add to the emetogenicity of a regimen, while adding one or more mild-moderate agents increases the combinations emetogenicity by 1 level.			

Recommended Antiemetic Regimens for Chemotherapy

The below is a guideline only, and individual regimens will have the suggested accompanying anti-emetic regimen printed on the chemo prescription chart.

Emesis Risk	Drug	Acute: Pre chemo	Delayed: Post chemo
High	Dexamethasone*	16-20mg IV/PO	8mg od-bd d2,3 8mg mane d4 (+/- d5)
	Ondansetron	8mg IV or 16mg PO	Nil
	Domperidone		20mg prn (qid)
Moderate	Dexamethasone	8mg IV/PO	4-8mg daily d2,3, +/- 4mg d4.
	Ondansetron	8mg IV or 16mg PO	Nil
	Domperidone		prn
Low	Dexamethasone Domperidone	4mg PO or 20mg PO	 prn
Minimal	Domperidone	Nil routine	prn

***Note**: If Aprepitant is given reduce dexamethasone doses by 50% when given on the same day as Aprepitant
If on 16mg of dexamethasone decrease to 12mg rather than by 50% if on Aprepitant when given on the same day.

AC and AC-Like regimens (e.g. FAC, FEC etc) have an altered antiemetic regimen as follows (between high and moderate) with attenuated steroid pre chemotherapy and tapered steroid for 5 days post chemotherapy, as the nausea with these regimens is more prolonged than with other highly emetogenic regimens.

	Drug	Acute: Pre chemo	Delayed: Post chemo
Anthracycline Cyclophosphamide combinations	Dexamethasone	12mg PO/ IV	8mg bd d2 8mg mane d3,4 +/- 4mg d5.
	Ondansetron	8mg IV or 16mg PO	Nil
	Domperidone		20mg prn (qid)

Use of 5HT3 antagonists

The literature supports the use of 5HT3 BEFORE chemotherapy and radiotherapy as a first line prophylactic antiemetic.
The data shows that 5HT3 are ineffective when given more than 24h after chemotherapy. The side effects of constipation and headache are also additive in patients who have these side effects from opioids and or chemotherapy.
Use of 5HT3 antagonists may occasionally be indicated in those who cannot tolerate steroids.
Non treatment related nausea should be treated with non 5HT3 agents in the first instance, as long term use of these can cause major constipation.
If a patient suffers CINV after low or moderate risk regimen, move to a higher level prevention regimen

Failed Prophylaxis

For next cycle:

1. Increase dexamethasone pre and/or post chemotherapy (pre if vomits in 1st 24h, pre and post if >24h)
2. Consider aprepitant
3. Some patients may benefit from regular 5HT3 antagonists post chemotherapy – only if other agents have failed

As rescue and to consider adding regularly next cycle:

- Ensure patient is taking regular dopamine antagonists. Domperidone appears not to cross the blood brain barrier and cause CNS effects as much as metoclopramide. This can be given 20mg q4h
- Cyclizine 50mg PO t.d.s (note drowsiness, dry mouth)
- Prochlorperazine (Stemetil) suppositories can “break the cycle” of vomiting up anti-emetics. Rx 25mg PR prn to bd. Note patients will pay a part fee for these
- Lorazepam 1mg PO up to q8h is particularly useful for anticipatory nausea (note sedation, driving)
- Methotrimeprazine (Nozinan) 6.25 – 12.5 mg PO nocte can be useful (note sedation)
- Haloperidol 0.5-1mg PO prn to t.d.s (note sedation)

If failed **high risk** regimen, also consider adding in drugs from the list below. In general addition of several agents is preferred to substitution unless a patient is not tolerating the side effects of a particular drug.

1. Ensure patient is taking routine **dopamine antagonist** (domperidone or metoclopramide): metoclopramide 10po q4h prn, or domperidone 20mg qid prn (domperidone less CNS side effects c.f. metoclopramide)

2. **Increase dexamethasone** pre and/or post chemotherapy (pre if vomits in 1st 24h, pre and post if >24h)**Extended steroid:** 8mg mane to b.d or 4mg b.d p.o. for up to one week is the most effective treatment for delayed nausea. (Note weight gain, proximal myopathy, hyperglycaemia, sleeplessness)

3. **Cyclizine** 50mg p.o. t.d.s (note drowsiness, dry mouth)

4. For patients who are unable to tolerate oral anti-emetics, or who vomit their tablets and thereafter lose control of their emesis, suppositories can be prescribed to ensure absorption and 'break the cycle' (e.g. **prochlorperazine (Stemetil)** 25mg B.D. prn rectally).

