Complete Summary

GUIDELINE TITLE

Use of 5-HT_3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy.

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Use of 5-HT3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 24 p. (Practice guideline; no. 12-3). [49 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Nausea and vomiting associated with chemotherapy given for cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To compare the antiemetic efficacy of the 5-HT_3 receptor antagonists ondansetron, granisetron, and dolasetron in terms of efficacy and adverse effects in patients receiving moderately or highly emetogenic chemotherapy
- To evaluate the extent to which administration of 5-HT_3 antagonists beyond the first 24 hours prevents delayed-onset emesis

TARGET POPULATION

Adult cancer patients receiving moderately or highly emetogenic chemotherapy

INTERVENTIONS AND PRACTICES CONSIDERED

Use of the following antiemetics (orally or intravenously) in the first 24 hours after chemotherapy and beyond 24 hours:

1. Ondansetron
2. Granisetron
3. Dolasetron
4. Tropisetron

Note: Alternative treatments, such as dexamethasone or domperidone are also considered.

MAJOR OUTCOMES CONSIDERED

- Proportion of patients without vomiting in the first 24 hours following chemotherapy
- Proportion of patients without nausea in the first 24 hours following chemotherapy
- Mean nausea severity according to a visual analog scale
- Quality of life
- Adverse effects of antiemetic therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original: March 2000

The MEDLINE and CANCERLIT databases were originally searched from January 1987 to November 1997. This search was updated in November 1998, April 1999 and October 1999. The search terms included the medical subject headings (MeSH) ondansetron, granisetron, neoplasms, practice guidelines, meta-analysis, randomized controlled trials, double-blind and single-blind method; and the text words ondansetron, granisetron, dolasetron, tropisetron, $5HT_3$ antagonist(s), serotonin antagonist(s), randomized controlled trial and random (truncated). The search also included the publication types practice guideline, meta-analysis and randomized controlled trial. The Physician Data Query (PDQ), the Cochrane Library and the proceedings of the annual meeting of the American Society of Clinical Oncology (ASCO) (1995-1999) were also searched for reports of new or ongoing trials. The lead author checked his personal files for reports of relevant studies. Articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials.

Update: January 2003

The original literature search has been updated using MEDLINE (through January 2003), CANCERLIT (through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query database, the Canadian Medical Association Infobase, the National Guideline Clearinghouse, and abstracts published in annual meeting proceedings of the American Society of Clinical Oncology (through 2002). Article bibliographies and personal files were also searched to January 2003 for evidence relevant to this practice guideline report.

Inclusion Criteria

Articles were selected for inclusion if they met the following criteria:

1. Reports of randomized trials comparing one or more $5\text{-}HT_3$ receptor antagonists (dolasetron, granisetron, ondansetron or tropisetron) with a suitable control group (placebo or antiemetic) in adult cancer patients receiving moderately or highly emetogenic chemotherapy.
2. Since emesis and nausea are subjective endpoints, only the results of randomized double-blind studies were used to formulate the recommendations of this guideline.
3. It has been demonstrated that antiemetics used prior to chemotherapy influence the frequency of delayed-onset emesis. Therefore, to address the question of duration of administration of $5\text{-}HT_3$ receptor antagonists, this overview includes only those studies in which the same antiemetics were administered in both the treatment group and the control group during the first 24 hours, or those in which randomization occurred 24 hours after the initial antiemetic therapy.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.
4. Studies where different 5-HT_3 antagonists were used during the first 24 hours were ineligible.

NUMBER OF SOURCE DOCUMENTS

Original: March 2000

Twenty-two randomized double-blind trials, six unblinded or single-blind trials

Update: January 2003

Two clinical practice guidelines, two meta-analyses, and four double-blind randomized controlled trials were identified in the update and were eligible for review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Synthesizing the Evidence

Original: March 2000

The intent was to combine (i.e., pool) data from all eligible trials in order to calculate overall estimates of treatment efficacy. Pooled results were expressed as a risk ratio (RR) with a 95% confidence interval (CI). The risk ratio is the proportion of patients in the experimental group, relative to the proportion of patients in the control group, who are likely to experience the event. When the event measured is unfavourable (e.g., emesis), estimates greater than 1.0 favour the control group (e.g., placebo, no antiemetic) and estimates less than 1.0 favour the experimental group (antiemetic therapy). The proportion of patients

experiencing emesis was extracted from the trials investigating the efficacy of 5-HT_3 receptor antagonists in delayed-onset emesis and pooled using the fixed effects model. The fixed effects model was used for the meta-analysis because there were too few studies to estimate random effects. The Q-test was used to measure the quantitative heterogeneity among study results. Calculations for the meta-analysis were performed on a Pentium personal computer using the software program, Metaanalyst[0.988], provided by Dr. Joseph Lau (Boston, MA).

