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Antiemetic Guidelines for Adult Patients Receiving Chemotherapy and Radiotherapy

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Introduction

Chemotherapy Induced Nausea and Vomiting (CINV) is one of the most frequently experienced side effects encountered by chemotherapy patients. Patients will often find the symptoms distressing, and develop anxiety about the potential for such symptoms to recur on future cycles of chemotherapy. Modern drug treatment can successfully control CINV for the majority of patients.

Scope

The purpose of this document is to provide guidance on the rationale use of antiemetics for prevention and treatment of chemotherapy and radiotherapy induced nausea and vomiting in adult patients. They are not intended to address nausea and vomiting in palliative care. These guidelines are intended to provide a framework to support clinical practice, they can not cover every clinical situation and good common clinical sense and clinical experience will be required when approaching the management of individual patients.

The guidance was prepared by reviewing practice across London and by reviewing published guidelines on the subject. It should be noted that the definitions for low, moderate, high and very high differ from ASCO, MASCC and MCCN guidance. This is deliberate as the definition of "moderate" in these sources is 30-90% which will encompass most of the chemotherapy drugs/regimens and therefore it will make it difficult to discern between such treatments.

Definitions

Acute	N&V experienced during the first 24-hour period immediately after chemotherapy administration
Delayed	N&V that occurs more than 24 hours after chemotherapy and may continue for up to 6 or 7 days after chemotherapy.
Anticipatory	N&V that occurs prior to the beginning of a new cycle of chemotherapy. It is either a learned response following chemotherapy induced N&V on a previous cycle or an anxiety response. It is most common after 3 to 4 cycles of chemotherapy with very badly controlled acute or delayed symptoms.
Breakthrough	Development of symptoms (nausea or vomiting), despite standard anti-emetic therapy, which require treatment with an additional pharmacological agent
Refractory	Patients who have failed on both standard and rescue medication

Grading of Nausea and Vomiting[1]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 h	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 h	Life-threatening consequences	Death
Vomiting	1 episode in 24 h	2–5 episodes in 24 h; IV fluids indicated <24 h	≥6 episodes in 24 h; IV fluids, or TPN indicated ≥24 h	Life-threatening consequences	Death

Guidance

Antiemetic recommendations for Chemotherapy and Radiotherapy

- Always commence antiemetics before chemotherapy.
- Give oral doses at least 30 minutes before chemotherapy is initiated.
- Antiemetics are best given regularly; not prn and ensure courses are completed.
- Optimal emetic control in the acute phase is essential to prevent nausea and vomiting in the delayed phase
- Dexamethasone should be given prophylactically where indicated, and not as a treatment for emesis.
- Dexamethasone should be given no later than 2pm to minimise wakefulness in the night.
- Consider initiating domperidone on the evening of chemotherapy.

Choice of Antiemetics

- Consult Table 1 for the emetogenic potential of individual cytotoxic drugs
- Refer to Table 2 and 3 for the emetogenic potential of individual protocols
- For combination chemotherapy choose the appropriate regimen for the most emetogenic drug included
- For haematology patients, where a steroid is not a desirable antiemetic, substitute for a short course of a 5HT3 inhibitor (preferably 1 day).
- For multi-day regimens choose appropriate pre-chemotherapy regimen for each day and on discharge give the antiemetics suggested for the day with the highest emetogenic potential
- Drugs acting on the same receptor e.g. domperidone and metoclopramide should not be used together as the risk of side effects will be increased without additional clinical benefit
- For patients <20 yrs the dose of metoclopramide should be 10mg or consider using domperidone
- Carefully consider the risks and benefits of the use of steroids in diabetic patients and in patients who are immunocompromised
- Omit dexamethasone pre-chemotherapy if patient is on a high dose steroid-containing regimen e.g. CHOP, ESHAP or if the patient is on high dose steroids for another medical reason.

