R E V I E W

Chemotherapy-induced Nausea and Vomiting: Pharmacotherapy Update and Trends for Better Control

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Abstract: Nausea and vomiting are major concerns for patients who have to receive chemotherapy for an underlying malignancy. In this review, these concerns faced by patients receiving chemotherapy are presented along with discussion of the mechanisms of chemotherapy induced nausea and vomiting. Major targets of the $5HT_3$ antagonists, the NK1 antagonists and the dopamine antagonists are discussed along with the commonly utilized anti-emetics. The guidelines for use of these supportive care measures are reviewed along with drug-drug interactions of the available anti-emetics and chemotherapy. The cost effectiveness of using antiemetics is presented with a discussion of the limitation of the currently available studies. The need for additional studies to guide health care providers regarding the best use of anti-emetics for chemotherapy induced nausea and vomiting is discussed.

Keywords: chemotherapy induced nausea and vomiting, anti-emetics, cancer chemotherapy

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Introduction

For most malignancies, the incidence increases with advancing age. As the population of those >65 years of age continues to increase, it is likely that an increasing number of cancers will be recognized. The current SEER data indicate that 1,479,350 men and women will be diagnosed with cancer in 2009 in the USA.[1]

Most malignancies are treated with surgery, radiotherapy and/or chemotherapy, depending on the location of the cancer, the opportunity to completely remove the tumor and the likelihood that the tumor will recur locally or metastasize. Of these therapeutic options for patients, the most dreaded is chemotherapy. It is not unusual for patients to make decisions about desired treatments on the basis of whether chemotherapy will be given or not. Chemotherapy administration brings to mind thoughts of extensive nausea and vomiting, two of the most feared side effects associated with chemotherapy administration.[2–4] It is not unusual for patients to either forego chemotherapy due to their fear of chemotherapy induced nausea and vomiting [CINV] or quit chemotherapy after the initial cycle or cycles of chemotherapy during which the patient experienced less than adequately controlled CINV.[2]

Several models have been developed for early breast cancer, based on the gene array profile of the patient and/or the tumor removed, that may predict with a large success rate, based on clinical trials, if a tumor will recur locally or spread distantly.[5] Such a tool is useful to clinicians and patients alike as a determination is made about the utility of chemotherapy. Unfortunately, such a tool is not yet available for most other also commonly occurring tumors. Thus, the choice to receive or not receive chemotherapy is not based on scientifically rigorous methods as in the early breast cancer model. Patients then face not only the uncertainty of whether the chemotherapy will provide any benefit but they also face the almost certainty of nausea and vomiting associated with the chemotherapy.

With the advent of personalized medicine, pharmacogenomics is a new field in which drug combinations and scheduling are optimized for an individual's unique genetic make-up. Identification of such genetic features that may predispose a patient to have more significant CINV problems without some apparent drug metabolism change has not been accomplished.

This review will further define the problems that patients face in regards to CINV, the mechanism of action of anti-emetics, what is known and not known about the currently recommended anti-emetic regimens, the cost effectiveness of these anti-emetics and what models exist that may be useful in the future to predict what can be done to minimize the problem for those requiring emetogenic chemotherapy.

What Patients Face

In the specialty of palliative medicine, younger age, tumor type and chemosensitivity are important predictors of patients receiving palliative chemotherapy.[6] However, on further analysis, it was the individual clinician who was the only predictor for continuing chemotherapy in the last 4 weeks of life. Prior to that time, it is commonly recognized that it is the patient who determines whether chemotherapy is continued or not. CINV has been and still is among the most feared adverse effects by patients before starting therapy.[4] It is always disconcerting when a patient with a potentially curable cancer decides to discontinue treatment due to intolerable CINV. Preconceived notions about chemotherapy however may not persist throughout an entire course of treatment.[7] When patients are properly educated about the management of CINV, patient attitudes may change as early as the third chemotherapy cycle.[7] A recent survey found that nurses have a zero tolerance for CINV and will often delay chemotherapy if CINV remained uncontrolled.[8] In the same survey, the intolerance for CINV when caring for patients was for physicians only half what it was for nurses.

