

# Controlling nausea and vomiting in patients undergoing chemotherapy

## Toward more effective clinical practice

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Chemotherapy-induced nausea and vomiting continues to be an issue for some patients receiving chemotherapy, despite widespread use of 5-HT<sub>3</sub> receptor antagonists and dexamethasone. Implementation of recommendations based on evidence from randomized, Phase III clinical trials would help address many of the situations where patients continue to experience nausea and vomiting.

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**T**he introduction of serotonin type 3 receptor antagonists (5-HT<sub>3</sub> RAs) plus dexamethasone in the early 1990s revolutionized the treatment of chemotherapy-induced nausea and vomiting (CINV). The change was very dramatic and altered practice in many ways. An economic analysis by David Stewart<sup>1</sup> showed a substantial reduction in the number and duration of hospital admissions and other costs associated with prevention and management of nausea and vomiting. In fact, this intervention has been one of only a few to actually reduce medical costs. Today, while it is rare to see patients refusing chemotherapy because they can no longer tolerate the nausea or vomiting, or visiting the emergency room because of CINV-induced dehydration, many patients still suffer from CINV and physicians underestimate its prevalence.

Newer agents, notably aprepitant, offer the possibility of better control. Evidence from clinical trials shows that their incorporation into care strategies would improve quality of life for many patients undergoing chemotherapy. Ongoing and future research will clarify optimal anti-CINV strategies in many scenarios including newer chemotherapy regimens.

### EVIDENCE-BASED GUIDELINES FOR CINV

Several international, evidence-based clinical guidelines for control of CINV have been developed, including the guideline of the Multinational Association of Supportive Care in Cancer (MASCC),<sup>2</sup> due to be updated in 2009, and the 2006 American Society of Clinical Oncology (ASCO) guideline.<sup>3</sup> The US National Comprehensive Cancer Network

(NCCN) also has a guideline for emesis that includes CINV, updated in March 2009.<sup>4</sup> Most of the recommendations in the international CINV guidelines are based on evidence from Phase III randomized, controlled clinical trials conducted in patients who received high-dose cisplatin or breast cancer chemotherapy (usually containing an anthracycline). Although these types of chemotherapy were common in the past, today they constitute a minority of the chemotherapy administered to cancer patients. Extension of antiemetic recommendations to other regimens is based upon consensus among oncologists and thus is subject to change as new studies are published.

The ASCO, MASCC and NCCN guidelines all recognize very similar classifications of chemotherapy emetogenicity: highly emetic chemotherapy (HEC), moderately emetic chemotherapy (MEC) and low-emetic chemotherapy (LEC).<sup>2,4</sup> In addition to cisplatin, they all recognize regimens that include carmustine, cyclophosphamide (> 1500 mg/m<sup>2</sup>), dacarbazine, mechlorethamine and streptozotocin as HEC. In all but ASCO's guideline, which does not consider oral agents, the oral agents hexamethylmelamine and procarbazine are classified as HEC. All three recommend that patients receiving HEC regimens receive 5-HT<sub>3</sub> RAs, dexamethasone and the neurokinin 1 receptor antagonist (NK<sub>1</sub> RA) aprepitant. In patients receiving a cyclophosphamide + anthracycline-based regimen (e.g. many women being treated for breast cancer), they all recommend that aprepitant be given in addition to 5-HT<sub>3</sub> RAs and dexamethasone. The NCCN guidelines recommend that aprepitant be given to patients receiving certain more emetogenic MEC agents such as carboplatin, ifosfamide and irinotecan.

Some Canadian provinces, including Ontario and British Columbia, have guidelines for CINV. Current British Columbia Cancer Agency (BCCA)<sup>5</sup> and Cancer Care Ontario (CCO)<sup>6</sup> guidelines recommend that aprep-

itant be used in patients receiving high-dose cisplatin and other HEC regimens. These guidelines have not been updated to address the published information on non-cisplatin chemotherapy.

