

Pharmacological Treatment of Cancer Induced Nausea and Vomiting: A Literature Review

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Abstract

Cancer induced nausea and vomiting has detrimental effects on health of patients. This review describes what causes this cancer induced nausea and vomiting as well as what are current available pharmacological treatments of this condition. The review concludes that although pharmacological treatments are a good way of treatment and it has many side effects and currently needs much improvement. The improvement can be brought by better understanding of functioning of receptors and pathways involved in causing nausea and vomiting.

Keywords: Anti-emetics; Nausea and vomiting; Cancer chemotherapy

Introduction

Nausea and vomiting are two unfortunate adverse effects of cancer chemotherapy. Antineoplastic drug induced nausea and vomiting (AINV), more commonly referred to as cancer induced nausea and vomiting (CINV), has detrimental impacts on not only the quality of life of the patient but also their caregivers [1]. Patients undergoing chemotherapy are subjected to the mental, emotional and physical strains of being diagnosed as a cancer patient, and when compounded with the destructive effects of treatment, make for an overall decline in their well-being. The loss of appetite that results from nausea and emesis can subsequently cause weight loss and thereafter malnutrition, further spurring the damaging effects of chemotherapy.

Nausea is defined by the National Cancer Institute as “a queasy sensation or the urge to vomit”, a sensation triggered by stimuli to the chemoreceptor trigger zone (CTZ) on the floor of the fourth ventricle, outside the blood brain barrier [2]. The CTZ contains acetylcholine, dopamine, serotonin, cannabinoid and opioid receptors [2], which thus serve as the targets for antiemetic therapy. Although it is difficult to measure nausea considering that it is a subjective sensation, an attempt has been made to quantify it using the Visual Analogue Scale (VAS) on a scale of 0-10 or 0-100 (10 or 100 is maximal nausea), or the Likert scale, where nausea is measured with in a discrete manner with ratings of non, mild, moderate or severe nausea [2].

Emesis, or vomiting, is the reflexive act of ejecting the stomach contents through the mouth. This reflex originates from the gastrointestinal tract, which sends afferent impulses *via* the cerebral cortex, CTZ, pharynx and vagal afferent fibres to the vomiting centre in the medulla. Efferent impulses from the vomiting centre travel to the abdominal muscles, salivation centre, cranial nerves and respiratory centre, producing the vomiting response [3]. The effects of emesis include not only dehydration, dyselectrolytemias, aspiration pneumonia, wound dehiscence, upper GI injury and or hemorrhage, malnutrition and psychological stress, but also poses the risk of

increased tendency to reduce compliance to treatment, thereby affecting the overall prognosis [1].

There are a number of predisposing factors for anticipatory nausea and vomiting (ANV) such as susceptibility to motion sickness, awareness of tastes or odor, younger age, lengthier infusions, greater autonomic sensitivity and general anxiety or emotional distress [4]. There are also numerous paediatric conditions which possess high emetic risk, including sarcomas, Wilms tumor, neuroblastoma, hepatoblastoma, medulloblastoma, lymphomas and myeloid leukemias [1]. Because the chemotherapy treatment for these conditions contain similar chemicals such as anthracyclines, cyclophosphamide, methotrexate etcetera, they all possess similar emetic risks.

While there are a number of non-anti emetic treatments and behavioral techniques that aim to reduce nausea and emesis, such as hypnosis, benzodiazepines and progressive muscle relaxation [4] and acupuncture, acupressure, music therapy and psychoeducational support [1], pharmacological treatments are the mainstay of treatment for CINV.

