



Baystate Health System

MEMORANDUM

DIVISION OF HEALTHCARE QUALITY (DHQ)

TO: Medical Staff

FROM: Wilson Mertens, MD
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DATE : February 4, 2002

SUBJECT: **Update to Clinical Practice Guideline: Anti-emetic Guidelines for Chemotherapy**

Since the initial distribution of the Antiemetic Guidelines for Chemotherapy there has been a change in the Baystate Medical Center Formulary. Dolasetron (Anzemet) is now the only 5ht-3 antagonist available. Enclosed please find 2 stickers to be attached to your copy of the clinical practice guideline and pocket card.

If you have any questions regarding this matter, or other issues related to this clinical practice guideline please contact Wilson Mertens, MD at 413-794-9355, Gary Kerr, RPh at 413-794-3178 or Jan Fitzgerald, RN at 413-794-2531.

Thank you.

Enclosures



October, 2001

RE: Baystate Health Systems Guidelines on Antiemetic Use With Chemotherapy

Dear Colleague,

Recent clinical trials and overviews, in addition to the release of new and effective agents, have led to refinements in the usage of antiemetic drugs in the prevention of chemotherapy-associated nausea and vomiting. While the improvements achieved have been impressive, the inconsistent application of best-evidenced practice in the use of these drugs, documented by a number of groups internationally, remains a concern.


As part of our quality improvement efforts and evidence-based guideline initiative, our committee has conducted a literature and guideline search and authored a Baystate Health System guideline on the use of antiemetics in the prevention of acute and delayed nausea and vomiting associated with cancer care. A draft of this document was previously widely circulated, and a gratifying number of comments were received, many of which were incorporated into the final document.

Important aspects of this guideline include classification of chemotherapy drugs by emetogenic potential, basic rules for prescribing of antiemetic drugs, and evidence-based guidelines with levels of evidence and greater recommendation for the prevention of both acute and delayed nausea and vomiting. Special emphasis has been made on the prevention of delayed nausea and vomiting and the use of corticosteroids, particularly dexamethasone, post chemotherapy to reduce the incidence of this symptom. Guidelines describing general rules for the use of antiemetic agents in the pediatric and radiation oncology populations are also included. These guidelines are generally consistent with those published by the National Cancer Center Network (NCCN), as well as those published by the American Society of Clinical Oncology.

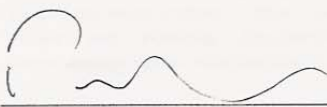
Please take the time to review these guidelines. We feel that these guidelines will result in a significant improvement in symptomatology patients experience as a result of anticancer treatment.

We commend the Medical Staff for your ongoing commitment in providing outstanding care. If you have any questions or comments regarding this guideline, please feel free to contact Wilson Mertens, MD, at (413) 794-5468 or wilson.mertens@bhs.org.

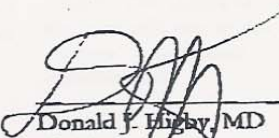
Sincerely,



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The Western Campus of Tufts University School of Medicine



Clinical Practice Guideline

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Task Force Members

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Antiemetic Guidelines for Chemotherapy

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Of more concern is the relatively low rate of appropriate usage of drugs by oncologists for nausea prevention proven effective in randomized clinical trials. Most of the drugs and drug dosages listed in this document are intended for adult patient who do not otherwise have a history of intolerance to these drugs and do not have medical conditions that preclude its use. For **pediatric dosing**, please see the section entitled "Nausea and Vomiting with Chemotherapy in Pediatric Oncology".