Anti-emetic failure

This is defined as prolonged, distressing nausea or 2 or more episodes of vomiting in 24 hours. Move onto suggested regimen for next level of emetogenic potential

On completion of chemotherapy

- Omit oral dexamethasone if the patient is on a steroid-containing chemotherapy regimen e.g. CHOP, PMitCeBo or if the patient is receiving regular low dose steroid doses.
- For patients receiving a taxane, the anti-emetic dose of dexamethasone should be the same as per the prophylaxis or hypersensitivity dose.
- Consider omitting the steroid or reducing length of course if the patient is on a weekly regimen or an oral cytotoxic course longer than 3 days.

Action of anti-emetics on main receptor sites

Drug	D_2 antagonist	H_1 antagonist	ACh antagonist	$5HT_2$ antagonist	$5HT_3$ antagonist	$5HT_4$ agonist	NK1 inhibitor
Metoclopramide	++					++	
Domperidone	++						
Cyclizine		++	++				
Hyoscine			+++				
Haloperidol	+++						
Levomepromazine	++	+++	++	+++			
Aprepitant							+++
Ondansetron					+++		
Granisetron					+++		

Table adapted from Twycross R, Wilcock A, - Palliative Care Formulary Third Edition (2007)

Anti-emetic information

Please refer to BNF/SPC for more information

$5HT_3$ antagonist	Patients may complain of constipation and headaches. Patients need to be advised accordingly, e.g. lactulose to relieve constipation and paracetamol to relieve headache. If severe consider an alternative anti-emetic. Long acting $5HT_3$ antagonists are available and may be used if locally approved.
Aprepitant	Aprepitant is an NK-1 receptor antagonist has been shown to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. In addition, studies show that aprepitant augments the antiemetic activity of the 5-HT_3-receptor antagonist and dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis When given in combinations with corticosteroids, the SPC suggests: reduce oral dexamethasone dose by 50%, reduce methylprednisolone IV dose by 25% and oral dose by 50%. NB for practical reasons it is not necessary to halve post chemotherapy dexamethasone doses as confirmed in the aprepitant trial data. Common side effects include headaches, hiccups and fatigue.
Cyclizine	Cyclizine may cause antimuscarinic side effects such as dryness of the mouth and drowsiness. Children and the elderly are more susceptible to these effects.
Dexamethasone	Corticosteroids can cause sleep disturbances, hyperactivity and excessive appetite. They also produce glucose-intolerance, use with care in patients with diabetes mellitus. Patients may experience perineal discomfort if the drug is given by iv bolus. This can be avoided by administration via IV infusion.
Domperidone	Domperidone should not be used when stimulation of the gastric motility could be harmful e.g. gastro-intestinal haemorrhage, mechanical obstruction or perforation.
Levomepromazine	Avoid in patients with liver dysfunction. Inhibits cytochrome P-450. Common side effects are somnolence, asthenia, dry mouth, hypotension, photosensitivity and skin reactions.
Lorazepam	Can cause drowsiness and may affect performance of skilled tasks (driving)
Metoclopramide	Can rarely cause agitation or the development of extra-pyramidal symptoms particularly in the young female patients. These can occur up to 24 hours after a dose and may vary from facial grimacing and dystonic movements to odd feelings in the mouth, restlessness, somnolence and irritability. Bowel transit time may be reduced and some patients experience diarrhoea.
Prochlorperazine	Prochlorperazine should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis, prostatic hypertrophy. A mild leukopenia occurs in up to 30% of patients on prolonged high dosage. May cause drowsiness.