Phases of Chemotherapy Induced Nausea and Vomiting

CINV is divided in three distinct phases: anticipatory, acute and delayed.[9,10] For single day administered systemic chemotherapy, acute CINV is defined as the first 24 hours and delayed CINV is defined as the time from 25 hrs to 120 hrs following administration. These arbitrary dividing times are useful for selecting therapies that work in concert to effectively control CINV in both phases since some therapy exerts a greater effect in one phase over another. However, these definitions do not adequately describe phases of chemotherapy administration that may last for more than one day.[9] When does the acute phase end and the delayed phase

begin? How long will the delayed phase last after multi-day chemotherapy administration? Considering the fact that even with preventive measures, CINV may persist unabated for several weeks after a single course of chemotherapy, these questions about multi-chemotherapy take on added importance for the clinicians managing the supportive care for cancer patients as they best determine, without adequate clinical guidelines, how to manage nausea and vomiting. In addition, patients may experience anticipatory and breakthrough nausea and vomiting, particularly if the prophylactic or preventive measures used fail to adequately cover the patient.[11,12]

The development of anticipatory nausea is particularly troublesome because studies in breast cancer patients have shown that once anticipatory nausea has been established, this conditioning may contribute to the severity of post-treatment nausea.[13,14]

Pathophysiology of Emesis and Active Sites of Antiemetic Drugs

Although there are a variety of neurotransmitters involved in CINV and the emetic reflex, including dopamine, acetylcholine, endorphins, serotonin (5-hydroxytryptamine: 5HT), gamma-aminobutyric acid and histamine, the two key transmitters targeted with more recently developed compounds are the substance P receptors and the $5HT_3$ receptors, involved in serotonin release.[9] Many of the agents used to control CINV target the release of these substances, which directly trigger the emetic response.[9]

The $5HT_3$ receptor is a member of the ligand-gated ion channels. When serotonin, for example, binds to the $5HT_3$ receptor, this opens the channel which in turn leads to an excitatory response in neurons. In the central nervous system, this excitatory response will be manifest as anxiety. In the peripheral nervous system, the excitatory response will be more likely emesis. Identification of the $5HT_3$ receptor did not take place until 1986 but it was soon discovered the prominent role played by the $5HT_3$ receptor in CINV and in radiation induced vomiting. The signal of the serotonin receptors associated with vagal afferents from the GI tract is abolished by $5HT_3$ antagonists, of which there are currently a variety approved and on the market (Table 1). In an early clinical study, patients with cancer received prophylactic antiemetics prior to cisplatin and the urinary 5-hydroxyindoleacetic acid (5-HIAA), a marker of serotonin released, was measured.[15–18] Of interest was that 5-HIAA was highest in the first 24 hours after cisplatin infusions and 5-HIAA excretion returned to pre-cisplatin levels on subsequent days after the first day of the chemotherapy administration, suggesting that serotonin was not the mediator of delayed emesis. However other studies have shown that urinary concentrations of 5-HIAA extended beyond the initial 24 hours after cisplatin administration, suggesting that serotonin release is not just confined to this acute period of time.[19] The approval and successful treatment with long-acting $5HT_3$ antagonists, that extend into the period of delayed CINV, suggest that serotonin mechanisms do indeed play a role in the period of delayed CINV.[19]

Dopamine receptors are implicated in many neurological processes, including motivation, pleasure, cognition, memory, learning, and fine motor control, and in neuroendocrine signaling. Dopamine receptors are common neurologic drug targets and a variety of compounds have been used to target these receptors to control CINV.[20] Unfortunately use of haloperidol and droperidol, pure dopamine antagonists, have significant central nervous system toxicity which limits their front-line application to prevent or control CINV.[20]

Like dopamine antagonists, neurokinin NK1 antagonists have shown a broad spectrum of action treating diverse causes of nausea and vomiting. They are thought to work at the dorsal vagal complex in the medulla, thereby inhibiting the response that leads to gastric emptying. Laboratory studies have provided evidence that substance P release, in patients receiving chemotherapy, binds to these neurokinin receptors and thus triggers the emetic response.[21] NK1 antagonists have their effect predominantly in the delayed phase of CINV, when substance P binding to the NK1 receptors is most notable. NK1 receptor antagonists prevent binding of substance P to the NK1 receptors, thereby blocking the vomiting response.