Baystate Health System Recommendations Regarding Prevention of Nausea Induced by Chemotherapy

These recommendations are based on the results of randomized clinical trials, published meta-analyses, and expert literature review such as that conducted by the American Society of Clinical Oncology. The use of the recommendations that follow depend on two basic principles:

Classification of Nausea and Vomiting Associated with Chemotherapy

Nausea and vomiting can occur in a number of ways, but nausea and vomiting associated with chemotherapy can be classified in terms of *acute* and *delayed* occurrence. Acute nausea and vomiting is defined as occurring within the first 24 hours after chemotherapy administration with delayed nausea and vomiting occurring after that (usually in the first 5 to 7 days after chemotherapy). Occasionally, medications taken orally, such as cyclophosphamide (Cytosan) may result in a low-grade nausea for the duration of the drug's administration. This can be handled reasonably well with commonly used and easily available anti-nausea drugs such as prochlorperazine (Compazine). For the most part, our discussion will revolve around the more common presentations of nausea and vomiting associated with chemotherapy agents administered by vein.

- Nausea prevention drugs should be used in the **lowest dose achieving maximal effectiveness**, as supported by research, commencing with the first course of chemotherapy.
- Nausea prevention drugs should be administered as **appropriate for the chemotherapy drug which has the greatest potential to cause nausea**. Thus, if a chemotherapy regimen contains cisplatin as well as other chemotherapy drugs less likely to cause nausea, nausea prevention strategies appropriate for cisplatin should be prescribed.

Cisplatin-Induced Emesis

Acute Nausea and Vomiting

The goal of therapy in the treatment of nausea and vomiting is, of course, total control of symptoms in all patients. This appears to be the same as total control of nausea. Two classes of drugs appear to be the most effective in this regard: serotonin receptor antagonists (blockers) and corticosteroids.

Nausea and Vomiting and Anticancer Therapy: Current Recommendations

Nausea and vomiting (or *emesis*) resulting from cancer therapy remains for most cancer patients the toxicity of greatest concern. Although many chemotherapy regimens now commonly employ chemotherapy agents with a reduced risk of nausea and new, more effective agents are now available to prevent or treat the condition, a significant proportion of patients continue to experience these unpleasant conditions.

Serotonin Receptor Antagonists

Ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet), have revolutionized the administration of cisplatin. These drugs are highly effective in preventing nausea when administered prior to chemotherapy and are responsible for the vastly improved tolerability of chemotherapy in recent years. Multiple randomized, controlled clinical trials and meta-analyses have confirmed their role in the prophylaxis of these symptoms. These studies have also confirmed that these drugs, when employed in sufficient dosage, are equally effective, and that the oral form of these drugs are as effective as the intravenous preparations and are cheaper and often more convenient.

Corticosteroids

Dexamethasone (Decadron) is often used prior to chemotherapy as an acute nausea preventative and are particularly valuable when used in conjunction with serotonin receptor antagonists in patients receiving highly or moderately nausea-inducing chemotherapy, as illustrated by the list above, and particularly by cisplatin.

Although other corticosteroids have been used with effect, dexamethasone is the agent with which oncologists have the greatest experience as well as the drug with the largest body of literature supporting its use.

Other Agents

Older drugs, which were commonly used prior to the introduction of serotonin receptor antagonists still have a role in the therapy of nausea and vomiting.

- Metoclopramide (Reglan) is useful as an anti-nauseant given prior to cisplatin in high doses, but is somewhat less effective than serotonin receptor antagonists and causes more side effects. Other drugs, such as antipsychotic agents (haloperidol [Haldol] and droperidol [Inapsine]) are similarly useful but have been supplanted by more the more effective regimens.

- Cannabinoids (marijuana derivatives available as plant extracts [dronabinol] or as semisynthetic drugs [nabilone]) have had some limited success in preventing nausea and vomiting due to chemotherapy in clinical trials, but appear to be less effective than newer drugs. In addition, inhalant marijuana was not effective in preventing nausea in one clinical trial. There is no group of patients, especially in the high-risk setting, for whom these agents are appropriate as a first choice for an antiemetic regimen.

Level of evidence:3;Grade of recommendation: B.

- Benzodiazepines such as lorazepam (Ativan) have some anti-nausea activity; its main value likely lies in its anti-anxiety effects. Consequently, these drugs have a role to play, particularly as adjuncts to serotonin receptor antagonists and corticosteroids, but not as the sole drug to prevent nausea.