Table 1. Antiemetic Selection

Emetogenic Potential	Pre Chemotherapy Schedule (for each day of chemotherapy)	Post Chemotherapy (day after chemotherapy finished)	Antiemetic Failure (Refer to Table 2)
Low Risk of emesis is < 30%	No routine antiemetics usually necessary.	No routine anti-emetics are necessary. For 1st course consider prescribing Domperidone 20mg tds prn PO 5/7 Or Metoclopramide 20mg tds prn PO 5/7	If no routine antiemetics taken: 1st line anti-emetics for breakthrough. Treat on subsequent courses the same. If routine antiemetics taken: 2nd line anti-emetics for breakthrough. Manage subsequent cycles as moderately emetogenic.
Moderate Risk of emesis is 30-60%	Dexamethasone 8mg PO/IV And Metoclopramide 20mg IV/PO	Dexamethasone 8mg PO daily in either one or two divided doses for 2-3/7 And Domperidone 20mg tds PO 3-5/7 or Metoclopramide 20mg tds PO 3-5/7	Commence with 2nd line antiemetics for breakthrough. Manage subsequent cycles as highly emetogenic. See Table 2
High Risk of emesis is 60-90%	locally approved $5HT_3$ antagonist e.g. Granisetron 2mg PO or Granisetron 1mg IV or Ondansetron 8mg PO/IV And Dexamethasone 20mg PO/IV	Dexamethasone 8mg PO daily in either one or two divided doses for 2-3/7 And Domperidone 20mg tds PO 5/7 or Metoclopramide 20mg tds PO 5/7 And Consider Levomepromazine 6mg (unlicensed) nocte prn.	Commence with 3rd line anti-emetics for breakthrough. Consider including these as part of take home medication. Manage subsequent cycles as very high emetogenic with the addition of aprepitant if locally approved and N&V has resulted in hospital admission.

Emetogenic Potential	Pre Chemotherapy Schedule (for each day of chemotherapy)	Post Chemotherapy (day after chemotherapy finished)	Antiemetic Failure (Refer to Table 2)
Very High Risk of emesis is >90%	**Single day treatment:** Aprepitant 125mg PO 1hour pre chemotherapy dexamethasone 12mg PO/IV and Granisetron 2mg PO or Granisetron 1mg IV or Ondansetron 8mg PO/IV or locally approved $5HT_3$ antagonist **Multiple day treatment** D1:Aprepitant 125mg PO 1 hour pre-chemotherapy Dexamethasone 12mg IV $5HT_3$ antagonist as above **subsequent days:** Aprepitant 80mg PO 1 hour pre-chemotherapy and Dexamethasone 8mg IV and $5HT_3$ antagonist as above Domperidone 20mg PO qds e.g. for a 3 day highly emetogenic regimen aprepitant is given as follows; Day1 125mg, Day2 –Day 5 80mg od	Aprepitant 80mg od PO 2/7 Dexamethasone 8mg PO daily in either one or two divided doses for 2-3/7 Domperidone 20mg qds PO 5/7 or Metoclopramide 20mg qds PO prn 5/7	If nausea/vomiting >7days consider corticosteroid induced dyspepsia and give a proton pump inhibitor (PPI)
Anticipatory Nausea and Vomiting	If nausea and vomiting is well controlled during and after chemotherapy, anticipatory nausea and vomiting is unlikely to occur.		Lorazepam 1mg orally, sublingually or IV 30 minutes before chemotherapy is given. Patients may benefit from oral lorazepam the night before and/or on the morning of chemotherapy

Table 2. Breakthrough nausea and vomiting for Chemotherapy

The following table describes additional anti-emetics that may be required to manage immediate episodes of nausea and vomiting. For subsequent cycles of chemotherapy prophylactic anti-emetics should be increased to the next level refer to Table 1.

