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# Chemotherapy Induced Nausea and Vomiting: Fear Makes the Wolf Bigger than He is

**Mansi Sharma and Jyoti Bajpai***

*Medical oncologist, Tata Memorial Cancer Centre, Mumbai, India*

***Corresponding author:** Jyoti Bajpai, Medical oncologist, Tata Memorial Cancer Centre, Mumbai, India, Tel: +919920640040; E-mail: dr_jyotibajpai@yahoo.co.in

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## Abstract

Chemotherapy induced nausea and vomiting (CINV) is one of the most feared and severe side effects of cancer treatment. It is broadly categorised as anticipatory (a conditioned reflex, due to past experience, generally triggered by same stimuli), acute (within 24 hours of chemotherapy administration), delayed (after 24 hours and lasting up to 7 days of chemotherapy), breakthrough (inspite of primary prophylaxis for CINV), and refractory (unresponsive to prophylactic and breakthrough medications). The chemotherapeutic regimens are having varying potential (high, moderate, low, or minimal) for CINV. Incidence and timing of CINV depends upon the emetogenic potential of chemotherapy and also patient factors. This perspective highlights the underlying mechanism of CINV, state of the art therapeutic options and nuances in the field to better control this dreaded complication and in turn enhance the quality of life of these patients.

## Article

One of the most important complications of cancer therapy is development of chemotherapy induced nausea and vomiting (CINV). It can be highly debilitating to the patient, leading to decreased quality of life. This has various therapeutic implications, and can lead to the patient receiving suboptimal therapy. CINV can cause poor compliance with therapy, nutritional deficiencies, metabolic derangements, need for in patient management, and can also result in mechanical issues like wound dehiscence and esophageal tears [1-3].

CINV is divided into three main subtypes, mainly acute, delayed and anticipatory. Acute emesis usually begins a few minutes to few hours after chemotherapy, peaks within four to six hours, and usually resolves within the first twenty four hours. Delayed emesis develops more than twenty four hours after chemotherapy, especially with drugs like cisplatin, carboplatin, doxorubicin, and cyclophosphamide [4-6]. Anticipatory emesis develops in patients prior to their next chemotherapy cycle as a conditioned response [7,8]. It occurs mostly in patients who have had poor control of emesis during previous chemotherapy cycles. Another type of CINV is known as breakthrough nausea and vomiting, which occurs in spite of prophylactic medications [9]. Refractory CINV is defined as vomiting and/or nausea occurring in subsequent chemotherapy cycles when prophylactic and/or rescue therapy has failed in previous cycles [10].

There are two main pathways through which chemotherapy can cause emesis [11,12]. Acute CINV is mostly caused by activation of the peripheral pathway. Chemotherapy drugs lead to activation of neurotransmitter receptors including 5HT3 receptors in the gastrointestinal tract. This leads to the transmission of afferent impulses to the vomiting centre, activation of which leads to vomiting. Efferent signals are transmitted via the vagus nerve to the salivation centre, abdominal muscles, respiratory centre and cranial nerves [13]. The central pathway is mostly responsible for causing delayed CINV. The vomiting centre is stimulated by afferent impulses from the chemoreceptor trigger zone and cerebral cortex [14,15]. Various neurotransmitters and their receptors are involved in these pathways, most importantly dopamine, 5HT 3 and substance P [16]. Most antiemetic drugs target these neurotransmitters and their receptors. Others include neurokinin-1, corticosteroids, acetylcholine, histamine, opioid and cannabinoid receptors [17].

