Trust Guideline for Prevention and Control of Chemotherapy and Radiotherapy Induced Nausea and Vomiting in Adults patients age 18 years and over

A Clinical Guideline

For Use in: Organisation-wide	All clinical areas
By:	Medical and Nursing staff
For:	Adults receiving Chemotherapy or Radiotherapy including recipients of haematopoietic stem cell transplants
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Name of document author:	Nicola Kaciubskyj, reviewed by Matthew Small
Job title of document author:	Specialist Pharmacist Oncology and Haematology
Name of document author's Line Manager:	Matthew Small
Job title of author's Line Manager:	Lead Oncology and Haematology Pharmacist
Supported by:	Dr Tom W Roques, Oncology Consultant Dr Angela Collins, Haematology Consultant
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Compliance links: *e.g. NICE*	None

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Abbreviations	
ANV	Anticipatory Nausea and Vomiting
SACT	Systemic Anticancer Therapy
CTZ	Chemotherapy Zone
IV	intravenous
N&V	Nausea and Vomiting
PO	per oral
PR	per rectum
RT	Radiotherapy
SC	subcutaneous

Table 1 Schedule for Patients receiving Systemic Anticancer Therapy (SACT)

- Suggested regimen will be included in Aria prescription
- For combination SACT the emetic level of the highest level agent on that day should be used
- See page 6 for suggested changes to anti-emetic regimen
- For anti-emetic failure increase to next level suggested for that regimen
- For persistent vomiting see page 7
- For precautions and side effects of anti-emetic agents see Table 9 page 14 and15

Emetogenic potential % = incidence of emesis	Pre chemo and for each day of regimen*	Post chemo – day after chemo finished
High >90% (previous Level 4)	Ondansetron 8mg** po Dexamethasone* 8mg po/IV Netupitant/palonosetron 300 mg / 0.5 mg po one hour prior to the start of each chemotherapy cycle. Ondansetron not required (cisplatin **> 75mg/m²** only) In swallowing difficulties or feeding tubes: Aprepitant*** 120mg (cisplatin **> 75mg/m²** only)	Ondansetron 8mg po bd 3/7 Dexamethasone* 4mg po bd d1-3 Domperidone 10mg po tds prn for a maximum of 1 week Ondansetron not required if patient on netupitant/palonosetron In swallowing difficulties or feeding tubes: Aprepitant*** 80mg days 2 and 3 (for cisplatin **> 75mg/m²** only)
Moderate 30-90% (previous Level 3)	Ondansetron 8mg** po Dexamethasone* 8mg po/IV	Dexamethasone* 4mg po bd d 1-3 Domperidone 10mg po tds prn for a maximum of 1 week
Low 10-30% (previous Level 2)	Metoclopramide 10mg po/IV	Domperidone 10mg po tds prn for a maximum of 1 week
Minimal <10% (previous Level 1)	Not required routinely	Not required routinely

For haematology patients omit if regimen contains steroids e.g. CHOP, ESHAPP. Consider omitting if neutropenic. Max duration 5 days e.g. AML regimen

***** If a patient is unable to take pre- chemo ondansetron orally e.g. swallowing difficulty, nurses are able to give the ondansetron IV infused in 100 ml 0.9% sodium chloridel over at least 15 minutes.***

***** Only for regimens containing cisplatin doses > 75mg/m²**

Table 2 Schedule for patients receiving radiotherapy

Risk Level	Radiotherapy	Anti-Emetic Schedule
High risk	Total Body Irradiation (TBI)	Not given at NNUH
Moderate risk	Upper abdomen (including low thoracic spine)	Prophylactic ondansetron 8mg po/IV before each fraction for the entire cycle
Low risk	Low thorax, pelvis, stereotactic cranial RT, craniospinal	Consider prophylaxis with ondansetron 8mg po/IV before each fraction for the entire cycle if large volume treated (e.g. whole pelvis) Otherwise use ondansetron 8mg po/IV before each fraction if symptoms develop continued for the entire cycle.
Minimal risk	other sites	No routine prophylaxis. Use ondansetron 8mg po or domperidone 20mg po before each fraction if symptoms develop, continued for the entire cycle

If breakthrough nausea continues in spite of the above consider:

- **Domperidone** 10mg po tds prn for a maximum of 1 week or **metoclopramide** 10mg po tds as a prokinetic if delayed gastric emptying is suspected
- A broad spectrum antiemetic - **levomepromazine** (6.25–12.5mg bd) increasing as necessary (higher doses may be sedating); **cyclizine** 50mg tds or **haloperidol** 1.5mg bd

Objective

To provide guidance on the use of antiemetics for prevention and treatment of systemic anticancer therapy (SACT) and radiotherapy (RT) induced nausea and vomiting (N&V) in adult patients.