Clinical Studies

Of the numerous studies that have been conducted over the years to improve the control of CINV for those who will receive moderately or highly emetogenic chemotherapy for an underlying malignancy, the most recently published study of casopitant highlights a number of difficulties with the design and conduct of any CINV study, the subsequent analyses

Table 1. Commonly used agents for CINV control.

Agent	Mechanism of action	Use	Usual dose, route and schedule
Ondansetron	Competitive inhibitor of 5-HT$_3$ receptor. Effect believed to be mediated primarily by inhibiting peripheral 5-HT$_3$ receptors.	Prevention of acute nausea/vomiting due to moderately or highly emetogenic chemotherapy.	Single (24 mg) or multiple (0.15 mg/kg every four hours × 3) doses given orally or intravenously; first dose given 30 minutes prior to chemotherapy. Doses of 32 mg IV used as prophylaxis in studies of antiemetics on day 1; doses of 8 mg IV and oral have been used on ongoing basic.
Palonosetron		Prevention of acute CINV due to highly emetogenic chemotherapy and acute and delayed CINV due to moderately emetogenic chemotherapy.	Single dose of 0.25 mg in adults is given intravenously 30 minutes prior to chemotherapy. Oral form 0.5 mg capsules for MEC only.
Granisetron		Prevention of CINV due to highly emetogenic and moderately emetogenic chemotherapy.	Oral 1 mg tablets taken as frequently as bid. Available as liquid for pediatric patients. Available as IV formulation, given in doses of 10 mcg/kg every 12 hours. Available as a transdermal patch, applied 24–48 hours prior to chemotherapy administration; patchcontains 34.3 mg Granisetron and delivers granisetron at a rate of 3.1 mg/24 hrs.
Aprepitant	Competitive inhibitor of NK$_1$ receptor. Effect believed to be mediated primarily by blocking central NK$_1$ receptors.	Prevention of acute and delayed CINV due to highly and select moderately emetogenic chemotherapy regimens.	125 mg orally 60 minutes prior to chemotherapy, then 80 mg every 24 hours × 2 more doses. IV prodrug fosaprepitant dimeglumine available 115 mg IV as a substitute for the 125 mg oral dose on day 1.
Dexamethasone (most frequently used glucocorticoid)	Precise mechanism of action has not been elucidated. Appears to work centrally. Appears to have meaningful effects against nausea and vomiting.	Adjunctive agent used in combination with 5-HT$_3$ antagonists +/– NK$_1$ antagonist.	8–12 mg per day given orally prior to chemotherapy and continued for 2–4 additional days. When given in conjunction with aprepitant, doses should not exceed 8 mg/day beginning day 2. No well established dosage. Steroid use in pediatric and adolescent patients often avoided due to long-term adverse events.
Olanzepine	Action may be mediated through blockade of one or multiple receptors including: central dopamine (D)1–4, peripheral 5-HT$_3$, muscarinic, or histamine.	Although not currently FDA-approved for prevention of CINV, Phase I and II clinical trials indicate the agent is effective when added to standard antiemetics.	A single 10 mg dose or 5 mg twice daily given orally beginning prior to chemotherapy, then continued for 2–4 days thereafter.
Metoclopramide	Although blockade of central and peripheral dopamine receptors may account for some of its efficacy, high concentrations appear to inhibit peripheral 5-HT$_3$ receptors.	Randomized trials indicate high-dose metoclopramide is superior to dexamethasone, prochlorperazine and haloperi-dol against cisplatin-induced emesis. Nonetheless, the better tolerability of the newer 5-HT$_3$ antagonist has resulted in less frequent use of this agent.	1–3 mg/kg intravenously every 2 hours for 3 doses, beginning 30 minutes prior to chemotherapy.

of these studies, and the potential problems that may develop.[22]