Chemotherapy drugs are classified according to their intrinsic emetogenicity. A classification scheme was developed by Hesketh and colleagues, which defined the emetogenicity of individual drugs as well combination chemotherapy regimens [18]. A modification of this classification proposed by Grunberg is presently in use [19,20]. This classification divides chemotherapy drugs into four main subtypes based on the risk of developing emesis in the absence of antiemetic prophylaxis (Tables 1 and 2). More than 90% patients develop acute emesis after administration of highly emetogenic chemotherapy. Similarly, after administration of moderately emetogenic chemotherapy, 30-90% patients develop acute emesis and 10-30% do so after low emetogenic chemotherapy administration. In drugs or chemotherapy regimens classified as minimal emetogenic, less than 10% patients develop acute emesis. The emetogenic potential of some chemotherapy agents may vary as per the dose used [18]. Cisplatin is classified as highly emetogenic at doses of ≥ 50mg/m$^2$ , and moderately emetogenic at doses of <50 mg/m$^2$ [18]. Tables 1 and 2 lists the other chemotherapeutic drugs with emetogenicity varying as per doses.

| High | Moderate | Low | Minimal |
|---|---|---|---|
| Anthracycline/cyclophosphamide combination | Aldesleukin >12-15 million IU/m$^2$ | Ado- trastuzumab emtansine | Alemtuzumab |

| | | | |
|---|---|---|---|
| Carmustine >250 mg/m$^2$ | Amifostine >300 mg/m$^2$ | Amifostine ≤ 300 mg/m$^2$ | Asparaginase |
| Cisplatin | Arsenic trioxide | Aldesleukin ≤ 12 million IU/m$^2$ | Bevacizumab |
| Cyclophosphamide >1500mg/m$^2$ | Azacitidine | Belinostat | Bleomycin |
| Dacarbazine | Bendamustine | Blinatumomab | Bortezomib |
| Doxorubicin ≥ 60 mg/m$^2$ | Busulfan | Brentuximab vedotin | Cetuximab |
| Epirubicin >90 mg/m$^2$ | Carboplatin | Cabazitaxel | Cladribine |
| Ifosfamide ≥ 2 g/m$^2$ per dose | Carmustine ≤ 250 mg/m$^2$ | Carfilzomib | Cytarabine <100 mg/m$^2$ |
| Mechlorethamine | Clofarabine | Cytarabine (low dose) 100-200 mg/m$^2$ | Daratumumab |
| Streptozocin | Cyclophosphamide ≤ 1500 mg/m$^2$ | Docetaxel | Decitabine |
| | Cytarabine >200 mg/m$^2$ | Doxorubicin (liposomal) | Denileukin diftitox |
| | Dactinomycin | Eribulin | Dexrazoxane |
| | Daunorubicin | Etoposide | Elotuzumab |
| | Dinutuximab | Fluorouracil | Fludarabine |
| | Doxorubicin <60 mg/m$^2$ | Floxuridine | Interferon alfa ≤ 5 million IU/m$^2$ |
| | Epirubicin ≤ 90 mg/m$^2$ | Gemcitabine | Ipilimumab |
| | idarubicin | Interferon alfa >5-<10 million IU/m$^2$ | Methotrexate ≤ 50 mg/m$^2$ |
| | Ifosfamide <2 g/m$^2$ per dose | Irinotecan ( liposomal) | Nelarabine |
| | Interferon alfa ≥ 10 million IU/m$^2$ | Ixabepilone | |
| | Irinotecan | Methotrexate >50 mg/m$^2$-<250 mg/m$^2$ | Obinutuzumab |
| | Melphalan | Mitomycin | Ofatumumab |
| | Methotrexate ≥ 250 mg/m$^2$ | Mitoxantrone | Panitumumab |
| | Oxaliplatin | Necitumumab | Pegaspargase |
| | Temozolamide | Omacetaxine | Peginterferon |
| | Trabectedin | Paclitaxel and nabpaclitaxel | Pembrolizumab |
| | | Pemetrexed | Pertuzumab |
| | | Pentostatin | Ramucirumab |
| | | Pralatrexate | Rituximab |
| | | Romidepsin | Siltuximab |
| | | Talimogene laherparepvec | Temsirolimus |
| | | Thiotepa | Trastuzumab |
| | | Topotecan | Valrubicin |
| | | Ziv-aflibercept | Vinblastine |
| | | | Vincristine |
| | | | Vincristine (liposomal) |