It is not intended to address N&V in palliative care. It is intended to provide a framework to support clinical practice, it cannot cover every clinical situation and good clinical common sense and experience will be required when approaching the management of individual patients.

Rationale

Prevention and control of N&V is an essential part of the management of patients receiving SACT and RT. N&V can result in serious metabolic derangements, nutritional depletion, oesophageal tears and deterioration of patients' physical and mental state with the development of anticipatory nausea and vomiting (ANV).

Modern drug treatment can successfully control N&V for the majority of patients.

General principles

- Ensure adequate hydration/ fluid balance
- Always commence any antiemetics before SACT or RT
- Give oral doses at least 30 minutes before SACT or RT 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 delayed N&V
- Drugs acting on the same receptor (see table 8 page 10) e.g. domperidone and metoclopramide should not be used together as the risk of side effects will be increased without additional clinical benefit

Choice of Antiemetics for Chemotherapy

- See Table 1 (page 3) for antiemetic schedule for SACT and table 2 (page 4) for RT
- All electronically prescribed SACT will have anti-emetics included in the prescription according to the emetic potential of the regimen (see Table 3 (pages 8 and 9 for individual intravenous cytotoxic drugs and table 4 (page 10 and 11) for oral cytotoxic drugs)
- For combination SACT the antiemetic schedule of highest level agent should be used
- For multi-day regimens the appropriate anti-emetic regimen for each day is chosen and on discharge give the antiemetics suggested for the day with the highest emetogenic potential

<u>Changes to the electronic prescription for SACT should be considered for</u>

Anti-emetic failure** if breakthrough nausea and vomiting occur (defined as prolonged, distressing nausea or 2 or more episodes of vomiting in 24 hrs), consider the following: **-**

- Move up to the next level of antiemetic treatment
- Lorazepam for anticipatory vomiting (1mg po morning of chemotherapy and 6-12 hourly; dose may be increased)
- Levomepromazine oral (6.25–12.5mg bd – quarter or half the 25 mg tablet) or by subcutaneous infusion if remains problematic (12.5-25 mg in 14mL water over 24 hours)
- Addition of cyclizine (50mg tds) or haloperidol (1.5mg bd) or buccal prochlorperazine (3-6 mg po bd)
- In patients with swallowing difficulties only - adding aprepitant for highly emetogenic regimens (125 mg 1 hour prior to day 1 SACT and 80 mg for days 2 and 3). Aprepitant capsules can be opened and mixed with water.
- Netupitant/palonosetron can be added. One 300 mg / 0.5 mg capsule should be administered approximately one hour prior to the start of each chemotherapy cycle. It is used for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and

moderately emetogenic cancer chemotherapy. Ondansetron must be removed from the prescription before and after chemotherapy.

Anticipatory nausea and vomiting (ANV**) -** the addition of lorazepam to antiemetic therapy is helpful due to its anxiolytic, sedative and amnesic effects. Behavioural interventions including hypnosis, acupuncture, distraction and psychological input may also be helpful for ANV

Diabetic patients - risks and benefits of dexamethasone should be assessed with consideration given to substitution with a $5HT_3$ inhibitor e.g. ondansetron

Patients on high dose steroids for another medical reason - dexamethasone may be omitted pre SACT or RT

Patients with severe Parkinson's disease - caution with metoclopramide, levomepromazine and prochlorperazine which may cause worsening of dyskinesia

**** NB also**

- Check electrolyte balance (particularly check creatinine, potassium)
- Review drug prescriptions and avoidance of opioids wherever possible
- Treat reversible causes wherever possible such as
  - Constipation
  - Gastric Irritation
  - Sepsis
  - Cough

Management of intractable vomiting

Contact the palliative care team (extension 3227 or through switch board) for advice

