Complete Summary

GUIDELINE TITLE

The role of gemcitabine in the management of metastatic breast cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Dent S, Messersmith H, Trudeau M, Breast Cancer Disease Site Group. The role of gemcitabine in the management of metastatic breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2007 Jan 22. 5 p. (Evidence-based series; no. 1-12). [11 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, 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.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Metastatic breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the role of gemcitabine, alone or in combination, as first-line chemotherapy in women with metastatic breast cancer
- To evaluate the role of gemcitabine, alone or in combination, as second-line or greater chemotherapy in women with metastatic breast cancer

TARGET POPULATION

Women with metastatic breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Gemcitabine plus docetaxel versus capecitabine plus docetaxel
2. Gemcitabine plus paclitaxel versus paclitaxel alone

Note: Single agent gemcitabine is not recommended for women with metastatic breast cancer who are being considered for first-line single agent anthracycline therapy

Note: The combination of gemcitabine, epirubicin, and paclitaxel (GET) is not recommended for women with metastatic breast cancer who are being considered for first-line anthracycline-based combination chemotherapy

MAJOR OUTCOMES CONSIDERED

- Overall response rate
- Duration of response
- Time-to-progression
- Overall survival
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

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

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

2007 Update

The systematic review portion of this evidence-based series was updated in October 2006 to reflect new evidence published since the previous search in August 2005. This new evidence generated no changes to the clinical practice guideline, and therefore the evidence-based series was not resubmitted to the RAP or for practitioner feedback.

Original Guideline

MEDLINE was searched in its entirety to September 2006 using a disease-specific medical subject heading (MeSH) descriptor ("breast neoplasms") and an agent-class MeSH descriptor with qualifier ("deoxycytidine/analog and derivatives"). The Excerpta Medica database (EMBASE) was also searched in its entirety to September 2006 using a disease-specific Excerpta Medica Tree (EMTREE) term ("breast cancer") and an agent-specific EMTREE term ("gemcitabine"). These terms were then combined with the publication-type search terms for clinical trials, systematic reviews, meta-analyses, and practice guidelines.

Issue 1 (2004) of the Cochrane Library and on-line conference proceedings from the American Society of Clinical Oncology (ASCO) (http://www.asco.org/portal/site/ASCO/; 1999-2006) and the San Antonio Breast Cancer Symposium (http://www.sabcs.org/EnduringMaterials/Index.asp#abstracts; 2001-2005) were also searched. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were examined for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Gemcitabine, alone or in combination with other systemic therapy agents, was evaluated in the metastatic setting, using any of the publication types listed in the search strategy (clinical trials, systematic reviews, meta-analyses, and practice guidelines). After August 2005, only randomized controlled trials were considered for inclusion.
- Reported outcomes included overall response rate (ORR), time to progression (TTP), duration of response, or overall survival.

- Clinical trial results were reported in full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. Those data often appear first in meeting abstracts and may not be published for several years.

Exclusion Criteria

- Trials published in a language other than English were excluded, as resources for translation were not available.
- Reports based on trials that have not completed patient accrual and were clearly ongoing were excluded, unless the report clearly stated that the analysis was pre-planned.
- Reports based on solely dose-finding phase I trials were excluded. Reports of combination phase I/II trials were included.

NUMBER OF SOURCE DOCUMENTS

Eighty-three studies were included in the 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

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Because of the low number of randomized controlled trials identified during the literature search, no systematic pooling of the results of trials was considered.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Gemcitabine has been studied extensively (83 studies) in women with advanced breast cancer, mainly in the phase II setting. While gemcitabine has demonstrated some activity and has generally been well tolerated, there appears to be no particular advantage of gemcitabine over existing chemotherapeutic

