Hull and East Yorkshire Hospitals NHS Trust

Management Chemotherapy and Radiotherapy Induced Nausea and Vomiting

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Version Control

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Signature Sheet

These guidelines have been agreed by:		
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Chemotherapy induced Nausea and Vomiting

Introduction

Nausea and Vomiting are among the most feared and distressing adverse effects of chemotherapy from a patient's standpoint. Substantial progress has been made in improving the control of chemotherapy-induced nausea and vomiting (CINV) due in large part to the introduction of selective type-three 5-hydroxytryptamine (5-HT3) receptor antagonists approximately 13 years ago. Nevertheless, often CINV remains sub optimally controlled for a significant number of cancer patients receiving chemotherapy.

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The following distinct types of CINV have been defined, with important implications for both prevention and management:

- Acute emesis, which most commonly begins within one to two hours of chemotherapy and usually peaks in the first four to six hours (<1 day post chemotherapy)
- Delayed emesis, occurring more than 24 hours after chemotherapy (1 - 7 days post chemotherapy)
- Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant nausea and vomiting during previous cycles of chemotherapy.
- Breakthrough emesis refers to vomiting despite pre-treatment and requires rescue with additional antiemetics.
- Refractory- continued emesis in subsequent treatment cycles when prophylaxis and rescue antiemetics have failed in previous cycles.

The **objective** of antiemetic therapy is the complete prevention of CINV, and this should be **achievable** in the majority of patients receiving chemotherapy, even with highly emetogenic agents.

The **three** categories of drugs with the highest therapeutic index for the management CINV include Corticosteroids, type three 5-hydroxytryptamine (5-HT3) receptor antagonists, and the neurokinin-1 (NK1) receptor antagonists.

The management of CINV has been greatly facilitated by the development of classification schemes that reflect the likelihood of emesis developing following treatment with a particular agent. A 1997 classification scheme gained broad acceptance and was utilized as the basis for treatment recommendations by guideline panels. A modification of this schema was proposed at the 2004 Perugia Antiemetic Consensus Guideline meeting.

Chemotherapy agents were divided into four categories

- High — >90 percent risk of emesis
- Moderate — >30 to 90 percent risk of emesis
- Low — 10 to 30 percent risk of emesis
- Minimal — <10 percent risk of emesis

This drug classification schema is utilized in both the updated antiemetic guidelines of the Multinational Association of Supportive Care in Cancer (MASCC) and the American Society of Clinical Oncology (for examples see **Table 1**).

For combination regimens, the emetic level is determined by identifying the most emetogenic agent in the combination and then assessing the relative contribution of the other agents.

The present guideline document is based mainly on the 2016 MASCC and ESMO guideline update (1); additional information has been obtained from the British National Formulary. Examples of compatible antiemetic regimens incorporating local experience are given in **table 2.**

High risk

For the prevention of non- anthracycline highly emetogenic chemotherapy, a three-drug regimen including single doses of a 5-HT3 inhibitors , dexamethasone and an NK1 inhibitor (aprepitant, fosaprepitant, netupitant or rolapitant), given before chemotherapy is recommended [MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence I; ESMO grade of recommendation: A]. In patients receiving non-AC highly emetogenic chemotherapy treated with a combination of an NK1 RA, a 5-HT3 inhibitors and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days 2–4 is suggested to prevent delayed nausea and vomiting [MASCC level of confidence: high; MASCC level of consensus: moderate; ESMO level of evidence I; ESMO grade of recommendation: B]. it is noted that when apprepitant is used as the NK1 inhibitor, day2 and 3 80mg doses can be used as an adjunct to prevent delayed emesis.
In women with breast cancer receiving doxorubicin / cyclophosphamide chemotherapy, a three-drug regimen including single doses of a 5-HT3 RA, dexamethasone and an NK1 inhibitors (aprepitant, fosaprepitant, netupitant or rolapitant), given before chemotherapy is recommended [MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence I;

ESMO grade of recommendation: A]. The addition of NK1 inhibitors increase the complete response rate by up to 9% on days 1-5 (2,3)
In women with breast cancer treated with a combination of a 5-HT3 RA, dexamethasone and an NK1 inhibitors to prevent acute nausea and vomiting, aprepitant or dexamethasone should be used on days 2 and 3 but not if fosaprepitant, netupitant or rolapitant has been used on day 1 [MASCC level of confidence: moderate; MASCC level of consensus: moderate; ESMO level of evidence II; ESMO grade of recommendation: B].
In patients having treatment with other agents, with whom randomised trials have not been conducted, the above recommendations can serve as guidance.

