



National Oncology Pharmacy Symposium 2008

Calgary, Alberta / October 17-19, 2008

Prevention and Management of Chemotherapy-induced Nausea and Vomiting

Calgary - Chemotherapy-induced nausea and vomiting (CINV) is a troublesome side effect of many cancer therapies. It affects almost all chemotherapy patients, some to the point where they discontinue their chemotherapy rather than suffer this distressing and debilitating condition. Clinicians often underestimate the risk of CINV, particularly the delayed form, which does not manifest itself until a day or more post-therapy. Consensus guidelines by the Multinational Association of Supportive Care in Cancer detail the principles of prevention and management of CINV and recommend preventative and therapeutic treatment regimens according to the specific chemotherapy involved. The British Columbia Cancer Agency has published detailed treatment guides and algorithms for management of breakthrough and refractory CINV.

For the past 25 years, nausea and vomiting have consistently been rated by patients as among the most severe side effects of chemotherapy, stated clinical oncology pharmacist Scott Edwards, PharmD, Eastern Health, St. John's, Newfoundland. These symptoms have an enormous impact on patients' quality of life, he added.

Chemotherapy-induced nausea and vomiting (CINV) can be categorized into several types. Acute CINV has an onset from minutes to a few hours after chemotherapy and typically resolves within 24 hours. Delayed CINV develops 24 hours or more following therapy and may last up to six days. In a study of 322 patients undergoing chemotherapy, 43% experienced acute nausea while 73% had delayed nausea; 39% of patients experienced both types. Vomiting is less common; while 76% of patients in this study experienced one or another type of nausea, only 30% suffered from vomiting. Anticipatory CINV occurs in patients who have had previous experience of nausea and vomiting with chemotherapy and occurs before the treatment. Breakthrough CINV occurs despite anti-nausea medication and may require rescue. Finally, patients with refractory CINV fail to respond to any antiemetic medication.

Risk Factors for CINV

Risk factors for CINV include patient-related aspects such as younger age, female and no or minimal alcohol use. Anxiety is a very important risk factor and may be associated with prior experience of CINV, leading to high expectation of further occurrences in subsequent treatment cycles. The predominant risk factor, however, is the inherent emetogenicity of the chemotherapeutic agent itself, Dr. Edwards told delegates. Nausea and vomiting may also be due to other factors surrounding the patient's condition, such as bowel obstruction, brain metastases, vestibular dysfunction, anxiety, concomitant therapies (e.g. opiates) and gastroparesis.

The ANCHOR (Anti-nausea Chemotherapy Registry) revealed that medical staff tend to underestimate the risk of CINV, particularly the delayed type, which may lead to undertreatment of CINV. Dr. Edwards investigated this problem

in a small study in Newfoundland and found that delayed nausea was far more common than acute nausea or any vomiting, and its incidence was underestimated by staff more than the other types. The greatest danger of unresolved CINV is discontinuation of therapy, remarked Dr. Edwards, adding that metabolic derangements, anorexia, esophageal tears and physical, psychological and social deterioration are also risks.

Treatment Strategies

It is believed that there are two mechanisms of CINV, explained Dr. Edwards. One is peripheral, and caused by irritation of the gut by the chemotherapeutic agent. The advent of 5-HT₃ antagonists used with corticosteroids, which appears to block the peripheral stimuli, has led to dramatic reductions in acute CINV due to peripheral effects. The other mechanism of CINV is central, and is believed to be the result of direct action of chemotherapeutics on the substance P receptor NK₁, which is present at high densities in areas of the brain implicated in the emetic reflex. Blockade of this receptor with aprepitant inhibits this central mechanism and, because the mechanism of action of aprepitant differs from that of 5-HT₃ antagonists, the two drugs may be administered concomitantly. Inhibition of NK₁ receptors by aprepitant is effective against delayed CINV as well as the acute form, noted Dr. Edwards.

Antiemetic Treatment Guidelines

In 2004, a conference of the Multinational Association of Supportive Care in Cancer (MASCC) formulated an international antiemetic treatment guideline consensus subscribed to by nine organizations, including ASCO and CCO in North America. These guidelines were updated in 2008. The guidelines categorize intravenous (i.v.) and oral anti-cancer drugs into high (risk in >90% of patients), moderate (risk in 30% to 90% of patients), low (risk in 10% to 30% of patients) and minimal (risk in <10% of patients) emetic risk groups and recommend therapy. Key principles for antiemetic treatment that achieved unanimous consensus with category I evidence included the following:

- Use the lowest tested fully effective dose.
- No schedule is better than a single dose given before chemotherapy.
- The antiemetic efficacy and adverse effects of serotonin antagonist agents are comparable in controlled trials.
- Intravenous and oral formulations are equally effective and safe.
- Always give dexamethasone with a 5-HT₃ antagonist before chemotherapy.

“These are the golden rules that we need to use when treating patients for CINV,” Dr. Edwards told delegates.

Specific treatments are recommended by the guidelines to prevent acute nausea and vomiting, based on the risk of the chemotherapy. For high-risk treatments, a single dose each of a 5-HT₃ antagonist, dexamethasone and aprepitant should be given before chemotherapy. For moderate-risk regimens, including anthracycline/cyclophosphamide, the same prophylaxis is recommended. If the regimen does not include anthracycline/cyclophosphamide, then only the 5-HT₃ antagonist and dexamethasone should be given.

Dr. Edwards recommended use of the antiemetic regimens that the British Columbia Cancer Agency (BCCA) has designed, based on these recommendations (Table 1). “These guidelines are fantastic and easy to use,” he confirmed. The BCCA chart includes recommendations for both acute and delayed CINV.

