NHS
Kent and Medway
Cancer Collaborative

Systemic Anti-cancer Therapy Care Pathway – Guidelines for the management of SACT induced nausea and vomiting in adult patients

Pathway of Care

Kent & Medway Cancer Collaborative

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1.0 BACKGROUND

Nausea and vomiting are known side effects of many of the systemic anti-cancer agents. The risk and severity of symptoms depends largely upon the dose and combination of the systemic anti-cancer agents used.

Patients may experience different levels of nausea and vomiting even though they are receiving the same regimen, and assessment of the patients' response needs to take this into account.

The prophylactic treatment of nausea and vomiting is essential, as uncontrolled symptoms can contribute to fluid and electrolyte imbalance, anorexia and lead to anticipatory nausea and vomiting.

In addition to drug therapy for SACT induced nausea and vomiting, it is essential that the patient receives adequate information with regard to other mechanisms of management. Patient education is essential at the pre-chemotherapy information appointment with regards this.

There are three areas of nausea and vomiting identified with systemic anti-cancer therapy:

- **ACUTE:** This usually happens during or within several hours of systemic anti-cancer therapy administration.
- **DELAYED:** Can happen and continue for several days after the treatment has been administered.
- **ANTICIPATORY:** If nausea and vomiting is not well controlled in the previous two phases, patients may experience a conditioned response of nausea and vomiting prior to receiving treatment.

Optimal emetic control at initiation of treatment is essential to prevent nausea and vomiting in the acute and delayed phase. Rigorous assessment by skilled chemotherapy nurses prior to each cycle of chemotherapy will ensure issues with uncontrolled emesis are identified, and these patients will be escalated up the anti-emetic ladder as deemed appropriate. Other causes of nausea and vomiting should also be considered such as constipation, acute bowel obstruction, opioid usage, hypercalcaemia and brain metastases.

Regimens are categorised as mildly, moderately or highly emetogenic (table 1). If a combination of drugs is used, the risk should be assessed according to the most emetogenic drug contained within the regimen. Intensive regimens with several highly emetogenic drugs or those delivered over many days, or those where the dosage is above the standard, should be treated as very highly emetogenic (table 2).

Notes:

1) For patients unable to tolerate metoclopramide or at high risk of extra pyramidal side-effects (e.g. patients under 20 years of age), domperidone may be considered (see MHRA guidance below on the use of domperidone and metoclopramide).
2) Although not approved as an anti-emetic, dexamethasone is widely used for the prevention of acute and delayed nausea and vomiting, and is a standard part of almost all anti-emetic regimens. Omit subsequent doses of dexamethasone in regimens incorporating prolonged usage of prednisolone. Where dexamethasone is given post chemotherapy for regimens of moderate emetogenic potential in which treatment is given more frequently than every 3 weeks (e.g. weekly paclitaxel), the dose of dexamethasone should be reduced to 4mg in the morning for 2 days after each treatment administration.
3) If vomiting lasts beyond 72 hours, give a prolonged course of dexamethasone 6mg om for up to 7 days. Also consider extending the course of metoclopramide to 5 days or the course of domperidone to 7 days. Also consider changing the drugs to alternatives.
4) Anticipatory nausea and vomiting is best prevented by adequate control of emesis in the first cycle. If it does develop, give haloperidol the evening before chemotherapy (1.5mg if <60 kg or >70 years) and/or lorazepam 1mg the evening before and on the morning of chemotherapy. As both these drugs cause drowsiness, patients must be counselled not to drive when taking this medication.
5) For patients with diabetes, patient education must be offered with regards to steroid usage and control of their diabetes.