Moderate risk

For patients receiving moderately emetogenic chemotherapy, recommend the combination of a 5-HT3 receptor antagonist plus dexamethasone [MASCC level of confidence: moderate; MASCC level of consensus: moderate; ESMO level of evidence II; ESMO grade of recommendation: B].. in patients receiving moderate emetogenic risk agents with a known potential for delayed emesis (e.g. oxaliplatin, doxorubicin, cyclophosphamide), the use of dexamethasone for days 2–3 can be considered [MASCC level of confidence: low; MASCC level of consensus: moderate; ESMO level of evidence III; ESMO grade of recommendation: C]. Treatment with a 5-HT3 receptor antagonist alone is a reasonable alternative and/or adjunct.
Patients who despite recommended treatment develop unacceptable emesis after a moderate emetogenic risk chemotherapeutic regimen, escalation to an antiemetic regimen used for high risk chemotherapy is a reasonable option. The ESMO guidelines specifically reviewed evidence for carboplatin-based regimens for which they suggest the addition of an NK1 inhibitor [grade of recommendation B]

Low risk

a single antiemetic agent, such as dexamethasone, a 5-HT3 RA or a dopamine RA, such as metoclopramide may be considered for prophylaxis in patients receiving chemotherapy of low emetic risk [MASCC level of confidence: no confidence possible; MASCC level of consensus: moderate; ESMO level of evidence: II; ESMO grade of recommendation: B].

Minimal risk

No antiemetic should be routinely administered before chemotherapy to patients without a history of nausea and vomiting receiving minimally emetogenic chemotherapy [MASCC level of confidence: no confidence possible; MASCC level of consensus: high; ESMO level of evidence: IV; ESMO grade of recommendation: D].

Anticipatory emesis

Once it develops, anticipatory nausea and vomiting is difficult to control by pharmacological treatment. The best approach for the prevention of anticipatory nausea and vomiting is the best possible control of acute and delayed nausea and

vomiting [MASCC level of confidence: moderate; MASCC level of consensus: high; ESMO level of evidence: III, ESMO grade of recommendation:A]. Benzodiazepines can be used to reduce the occurrence and behavioural interventions can be useful in in managing anticipatory nausea and emesis.

High-dose chemotherapy

For patients receiving high-dose chemotherapy for stem cell transplant, a combination of a 5-HT3 RA with dexamethasone and aprepitant (125 mg orally on day 1 and 80 mg on days 2–4) is recommended before chemotherapy [MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence: I; ESMO grade of recommendation: A].

Multiday regimens

For patients receiving multiday (three or more) regimens that are moderately or highly emetogenic the use of a daily dose of a first-generation 5-HT3 receptor antagonist, or a single application of a granisetron transdermal patch or palonosetron on days 1, 3, and 5 plus daily dexamethasone, with the addition of aprepitant (days 1, 2, and 3), fosaprepitant (day 1), or another NK1R antagonist (eg, netupitant plus palonosetron [NEPA] or rolapitant) on day 1 for highly emetogenic regimens (eg, five days of cisplatin in regimens for testicular or ovarian germ cell cancer). Based on available randomised data ESMO/MASCC recommend a 5-HT3 RA plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for delayed nausea and vomiting for patients patients affected by metastatic germ cell tumours receiving multiple-day cisplatin.

Poor emesis control

For patients who do not achieve adequate control of CINV with their initial antiemetic regimen, the patient's management should be reviewed to ensure that there are no other factors responsible for continued emesis and that adequate antiemetic therapy actually was administered for the given chemotherapy regimen. If CINV remains an issue, the addition or substitution of a second line agent or changing from one 5-HT3 receptor antagonist to another may be useful. In some cases chemotherapy needs to be altered, i.e. substituting with less emetogenic agents or changing schedule, infusion duration etc.
Olanzapine can be used for breakthrough emesis (4) but the mild to moderate sedation it can cause may be a problem for elderly or frail patients.
Agents like metoclopramide, cyclizine, prochloperazine, levomepromazine, haloperidol most of which have indications for nausea and vomiting from other causes or within palliative care may be used as adjuncts in selected cases..