Level of evidence:2;Grade of recommendation: B.

These agents may play a role in the prevention or treatment of patients who suffer nausea and vomiting despite the optimal use of modern anti-nausea agents, or who cannot tolerate the use of these new drugs.

However, panelists from the American Society of Clinical Oncology have stated that “there is no group of patients [in the high-risk setting] for whom agents of lower therapeutic index... are appropriate as first-choice antiemetic [anti-nausea] drugs.”

Delayed Nausea and Vomiting

Delayed nausea and vomiting occurs more than 24 hours after chemotherapy administration. It is a troublesome symptom that often occurs after every chemotherapy course, and may become increasingly resistant to therapy. In some cases, delayed symptoms, if unchecked, may evolve into anticipatory nausea or vomiting, which occurs prior to the next chemotherapy administration.

The root cause of delayed symptoms is unclear and only recent clinical trials have clarified the role of anti-nausea agents in the treatment of this symptom. Corticosteroids have been the mainstay of preventative therapy for delayed nausea and vomiting. Dexamethasone is typically used, usually for 2 to 4 days after chemotherapy. Most clinical trials have employed 8 mg orally twice daily for 2 or 3 days after chemotherapy, some trials tapering to 4 mg twice daily for an additional 2 days.

Studies evaluating delayed nausea after cisplatin have also incorporated metoclopramide (Reglan) or serotonin receptor antagonists. In one clinical trial evaluating cisplatin-containing chemotherapy anti-nausea prophylaxis, metoclopramide with dexamethasone improved delayed vomiting control over dexamethasone alone. This trial was conducted prior to the introduction of serotonin receptor antagonists, however, and it is not known if pretreatment with such agents would permit therapy with dexamethasone alone. Although studies of serotonin receptor antagonists as single drugs have had a salutary effect on this symptom, studies of these drugs with dexamethasone for cisplatin-containing chemotherapy regimens have yielded conflicting results: one clinical trial showed no additional benefit to the addition of these drugs to dexamethasone, while another demonstrated equivalent efficacy of ondansetron and dexamethasone to metoclopramide and dexamethasone.

Recommendations

Prevention of Acute Nausea and Vomiting
Dexamethasone (20 mg IV) or equivalent with a serotonin receptor antagonist (ondansetron 20-32 mg IV or 24 mg orally, granisetron 2 mg orally or dolasetron 100 mg IV or orally).

Level of evidence: 1; Grade of recommendation: A.

The initial use of less effective drugs is not recommended.

Prevention of Delayed Nausea and Vomiting

Dexamethasone (8 mg orally twice daily for 2 days, followed by 4 mg twice daily for 2 days, or 8 mg orally twice daily for 3 to 4 days), therapy to begin the day after completion of chemotherapy administration.

Level of evidence: 1; Grade of recommendation: A.

or

Dexamethasone as above with metoclopramide (20 mg four times daily or 40 mg twice daily for 2 to 4 days), therapy to begin the day after completion of chemotherapy administration.

Level of evidence: 2; Grade of recommendation: B.

or

Dexamethasone as above with a serotonin receptor antagonist (ondansetron [Zofran] 8 mg orally twice daily, granisetron [Kytril] 2 mg once daily or dolasetron [Anzemet] (Now the sole 5HT-3 antagonist on the BMC formulary) 100 mg orally) for 3 to 4 days; therapy to begin the day after completion of chemotherapy administration.

Level of evidence: 2; Grade of recommendation: C.