Table 3 Emetogenic potential of intravenous cytotoxic agents

Agent	Degree of emetogenicity (incidence)
Alemtuzumab	Minimal
Amsacrine	Low
Arsenic	Moderate
Atezolizumab	Low
Avelumab	Low
Azacitidine	Moderate
Bendamustine	Moderate
Bevacizumab	Minimal
Bleomycin	Low
Blinatumomab	Low
Bortezomib	Minimal
Brentuximab	Low
Cabazitaxel	Low
Carboplatin	Moderate
Carfilzomib	Low
Carmustine >250mg/m^2	High
Cetuximab	Minimal
Cisplatin ≥ 60mg/m^2	HIgh
Cladribine	Minimal
Clofarabine	Moderate
Cyclophosphamide <1500mg/m^2	Moderate
Cyclophosphamide ≥1500mg/m^2	High
Cytarabine <1000mg/m^2	Low
Cytarabine ≥1000mg/m^2	Moderate
Dacarbazine	High
Dactinomycin	Moderate
Daratumumab	Low
Daunorubicin	Moderate
Docetaxel	Low
Doxorubicin	Moderate
Durvalumab	Low
Epirubicin	Moderate
Eribulin	Low
Etoposide	Low
Fludarabine	Minimal
Fluourouracil	Low
Gemcitabine	Low
Gemtuzumab	Minimal
Idarubicin	Moderate
Ifosfamide <1500mg/m^2	Moderate
Ifosfamide ≥1500mg/m^2	High
Inotuzumab	Moderate
Ipilimumab	Minimal

Agent	Degree of emetogenicity (incidence)
Irinotecan	Moderate
Liposomal doxorubicin	Low
Melphalan	High
Methotrexate	Low
Mitomycin	Low
Mitozantrone	Moderate
Nivolumab	Minimal
Obinutuzumab	Minimal
Ofatumumab	Minimal
Olaratumab	Low
Oxaliplatin	Moderate
Paclitaxel	Low
Paclitaxel albumin	Low
Pembrolizumab	Minimal
Pemetrexed	Low
Pentostatin	Minimal
Pertuzumab	Low
Pixantrone	Minimal
Rituximab	Minimal
Streptozotocin	HIgh
Temsirolimus	Minimal
Thiotepa	Low
Topotecan	Low
Trabectedin	High
Trasatuzumab	Minimal
Trastuzumab Emtansine	Low
Ublituximab	Moderate
Vinblastine	Minimal
Vincristine	Minimal
Vinorelbine	Minimal

Table 4 Emetogenic potential of oral antineoplastic drugs
Generally for oral agents, the pre-chemo are not given

Agent	Degree of emetogenicity (incidence)
Afatinib	Minimal
Axitinib	Minimal
Bexarotene	Minimal
Bosutinib	Moderate
Busulfan <10mg	Low
Cabozantinib	Low
Capecitabine	Minimal
Ceritinib	Moderate
Chlorambucil	Minimal
Crizotinib	Moderate
Cyclophosphamide	Moderate
Dabrafenib	Low
Dasatinib	Minimal
Erlotinib	Minimal
Etoposide	Low
Everolimus	Low
Fludarabine	Low
Gefitinib	Minimal
Hydroxycarbamide	Minimal
Ibrutinib	Low
Idelalisib	Low
Imatinib	Minimal
Lapatinib	Minimal
Lenalidomide	Minimal
Lenvatinib	Low
Lomustine	Low
Methotrexate	Minimal
Nilotinib	Minimal
Nintedanib	Minimal
Olaparib	Moderate
Osimertinib	Low
Palbociclib	Minimal
Panobinostat	Moderate
Pazopanib	Minimal
Pomalidomide	Minimal
Ponatinib	Low
Procarbazine	High
Regorafenib	Low
Ribociclib	Moderate

| Agent | Degree of emetogenicity (incidence) |

Table 5 Definitions

Acute	N&V during the first 24-hour period immediately after SACT administration
Delayed	N&V that occurs more than 24 hours after chemotherapy and may continue for up to 6 or 7 days after SACT.
Anticipatory	N&V that occurs prior to the beginning of a new cycle of SACT. It is either a learned response following SACT induced N&V on a previous cycle or an anxiety response. It is most common after 3 to 4 cycles of SA CT 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

Table 6 Criteria for Grading Severity of Nausea and Vomiting[1]

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	Loss of appetite, mild nausea, able to eat, reasonable intake	Oral intake decreased without significant weight loss dehydration or malnutrition IV fluids indicated < 24hr	no significant food intake Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 h	Life-threatening consequences
Vomiting	once in 24 hours	2-5 times in 24 hours IV fluids indicated <24 hrs	≥6 episodes in 24 h; IV fluids, or TPN indicated ≥24 h	Life-threatening consequences >10 times in 24 hours,or requiring IV support

Table 7 Risk Factors for chemotherapy-associated emesis

The following have been associated with increased incidence of chemotherapy-associated emesis

- age <50 years
- female gender
- susceptibility to motion sickness or morning sickness during pregnancy
- anxiety

Other possible causes include:

- fluid and electrolyte imbalances (hypercalcaemia, volume depletion, water intoxication)
- constipation
- drugs such as opioids;
- infection
- uraemia
- psychological variables (i.e. expectations of chemotherapy-related nausea before beginning treatment)