Safety of antiemetic agents

With the 5- HT3 inhibitorss, electrocardiographic changes, particularly QTc prolongation, are a class effect. The risk may differ between these agents and palonosetron seems to induce the lowest risk. Due to cardiac adverse effects, FDA warnings against both the i.v. dose of dolasetron (Drug Safety Communication, December 2010) and the high 32 mg i.v. dose of ondansetron (Drug Safety Communication, June 2012) have been released. These formulations have therefore been withdrawn. The EMA has recommended a change in the use of metoclopramide due to the risk of neurological effects such as short term extrapyramidal disorders [EMA/443003/2013]. The EMA recommends metoclopramide not to be used in children below 1 year of age and for adults to be used in a daily maximum dose of 30 mg (e.g. 10 mg × 3 orally) for a maximum of 5 days. The authors of the ESMO/MASCC guideline recorded their opinion that 10 mg of metoclopramide is not superior to placebo in the effect against chemotherapy induced nausea and vomiting and that higher doses are tolerable, when given for 2–3 days. Olanzapine may be considered with a 5-HT3 RA plus dexamethasone, particularly when nausea is an issue, but using the 10 mg dose, patient sedation may be a concern [MASCC level of confidence: low; MASCC level of consensus: low; ESMO level of evidence II; ESMO grade of recommendation: B].

Prevention of radiotherapy-induced nausea and vomiting

In the current ESMO/MASCC guidelines, mainly based on expert opinions the following risk categories were addressed:
made.

High- **Total body irradiation** – Prophylaxis with 5-HT3 inhibitor and dexamethasone
Moderate – **Upper abdomen, craniospinal** – Prophylaxis with a 5-HT3 inhibitor with optional dexamethasone
Low – **Cranium,**– Prophylaxis or rescue with Dexamethasone.- **Head and neck, thorax, pelvis**- Prophylaxis or rescue with Dexamethasone, a Dopamine receptor antagonist (metoclopramide) or a 5-HT3 inhibitor.
Minimal – **extremities, breast** – rescue with Dexamethasone, D-receptor antagonist or 5-HT3 inhibitor.
Concomitant CRT: The antiemetic prophylaxis should be according the the guidelines for CINV for the used chemotherapy. If the emetic risk level of the involved RT field is higher than the concomitant Chemotherapy then the risk level of RT has to be chosen to tailor the antiemetic treatment.

Tables

Table 1. Classiffication of antineoplastic agents according to emetogenic potential			
	IV agents		**Oral agents**
High	Anthracycline/cyclophosphamide combination Carmustine Cisplatin >50mg/m^2 Cyclophosphamide ≥1500 mg/m2 Dacarbazine Mechlorethamine Streptozocin		Hexamethylmelamine Procarbazine
Moderate	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide <1500 mg/m2 Cytarabine >1000 mg/m2 Daunorubicin	Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin Romidepsin Temozolomidec Thiotepad Trabectedin	Bosutinib Ceritinib Crizotinib Cyclophosphamide Imatinib Temozolomide Vinorelbine
Low	Aflibercept Belinostat Blinatumomab Bortezomib Brentuximab Cabazitaxel Carfilzomib Catumaxumab Cetuximab Cytarabine ≤1000 mg/m2 Docetaxel Eribulin Etoposide 5-Fluorouracil Gemcitabine	Ipilimumab Ixabepilone Methotrexate Mitomycin Mitoxantrone Nab-paclitaxel Paclitaxel Panitumumab Pemetrexed Pegylated liposomal doxorubicin Pertuzumab Temsirolimus Topotecan Trastuzumab-emtansine Vinflunine	Afatinib Axatinib Capecitabine Dabrafenib Dasatinib Everolimus Etoposide Fludarabine Ibrutinib Idelalisib Lapatinib Lenalidomide Olaparib Nilotinib Pazopanib Ponatinib Regorafenib Sunitinib Tegafur uracil Thalidomide Vandetanib Vorinostat
Minimal	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Cladribine Fludarabine Nivolumab Ofatumumab	Pembrolizumab Pixantrone Pralatrexate Rituximab Trastuzumab Vinblastine Vincristine Vinorelbine	Chlorambucil Erlotinib Gefitinib Hydroxyurea Melphalan Methotrexate L-phenylalanine mustard Pomalidomide Ruxolitinib Sorafenib 6-Thioguanine Vemurafenib Vismodegib