| | | | |
|---|---|---|---|
| | | | Vinorelbine |

**Table 1:** Classification of Intravenous chemotherapy drugs/regimens based on emitogenic potential.

| High /moderate | Low /Minimal |
|---|---|
| Altretamine | Afatinib |
| Busulfan | Alectinib |
| Ceritinib | Axitinib |
| Crizotinib | Bexarotene |
| Cyclophosphamide ≥ 100 mg/m$^2$/day | Bosutinib |
| Estramustine | Busulfan (<4 mg/day) |
| Etoposide | Cabozantinib |
| Lenvatinib | Capecitabine |
| Lomustine (single day) | Chlorambucil |
| Mitotane | Cobimetinib |
| Olaparib | Cyclophosphamide <100 mg/m$^2$/day |
| Panobinostat | Dasatinib |
| Procarbazine | Dabrafenib |
| Temozolomide (>75 mg/m$^2$/day) | Erlotinib |
| Trifluridine/tipiracil | Everolimus |
| | Fludarabine |
| | Gefitinib |
| | Hydroxyurea |
| | Ibrutinib |
| | Idelalisib |
| | Imatinib |
| | Ixazomib |
| | Lapatinib |
| | Lenalidomide |
| | Melphalan |
| | Mercaptopurine |
| | Methotrexate |
| | Nilotinib |
| | Osimertinib |
| | Palbociclib |
| | Pazopanib |
| | Pomalidomide |
| | Ponatinib |
| | Regorafenib |
| | Ruxolitinib |
| | Sonidegib |
| | Sorafenib |
| | Sunitinib |
| | Temozolamide (≤ 75 mg/m$^2$/day) |
| | Thalidomide |
| | Thioguanine |
| | Topotecan |
| | Trametinib |
| | Tretinoin |
| | Vandetanib |
| | Vemurafenib |
| | Vismodegib |
| | Vorinostat |

**Table 2:** Classification of oral chemotherapy drugs based on emitogenic potential.

Complete prevention of CINV should be the goal for any antiemetic regimen. Four major classes of agents are used for the same, either as a single agent, or as part of a combination regimen. These are type three 5hydroxytryptamine (5HT3) receptor antagonists, the neurokinin1 receptor (NK1R) antagonists, glucocorticoids and the antipsychotic medication olanzapine.

Various studies have demonstrated that 5HT3 antagonists used in combination with dexamethasone are more effective for the treatment and prophylaxis of CINV, with a better side effect profile than high dose metoclopramide plus dexamethasone [21-24]. The first generation 5HT3 antagonists include ondansetron, granisetron, dolasetron, ramosetron and tropisetron. Commonly used are ondansetron and granisetron. They appear equally effective in preventing acute or delayed CINV [25]. Oral formulations are equally effective as intravenous (IV) formulations [26-28]. Common side effects include headache, malaise, constipation and ECG changes. All first generation 5HT3 antagonists can cause ECG interval changes. These are most commonly seen after one to two hours and usually return to baseline within 24 hours [29-31]. Most changes are insignificant; however there have been case reports of QTc prolongation leading to development of serious arrhythmias like torsade de pointes [29,31,32]. ECG changes have not yet been reported in transdermal and extended release subcutaneous granisetron formulations [33,34]. Care must be taken while prescribing 5HT3 receptor antagonists in patients with cardiac disease, bradyarrythmias, and older patients, those with renal impairment and on other drugs known to cause QT interval prolongation. ECG monitoring and QTc

interval monitoring must be done regularly in such patients, and dyselectrolytemias should be corrected. Oral dosing of ondansetron has fewer propensities for causing arrhythmias as compared to the IV dosing [35]. As per the FDA recommendations single IV dose of ondansetron should not exceed 16 mg and its use should be avoided in patients with congenital long QT syndrome [36].