agents in the third-line or greater setting. Four randomized phase III trials of gemcitabine-based chemotherapy in women with advanced breast cancer have been reported in the literature. The results of those randomized trials, while difficult to compare directly, suggest that gemcitabine as a single agent is inferior to standard anthracycline-based chemotherapy in patients who are anthracycline naïve. The data suggest that the greatest benefit to be derived from gemcitabine in women with metastatic breast cancer is achieved when it is administered in the first- or second-line setting with a taxane. In particular, the phase III study by Chan et al demonstrated that gemcitabine plus docetaxel was as efficacious as the standard arm of capecitabine and docetaxel in the first- or second-line setting, with significantly reduced toxicity. The trial by O'Shaughnessy et al, combining capecitabine and docetaxel, is one of the few phase III trials to have reported an overall survival advantage in women with advanced breast cancer. The utility of that regimen, however, was hampered by the significant toxicities seen clinically, especially hand-foot syndrome and mucositis Thus, one can hypothesize that the combination of gemcitabine and docetaxel might be a better-tolerated alternative to the capecitabine–docetaxel regimen. Although at this time the results of the Chan study have yet to be fully published, the Breast Cancer Disease Site Group (DSG) believes it very unlikely that those results will change with the final publication, given the strength of the evidence presented in the abstract and the maturity of the data, and barring any major error on the part of the researchers.

The results of the gemcitabine plus paclitaxel trial, showing the superiority of gemcitabine–paclitaxel over paclitaxel alone, led to the approval by the US Food and Drug Administration, and the recent approval by Health Canada, of that combination for women with metastatic breast cancer after failure of prior anthracycline-containing adjuvant therapy. Based on those approvals, the Breast Cancer DSG believes the results to be sufficient to warrant a recommendation at this time, while awaiting the peer-reviewed publication. Single-agent paclitaxel has generally not been considered as efficacious as single-agent docetaxel in the treatment of women with metastatic breast cancer, and one might expect a paclitaxel doublet to be superior to paclitaxel alone. Docetaxel, given as a single agent or in combination has generally been accepted as the standard taxane in the treatment of women with metastatic breast cancer. However the randomized phase II trial by Khoo et al suggests that the choice of taxane, paclitaxel or docetaxel, may not make any meaningful difference in the efficacy of gemcitabine plus taxane combinations.

While gemcitabine appears to be generally well tolerated when administered with a taxane doublet, one phase III study by Zielinkski et al demonstrated equal efficacy with significantly higher hematological toxicity in patients treated with a gemcitabine/taxane triplet (GET) over those treated with 5-fluorouracil plus epirubicin plus cyclophosphamide (FEC) chemotherapy. Patients receiving gemcitabine/taxane triplet also experienced significantly more grade 3/4 polyneuropathy and mucositis. This trial suggests that there is no additional benefit, and more toxicity, to the addition of a third chemotherapeutic agent to a gemcitabine/taxane doublet.

The large number of non-randomized phase II trials identified indicates that gemcitabine, alone or in combination, is generally effective with acceptable toxicity but not more so than other currently accepted regimens. The results of the phase II trials do not support the acceptance of gemcitabine as a standard

therapeutic option in women with metastatic breast cancer in the third-line or greater setting. Gemcitabine should not be considered as first-line therapy in women with metastatic breast cancer who are anthracycline naïve. Gemcitabine is most effective when administered with a taxane (docetaxel/paclitaxel) in the first- or second-line setting. Gemcitabine/taxane combinations represent a viable alternative to currently accepted taxane combinations such as capecitabine–docetaxel. There is no evidence at the present time to support the use of gemcitabine triplets, given the equal efficacy to anthracycline triplets and the added toxicity.

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

2007 Update

The systematic review portion of this evidence-based series was updated in October 2006 to reflect new evidence published since the previous search in August 2005. This new evidence generated no changes to the clinical practice guideline, and therefore the evidence-based series was not resubmitted to the Report Approval Panel or for practitioner feedback.

Original Guideline

Report Approval Panel Review

Prior to submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodology issues.

External Review

Following the review and discussion of Sections 1 and 2 of the original guideline document and review and approval of the report by the PEBC Report Approval Panel, the Breast Cancer Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 112 practitioners in Ontario: 75 medical oncologists and 37 radiation oncologists and surgeons. 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. The survey was mailed out on April 8, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer Disease Site Group (DSG) reviewed the results of the survey.

No modifications to the document were made in response to the practitioner feedback.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the Program in Evidence-based Care (PEBC) and National Guidelines Clearinghouse (NGC): 2007 Update: The systematic review portion of this evidence-based series was updated in October 2006 to reflect new evidence published since the previous search in August 2005. This new evidence generated no changes to the clinical practice guideline, and therefore the evidence-based series was not resubmitted to the Report Approval Panel (RAP) or for practitioner feedback.