### ADDRESSING CHALLENGES IN CLINICAL PRACTICE DELAYED NAUSEA AND VOMITING

Before the era of 5-HT<sub>3</sub> RAs, CINV was problematic in the first 12–18 hours following chemotherapy. Then the emphasis shifted to the so-called delayed phase, conventionally defined as beyond 24 hours (although evidence is surfacing that it may be reasonable to think about the delayed phase as beginning late in the first 24-hour period and continuing on).<sup>13</sup>

Dexamethasone has effects in both acute and delayed CINV, but many oncologists are reluctant to give corticosteroids beyond 24 hours. Short-term concerns include effects on sleep and increased anxiety — however, this is actually less likely on subsequent days, when the recommended dose is lower than on Day 1. The tradeoff between benefits and side effects of prolonged corticosteroid administration is being evaluated.<sup>14</sup> Long-term effects on bone loss are another voiced concern; the extent of any corticosteroid-induced bone loss beyond that induced by changes in ovarian function and the use of adjuvant hormonal therapy has not been studied. Recent guidelines on the subject of treatment-induced bone loss in women with breast cancer do not identify this as an issue.<sup>15</sup>

The NK<sub>1</sub> RA aprepitant has been shown to have activity mainly in delayed CINV, with some activity during the acute phase. A reduced dose of dexamethasone is recommended when giving aprepitant because of a drug interaction involving the liver enzyme CYP3A4. For patients receiving HEC chemotherapy, current ASCO guidelines for prevention of CINV recommend the three-drug combination of a 5-HT<sub>3</sub> RA + dexamethasone + aprepitant before chemotherapy, with

## CINV chemoreceptors and agents

While the pathophysiology of CINV is not fully understood, 5-HT<sub>3</sub> receptors (a type of serotonin receptor) and NK<sub>1</sub> receptors (receptors for substance P) are believed to play key roles. The 5-HT<sub>3</sub> receptors appear to be more important in acute CINV, while the NK<sub>1</sub> receptors are involved in delayed CINV although activity may begin earlier. Emetogenic chemotherapy agents cause CINV primarily through peripheral mechanisms involving the release of serotonin from enterochromaffin cells located in the small intestine. Serotonin activates vagal afferents that transmit signals centrally, principally to the nucleus tractus solitarius (NTS) and to a lesser extent the area postrema (AP), sometimes referred to as the chemoreceptor trigger zone (CTZ), located outside the blood-brain barrier in the 4<sup>th</sup> ventricle of the brain. The NTS and AP are known collectively as the dorsal vagal complex, which contains many receptors thought to be important in CINV including the 5-HT<sub>3</sub> receptors, NK<sub>1</sub> receptors and dopamine 2 receptors. Substance P released in the NTS passes the signal to the vomiting centre.<sup>7,8</sup>

5-HT<sub>3</sub> RAs (e.g. dolasetron, granisetron, ondansetron and palonosetron) block the 5-HT<sub>3</sub> receptors, and NK<sub>1</sub> RAs (e.g. aprepitant) block the NK<sub>1</sub> receptors. Dexamethasone has activity in both acute and delayed CINV; its mechanism of action is poorly understood.

Despite our improved understanding of the mechanisms underlying CINV, there is much to be learned. Clinical trial results and observation in the clinic associated with the use of current medications for CINV suggest that while vomiting can be relatively well controlled, nausea still remains a problem. This suggests that there may be distinct pathophysiologic mechanisms associated with the occurrence of vomiting and nausea following emetogenic chemotherapy.<sup>7,8</sup>

## Current and future aprepitant evidence

The addition of aprepitant to HEC antiemetic regimens is based on the combined analysis of two pivotal trials of patients receiving cisplatin-based chemotherapy that clearly showed aprepitant to be an effective agent in the delayed phase, and even suggested some efficacy in the first 24 hours.<sup>9</sup> The recommendations of aprepitant for MEC antiemetic regimens are based on a study that showed significantly better control of emesis (but not nausea) in women receiving a cyclophosphamide + anthracycline-based regimen for treatment of breast cancer.<sup>10</sup> The range in emetogenic potential of MEC agents is quite wide, from 30% to 90%.<sup>11</sup> Preliminary data for the role of aprepitant with other MEC regimens is promising and awaits confirmation by properly controlled Phase III trials.<sup>12</sup>

dexamethasone + aprepitant on Days 2 and 3. For patients receiving MEC chemotherapy including an anthracycline + cyclophosphamide, ASCO guidelines recommend a 5-HT<sub>3</sub> RA + dexamethasone + aprepitant on Day 1, and aprepitant on Days 2 and 3. Recommendations in other international guidelines are similar.