Non-Cisplatin Highly Emetogenic Chemotherapy

Clinical trials have evaluated the same issues in highly emetogenic chemotherapy regimens that do not include cisplatin. These include:

- dacarbazine (DTIC)
- carboplatin
- cyclophosphamide (intravenous administration, dose greater than 600 mg/m², or any dose in combination with other chemotherapy agents)
- doxorubicin (any dose)
- daunorubicin (any dose)
- epirubicin (any dose)
- idarubicin (any dose)
- ifosfamide
- cytarabine
- actinomycin-D
- methotrexate \geq 1000 mg/m²
- nitrogen mustard
- hexamethylmelamine
- streptozotocin
- lomustine (CCNU)
- carmustine (BCNU)

A recent clinical trial evaluated the value of adding dexamethasone and ondansetron, a serotonin receptor antagonist, after completing chemotherapy.

Dexamethasone significantly improved delayed nausea and vomiting, while the further addition of ondansetron added relatively little in the way of improvement in symptoms. This study also demonstrated a significant association between acute (early onset) nausea and vomiting and delayed nausea and vomiting, underscoring the need for optimal pretreatment prior to chemotherapy.

Recommendations

Prevention of Acute Nausea and Vomiting

Dexamethasone (10-20 mg IV) or equivalent with a serotonin receptor antagonist (ondansetron 20-32 mg IV, 0.15 mg/Kg IV or 24 mg orally, or granisetron 2 mg orally, or dolasetron 100 mg IV or orally).

Level of evidence: 1,2; Grade of recommendation: A,B.

The initial use of less effective drugs is not recommended. For regimens such as CHOP, which include several days of high-dose prednisone or other corticosteroids, post-chemotherapy dexamethasone should be omitted.

Prevention of Delayed Nausea and Vomiting

Dexamethasone (8 mg orally twice daily for 2 days, followed by 4 mg twice daily for 2 days, or 4 mg orally twice daily for 4 days), therapy to begin the day after completion of chemotherapy administration

Level of evidence: 1; Grade of recommendation: A.

Intermediate Emetogenic Potential Chemotherapy

Intermediate risk agents cause nausea and vomiting between 10% and 30% of administrations. Representative drugs that fall into this class include:

- irinotecan (Camptosar)
- mitoxantrone
- paclitaxel (Taxol)
- docetaxel (Taxotere)
- mitomycin (Mutamycin)
- methotrexate >100 mg/m² but <1000 mg/m²
- topotecan (Hycamtin)
- gemcitabine (Gemzar)
- etoposide (Vepesid)
- teniposide (Vumon)

There are few clinical trials that address which antiemetic regimen is most appropriate for these drugs. Most information arises from the early, developmental clinical trials used to determine the anticancer efficacy of these agents. General consensus is that, if these drugs are the most emetogenic agents in the regimen, corticosteroids (dexamethasone) should be employed as the antiemetic of choice. The addition of a serotonin receptor antagonist and/or an agent such as prochlorperazine (Compazine) is often recommended or offered, no evidence in the medical literature documents the benefits of this approach.

Recommendations

Prevention of Acute Nausea and Vomiting

Corticosteroids (dexamethasone) or equivalent prior to chemotherapy alone. Addition of other agents of uncertain benefit.

Level of evidence: 3,4; Grade of recommendation: B,D.

Prevention of Delayed Nausea and Vomiting

No routine use of regimens for prevention of delayed nausea and vomiting are recommended. Combinations of these agents have not been studied systematically, and may require antiemetic prophylaxis similar to more emetogenic regimens.

Low Emetogenic Potential Chemotherapy

Many chemotherapy agents do not cause nausea frequently. Examples of these include:

- fluorouracil (5-FU)
- methotrexate <100 mg/m² as a single agent
- thioguanine
- mercaptopurine
- bleomycin
- L-asparaginase
- vindesine
- vinorelbine (Navelbine)
- vincristine
- busulphan
- chlorambucil
- melphalan
- hydroxyurea
- fludarabine
- 2-chlorodeoxyadenosine (2-CDA, Leustatin)
- tamoxifen (Novaldex)

For these drugs, preventative treatment to avoid nausea or vomiting is not required. Occasionally, these agents do cause nausea or vomiting. When this occurs, treatment directed at controlling the symptoms is warranted and consideration should be given to preventative treatment with corticosteroids, prochlorperazine, or other anti-nausea measures.