2.0 TABLE 1: Emetogenic potential of individual chemotherapy drugs

Emetic Risk <10% (equivalent to "Mildly")	Emetic Risk 10 – 30% (equivalent to "Mildly" or "Moderately" as indicated)		Emetic Risk 30 - 90% ("Highly")	Emetic Risk >90% (equivalent to "Highly")	Emetic Risk >90% and warranting addition of NK1 antagonist (equivalent to "Very High Risk")
	Mildly	Moderately			
Asparaginase	Capecitabine	Bortezomib	Amsacrine	Carmustine	High dose Cisplatin >/=75mg/m^2
Bevacizumab	Cetuximab	Cabazitaxel	Azacitidine	Cisplatin	Folfirinox
Bleomycin	Cyclophos PO	Caelyx	Bendamustine	Cyclophosphamide ≥ 1.5g/m^2	
Busulfan PO	Fluorouracil	Cytarabine ≤1g/m^2	Bosutinib	Dacarbazine	
Chlorambucil PO	Methotrexate 50-250mg/m^2	Docetaxel	Cabozantinib	Dactinomycin	
Cladribine	Mitomycin	Eribulin	Carboplatin	Procarbazine	
Daratumumab	Paclitaxel	Etoposide IV	Ceritinib	Streptozocin	
Fludarabine	Pemetrexed	Mitoxantrone	Cyclophosphamide < 1.5g/m^2		
Hydroxycarbamide	Pentostatin	Nab-paclitaxel	Cytarabine > 1g/m^2		
Melphalan PO	Pertuzumab	Raltitrexed	Daunorubicin		
Mercaptopurine	Topotecan IV		Doxorubicin		
Methotrexate PO	Trastuzumab		Epirubicin		
Nivolumab	Trastuzumab emtansine		Idarubicin IV		
Obinutuzumab	Trifluridine-tipiracil		Ifosfamide		
Pembrolizumab			Irinotecan		
Pixantrone			Lenvatinib		
Rituximab			Lomustine		
Ruxolitinib			Melphalan IV		
Vinblastine			Methotrexate >250mg/m^2		
Vincristine			Oxaliplatin		
Vindesine			Temozolomide		
Vinorelbine			Thiotepa		

This table (table 1) is not an exhaustive list, and the individual performing the administration should familiarise themselves with the emetogenic potential of the agent or regimen.

For adult patients, the addition of a check point inhibitor (e.g pembrolizumab, atezolizumab, ipilumumab or nivolumab) to chemotherapy does not change the guideline recommendation for an antiemetic regimen based on the emetogenicity of the agents administered (ie steroids may be given as anti-emetics). Check point inhibitors administered alone or in combination with another check point inhibitor are minimally emetogenic and do not require the routine use of a prophylactic antiemetic.

Antiemetic regimens should be based on the agent in the regime which has the highest emetogenic potential, however combinations of highly emetogenic agents, and some haematology regimes should be classified as having a **"very high" emetogenic potential.**

The emetogenic potential of each SACT protocol is assessed by the non-surgical oncology group when the collaborative chemotherapy prescribing protocol is written and the necessary anti emetics are added to the protocol.

It must be remembered above all that each patient must be treated on an individual basis.

3.0 TABLE 2: Recommended antiemetic regimes for prevention and control of nausea and vomiting

ACUTE PHASE (1st Line)	DELAYED PHASE (24 to 72 hours post chemo)	IF NO RESPONSE / FAILURE WITH PREVIOUS CYCLE (2nd Line)
VERY HIGH EMETOGENIC POTENTIAL CHEMOTHERAPY (e.g High dose Cisplatin ≥75mg/m2 & FOLFIRINOX)		
5-HT_3 receptor antagonist Dexamethasone 8mg IV or oral Aprepitant*** 125 mg od orally In addition, consider adding olanzapine 5mg po	METOCLOPRAMIDE# 10mgs tds for 3 days then 10mg up to 3 times a day as required Or DOMPERIDONE 10mgs tds as required DEXAMETHASONE 6mg in the morning for 3 days Aprepitant 80mg orally daily for 2 days ONDANSETRON 8mg po bd for 3-5 days may also be added if deemed appropriate by the relevant non-surgical oncology group. Consider substituting domperidone / metoclopramide for olanzapine 5mg po od – bd for up to 3 days (patients >65 years should receive olanzapine 5mg po od)	Increase duration of 5-HT_3 receptor antagonist or consider alternative strategies (e.g. s/c infusion) (NB: Dexamethasone TTO should not exceed 6mg om when given with Aprepitant) Alternatively, 300 mg / 0.5 mg netupitant and palonosetron hydrochloride may be given orally once on the day of chemotherapy (not required on days 2 and 3) with Dexamethasone 8mg iv/po. (NB: Dexamethasone TTO should not exceed 6mg om when given with netupitant / palonosetron) If not received previously, consider substituting domperidone / metoclopramide for olanzapine 5mg po od – bd for up to 3 days (patients >65 years should receive olanzapine 5mg po od)
HIGH EMETOGENIC POTENTIAL CHEMOTHERAPY + Anthracycline and cyclophosphamide combinations		
5-HT_3 receptor antagonist + DEXAMETHASONE 8mg oral/IV	METOCLOPRAMIDE# 10mgs tds for 3 days then 10mg up to 3 times a day as required or DOMPERIDONE 10mgs tds for 3 days then as required DEXAMETHASONE 6mg in the morning for 3 days ONDANSETRON 8mg po bd for 3-5 days may also be added if deemed appropriate by the relevant non-surgical oncology group.	Increase dose* and/or duration of 5-HT_3 receptor antagonist and Dexamethasone or add Aprepitant 125 mg od orally Day 1 followed by 80mg orally daily for 2 days (NB: Dexamethasone TTO should not exceed 6mg om when given with Aprepitant) * N.B. See Section 5 NB Netupitant and palonosetron may be used as an alternative to aprepitant with 5-HT3 receptor antagonist, see above.