	Drug and Schedule	**Comments**
1st Line For patients not taking regular antiemetics)	Domperidone 20mg tds PO or 30-60mg rectally tds Or Metoclopramide 20mg po / iv tds	Prescribe regularly in addition to recommended post chemotherapy antiemetics Do NOT use domperidone and metoclopramide together. If unable to tolerate PO domperidone, use rectal domperidone (if the platelet count is normal) or IV metoclopramide.
2nd Line	Levomepromazine 6mg (unlicensed) BD PO Or Prochlorperazine 5-10mg PO TDS or 25mg PR TDS Or Cyclizine 50mg PO/IV tds	Levomepromazine/Prochlorperazine/cyclizine – replaces Metoclopramide as post chemotherapy antiemetic
3rd Line	Granisetron 1mg IV or Ondansetron 8mg PO/IV or locally approved $5HT_3$ antagonist or Levomepromazine 6 mg (unlicensed) PO up to tds or 6.25-12.5mg SC or Lorazepam 1mg PO/IV/Sublingual tds or Cyclizine 150mg continuous subcutaneous infusion over 24 hours or Haloperidol 1-2mg qds PO or 1-3mg IV TDS Or Nabilone 1mg PO TDS	Use short course only Consider instituting S/C infusion of Cyclizine 1st or 2nd line if severe vomiting occurs in inpatients. Levomepromazine/Prochlorperazine/cyclizine – replaces Metoclopramide as post chemotherapy antiemetic

Table 3. Emetic Potential for Individual Drugs

Low emesis (<30% incidence)	Moderate Emesis (30%-60% incidence)	High Emesis (60% to 90% incidence)	Very High Emesis (>90% incidence)
Alemtuzumab	Arsenic	Altretamine	Busulfan high doses
Asparaginase	Carmustine <100mg/m^2	Amsacrine	Carmustine > 250mg/m^2
Bevacizumab	Cyclophosphamide <750mg/m2	5 Azacitadine	Cisplatin >60mg/m^2
Bleomycin	Cytarabine <900mg/m^2	Carboplatin	Cyclophosphamide >1500mg/m^2
Bortezomib	Daunorubicin <50mg/m^2	Clofarabine	Dacarbazine
Busulfan <10mg	Doxorubicin <60mg/m^2	Carmustine >100mg/m^2 ', < 250mg/m^2	Ifosfamide >3g/m2
Cetuximab	Etoposide>120mg/m2	Cisplatin < 60mg/m^2	Streptozocin
Capecitabine	Gemcitabine	Cyclophosphamide >750mg/m^2 - <1500mg/m^2	
Chlorambucil	Methotrexate 250mg/m2 -<1000mg/m^2	Cytarabine > 900mg/m^2	
Cladrabine	Mitomycin C	Dactinomycin	
Dasatinib	Mitoxantrone	Daunorubicin > 50mg/m^2	
Erlotinib	Paclitaxel	Docetaxel	
Etoposide ≤120mg/m2	Procarbazine	Doxorubicin > 60mg/m^2	
Fludarabine	Temozolomide	Epirubicin	
Fluorouracil	Raltitrexed	Estramustine	
Gefitnib	Trabectedin	Idarubicin	
Gemtuzumab	Topotecan PO/IV	Ifosfamide <3g/m^2	
Hydroxycarbamide	Vinorelbine PO	Irinotecan	
Imatinib		Lomustine	
Lapatinib		Melphalan IV >100mg/m^2	
Lenolidamide		Methotrexate >1000mg/m^2	
Liposomal Daunorubicin		Oxaliplatin	
Liposomal Doxorubicin			
Melphalan oral			
Mercaptopurine			
Methotrexate <250mg/m^2			
Nelarabine			
Nilotinib			
Pemetrexed			
Pentostatin			
Rituximab			
Sorafenib			
Thalidomide			
Thioguanine			
Trastuzumab			
Vinblastine			
Vincristine			
Vindesine			
Vinorelbine IV			