Casopitant is an NK1 receptor antagonist and has been shown in earlier phase 2 studies to prevent CINV in those receiving MEC and HEC for treatment of underlying malignancies.[23] In a subsequent phase 3 study recently published, 810 patients with a variety of malignancies [slightly more than half of the patients had non-small cell lung cancer] all receiving highly emetogenic chemotherapy [HEC], were randomized to one of three study arms: study arm #1: Ondansetron 32 mg IV on day 1, dexamethasone 12 mg oral on day 1 and 8 mg bid on days 2, 3, and 4, and casopitant 150 mg oral on day 1; study arm #2: ondansetron 32 mg IV on day 1, dexamethasone 12 mg oral on day 1 and 8 mg qd on days 2, 3 and 4, and casopitant 90 mg IV on day 1 and 50 mg oral on days 2 and 3; and study arm #3: ondansetron 32 mg IV on day 1 and dexamethasone 20 mg oral on day 1 and 8 mg bid on days 2, 3 and 4.[22]

The results were exceptionally excellent when looking at the absolute percentages of patients who had complete control and showed a statistically significant improvement in complete control [defined as no vomiting and no use of rescue medication] when assessing the results of the two casopitant study arms over the control arm. There was a 20% improvement in the number of patients who achieved a complete response to a total of more than 80% of the study patients achieving a complete response. The study was not powered to demonstrate whether a single oral dose of the NK1 antagonist casopitant achieved better or worse control than the study arm with a dose of casopitant IV on day 1 and then followed by two smaller oral doses on days 2 and 3. Few studies have ever resulted in complete response rates of 80% or more as this one did.

However the design of the casopitant study in HEC patients highlights 3 significant problems. The first

is that the control group without the addition of the NK1 antagonist demonstrated a CR of 66%. Thus a majority of the control patients did not need the addition of the NK1 antagonist and this then predicts the difficulty that clinicians will have to identify those patients who will have adequate control with a two drug regimen versus a 3 drug regimen. This issue of developing models of predicting which patients will benefit from the addition of agents to control CINV is discussed in a subsequent section of this manuscript.

The second problem identified with this study is the determination of what is an adequate control group. For a number of years, the various scientific and clinical oncology societies have recommended a 3 drug regimen, including a $5HT_3$ antagonist, an NK1 antagonist and a steroid, as the standard antiemetic preventive treatment for those receiving HEC.[9] The study with casopitant used a regimen in the control study arm that was considered inferior to the 3 drug regimen in the published guidelines for oncologists and those working in the oncology field. Although the results indicated a statistically significant improvement in the complete control of CINV with the addition of an NK1 antagonist, this result had already been published with another NK1 antagonist several years before.[24,25] Now the oncology health care providers were left with the decision as to which NK1 antagonist to prescribe if studies with casopitant lead to the approval of this new compound.

The third problem identified with this study is best displayed in Tables 2 and 3, which highlight the adverse events that occurred with this NK1 antagonist. Casopitant is a moderate inhibitor of CYP3A, which is discussed in the next section on drug-drug interactions. A number of chemotherapy agents are also metabolized by CYP3A, such as etoposide and vinorelbine. It was thought that the co-administration of these agents [casopitant and etoposide or vinorelbine] may

Table 2. Casopitant data on adverse events.

Serious adverse events*	Control (n = 265)	Single dose oral (n = 267)	3 Day IV plus oral (n = 270)
Neutropenia	5 (2%)	3 (1%)	11 (4%)
Neutropenia as a common adverse event	80 (30%)	83 (31%)	108 (40%)
Febrile Neutropenia	1 (<1%)	4 (1%)	6 (2%)
Leukopenia	44 (17%)	53 (20%)	60 (22%)

Adapted from Grunberg S, et al.[22]

Table 3. Chemotherapy regimens potentially affected by casopitant—grade 4 neutropenia by chemotherapy type.