The guidelines of ASCO, MASCC and NCCN all recommend more widespread use of both dexamethasone and aprepitant than currently appears to be occurring in practice. Anecdotally, it seems that even patients with good drug plan coverage are often not offered the option of receiving an NK<sub>1</sub> RA. Why is this happening? A survey of oncologists and oncology nurses indicated that their patients experienced more frequent nausea and vomiting than the healthcare professionals predicted, particularly in the delayed phase.<sup>16</sup> Perhaps this discrepancy between perception and reality is due to imperfect communication between doctor and patient. While some oncologists routinely ask their patients in the post-chemotherapy followup visit about nausea and vomiting, along with other issues such as mucositis and neuropathy, others operate on the principal that unless the patient mentions otherwise, the treatment has been tolerated well. This assumption is incorrect: patients may not mention a side effect that they were told might happen, they may not wish to bother an oncologist in a busy clinic or they may worry that complaints will lead to a dose reduction and a consequent lesser chance of winning the battle against cancer. A routine assessment of the effects of cancer therapies by a physician who is well informed of the options available to reduce side effects could help improve a patient's experience without compromising treatment effectiveness.

### NAUSEA WITHOUT VOMITING

Nausea and vomiting are closely related symptoms: nausea is more common than vomiting, and vomiting without nausea is rare. As vomiting is objective, it is more compelling to treat, while nausea attracts less attention — although patients seem to rate it as being at least as important in its effect on quality of life.<sup>17</sup> Interventions have been more effective in controlling vomiting than in eliminating nausea. 5-HT<sub>3</sub> RAs and dexamethasone are very effective in the management

of vomiting, but they seem to be less so with respect to nausea.<sup>8-10,18,19</sup>

The NK<sub>1</sub> RA aprepitant has been shown to have efficacy against nausea for HEC,<sup>9</sup> but in the clinical trials on nausea in the MEC population no impact was shown.<sup>9,10</sup> Casopitant, another NK<sub>1</sub> RA now in Phase III clinical trials for CINV in patients receiving highly- and moderately-emetogenic chemotherapy, has shown similar results. Subgroup analyses suggest that the difference in impact of NK<sub>1</sub> RAs upon nausea in HEC vs MEC studies may not be due to the cyclophosphamide or anthracycline,<sup>20</sup> or to gender differences.<sup>21</sup> The explanation for the differing impact upon nausea is not known, but a contributing factor in the control of nausea during the delayed phase might be the protocol-specified use of dexamethasone, which was not used beyond the first 24 hours in the MEC studies, whereas it was administered in the HEC studies.

### ANTICIPATORY NAUSEA AND VOMITING

A third type of type of chemotherapy-related nausea and vomiting (besides acute and delayed) is anticipatory CINV, which occurs in patients who have had CINV in previous experiences with chemotherapy. There have been no studies on the prevalence of this problem in the era since 5-HT<sub>3</sub> RAs were introduced but, anecdotally, it still exists.<sup>22</sup>

Anticipatory symptoms develop only in those with poor antiemetic control, and our interventions for these conditioned responses are only modestly effective. Systematic desensitization has been shown to reduce pre- and post-chemotherapy emesis but very few centres have expertise in its application. The 2006 ASCO guideline recommends “use of the most active antiemetic regimens appropriate for the chemotherapy being administered” to prevent anticipatory CINV.<sup>3</sup> The MASCC and NCCN guidelines both state “the best management of anticipatory emesis is the best possible control of acute and delayed emesis.”<sup>2,4</sup> Thus, primary prevention is the approach recommended by experts.