Table 4. Emetic Potential for Combination Regimens for Common Tumour Types

NB- This list is not comprehensive

Tumour Type	Regimen	Risk of Emesis	Comments
Lung	Gem/carbo	High	
	Carbo/etop	High	
	Cis/pemetrexed	Very High	
	Cisplatin/Vinorelbine	Very High	
Breast	EC90	High	
	FEC100	High	
	AC	Very High	
	CMF	High	
	EC	High	
Upper GI	Cis/5FU	Very High	Cisplatin dose =75mg
	ECF	Very High	
	Mitomycin/5FU	Moderate	
	Gem/cis (ca pancreas)	Very High	
	Gem/Cap	Moderate	
Lower GI	OxMDG	High	
	OxCap	High	
	IrMdg	Moderate	
	Cetuximab+ OxMdg	High	
	Cetuximab+OxCap	High	
	IrMdg+cetuximab	High	
	Bevacizumab+IrMdg	High	
	Mitomycin/5FU	Moderate	
H&N	Cis100/5FU	Very High	
Gynaecology	Carbo/taxol	High	
	Carbo/lipo dox	High	
	Cis/Etop (van der Berg)	Very High	
	Cisplatin/topotecan	Very high D1	Moderate days 2 and 3
CNS	PCV	High	
Lymphoma	RCHOP	High	
	ABVD	Very High	
	ESHAP	High	
	IVE	Very High	
	Mini Beam	Very high	
	Codox-M	High	
	IVAC	Very High	
	RCVP	Moderate	
	Esc BEACOPP	High/Moderate/Low	High D1 Moderate D2-7 Low D8
	BEACOPP	High/Moderate/Low	High D1 Moderate D2-3 Low D8
GU	Gem/Cis 35	High	
	ECarboF	High	Low on Day 15
	POMB-ACE	Moderate/Low and very high	Moderate D1 Low D2 Very high D3.
	BEP	Very High	

Table 5. Emetic Potential for Combination Regimens for other Tumour Types

Tumour Type	Regimen	Risk of Emesis	Comments
Sarcoma	Dox/cis (MAP)	Very High	Consider aprepitant
	Cyclo/topotecan	Moderate	
	VIDE	Very High	
	VAI	High	
	VAC	High	
	Ifos(>3gm^2)/Etop	Very high	
	Cis 60/dox	Very high	
	Gem/Docetaxel	High	

Radiation Induced Nausea and Vomiting

Principles of Management

• As for chemotherapy-induced nausea and vomiting, the goal of anti-emetic therapy is to prevent nausea and vomiting.
• The risk of radiation induced emesis varies with the treatment administered.

Determinants of Emetic Risk

The determinants of emetic risk in relation to radiotherapy are as follows:
• The actual treatment field
• The dose of radiotherapy administered per fraction
• The pattern of fractionation

ChemoRadiation

For patients receiving chemoradiation schedules, treat with antiemetic therapy according to the highest emetogenic risk based on the chemotherapy regimen or the radiotherapy treatment field.

Guidance

Risk Level	Irradiated Area	Pre-Radiotherapy Antiemetic – 1 hour before each fraction	Anti-emetic breakthrough
Low	Head and neck, extremities, cranium and breast Lower thorax region and pelvis Cranium (radiosurgery) and cranospinal	Domperidone 20mg tds PO PRN or Metoclopramide 20mg tds PO PRN	• Commence with 1st level anti-emetics for breakthrough nausea and vomiting. • Treat on subsequent fractions as moderately emetogenic.
Moderate	Upper abdomen hemibody irradiation, upper abdomen, abdominal-pelvic, mantle, craniospinal irradiation, and cranial radiosurgery	locally approved $5HT_3$ antagonist e.g. Granisetron 2mg PO or Ondansetron 8mg PO	• Commence with 2nd level anti-emetics for breakthrough nausea and vomiting. • Treat on subsequent fractions as highly emetogenic.
High	Total body irradiation (TBI)	locally approved $5HT_3$ antagonist e.g. Granisetron 2mg PO or Ondansetron 8mg PO and Dexamethasone 8mg PO/IV and Domperidone 20mg tds PO PRN or Metoclopramide 20mg tds PO PRN Continue for 24 hours after fraction	Commence with 2nd level anti-emetics for breakthrough nausea and vomiting.

Breakthrough Anti-emetic Schedule for Radiotherapy Induced Nausea and Vomiting

Refer to the chemotherapy section and the table for treatment of breakthrough nausea and vomiting on pages 7 and 8.

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