Adapted from *2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients*. Roila et all Ann Onc 27 (S5):V119-v133, 2016

Table 2. Examples of antiemetic regimens according to emetogenic potential.			
Emetogenic risk	**Prophylaxis of acute CINV**	**Prophylaxis of delayed CINV**	**Options for secondary prophylaxis / breakthrough emesis**
High (>90%)	**Ondansetron** 8mg IVstat or 8-16mg PO **Dexamethasone** 8mg IV stat (not haem) **Aprepitant** 125mg po if Cisplatin >70mg/m2, Cyclophosphamide >1500mg/m2	**Dexamethsone** 2mg tds 3/7 up to 8mg BD for 3/7 (in regimens not containing a steroid) **Ondansetron** 8mg bd 3/7 **Aprepitant** 80mg days 2 and 3 if given 125mg on day 1. **Metoclopramide** 10mg tds prn for 5 days	Add in **ondansetron** 8mg bd 5/7 Consider **Levomepromazine** 6.25mg prn up to qds Consider **Lorazepam** 1mg tds, especially in anticipatory nausea. Consider adding **Aprepitant / other NK1** for subsequent cycles (once other options exhausted) if not previously used Consider **olanzapine** 5-10mg daily on days 2-4
2nd Option: Netupitant / palonosetron combination with **Dexamethasone** 8-12mg IV day1, with **Dexamethasone** 4mg BD day2-day4			
Moderate (30-90%)	**Ondansetron** 8mg pos 30 min prior to infusion **Dexamethasone** 8mg IV stat (not haematology)	**Dexamethasone** 2mg tds 3/7 up to 4mgBD (in regimens not containing steroids or haem) [With **Ondansetron** 8mg bd 3/7 for anthracycline / cyclophosphamide regimens)] **Metoclopramide** 10mg tds prn for 5 days	**Ondansetron** 8mg bd 5/7 +/- dexamethasone 2mg tds 3/7 (if not already used) **Metoclopramide** 10mg tds prn (if not already used) Consider **Aprepitant / other NK1** in patients with previously poorly controlled CINV
Low (10-30%)	**Dexamethasone 4-**8mg IV stat (not haematology)	**Metoclopramide** 10mg tds prn	**Dexamethasone** 2mg tds 3/7 (in regimens not containing steroids) With **Ondansetron** 8mg bd 3/7
Minimal(<10%)	None	None	**Metoclopramide** 10mg tds prn **Dexamethasone** 2mg tds 3/7 (in regimens not containing steroids) With **Ondansetron** 8mg bd 3/7

Table 3. Active agents in managing CINV		
Included in ESMO / MASCC guidelines 2016		
	Acute Emesis (day1)	**Delayed Emesis**
Corticosteroids		
Dexamethasone	Various doses from 4mg for low risk, up to 20mg for high risk.	8-16mg daily for 3-4 days
5-HT_3 inhibitors (receptor antagonists)		
Ondasentron	8mg-16mg pos / IV (preference to oral administration)	8mg pos bd for delayed emesis
Granisetron	IV 1 mg or 0.01 mg/kg Oral 2 mg (or 1 mgb)	
Palonosetron	IV 0.25 mg Oral 0.5 mg	
NK1-inhibitors (receptor antagonists)		
Aprepitant	125mg	80mg days2-3
Fosaprepitant	150mg	none
Rolapitant	180mg	none
Combination 5-HT_3 and NK1 inhibitors		
Palonosetron with netupitant	0.5 mg + 300mg	
Antipsychotics		
Olanzapine	5-10mg daily	
Dopamine receptor inhibitors		
Metoclopramide	10mg tds	
Not included in MASCC / ESMO guidelines but possibly useful in selected cases		
Levopepromazine	6.25 mg od to 6.25bd	
Prochloperazine	5-10mg bd or tds, acute attack: 20mg	
Haloperidol	1.5 mg od or bd	
Cyclizine	50mg tds	

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