Chemotherapy Regimens	Control n = 267	Casopitant-Single oral dose, n = 267	Casopitant-3 day IV plus oral, n = 270
Containing etoposide or vinorelbine	18 of 98 (18%)	28 of 82 (34%)	30 of 89 (34%)
Containing other CYP3A-metabolised agents	3 of 54 (6%)	5 of 49 (10%)	10 of 54 (18%)
Non-CYP3A-metabolised agents	4 of 111 (4%)	8 of 132 (6%)	5 of 120 (4%)

Adapted from Grunberg S, et al.[22]

have resulted in higher levels of the chemotherapeutic agents, which in turn might have lead to the higher incidence of grade 4 neutropenia. Although most drug-drug interactions are insignificant, this was an example of a supportive care medication to prevent CINV that may have resulted in the accentuation of the adverse events associated with the administration of chemotherapy. Thus, health care providers would have to keep in mind when prescribing antiemetics which ones would potentially interact with the chemotherapy to be co-administered at the time and which ones would result in no drug-drug interactions. The addition of this NK1 antagonist highlighted the problem of not only deciding whether it was necessary but also deciding which patients would benefit most from this additional agent and which patients would fare worse, due to toxicity from the administration of this agent.

Another question also not addressed in the recent casopitant studies is the choice of the $5HT_3$ antagonist. More recent data suggest that a longer acting $5HT_3$ antagonist (palonosetron) may provide more durable CINV prevention, particularly when combined with an NK1 antagonist and a steroid.[26,27] These recent studies highlight the contribution of serotonin release to the various triggers of CINV occurring following single or multi-day chemotherapy and the importance of $5HT_3$ antagonists.

Drug-Drug Interactions and Effect on Antiemetic Control

Patients with cancer are often on multiple drugs at the same time. Thus, not only are they often on multiple chemotherapeutic agents at the same time, they may also be on compounds for analgesia, anemia, neutropenia, depression, fluid overload, blood pressure related problems, and gastro-intestinal motility related difficulties. Because of the number of metabolic pathways involved in drug metabolism and the number of agents patients with cancer may be taking at the same time, drug-drug interactions are common and a valid concern.

The cytochrome P450 isoenzyme system is a major metabolic pathway for drugs in the human body and specifically, isoenzyme 3A4 [CYP3A4], is of concern in regards many chemotherapeutic agents.[28] Inhibitors of CYP3A4 may result in an increase in the concentration of a chemotherapeutic agent resulting in changes in the toxicity and the safety profile, and inducers of the CYP3A4 may expedite metabolism thereby shortening the half-life and reducing the efficacy of a given agent. Cancer drugs known to be metabolized by CYP3A4 include all the vinca alkaloids, paclitaxel, docetaxel, ironotecan, etoposide, ifosfamide, imatinib, gefitinib and desatinib. CYP3A4 does not play a major role in the metabolism of cyclophosphamide nor its conversion to its active metabolite.[28,29] The use of aprepitant, known to be a moderate inhibitor of CYP3A4, is important in combination with a $5HT_3$ antagonist and a steroid for control of CINV in patients receiving moderately emetogenic chemotherapy [MEC] or HEC therapy. For that reason, there is concern about the interaction of aprepitant with many of these chemotherapy agents. However, trials of aprepitant with regimens including etoposide, taxanes, vinca alkaloids, cyclophosphamide, vinorelbine, and irinotecan have failed to produce any clinically significant interaction.[30] Potential interactions with cyclophosphamide had been studied not only in patients with breast cancer receiving ordinary doses of cyclophosphamide but also in bone marrow transplant patients receiving extraordinarily high

doses of cyclophosphamide, which are often given as part of the preparative therapy.[31,32]

Antiemetic Guidelines and Clinical Predictive Profiles

Evidence based consensus statements or guidelines have been developed to assist oncology practitioners to optimize the management of CINV. The major antiemetic guidelines include those developed by the American Society of Clinical Oncology [ASCO],[9] the National Comprehensive Cancer Network [NCCN],[33] the Multinational Association of Supportive Care in Cancer [MASCC],[34] the American Society of Health-System Pharmacists [ASHP],[35] the European Society of Medical Oncology [ESMO][36] and the Oncology Nursing Society [ONS].[37] Although the guidelines of these 6 different societies are very similar, they do differ in how they were developed, how the evidence-based studies were interpreted and how often the guidelines will be updated. For example, the NCCN guidelines may be updated more than once per year, depending on available clinical experience and new peer-reviewed publications, whereas other guidelines may only be updated every 4–5 years. NCCN guidelines, for the first time, have included recommendations on how to protect patients from anticipated CINV caused by oral agents and have also included off-label recommendations for use of systemic antiemetics for multi-day chemotherapy administrations.[33]