Literature Review

This Chemotherapeutic agent are known to induce nausea and vomiting, but the risks vary between drugs. Such pharmacological treatments are classified as having minimal, low, moderate, and high emetic risk based on their potential to cause emesis in the absence of prophylaxis [1]. The label high emetic risk (HEC) is given for agents that carry a greater than 90% risk of emesis, moderate emetic risk (MEC) if the risk is 30-90%, and low emetic risk (LEC) if the risk is 10-30%. Minimal emetogenic therapy indicates chemotherapeutic agents whose risk in developing emesis is less than 10%. Minimal emetogenic drugs include bortezomib, hormones, vinblastine, vinca alkaloids, vinorelbine and bleomycin [5]. Examples of LEC drugs include etoposide, 5-fluorouracil, gemcitabine, mitoxantrone, taxanes and topotecan. MEC drugs include anthracyclines, carboplatin, carmustine (high dose), cyclophosphamide, ifosfamide, irinotecan, methotrexate (high dose) and oxaliplatin. Examples of drugs with high emetogenic potential include: Cisplatin, dacarbazine, melphalan,

nitrogen mustard, and the combination of cyclophosphamide plus an anthracycline. These drugs induce emesis in nearly all patients.

Serotonin antagonists, or 5-HT₃ antagonists, are one class of chemotherapeutic agents. These drugs target the serotonin receptor in the vagus nerve, brain and gut enterochromaffin cells. Serotonin is produced in the small intestine in response to chemotherapy. There are two generations of serotonin antagonists, the first of which has a higher potency, longer half-life and different molecular interaction than the second generation [2]. Examples of first-generation drugs include dolasetron, granisetron, palonosetron, tropisetron and most popularly, ondansetron. The early generation 5-HT₃ receptor antagonists (5-HT₃ RA) are more efficacious and tolerable than older antiemetics such as phenothiazines and metoclopramide. Second generation serotonin receptor antagonists such as palonosetron have a 30x higher affinity to the serotonin receptor at central and gastrointestinal (GI) sites, although the main site of action was found to be at the gastrointestinal tract [2]. Palonosetron is the drug of choice for prechemotherapy as well as acute and delayed CINV due to its pharmacokinetic and pharmacodynamic profile, but ondansetron and granisetron are viable substitutes [5]. However, there are a few adverse effects associated with 5-HT₃ RA such as mild headache, constipation, and increased risk for developing abnormal electrical heart activity [5], which will be discussed later.

Another class of drugs used in the pharmacological treatment of CINV are dopamine antagonists. The phenothiazines such as chlorpromazine and levomepromazine act on the dopamine (D₂) receptors in the CTZ and the periphery, but their use may be limited by side effects [5]. One of the more popular dopaminergic competitive antagonists is metoclopramide, a drug commonly used to increase gastric motility [5]. The side effects of metoclopramide are thus commonly related to disturbances in the GI tract such as diarrhea, however extrapyramidal side effects such as akathisia, dystonic reactions and sedation have also been noted [4].

Neurokinin-1 receptor antagonists (NK1RA) are upcoming antiemetics used to relieve the discomforts of CINV. Since Substance P can cause emesis mediated through NK-1 receptors, the NK1RAs are effective in inhibiting the vomiting reflex [4]. Oral aprepitant and the prodrug fosaprepitant are NK1RAs recently approved for the treatment of CINV for patients receiving HEC and MEC. However, the side effects were notable, including alopecia, anorexia, asthenia and fatigue, constipation, diarrhea, headache, hiccups and nausea [5]. Rolapitant is a highly selective, long acting NK1RA commended for its high CNS penetrance [5].

For less severe cases, notably the treatments associated with LEC regimens, corticosteroids are administered. Currently, the way in which corticosteroids deliver their antiemetic action is unclear. Dexamethasone and methylprednisolone are two of the most widely used corticosteroids for CINV, both of which are clinically similar in terms of their efficiency [4].

In many cases, physicians do not prescribe a single agent but rather a combination of drugs from different classes in order to provide optimal antiemetic action. For example, while corticosteroids were found to be useful in treating LEC, they were found to be more effective when combined with a 5-HT₃ antagonist including ondansetron and granisetron, especially for MEC [4].