- The combination of gemcitabine and docetaxel may be considered as an alternative to capecitabine and docetaxel for first- or second-line chemotherapy in patients in whom the toxicity of the capecitabine and docetaxel regimen is a concern.
- For patients with metastatic breast cancer who have received prior (neo)adjuvant anthracycline therapy, the combination of gemcitabine plus paclitaxel is superior compared to paclitaxel alone as first-line chemotherapy.
- Single-agent gemcitabine is NOT recommended for women with metastatic breast cancer who are being considered for first-line single-agent anthracycline chemotherapy.
- The combination of gemcitabine, epirubicin, and paclitaxel (GET) is NOT recommended as first-line chemotherapy for women with metastatic breast cancer who are being considered for anthracycline-based combination chemotherapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and single-arm trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized phase III study reported by Chan et al in abstract form found no significant difference between the combination of gemcitabine (1000 mg/m^2 on days one and eight) and docetaxel (75 mg/m^2 on day one) every 21 days and the combination of capecitabine (1250 mg/m^2 twice a day for 14 days) and docetaxel (as above) every 21 days in terms of objective response rate (ORR), progression-free survival (PFS), duration of response, or time-to-progression (TTP). However, patients receiving gemcitabine plus docetaxel experienced significantly less hand-foot syndrome, diarrhea, and mucositis than those receiving capecitabine plus docetaxel.
- A randomized controlled trial reported at the 2003 and 2004 American Society of Clinical Oncology (ASCO) meetings compared the combination of gemcitabine (1250 mg/m^2 of on days one and eight) and paclitaxel (175 mg/m on day one) every 21 days to the same dosage and schedule of paclitaxel without gemcitabine in patients with metastatic breast cancer who had previously received adjuvant or neoadjuvant anthracycline chemotherapy. That trial found a significantly superior ORR (40.8% versus 22.1%, $p<0.0001$), median TTP (5.2 months versus 2.9 months, hazard ratio [HR] 0.650, 95% confidence interval [CI] 0.524 to 0.805), and overall survival (18.5 months versus 15.8 months, HR 0.775, 95% CI 0.627 to 0.959) in patients treated with the combination regimen.

POTENTIAL HARMS

A randomized controlled trial reported by Zielinski et al compared the combination of gemcitabine (1000 mg/m^2 on days one and four), epirubicin (90 mg/m^2 on day one), and paclitaxel (175 mg/m^2 on day one), with the combination of 5-fluorouracil (500 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (500 mg/m^2), all on day one. That trial found significantly higher haematological toxicities, polyneuropathy, and mucositis in the gemcitabine-containing arm.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The efficacy of capecitabine and docetaxel over docetaxel alone was demonstrated in a trial by O'Shaughnessy et al but the clinical utility of this regimen has been hampered by significant toxicities, especially hand-foot syndrome and mucositis.
- Patients who received the combination regimen (gemcitabine plus paclitaxel) experienced a higher rate of neutropenia (48% versus 11%) over those treated with paclitaxel alone.
- The clinical relevance of this regimen (gemcitabine plus paclitaxel) in Ontario is questionable as docetaxel has been the standard taxane used in the metastatic setting.
- Doxorubicin given as a single agent or in combination is currently approved and funded for women with metastatic breast cancer in Ontario. Epirubicin-

based combinations are not funded for women with metastatic breast cancer in Ontario.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series 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 guarantees of any kind whatsoever regarding their content or use or application and disclaims any 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

2006 Jun 27 (revised 2007 Jan 22)

GUIDELINE DEVELOPER(S)

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

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is 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 Breast Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The following potential conflicts of interest were declared by the lead authors of this review (SD, MT, and HM). SD was the primary investigator of a phase II trial of gemcitabine and pemetrexed in women with metastatic breast cancer, funded by Eli Lilly and Company. MT reported receiving some free gemcitabine for several patients from the same company.

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:

- The role of gemcitabine in the management of metastatic breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO), 2007 Jan 22. Various p. (Practice guideline; no. 1-12. 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 August 21, 2006. The information was verified by the guideline developer on August 23, 2006. This NGC summary was updated by ECRI Institute on April 30, 2007. The updated information was verified by the guideline developer on May 9, 2007.

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