		If not received previously consider substituting domperidone / metoclopramide for olanzapine 5mg po od – bd for up to 3 days (patients >65 years should receive olanzapine 5mg po od)
MODERATE EMETOGENIC POTENTIAL CHEMOTHERAPY		
METOCLOPRAMIDE 10-20mg iv + DEXAMETHASONE 8mg oral	METOCLOPRAMIDE[#] 10mgs tds for 3 days then 10mg up to 3 times a day as required OR Domperidone 10mgs tds for 3 days then as required PLUS DEXAMETHASONE 6mg in the morning for 3 days**	5-HT_3 receptor antagonist
Minimal EMETOGENIC POTENTIAL CHEMOTHERAPY		
METOCLOPRAMIDE 10-20mg oral Domperidone 10mgs oral Some patients / regimes do not require any anti-emetics	METOCLOPRAMIDE[#] 10mgs tds for 3 days then 10mg up to 3 times a day as required OR Domperidone 10mgs tds prn	Add DEXAMETHASONE 8mg oral plus Dexamethasone 6mg in the morning for 3 days for delayed emesis

[#]Please note some of the doses recommended exceed the UK licensed marketing authorisation.

** Where dexamethasone is given post chemotherapy for regimens of moderate emetogenic potential in which treatment is given more frequently than every 3 weeks (e.g. weekly paclitaxel), the dose of dexamethasone should be reduced to 4mg in the morning for 2 days after each treatment administration.

*** For patients who cannot swallow capsules, the aprepitant capsule may be opened and the contents sprinkled on the tongue and swallowed.
For patients who have a feeding tube, it is not recommended to use the feeding tube for administration of the contents of the capsule. Instead, a single dose of **fosaprepitant** 150mg IV over 20-30 minutes is recommended immediately before chemotherapy. When fosaprepitant is given, dexamethasone TTO should not exceed 6mg om.

4.0 TABLE 3: Recommended dosages for 5-HT$_3$ receptor antagonist

Drug	I.V.	Oral
GRANISETRON	1-3mg od	1-2mg od
ONDANSETRON	8mg od (up to a max 16mg a day) ***N.B. please see below**	8mg bd (up to a max of 32mg a day)

Once daily doses are recommended to be administered prior to chemotherapy.
Evidence for the use of 5-HT3 receptor antagonists for an additional day for delayed nausea and vomiting is limited.