Researchers found higher rates of complete response when NK1RAs were combined with serotonin antagonists and corticosteroids [4]. Overall, rolapitant (200 mg) combined with 5-HT₃RAs and

dexamethasone are considered safe and well tolerated for MEC or HEC [5]. The addition of NK-1 inhibitors was found to be effective when two moderately emetogenic agents such as adriamycin and cyclophosphamide were employed [4]. Another recently approved treatment for delayed CINV is NEPA, which contains a fixed dose of combination of netupitant and palonosetron, which targets NK-1 and 5-HT₃ receptors, in cases where cyclophosphamide is employed [5].

While different combinations of anti-emetic medications exist, there are also other factors which contribute to nausea and subsequently emesis, as mentioned previously. Lorazepam may be added to alleviate anxiety-related symptoms, and scopolamine can be effective for patients with motion sickness [4].

Although the anti-emetic drugs previously described are frequently used and efficacious, there are certain side effects which need to be considered. One of the most severe adverse effects of antiemetic drugs is cardiotoxicity. Although rare, the prolongation of the QT interval is a potentially fatal side effect due to its tendency to progress to Torsades de pointes, an abnormal electrical heart rhythm [6]. Torsades de pointes secondary to QT prolongation is most closely associated with serotonin antagonist anti-emetics, specifically ondansetron, however this can be avoided by reducing the dose and increasing the infusion duration [6]. Other drugs associated with QT prolongation include dolasetron, metoclopramide and olanzapine, and are thus advised to be closely monitored when prescribed. Other cardiotoxicities include arrhythmias and ECG changes, notably granisetron and betamethasone, a dopamine receptor antagonist.

Another cardiac-related adverse effect is heart rate reduction. Heart rate reduction is a poorly understood side effect of anti-emetics. Tropisetron, palonosetron, aprepitant, fosaprepitant and NEPA are all noted to have decreased heart rate, however the QT interval does not appear to be affected [6]. Thus, physicians must be aware of the patient's full medical history before prescribing anti-emetics. Patients with electrolyte abnormalities such as hypokalemia or hypomagnesia must be treated prior to anti-emetic treatment so as not to exacerbate the pre-existing condition. Congestive heart failure and bradyarrhythmias are contraindications for the drugs which reduce heart rate. Physicians must also be aware of the patient's current medications, as other drugs known to prolong QT interval or cause electrolyte abnormalities can have synergistic effects and have potentially fatal consequences [6].

Physicians must also be aware of antiemetic drug overuse. According to Lancet Oncology, researchers noted overuse of antiemetic drugs in 163, 451 patients (24.1%) in the United States in a study of 678, 220 cancer patients undergoing chemotherapy. The overuse of antiemetic drugs was an "unnecessary treatment...which generates unnecessary patient and societal costs", according to Amy Davidoff, a Yale School of Medicine graduate and researcher of patients undergoing chemotherapy [7].

Researchers are continuously coming up with new treatments for nausea and vomiting in chemotherapy. Currently, the oral route is recommended for anti-emetic treatment, but it is not always convenient. For certain populations, such as the elderly or for young children, it should be noted that the oral route is not always effective, such as when motor coordination is impaired or has yet to be matured, respectively. Additionally, ondansetron has a short half-life and a high first pass metabolism [8]. Considering that the intravenous route is uncomfortable, especially when it is potentially being used frequently, it is perhaps more appropriate to explore different routes of

administration. Researchers are currently investigating a transdermal formulation containing three antiemetics: ondansetron, dexamethasone and aprepitant. Five vehicles are highlighted by Fagron's company for the administration of transdermal antiemetics, named Phytobase, Lipovan, Pentravan, Pentravan Plus and Pluronic Lecithin Organogel (PLO). It is important to note that the transdermal route of administration requires complex vehicles to solubilize, release and permeate the drug through the skin, all while still maintaining skin hydration and limiting irritation [8]. Although this research is still in the process of being developed, there has been notable interest to use Fagron vehicles to deliver semi-solid transdermal anti-emetics to treat CINV.