Treatment of (Established) Nausea and Vomiting

Nausea and vomiting may still develop after therapy with chemotherapy despite adequate preventative measures and the established symptom must be treated. This is often a challenge as most medications are taken orally and patient nutrition and hydration is often at risk. Patients who develop nausea or vomiting after chemotherapy should let their oncologist know promptly; the earlier therapy is initiated, the faster and more completely the symptom will be controlled. More importantly, the danger of dehydration may be magnified after certain chemotherapy agents, as adequate kidney function could be crucial to avoiding further chemotherapy-associated side effects.

Prochlorperazine (Compazine) is often employed to treat nausea and vomiting caused by chemotherapy, and is available in oral, suppository, and intramuscular and intravenous preparations. Occasionally, serotonin receptor antagonists are used to treat established nausea and vomiting, but there is little medical evidence to support this practice. In difficult situations, aggressive intravenous hydration with or without corticosteroids (dexamethasone, most commonly) may help; this is usually performed in an outpatient setting.

We recommend that all patients receiving moderately-emetogenic chemotherapy be provided with medications designed to treat nausea and emesis when they develop.

Anticipatory Emesis

Anticipatory emesis describes nausea or vomiting which occurs prior to scheduled chemotherapy, before chemotherapy drugs are administered.

It is a *conditioned* response which may develop in patients who have had poor control of either acute or delayed nausea or vomiting with previous chemotherapy, or who have predisposing factors such as intense anxiety about chemotherapy or a history of motion sickness. In general, prevention of this symptom is the best approach, as treatment is often only partially successful. Therefore, the use of the most active and evidenced-based antiemetic regimens for chemotherapy agents and combinations as described above is recommended. Their use with the initiation of treatment is imperative; employment of less effective and less aggressive regimens may result in a proportion of patients experiencing unnecessary symptoms, and a proportion of those may go on to develop anticipatory nausea. If anticipatory nausea develops, behavioral therapy with desensitization or hypnosis in addition to aggressive anti-nausea therapy including lorazepam (Ativan) may be helpful.

Nausea and Vomiting with Chemotherapy in Pediatric Oncology

Studies of patients with childhood cancer have documented the efficacy of a variety of antiemetic regimens, with the best-documented success achieved with the serotonin receptor antagonists, which are often administered with corticosteroids. However, dosing studies have not clearly established the optimal dosage or dosing regimens for these drugs.

Recommendations

Typical dosages for serotonin receptor antagonists are:

ondansetron 0.15 mg/Kg per dose every 4-8 hours,

granisetron 15-20 micrograms/Kg per dose every 12-24 hours

dolasetron 1.8 mg/kg IV or orally 1 hour before treatment.

dexamethasone 10 mg/meter squared to maximum of 10 to 20 mg prior to chemotherapy, then 5 mg/square meter IV every 6 to 12 hours or equivalent.

Level of evidence: 3; grade of recommendation: B.

Rules for the prevention of acute and delayed nausea and vomiting follow those for adults, with appropriate dose adjustments. A major exception is the use of metoclopramide (Reglan), droperidol (Inapsine) and similar agents for both acute and delayed nausea prevention: children do not tolerate these drugs well, and a high incidence of *dystonic reactions* (characterized in part by temporary stiffening of parts of the body and an inability to move) suggest that these agents are poor choices for the pediatric population.

Occasionally, *promethazine* (Phenergan) is used employing dosages of 0.25 - 1 mg/Kg PO, PR or IM every 4 to 6 hours as needed.

Special Situations

Regimens with Multiple Consecutive Days of Chemotherapy

Antiemetics, as outlined above, appropriate for the risk class of the chemotherapy drugs employed, should be administered each day of chemotherapy delivery.

Level of evidence: 2, 3; Grade of evidence: B.