As indicated in all the guidelines, the emetogenic potential of a particular chemotherapeutic agent or combination of agents and the dose are the most critical factors that may influence the likelihood of developing CINV.[9] However, there are a variety of patient-specific facts that are also important in predicting the likelihood of CINV [i.e. female gender, young age, prior history of nausea and vomiting with chemotherapy, history of motion sickness, history of nausea and vomiting associated with pregnancy, and a low alcohol intake (<1.5 oz/day)].[9]

An interesting tool has recently been developed and reported to predict another group of patients who may be at risk of developing moderate to severe acute CINV and at risk for the development of delayed CINV.[38,39] The model distinguishes between risk factors and predictive factors. Risk factors were treatment or patient characteristics, as indicated above, such as emetogenicity of certain chemotherapeutic agents or combinations. Predictive factors, unlike risk factors, seem to have some association with CINV although the causal link is not known or well understood. The authors of this new tool found that predictive factors for acute and/or delayed CINV included age, disease site and state, existing co-morbidity in the patients, use of dexamethasone and a 5-HT$_3$ pre-chemotherapy, anxiety, patients' expectation to have CINV, use of non-prescription treatments taken at home for emesis control, and hours slept the night before treatment. The model has the significant limitation in that it was developed in an area where, at the time of the study, an NK1 antagonist was not available and thus the patient outcome was influenced by inadequate anti-emetic prophylaxis. If the NK1 antagonist had been available, this may have altered the types and associated links for these predictive factors.

Measurement of substance P levels and serotonin metabolite levels may also assist in more accurate proactive treatment to prevent CINV when questions arise to which measures to use.[21] Such measurements could be done in large groups of patients receiving specific multi-day chemotherapy treatments and the patterns of these levels most probably would assist practitioners to determine in a more objective way the risk levels that patients have at certain post-chemotherapy administration times for developing CINV. In addition, in the patient who persists in having prolonged delayed CINV, such levels may shed light on the mechanism for the CINV, potentially leading to a suggested pharmacotherapeutic approach to prevention or treatment.

Another recent update on substance P levels provides corroborative biochemical evidence for the use of an NK1 antagonist and support for the current antiemetic guidelines from various societies.[21] In this recent study, 22 of 37 enrolled patients in a study of substance P levels received cisplatin in a variety of doses from 20 mg/m^2 to 120 mg/m^2. When patients were divided into two groups on the basis of cisplatin doses $>$ or <50 mg/m^2 or $>$ or <70 mg/m^2, the difference in measured substance P levels was significant. Enrolled patients had samples drawn at baseline and then 4–6, 24, 48 and 72 hours after the initiation of single day chemotherapy. A small increase in substance P levels was seen in the acute phase and the marked divergence in substance P levels was seen

during the delayed phase of CINV, which begins 24 hours after initiation of single day chemotherapy. There were no reported data on what happened with the substance P levels after hour 72, if they continued to rise, how long it took for substance P levels to return to baseline and if there were any correlation with CINV that persisted beyond 5 days [120 hours]. There was no indication on how long elevated substance P levels may have persisted. These will be important questions to address in further studies of substance P levels, with the potential anticipation that measurement of substance P levels may be warranted in those individuals who continue to have vomiting long after the chemotherapy effects are supposed to have abated.