5. **Lorazepam** 1mg p.o up to 8 hourly. Particularly useful if anxious / anticipatory nausea, to be given pre-chemotherapy. Note can be sedating and impair ability to drive.

6. Methotrimeprazine **(Nozinan)** 6.25 – 12.5 mg p.o as a single dose in the evening, or can be split up during the day i.e. 6.25mg BD. Note can be sedating.

7. **Haloperidol** 0.5-1mg po t.d.s (prn). Also can be sedating.

8. If significant *acute* emesis/nausea, trial **alternative 5HT3 antagonist pre chemo** ie tropisetron (some studies suggest up to 50% patients will respond to alternative 5HT3)

9. Consider **aprepitant.** Note patients must pay for this unless they fulfill criteria.

10. 5HT3 antagonists should only be included post chemotherapy when other agents have failed. There is no evidence to support using 5-HT3 antagonists beyond 24 hours after chemotherapy routinely, but one patient in 12 may benefit

11. May need to consider S/C syringe driver regimen if failed all attempts at oral/PR/IV regimens

12. Look for other triggering factors – tumour related, metabolic, constipation, CNS

Radiation Induced Emesis

Emetogenicity	Treatment Field	Drug	Dose	Frequency	Route
Minimal	Breast Extremities (pelvis/thorax)	Nil or metoclopramide or Domperidone	10mg	QID PRN	oral
Low	Cranium Head and neck Lower thorax region Pelvis	Nil or metoclopramide or Domperidone	10mg	QID PRN	oral
Moderate	Abdomen Craniospinal Lower hemi-body	Ondansetron	8mg	1-2 hours before each fraction	oral
High	Upper hemi-body	Ondansetron Dexamethasone	8mg 4mg	1-2 hours before each fraction and repeat Q12H for at least 24 hours post treatment 4mg pre treatment then 2mg BD for 2 further doses	oral

1. If nausea or vomiting occurs despite these measures, give metoclopramide/ domperidone regularly and treat at next level of emetogenicity.

2. 4mg of ondansetron may be as effective as 8mg in the prevention of chemotherapy induced vomiting and anecdotal evidence supports 4mg for radiotherapy also.

   If a patient experiences nausea despite 4mg, increase to 8mg.

3. If it is not possible to administer ondansetron more than one hour before RT,

administration less than one hour before RT or immediately after RT is likely to provide some benefit.

Drug Information

5HT3 RECEPTOR ANTAGONISTS

PRE-CHEMO (Preventing **acute** nausea and vomiting**)**

- 5HT3 receptor antagonists **are all considered to be equally effective**. More than 50 randomised trials have compared the clinical effect of two or more of these agents and have been unable to find clinically meaningful differences[i,ii]. Ondansetron is the most studied, and least expensive, and therefore the drug of choice.

- **A single pre-chemo dose works as well as splitting the dose over 24 hours,** and is less complicated. [iii,iv,v, 13.] Multiple doses only provide a better outcome if the initial dose was suboptimal.[1]

- **Optimal dose:** 5HT3 antagonists are characterised by a threshold dose, followed by a short dose response curve, then a plateau of therapeutic efficacy. The vast majority of trials have used IV doses of ondansetron ranging between 8 and 32mg, and oral doses of 16 to 32mg, and. There are only 3 trials comparing 8mg of ondansetron vs. higher doses (32mg); these were all IV trials. One showed benefit for the higher dose and the other 2 showed equivalent efficacy[vi, vii] there are no data on the 8mg PO dose.

- Common side effects of 5HT3 receptor antagonists include constipation, headache, and transient asymptomatic elevations of serum aminotransferases.