5.0 MHRA advice for healthcare professionals

5.1 On the use of ondansetron

New Advice

Patients age 75 years or older:

- A single dose of intravenous ondansetron for the prevention of CINV must not exceed 8 mg (infused over at least 15 minutes)

Adult patients younger than 75 years:

- A single dose of intravenous ondansetron prevention of CINV must not exceed 16 mg (infused over at least 15 minutes)

Dilution and administration in patients age 65 years or older:

- All intravenous doses should be diluted in 50–100 mL saline or other compatible fluid and infused over at least 15 minutes

Repeat dosing in all adults (including elderly patients):

- Repeat intravenous doses of ondansetron should be given no less than 4 hours apart

Reminder of previous advice (from August 2012)

- Ondansetron should be avoided in patients with congenital long QT syndrome
- 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 QT interval (including cytotoxic drugs) or that may lead to electrolyte abnormalities; congestive heart failure; bradyarrhythmias; or use of medicines that lower heart rate
- Hypokalaemia and hypomagnesaemia should be corrected before ondansetron administration

5.2 On the use of domperidone

- Domperidone should be used at the lowest effective dose.
- Domperidone should not be used in patients with underlying cardiac disease.
- Patients should not take more than three 10mg tablets per day for up to 7 days.
- Domperidone should be avoided in patients who are taking concomitant medication known to cause QT prolongation (e.g., ketoconazole or erythromycin)
- Patients should be advised to seek prompt medical attention if symptoms such as syncope or tachyarrhythmias appear during treatment

5.3 On the use of metoclopramide

- Metoclopramide should only be prescribed for short-term use (up to 5 days), to reduce the risk of tardive dyskinesia.
- Maximum dose is 30mg in 24 hours (usually 10mg tds).
- Intravenous doses should be administered as a slow bolus over 3 minutes.

6.0 ALTERNATIVE STRATEGIES

If emesis control is not achieved using above recommendations, consider the use of alternatives such as levomepromazine 6.25mg tds, haloperidol 1.5mg od-bd, lorazepam 1mg 1 hour prior to treatment or cyclizine 50mgs tds.
For patients who are unable to tolerate oral anti-emetics, suppositories can be prescribed to increase absorption, or a subcutaneous infusion may be considered.
If not received previously consider substituting domperidone / metoclopramide for olanzapine 5mg po od – bd for up to 3 days (patients >65 years should receive olanzapine 5mg po od).

7.0 SIDE EFFECTS OF COMMONLY USED ANTI EMETICS

- Domperidone: generally, well tolerated but can increase gut motility leading to diarrhoea. A European Medicines Agency's (EMA) review on the safety and effectiveness of domperidone found that people who take the drug may have a small increased risk of potentially life-threatening effects on the heart.
- These risks may be higher in patients older than 60 years and in patients who receive daily oral doses of more than 30 mg.
- Metoclopramide: can cause extra pyramidal symptoms up to 24 hours after administration. It should be avoided in patients with Parkinson's disease and used with caution in patients under 20 years of age.
- Dexamethasone: can cause an increase in appetite and activity, or steroid induced psychosis. Some patients experience perianeal discomfort if the drug is given by fast bolus, and should therefore always be given slowly. Should be used with extreme caution in diabetic patients, and those already receiving dexamethasone as part of their treatment protocol.
- 5-HT3 receptor antagonist: can induce constipation in a high proportion of patients, and may also complain about headaches.
- Aprepitant: may include side effects such as hiccups, and gastrointestinal symptoms.

8.0 REFERENCES

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9.0 GLOSSARY

Acronyms in common usage throughout KMCC documentation

BNF	British National Formulary
BOPA	British Oncology Pharmacist Association
CNB	Cancer Network Board
COSHH	Control of substances hazardous to health regulations.
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
DGT	Dartford and Gravesham NHS Trust
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
EPS	Electronic Prescribing System
FP10(HNC)	Prescriptions issued by hospital doctors for dispensing in the community
GP	General Practitioner
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
IV	Intravenous
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network
KOMS	Kent Oncology Management System
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NHS	National Health Service
NMP	Non-medical prescriber
NPSA	National Patient Safety agency
NOG	Non Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
QSIS	Quality service information system
QST	Quality Surveillance Team
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
SACT	Systemic Anti-Cancer therapy
SACT regimen	Systemic Anti-cancer prescription on the electronic prescribing system
SACT protocol	Systemic Anti-cancer protocol on KMCC website
TTO	Treatment to take home
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

10.0 DOCUMENT ADMINISTRATION

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