### PATIENT SUBGROUPS

Certain groups of patients have a higher risk of CINV, including younger people, females and those who consume little or no alcohol.<sup>23</sup> At this time, however,

research evidence does not support using patient risk factors in daily planning of interventions, as analyses of patients who received high-dose cisplatin have failed to identify any low-risk subgroups that will not benefit from the addition of an NK<sub>1</sub> RA.<sup>11,23</sup>

### REFRACTORY NAUSEA AND VOMITING

Some patients have emesis despite receiving the recommended antiemetic regimen. When this occurs in the setting of chemotherapy for which “triple therapy” (i.e. corticosteroid + 5-HT<sub>3</sub> RA + NK<sub>1</sub> RA) is not considered standard, some recommend adopting an approach usually reserved for more emetogenic chemotherapy. If the patient has already received triple therapy, no evidence-based approach is available. It is, however, important to make sure that the antiemetics were given in optimal dose and schedule. For example, a patient with late-onset emesis who was not prescribed dexamethasone beyond the first 24 hours cannot be said to have been given optimal therapy. Other options exist but are not supported by evidence from Phase III studies. The atypical antipsychotic olanzapine has been shown to help some patients.<sup>24,25</sup> Olanzapine blocks multiple receptors and has intriguing activity beyond that expected for a dopamine receptor antagonist. Another option sometimes considered is use of a cannabinoid, but again, data from recent Phase III trials is lacking and their side effect profile has made many oncologists reluctant to prescribe cannabinoids.

A particular group in need of a better approach to CINV is patients receiving high-dose chemotherapy regimens prior to stem cell transplant for hematologic malignancy. Even the best strategies, using multiple drug combinations, fail in 30% to 40% of patients.<sup>26,27</sup>

### CANCER CARE SYSTEM ISSUES

#### ROUTINE ASSESSMENT OF SIDE EFFECTS

Few if any North American oncology care centres have a consistent and standardized way of assessing CINV or any other side effects from chemotherapy in day-to-day practice. Without standardized tools, the oncology care team relies on how the patients report symptoms. Some clinicians propose that provincial or even national standards be set, for example, “80% of the patients walking through the door should be free of nausea and vomiting,” with a system to audit the standards and allow each centre to compare itself to others. At the level of individual cancer centres, provision of feedback to physicians regarding the differences in outcomes once a new measure is adopted has been shown to facilitate implementation of practice changes.<sup>28</sup> The Odette Cancer Centre (Sunnybrook) is working on a project to develop a standardized approach to assessment and feedback to physicians, likely via technology that collects data directly from patients.

#### LACK OF PUBLIC FUNDING FOR NEW THERAPIES

Many cancer centres, including the Odette Cancer Centre and Princess Margaret Hospital, have developed standardized antiemetic regimens for each chemotherapy regimen. These are linked in an electronic ordering system and ordered automatically. Drugs that are not funded for outpatients, however (for example aprepitant in Ontario as of April 2009), are not included in these regimens, so ordering such drugs is cumbersome: the oncologist has to manually make a specific order that will be funded either by the patient's insurance, self-pay or the manufacturer's compassionate use program. As well, in the case of aprepitant, the dose of dexamethasone must be manually reduced. ↑

## Toward better control of CINV in Canada

In many settings where CINV continues to be problematic for patients, Canadian cancer care centres need to use available agents more effectively, based on evidence from large, randomized Phase III clinical trials.

- all patients receiving chemotherapy should be asked routinely about chemotherapy-related symptoms including nausea and vomiting
- every effort should be made to prevent CINV in the first cycle of chemotherapy to prevent subsequent problems
- for controlling delayed nausea and vomiting, dexamethasone given on subsequent days following chemotherapy administration is effective
- aprepitant combined with dexamethasone improves control of delayed CINV in patients receiving HEC (including cisplatin-based chemotherapy)
- aprepitant + dexamethasone also improves control of CINV in women receiving anthracycline + cyclophosphamide-based MEC regimens; research is ongoing for other MEC regimens.
- for patients whose nausea and vomiting is not controlled by the recommended regimen, a more aggressive regimen should be used, which could mean adding dexamethasone, aprepitant and a number of other agents

Further research is needed regarding:

- emetogenicity of and interventions for MEC regimens
- emetogenicity of oral antineoplastic agents with development of antiemetic regimens specific for these agents
- effective regimens for ultra-HEC regimens
- risks vs benefits of dexamethasone given for a few days in each chemotherapy cycle
- new interventions to target nausea, especially in MEC regimens

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