Antiemetic Guidelines

There are several bodies that provide recommendations on antiemetic regimens, tailored to the emetic risk of chemotherapy agents a patient is taking. The American Society of Clinical Oncology (ASCO) provides guidelines to help clinicians personalise antiemetic treatment for various antineoplastic regimens and/or radiation therapy for cancer [9]. The ASCO guidelines stem from a systematic review of the most recent research pertaining to antiemetics in chemotherapy, conducted by an expert panel. The first version was published in 1999, and it was most recently revised in 2017, taking into account studies performed within the period of 2009-2016. The European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) produce their own guidelines for both chemotherapy and nausea induced emesis [10]. The first set of guidelines were published in 2010 in the Annals of Cancer, and the latest version included a revision in 2016 to include studies from 2009-2015. The MASCC guidelines are also based on the conclusions of an expert panel, after discussing the most recent research in the field. The NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines) were first published in 1997, and updated almost yearly by an expert panel. Contrasting from ASCO and MASCC, they provide specific antiemetic treatment regimens including specific drugs, rather than broader recommendations involving classes of antiemetics [11].

Antiemetics for low and minimal emetic risk chemotherapy

There is consensus among the ASOC and MASCC guidelines that patients receiving low emetic risk treatments should be given a single antiemetic agent. The MASCC guidelines recommend selecting one from dexamethasone, 5-HT₃ RA or a dopamine RA [10], whereas the ASOC guidelines do not include the dopamine RA in their recommendations [9]. Both guidelines agree that no prophylactic antiemetics should be given with minimal emetic risk agents. The NCCN guidelines as of 2017 do not provide any specific guidelines with regards to this.

Antiemetics for moderate emetic risk chemotherapy

Both ASOC and MASCC conclude that patients treated with carboplatin (Area under the curve <4 mg/mL per minute, classified as MEC) should be given a three-drug combination of NK1 RA, a 5-HT₃ RA, and dexamethasone [9,10]. The addition of the NK1 RA has been adopted by both guidelines in their newest revision, and is based on multiple phase II and III trials. The guidelines differ slightly in the course of administration; ASOC guidelines suggest that antiemetic treatment on the day of chemotherapy is sufficient whereas MASCC guidelines recommend continuing the use of aprepitant on days 2 and 3 if it is the chosen NK1 inhibitor on day 1. The ASOC guidelines

provide recommendations for treatment with other antiemetics in the event that carboplatin is not the moderate emetic risk drug of choice, and recommend a two drug combination of a 5-HT₃RA, and dexamethasone given on day 1. The NCCN [11] guidelines give six options for moderate emetic risk chemotherapy. Three of these are similar to the treatment for high emetic risk drugs, whereby the regimen is a combination of an NK1 RA (Aprepitant, Fosaprepitant or Rolapitant), a 5-HT₃ RA, and dexamethasone given on the first day of treatment. The NK1 RA chosen determines the subsequent treatment regimen on days 2 and 3. The other options are to use either an NK1 RA (Netupitant) or 5-HT₃ RA (Palonosetron) with dexamethasone and continue the dexamethasone on days 2 and 3, Olanzapine, Palonosetron, and dexamethasone and continue olanzapine on days 2 and 3, or choose from a selection of 5-HT₃ RA alongside dexamethasone, and continue both on days 2 and 3.