Update: January 2003

New studies investigating the efficacy of 5-HT_3 receptor antagonists in delayed-onset emesis that report on the proportion of patients experiencing emesis were added to the original meta-analysis.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

There was a lengthy discussion among the Disease Site Group members regarding the statistical analysis of the data for delayed-onset emesis. Although prolonged administration of 5-HT_3 receptor antagonists is associated with a statistically significant reduction in the rate of emesis, the difference in absolute terms is very small and the upper limit on the 95% confidence interval on the risk ratio (0.98) approaches 1.0.

There is no accepted standard for clinical as opposed to statistical significance. A similar risk ratio would likely be regarded as important for an endpoint of survival, particularly if the confidence limits were narrow. Unlike many other clinical problems, one could reserve the prescription of prolonged 5-HT_3 receptor antagonists for the minority who experience delayed-onset emesis after the first cycle of chemotherapy. The concept of salvage with second-line therapy has been demonstrated in several antiemetic studies. A cost-effectiveness analysis of this strategy would be ideal but is not possible with the current data.

It was felt that the most prevalent practice was administration of these agents for 48 hours after chemotherapy. Since the 5-HT_3 receptor antagonists are generally well tolerated and there is probably a benefit for a very small number of patients, practitioners may choose not to alter their practice for a majority of their patients. However, administration of these agents for the first 24 hours following chemotherapy should be regarded as an appropriate first-line approach. Limiting administration of these agents to the first 24 hours may be particularly desirable where the financial burden of treatment is of importance, or there is concern about the potential for additional constipation. The alternative drugs that have been shown to reduce delayed-onset emesis (dexamethasone and dopamine receptor antagonists) are less costly than 5-HT_3 receptor antagonists.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 150 practitioners in Ontario (100 medical oncologists and 50 pharmacists). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Systemic Treatment Disease Site Group.

The practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the Systemic Treatment Disease Site Group and the Practice Guideline Coordinating Committee.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Intravenous dolasetron, granisetron and ondansetron should be regarded as equally efficacious and well tolerated.
- As a first-line approach, 5-HT_3 receptor antagonists should be administered for 24 hours following chemotherapy.
- There are insufficient data to draw conclusions about the equivalence of the 5-HT_3 receptor antagonists when given orally. A single study comparing dolasetron and ondansetron suggests that a higher than recommended dose of oral dolasetron is at least as efficacious as oral ondansetron.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Original: March 2000

Twelve double-blind randomized controlled trials (RCTs) addressing the question of the relative efficacy and adverse effects of ondansetron, dolasetron and granisetron were eligible for inclusion in this guideline report. Nine additional double-blind randomized studies addressed the value of the administration of these agents beyond the first 24 hours.

An additional double-blind study, which randomized patients to receive either ondansetron or low-dose metoclopramide, was reviewed. Six studies of unblinded or single-blind design were identified and reviewed.

Update: January 2003

Two clinical practice guidelines, two meta-analyses, and four double-blind randomized controlled trials were identified in the update search and were eligible for review.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Original: March 2000

- When 5-HT_3 receptor antagonists are administered for more than 24 hours, the results of a meta-analysis indicate a small (4.1%) decrease in the absolute proportion of patients with delayed-onset emesis.
- A randomized trial showed no advantage when prolonged ondansetron administration was compared with metoclopramide 20 mg orally four times daily.
- No studies have compared the same 5-HT_3 receptor antagonist when given by the oral versus the intravenous route. Two studies of high-dose intravenous ondansetron versus oral granisetron suggest that the recommended dose of the latter is effective and may be regarded as equivalent to administration by the intravenous route.

Update: January 2003

A meta-analysis of 14 randomized trials (including seven non-blinded trials) did not detect statistically significant differences between granisetron and ondansetron for the prevention of acute or delayed nausea or vomiting for either moderately or highly emetogenic chemotherapy. Another meta-analysis, published in abstract form, with data from 28 randomized controlled trials detected no significant differences in acute or delayed nausea or vomiting between ondansetron, granisetron and tropisetron.

POTENTIAL HARMS

The adverse effect profile of all three 5-HT_3 receptor antagonists appears to be similar, apart from a higher frequency of electrocardiographic changes with dolasetron and a higher frequency of dizziness and abnormal vision with high-

dose intravenous ondansetron. Since ondansetron, granisetron and dolasetron are all regarded as well tolerated by the vast majority of patients, it is uncertain whether these observed differences have any clinical relevance.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Mar 7 (updated online 2003 Jan)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Systemic Treatment Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Systemic Treatment Disease Site Group (DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of 5-HT_3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2000 Mar (updated online 2003 Jan). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 19, 2002. The information was verified by the guideline developer on August 19, 2002. This summary was updated by ECRI on August 6, 2003. The updated information was verified by the guideline developer on September 2, 2003.

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Date Modified: 9/15/2008