Despite the guidelines recommending a combination of a $5HT_3$ antagonist, and NK1 antagonist and a steroid for MEC, such as an anthracyline and cyclophosphamide, and HEC, many patients are presumed with their first cycle of chemotherapy to not need a regimen with such broad coverage. A substantial portion of these patients will experience CINV and a study has been published to provide an NK1 antagonist as salvage antiemetic therapy in breast cancer patients who failed to received a triple antiemetic regimen with the onset of the first cycle. Although not an ideal way to provide supportive care to patients receiving MEC and HEC, the addition of an NK1 antagonist to the antiemetic regimen of those with persistent CINV, who did not receive an NK1 antagonist with their first cycle of chemotherapy, provides substantial benefit.[40]

Cost Effectiveness of Preventing CINV

CINV results in reduced quality of life and substantial adverse functional impact.[41] The economic consequences of CINV that has not been well prevented or treated are that patients require additional medical care to treat the symptoms and consequences.[42,43] One of the more serious consequences would be dehydration. In one study, rescue medication, additional office visits to engage the nurses and/or physicians, outpatient visits and hospital admissions are among the many resources that are used to assist patients who experienced inadequate CINV prevention and treatment.[44] A recent chart review study found in the USA an average cost of uncontrolled CINV is

US$500 per patient receiving moderately or highly emetogenic chemotherapy and this figure did not include the charges for nursing and physician time.[45] In addition, this figure did not include any additional expenses that patients may have incurred at local pharmacies and other medical facilities outside of the hospital where the survey was taken. Complementary care purchased by patients, lost wages from missed work by patients and their caregivers, and nutritional supplements were also not figured in the cost of uncontrolled CINV.

Poorly controlled or uncontrolled CINV may potentially delay the administration of subsequent cycles of chemotherapy or result in decreases in the dose of chemotherapy administered. In addition, patients have been known to quit subsequent chemotherapy administrations due to the uncontrolled or poorly controlled CINV. Such surveys and data collection have not been done on a large scale basis to provide this missing information. A recent study using palonosetron and dexamethasone to control CINV in patients treated with HEC showed very significant reductions in food intake [to 34% of normal daily food intake] by day 3 in those patients with persistent nausea. This result was not correlated with decisions to continue or to discontinue chemotherapy nor was it correlated with any quality of life measurements, such as absenteeism from work, inability to carry out routine daily chores, or to meet previous commitments.[46]

Because CINV has such a major impact on patients undergoing chemotherapy, various tools have been developed to assess the impact of CINV control.[40] One of these tools is the FLIE or Functional Living Index-Emesis tool, a validated nausea and vomiting patient report outcome measure. This index looks at the effect of nausea and vomiting on an individual patient. The specific items to assess the effect of the antiemetic control on the patient include ability to enjoy meals/liquids, prepare meals/do household tasks, perform daily functions, perform usual recreational/leisure activities, willingness to spend time with family/friends, the extent of personal hardship and hardship on others. Although studies have shown in some cases that the FLIE tool permitted an assessment that one antiemetic regimen compared to another reduced the impact of CINV on patients' daily lives, this was not assessed from a cost point of view. However it

may make intuitive sense that a favorable FLIE score might have an impact on reducing costs by limiting the need for additional clinic visits, additional phone calls to the health care providers and the need for additional medications for CINV control.

Conclusions

Basic understandings of the mechanisms of how the currently available anti-emetics work have permitted the design of rational combinations of anti-emetics for MEC and HEC. However, current methods of risk factor identification do not permit the selection of patients who will not need anything more than a single agent anti-emetic and those who will definitely need a combination of anti-emetics targeting the peripheral and central triggering receptors of CINV. In addition, studies are lacking on the best use of the currently available anti-emetics for multi-day chemotherapy administrations and for long-term oral chemotherapy use. In the era of health care reform, discussions of cost effectiveness of anti-emetic combinations are significant as health care providers learn to utilize the consensus guidelines to minimize complications and return patient visits for inadequately controlled CINV. Well designed trials are still needed for newer chemotherapy combinations, particularly multi-day regimens, to determine the most effective administration times, and further work on identification of predictive risk factors that may assist clinicians to determine which patients will benefit from anti-emetic regimens that are targeting specific emetic mechanisms. In addition, clinicians are at a loss on how to provide CINV prophylaxis for the patients required to take daily oral chemotherapy, for long periods of time. Questions for future studies that combine these well known anti-emetics with non-pharmacologic approaches to controlling CINV, which were beyond the scope of this review, may enhance the supportive care of patients receiving chemotherapy and enable them to maintain compliance with recommended therapies.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. Dr. Trigg is an employee at Merck & Co., Inc.

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