Table 8 Anti-emetic agents - Action on main receptor sites

Drug	D2 antagonist	H1 antagonist	ACh antagonist	5HT2 antagonist	5HT3 antagonist	5HT4 agonist	NK1 inhibitor
Aprepitant							+++
Cyclizine		++	++				
Domperidone	++						
Haloperidol	+++						
Hyoscine			+++				
Levomepromazine	++	+++	++	+++			
Metoclopramide	++					++	
Prochlorperazine	++						
Ondansetron					+++		
Netupitant/ palonosetron					+++		+++

Table 9 Individual anti emetic agents: side effects and cautions

Please refer to BNF/SPC for more information

Aprepitant	Augments the antiemetic activity of the 5-HT3-receptor antagonist and dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis Common side effects include headaches, hiccups and fatigue.
Cyclizine	May cause antimuscarinic side effects such as dryness of the mouth and drowsiness. Children and the elderly are more susceptible. Avoid in severe heart failure
Dexamethasone	Should be used prophylactically not to treat N&V. Can cause sleep disturbances so ideally should be given no later than 2pm to minimise wakefulness in the night, 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 so advice to give over 10-15 minutes. Avoid long term use may cause substantial morbidity, including immunosuppression, proximal muscle weakness, aseptic necrosis of the long bones, hyperglycemia and adrenal suppression.
Domperidone	Do not use when stimulation of the gastric motility could be harmful e.g. gastro-intestinal haemorrhage, mechanical obstruction or perforation. A review of the evidence confirms a small increased risk of serious cardiac adverse drug reactions related to the use of domperidone, including QTc prolongation, torsade de pointes, serious ventricular arrhythmia and sudden cardiac death. A higher risk was observed in patients older than 60 years, adults taking daily oral doses of more than 30 mg, and those taking QT-prolonging medicines or CYP3A4 inhibitors concomitantly.
Haloperidol	Avoid or use smaller dose in renal failure (eGFR <10mL/min/1.73m^2) - increased risk of extrapyramidal reactions[$]
Levomepromazine	Avoid in patients with liver dysfunction. Inhibits cytochrome P-450. Common side effects are somnolence, asthenia, dry mouth, hypotension, photosensitivity and skin reactions. Can cause extra-pyramidal symptoms[$]
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. Avoid or use smaller dose in renal failure (eGFR <10mL/min/1.73m^2)
Netupitant/ palonosetron	Use with caution in patients over 75 years. Can commonly cause fatigue. As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of subacute intestinal obstruction should be monitored following administration. Appropriate observation of patients for serotonin syndrome-like symptoms is advised. Caution should be exercised in concomitant use with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval. These conditions include patients with a personal or family history of QT prolongation, electrolyte abnormalities, congestive heart failure, bradyarrhythmia, conduction disturbances and in patients taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to administration. Netupitant is a moderate inhibitor of CYP3A4
Ondansetron	Can cause constipation and headaches if severe, consider an alternative anti-emetic. Severe liver impairment consider reduction of dose to 8mg daily (instead or BD). Cardiac risk: caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include: electrolyte abnormalities, use of other medicines that prolong the QT interval (including cytotoxic drugs) or may lead to electrolyte abnormalities; congestive heart failure: bradyarrhythmias: and use of medicines which lower the heart rate. Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.
Prochlorperazine	Avoid 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. Can cause extra-pyramidal symptoms[$] May cause drowsiness.

Management of induced extra pyramidal reactions

$ Extra pyramidal reactions - may occur (rarely) with metoclopramide, levomepromazine and prochlorperazine; consider stopping causative drug or switching metoclopramide to domperidone for a maximum of 1 week.

Treatment - Procyclidine 5 mg IV (usually effective within 5 mins); an occasional patient may need 10 mg or more and may require up to half an hour to obtain relief

Patient Information

Available from Macmillan website

Clinical audit standards

Audit will be against these recommendations for the use of antiemetic agents

Summary of development and consultation process undertaken before registration and dissemination

This guideline was originally developed for the Oncology Directorate by Matthew Small (Oncology Pharmacist). It was updated to add new chemotherapy and has been circulated to all consultants and senior nursing staff of the Oncology Directorate (Oncology, Haematology and Palliative Care); amendments were made to incorporate suggestions and comments especially those made by Dr Holtom.

In 2019 it was reviewed and only minor changes made. This version is endorsed by The Clinical Guidelines Assessment Panel

Distribution list/ dissemination method

Trustdocs

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