Palonosetron is a second generation 5-HT3 receptor antagonist, with a 30 to 100 fold higher affinity for the receptor, as well as a long half-life of 40 hours [37]. As seen in several large randomised phase three trials, palonosetron is equally effective when compared to ondansetron [38], granisetron [39] and dolasetron [40] in preventing acute emesis and more effective in preventing delayed emesis. Importantly, QTc prolongation has not been described with palonosetron [41,42]. Updated antiemetic guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend palonosetron as the preferred 5HT3 antagonist for patients who receive moderately emetogenic chemotherapy [43-45].

Neurokinin 1 (NK1) receptor antagonists include aprepitant and fosaprepitant. Aprepitant selectively blocks the binding of substance P at the NK1 receptor in the central nervous system and fosaprepitant is a parenteral water soluble prodrug of aprepitant. Various trials have evaluated the efficacy of these drugs in patients receiving highly emetogenic chemotherapy regimens. A metaanalysis of 17 trials evaluated the benefit of combining aprepitant with standard antiemetics in highly and moderately emetic chemotherapy regimens. The addition of aprepitant was associated with a significant improvement in the rate of complete response, i.e. absence of emesis and no need for rescue antiemetics [46].

Various other trials have demonstrated similar results in highly emetic chemotherapy regimens [47,48]. Aprepitant also significantly improved the ability to prevent nausea and vomiting in carboplatin containing regimens when combined with dexamethasone and a 5HT3 receptor antagonist [49-52]. Aprepitant needs to be combined with dexamethasone and a 5HT3 receptor antagonist to provide maximum efficacy as compared with only aprepitant and dexamethasone, especially in cisplatin based regimens [53]. Aprepitant is a substrate of, and induces as well as inhibits cytochrome p450 3A4 (CYP3A4). Is also induces CYP2C9 [54]. Hence care must be taken while using other drugs which are known to be metabolised by these enzymes.

Netupitant is a highly selective NK1 receptor antagonist and its oral fixed drug combination with palonosetron-NEPA, containing 300 mg of netupitant and 0.5 mg of palonosetron has been studied in combination with dexamethasone in patients receiving moderately or highly emetogenic chemotherapy. FDA has approved NEPA for the prevention of CINV based on the results of 2 randomised trials [55,56], which showed superior prevention of CINV by NEPA and steroid combination as compared to a combination of aprepitant, 5HT3 antagonist and dexamethasone.

Dexamethasone is an important component of most anti-emetic regimens. A number of randomised trials have established efficacy either as a single agent or in combination. Dexamethasone was found to be superior to placebo or no treatment with regard to both acute and delayed emesis in a meta-analysis of 32 randomised trials in patients receiving moderately or highly emetogenic chemotherapy regimens [57].

Olanzapine is an atypical antipsychotic drug, with antagonism of multiple receptors including dopamine D2 receptors, serotonin, 5HT2 receptors and acetylcholine- muscarinic receptors. Various trials have explored the efficacy of olanzapine in preventing both acute and delayed CINV. A metaanalysis of 10 randomised trials in patients receiving highly or moderately emetogenic chemotherapy [58] demonstrated the efficacy of olanzapine in preventing both acute and delayed emesis. However some of these studies did not use standard antiemetic regimens, especially use of a NK1 receptor antagonist. Two phase three trials have shown the efficacy of adding olanzapine to regimens containing NK1R antagonist, a 5HT3 antagonist, and a glucocorticoid [59,60]. The drug seems especially beneficial in preventing delayed nausea. Guidelines have included olanzapine in antiemetic regimens for both moderately and highly emetic chemotherapy [45].

While prescribing antiemetics, it is important to know the period of risk, and hence use drugs for the appropriate amount of time. The risk of vomiting lasts for 3 days for highly emetogenic regimens and for 2 days for moderately emetogenic chemotherapy regimens [45]. Antiemetic therapy is based on the drug with the highest emetic risk in patients receiving multi drug regimens.