POST CHEMO (Preventing **delayed** Nausea and vomiting**)**

- **There is no place for the routine use of 5HT3 receptor antagonists after chemotherapy. Do not give after chemotherapy except after discussion with consultant**. A meta-analysis of 10 randomised trials of 3,956 patients concluded that neither clinical evidence nor cost considerations justified the use of these agents beyond 24h after chemotherapy[viii]. In the 5 randomised trials comparing ondansetron alone versus placebo, there was an 8% (CI 3-13%) reduction in emesis, however in the other 5 trials where all patients were receiving dexamethasone post chemotherapy, ondansetron did not improve control. In patients not receiving dexamethasone after chemotherapy, 74 doses need to be administered to 12 patients to prevent 1 patient from delayed emesis.

CORTICOSTEROIDS

PRE-CHEMO (Preventing **acute** nausea and vomiting**)**

- Corticosteroids are an essential component in the anti-emetic regimen to prevent emesis in high and moderate emetogenic risk chemotherapy[1].

- Corticosteroids have equivalent anti-emetic efficacy at equivalent doses and can be used interchangeably, but dexamethasone is the most studied and widely used.

- **20mg of dexamethasone appears more efficacious** than lower doses in patients receiving chemotherapy of high emetic risk, and to have **equivalent adverse effects to lower doses**.[ix] Complete protection from vomiting was significantly superior in patients who received 20 mg compared with those who received 4 and 8 mg of dexamethasone *(*83% vs. 69%& 69% P < .005) and was superior, but not significantly, compared with those who received 12 mg.

POST CHEMO (Preventing **delayed** Nausea and vomiting**)**

- Corticosteroids are the most effective agent for the prevention of delayed emesis in moderate and low-risk regimens.[1,x,xi]

- **Single daily doses** are recommended[3], but larger doses may be split if patient experiences

indigestion or hyperglycaemia.

APREPITANT

- Aprepitant is an NK1 receptor antagonist, the first drug of a new class of oral anti-emetics for chemo-induced emesis and nausea.
- **Evidence:** Three randomized controlled trials including over 1,800 patients have demonstrated significant improvements in complete response of 20% in highly emetogenic regimens and 8% in AC-like regimens. [xii] [xiii] [xiv] [xv]
- Consensus recommendations from MASCC and ASCO guidelines state:
  'Following randomized trials Aprepitant has shown a significantly higher rate of protection from acute and delayed emesis when **added to a 5HT3 antagonist and dexamethasone** for **high risk chemotherapy and anthracycline/cyclophosphamide** combination regimes. It is not effective for low or intermediate risk regimens (Level 1,A evidence)'
- **Availability:** Aprepitant is not funded by Pharmac. CDHB pharmacy will dispense funded aprepitant for subsequent cycles for those patients admitted (to Ward 27 or the Day ward) for treatment of CINV.
- **Recommended dose:** 125mg PO pre-chemotherapy, 80mg PO daily days 2-3.
  Note; ***When aprepitant is combined with corticosteroids, the dose of steroids is reduced by ~ 50% i.e. Dexamethasone 12mg pre chemo and 8 mg daily days 2-4***.
- **Adverse effects/interactions:** Generally well tolerated with fatigue the most common adverse effect. As aprepitant is an inhibitor and inducer of CYP3A4 and other CYPs, there are multiple drug interactions. Aprepitant should not be used concurrently with terfenadine, astemizole, cisapride and pimozide. Patients on warfarin should be monitored for the 2 weeks after therapy as INR may decrease. Serum benzodiazepine concentrations may be increased. See full prescribing data.

OTHER AGENTS

- Metoclopramide traverses the blood brain barrier, and can cause sedation and extra-pyramidal reactions. Dystonic reactions occur in approximately 1% of patients.[xvi]
- Domperidone does not readily cross the blood-brain barrier and is the drug of choice for delayed nausea. It seldom causes extrapyramidal side effects.[xvii] The maximum dose is 80mg/day (2 tablets qid).

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[xvi] Medsafe data sheet. Maxolon tablets
http://www.medsafe.govt.nz/profs/datasheet/m/Maxolontabsyrinjsupp.htm
[xvii] Medsafe data sheet. Motilium tablets http://www.medsafe.govt.nz/profs/datasheet/m/motiliumtab.htm

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