Antiemetics for high emetic risk chemotherapy

For single day treatment with HEC agents like cisplatin, the ASOC guidelines recommend a NK1 RA, a 5-HT₃ RA, dexamethasone and olanzapine given on the first day of treatment (day 1), with the continuation of the latter two on days 2-4. An important change in the 2017 guidelines is the addition of olanzapine (an atypical antipsychotic commonly used in the treatment of conditions like schizophrenia) [9]. This is in contrast to the MASCC guidelines, which suggests that olanzapine for cisplatin therapy should be used with caution, as the studies recommending its use are of 'moderate to low quality' [10]. The same study [12] that led to ASCO's changing guidelines was regarded by MASCC as having several shortcomings including its being an open study and having a small sample size, leading to the conclusion that the 10mg recommended by the study may have adverse side effects like sedation, and has no added effect on emesis treatment for HEC. Hence, MASCC recommends a three-drug regimen including a single dose of a 5-HT₃ RA, dexamethasone and an NK1 RA, while acknowledging that olanzapine may be an option for delayed emesis, or if nausea remains a problem. For both guidelines, other updates for this category include the use of Rolapitant as an option when choosing an NK1 inhibitor, following its approval by the FDA in 2015. The NCCN guidelines suggest six different treatment regimens, in no order of preference [13]. The first three are a combination of an NK1 RA (Aprepitant, Fosaprepitant or Rolapitant), a 5-HT₃ RA, and dexamethasone given on the first day of treatment. The NK1 RA chosen determines the subsequent treatment regimen on days 2, 3, 4, with aprepitant and dexamethasone being continued if administered in combination on day 1, or only dexamethasone if another NK1 RA was selected. The fourth treatment is either a 5HT₃ RA or NK1 RA, with dexamethasone on day 1, and dexamethasone being continued on days 2-4. The fifth regimen is Olanzapine, Palonosetron (5-HT₃ RA) and dexamethasone, with the olanzapine continued on days 2-4 [14].

Antiemetics for combination therapy and chemotherapy preceding stem cell transplant

Both ASOC and MASCC guidelines agree that with combination therapy, the antiemetic therapy should be based on the agent with the highest emetic risk [9,10]. When treating with chemotherapy preceding a stem cell transplant, both ASOC and MASCC recommend a three-drug combination of dexamethasone, 5-HT₃ RA, and an NK1 inhibitor. The MASCC guidelines specify aprepitant as the NK1 inhibitor of choice and recommend that it be continued on days 2-4.

Antiemetics for breakthrough emesis

The MASCC guidelines define breakthrough emesis as ‘emesis and/or nausea occurring on the day of chemotherapy despite guideline-recommended prophylaxis’ [10], and suggest olanzapine at 10mg for 3 days, but being mindful of side effects such as sedation, especially in elderly patients. While not a formal recommendation, they also cite it as ‘reasonable’ to add another antiemetic agent with a different mechanism of action to the ones already being used. The ASCO guidelines suggest reevaluating emesis risks and comorbidities, and interactions with other medications, and then re-evaluate the prophylactic emesis treatment regimen [9]. The NCCN guidelines follow a similar approach, giving a list of potential antiemetics that can be added, and re-evaluated depending on the response [11].

Discussion and Conclusion

The cancer chemotherapy regimen is a physically and emotionally taxing process. One of the most detrimental effects of this process is the sensation of nausea and subsequent emesis. Such effects subsequently result in appetite loss and general health decline in addition to the detrimental effects of chemotherapy.

Current anti-emetic treatments aim to cater to different emetic potentials of chemotherapeutic agents. Each of the drug classes are specifically directed to a single receptor, but unfortunately, the sensation of nausea involves a myriad of receptors and pathways. In an attempt to target multiple pathways, combination therapies have been proposed and found to be effective. However, like all other drug regimens, the anti-emetics have other side effects, some of which are potentially fatal, such as cardiotoxicity.

There are a number of bodies that provide guidance on different treatments which are constantly reappraised and re-evaluated, reflecting the evolving field of antiemetic treatment. Research is being developed and new pharmacological treatments are being explored in an effort to ease the physical and subsequently emotional burden of cancer chemotherapy. Cancer is still a poorly understood disease process, and although there has yet to be a cure, it is still in the best interests of the global community to continue research into the pharmacological treatment of CINV to alleviate the suffering of the individuals still fighting for a chance to survive.

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