NCCN guidelines recommend regimens containing combinations of 5HT3 antagonist, dexamethasone, NK1 receptor antagonist and olanzapine for highly emetogenic chemotherapy regimens [45]. Aprepitant is used at an oral dosage of 125 mg on day 1, 80 mg on day 2 and 3. If fosaprepitant is used, it is given as a single IV dose of 150 mg on day 1 only. Dexamethasone is used either as an oral or IV dose of 12 mg on day 1. Either dolasetron 100 mg, granisetron 0.01 mg/kg ( max 1mg) IV, ondansetron 16-24 mg PO once or 8-16 mg IV once or palonosetron 0.25 mg IV once on day 1 can be used. Dexamethasone is continued at 8 mg PO/IV daily from day 2 to day 4. MASCC-ESMO guidelines recommend similar regimens [61]. An alternate regimen consists of olanzapine 10 mg orally on days 1 to 4 with palonosetron 0.25 mg and dexamethasone 20 mg IV on day 1. A third regimen consists of giving NEPA on day 1, with dexamethasone 12 MG PO/IV on day 1, continued as 8 mg PO/IV on days 2 to 4. Lorazepam, can also be added, as it decreases anxiety, and is especially useful to prevent anticipatory nausea and vomiting [62]. Antacids (proton pump inhibitors, H2 blockers) may also be added, especially if patients have dyspepsia.

For chemotherapy regimens at moderate risk for emesis, NCCN guidelines recommend a 5 HT3 antagonist, steroid with or without a NK1 receptor antagonist on the first day [45]. If an NK1 antagonist is not used, then either 5HT3 receptor antagonists or steroids are to be given on day 2 and day 3. If an NK 1 receptor antagonist is given on day 1, then steroids may be given on days 2 and 3. MASCC-ESMO as well as NCCN recommends adding NK 1 receptor antagonists to patients receiving carboplatin based chemotherapy [45,61]. Patients receiving chemotherapy drugs or regimens with low risk of emesis should receive either dexamethasone or metoclopramide or a 5HT3 receptor antagonist, repeated daily in case of multi day protocols. Patients receiving chemotherapy with minimal emetogenic potential do not require any routine prophylaxis [45].

Breakthrough nausea and vomiting may be treated with adding an agent from a different drug class [9]. Refractory CINV may need a change in the prophylactic regimen. Various drugs include olanzapine, metoclopramide, haloperidol, lorazepam, and cannabinoids [45]. The antiemetic regimen used should be reassessed and it should be confirmed that adequate drugs were used according to the risk of emetogenicity in the first place. The appropriate drugs should be added if not used initially. Other potential causes causing breakthrough

nausea and vomiting should be excluded. These include dyselectrolytemia, bowel obstruction or brain metastasis [45]. A Cochrane database analysis review of 23 randomised trials found that patients who received cannabis based medicines experienced lesser nausea and vomiting as compared to conventional anti-emetics. More patients experienced side effects, in spite of which cannabis based medications were preferred over conventional medications [63]. There may be a place for these in patients with refractory nausea and vomiting. Similarly, low alcohol consumption is a known risk factor for increased CINV along with various other risk factors like female patients, younger age, presence of anxiety [64-66]. These factors are currently not used to choose or change the antiemetic regimens. Randomised controlled trials or the development of nomograms based on these risk factors may have a role in personalised anti-emetic regimens in the future.

## Conclusions

Oncology care providers are concerned about oncologic outcome so much that they start undermining the complications of therapy which directly affects quality of life. One must be careful in assessing the real depth of the iceberg and not only the tip when handling one of the distressing complications of chemotherapy like CINV. Adequate control of CINV can lead to better patient compliance and might be having bearing on ultimate outcomes also. The optimization of the treatment should be made according to the emetogenicity of the chemotherapy regimen with different permutation-combination of NK1 receptor antagonist, 5HT3 receptor antagonist and corticosteroid. Ancillary drugs like olanzapine and lorazepam may also prove beneficial and should be judiciously used to their full potential. There might be scope for personalised management of CINV based on individual risk factors. Let's not allow the fear of CINV to make "the wolf bigger than he is!"

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