Table 1. British Columbia Cancer Agency Antiemetic Regimens

| Emetogenicity | Pre-Chemotherapy | Post-Chemotherapy |
|-------------------------------|---|---|
| High | One 5-HT ₃ antagonist: Ondansetron 8 mg po Dolasetron 100 mg po Granisetron 1 mg po PLUS Dexamethasone 8-12 mg po PLUS Aprepitant 125 mg po | Aprepitant 80 mg po daily x two days PLUS Dexamethasone 4 mg po evening of chemo then 4 mg po b.i.d. x 2-5 days AND ONE ANTI-EMETIC AS NEEDED: Prochlorperazine 10 mg po every 4-6 hrs PRN x 3-4 days OR Metoclopramide 10-40 mg po every 4-6 hrs PRN x 3-4 days |
| High-moderate Low-moderate | One 5-HT ₃ antagonist: Ondansetron 8 mg po Dolasetron 100 mg po Granisetron 1 mg po PLUS Dexamethasone 8-12 mg po | Dexamethasone 4 mg po evening of chemo then 4 mg po b.i.d. x 2-3 days AND ONE ANTI-EMETIC AS NEEDED: Prochlorperazine 10 mg po every 4-6 hrs PRN x 3-4 days OR Metoclopramide 10-40 mg po every 4-6 hrs PRN x 3-4 days |
| Low | <i>PREFERRED:</i> Dexamethasone 4-12 mg po <i>ALTERNATE:</i> Prochlorperazine 10 mg po OR Metoclopramide 20-40 mg po | Dexamethasone 4 mg b.i.d. for up to 2-3 days OR Prochlorperazine 10 mg po every 4-6 hrs PRN x 3-4 days OR Metoclopramide 10-40 mg po every 4-6 hrs PRN x 3-4 days |
| Rare | Prophylactic treatment not normally required | Prochlorperazine 10 mg po every 4-6 hrs PRN x 3-4 days OR Metoclopramide 10-40 mg po every 4-6 hrs PRN x 3-4 days |

Challenges in CINV

According to Dr. Edwards, certain situations present specific challenges to providing suitable therapy. Multiple-day chemotherapy may result in both acute and delayed CINV being present during the therapy. It should be borne in mind that

the period of risk for CINV depends on the emetogenic potential of the last chemotherapy agent administered in the regimen. Recommendations for moderately to highly emetogenic chemotherapy are to use a 5-HT₃ antagonist prior to each day’s use of the moderately to highly emetogenic drug. Dexamethasone should also be administered once the evening of chemotherapy then twice daily for two to three days post-chemotherapy for delayed CINV. Aprepitant may be used at a dose of 125 mg on day 1 followed by 80 mg for days 2 and 3. Phase III data indicate that it may also be administered for a further two days post-chemotherapy.

Breakthrough and refractory CINV are particularly challenging. Strategies include around-the-clock administration and use of additional agents from different drug classes. There is no specific preferred agent, so order of usage is not important. Possible choices include dopamine antagonists, metoclopramide, haloperidol, cannabinoids, corticosteroids and benzodiazepines. After failure, the nausea should be assessed, as well as the regimen that failed to prevent it, and another modality added for the next cycle. Antacid therapy using an H₂ blocker or proton pump inhibitor may also be useful.

Dr. Edwards stressed that care should be taken to ensure adequate hydration. The presence of other treatable causes (obstruction, poor gut motility, pain, increased intracranial pressure) should also be investigated.

Anticipatory CINV occurs in 18% to 57% of chemotherapy patients, particularly in younger individuals, who are often treated more aggressively. Because this form of CINV is a conditioned response to previous CINV episodes, the most effective treatment is to assiduously prevent CINV during chemotherapy by using optimal antiemetics during every cycle of therapy. Pre-chemotherapy alprazolam or lorazepam may be beneficial, as may cognitive behavioural therapy and systemic desensitization, if available.

The final challenge in the management of nausea and vomiting is delayed CINV. “We are doing a poor job of treating delayed CINV,” remarked Dr. Edwards, adding that it is 2.5 times more prevalent than the acute form. Delayed CINV is predicted by female sex, age <52 years, the expectation of nausea and, most markedly, by the presence of acute CINV, he told delegates. The severity of delayed nausea and vomiting was worse in patients who also had acute CINV. Good control of acute CINV correlates with good control of the delayed form, so prevention of acute CINV by appropriate prophylaxis is crucial. It is very important to identify patient risk factors before chemotherapy is given in order to ensure the most appropriate antiemetics are used prophylactically. Additionally, Dr. Edwards concluded, patient follow-up is essential to make sure that delayed symptoms are not missed by the treating clinicians. □

To view an electronic version of this publication along with related slides if available, please visit www.mednet.ca/2008/pp09-072e.

© 2008 Medical Education Network Canada Inc. All rights reserved. Priority Press™ is an independent medical news reporting service providing educational updates reflecting peer opinion from accredited scientific medical meetings worldwide and/or published peer-reviewed medical literature. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsor. Distribution of this educational publication is made possible through the support of industry under written agreement that ensures independence. Any therapies mentioned in this publication should be used in accordance with the recognized prescribing information in Canada. No claims or endorsements are made for any products, uses or doses presently under investigation. No part of this publication may be reproduced in any form or distributed without written consent of the publisher. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate physicians’ and allied health care providers’ understanding of current trends in medicine. Your comments are encouraged.

Medical Education Network Canada Inc. 132 chemin de l’Anse, Vaudreuil, Quebec J7V 8P3