Nausea and Vomiting despite Appropriate Prophylaxis

There are no good guidelines to assist the physician and patient as to the appropriate management in this situation. Often the problem is compounded by other medications taken by the patient (for example, narcotic pain medication) as well as tumor factors (tumor deposits in the liver, and secondary tumors in the brain, are often associated with nausea, as is the simple presence of cancer anywhere in a few patients).

Consideration should be given to optimizing the anti-nausea regimen (that is, to administer anti-nausea drugs as if the patient were taking highly emetogenic chemotherapy), adding an anti-anxiety drug such as lorazepam (Ativan), and substituting metoclopramide (Reglan) or droperidol (Inapsine) for the serotonin receptor antagonist.

Other therapies which have been employed include those often termed *complementary* or *alternative*. Hypnosis and relaxation have been shown to be helpful to a number of patients, particularly in terms of treating delayed nausea and vomiting. *Acupuncture* been shown to effectively avoid chemotherapy nausea and vomiting in one randomized clinical trial published in Britain in the late 1980's, prior to the release of serotonin receptor antagonists.

Radiation-Induced Nausea

Nausea may be caused by radiation therapy, but fortunately only a small proportion of patients experience this symptom. Those at highest risk for the symptom include:

- Patients receiving total body radiation (in preparation for bone marrow transplantation),
- Hemibody radiation (half of the body being treated, usually to relieve pain from bony tumors),
- Radiation to the upper abdomen (as in stomach and pancreatic therapy).

Children who receive radiation to any part of the abdomen are also at higher risk for nausea, and seem to suffer more nausea during cranial radiotherapy than do adults, and require more aggressive therapy.

In these groups intervention with preventative therapy appears to be preferable to waiting to see if the patient develops symptoms.

Serotonin receptor antagonists appear to be the most effective agents, and are usually administered orally 30 to 60 minutes prior to each radiation treatment, with or without a corticosteroid (refer to page 5 for dosing recommendations).

Level of evidence: 2,3; Grade of recommendation B, C.

For those at somewhat less risk, such as brain and spinal cord therapy, initial pretreatment with prochlorperazine or metoclopramide may be sufficient, but the development of symptoms should trigger the introduction of more aggressive therapy as outlined above.

Radiation treatments are often administered of several days and weeks, with each treatment termed a *fraction* of radiation therapy. Some investigators have demonstrated that the efficacy of serotonin receptor antagonist may wane after the first week of treatment, which makes the determination of the optimal duration of therapy (some fractions, all fractions, or only the early fractions) somewhat difficult.

References

Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidenced-based, clinical practice guidelines. *J Clin Oncol* 1999; 17: 2971-2994. American Society of Clinical Oncology guidelines. Comprehensive.

The Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *N Engl J Med* 2000; 342: 1554-1559.

Ioannidis JPA, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. *J Clin Oncol* 2000; 19: 3409-3422.

Kris MG, Gralla RJ, Tyson LB, et al. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989; 7: 108-114.

The above articles evaluate post-chemotherapy corticosteroids in an effort to avoid delayed nausea and vomiting.

Morrow GR, Morrell C. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. *N Engl J Med* 1982; 307: 1474-1480. Relaxation may be helpful to alleviate this troubling symptom.

Levels and Grades of Evidence

Levels

1. Evidence is obtained from meta-analysis of multiple, well-designed controlled trials. Randomized trials have low false-positive and low false-negative errors (high power).
2. Evidence is obtained from at least one well-designed experimental study. Randomized trials have high false-positive and or –negative errors (low power).
3. Evidence is obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled, single-group, pre-post, cohort, time, or matched case-control series.
4. Evidence is from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies.
5. Evidence is from case reports and clinical examples.

Grades

- A. There is evidence of type 1 or consistent findings from multiple studies of types 2, 3 and 4.
- B. There is evidence of types 2, 3, and 4, and findings are generally consistent.
- C. There is evidence of types 2, 3, and 4, but findings are inconsistent.
- D. There is little or no systematic empirical evidence.