Evidence-based Series 1-12: EDUCATION AND INFORMATION 2014

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Role of Gemcitabine in the Management of Metastatic Breast Cancer

Members of the Breast Cancer Disease Site Group

An assessment conducted in January 2014 put Evidence-based Series (EBS) 1-12 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 1-12: TO BE UPDATED is comprised of the following 4 sections:

1. Guideline Report Overview
2. Section 1: Guideline Recommendations
3. Section 2: Systematic Review
4. Section 3: EBS Development Methods and External Review Process
5. Document Assessment and Review Tool

and is available on the CCO Web site (http://www.cancercare.on.ca)
PEBC Breast Cancer DSG page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/

Release Date: September 15, 2011

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The Role of Gemcitabine in the Management of Metastatic Breast Cancer

Guideline Report History

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<tr>
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<th>SYSTEMATIC REVIEW</th>
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<td>Search Dates: 1966 to 2005</td>
<td>Data: Full Report</td>
<td>Peer review publication¹ Web publication</td>
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<td>Update</td>
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<td>Data: New data added to original Full Report</td>
<td>Updated Web publication</td>
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<td>Jan 2007</td>
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<tr>
<td>Reviewed version</td>
<td>Search Dates: 2006 to 2010</td>
<td>Data: New data found in Document Assessment and Review Tool</td>
<td>2007 Recommendations require an UPDATE</td>
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<td>Sep 2011</td>
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</table>

Evidence-based Series 1-12 TO BE UPDATED

The Role of Gemcitabine in the Management of Metastatic Breast Cancer

Guideline Review Summary

Review Date: November 19, 2010

The 2007 guideline recommendations require UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making.

OVERVIEW
Evidence-based Series History
This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 2006 and its first update released in January 2007. In November 2010, the PEBC guideline update strategy was applied, and it was determined that the document needs to be updated. The Practice Guideline and Systematic Review in this version are the same as in the January 2007 version.

Update Strategy
Using the Document Assessment and Review Tool, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered
- What is the role of gemcitabine, alone or in combination, as first-line chemotherapy in women with metastatic breast cancer?
- What is the role of gemcitabine, alone or in combination, as second-line or greater chemotherapy in women with metastatic breast cancer?
Literature Search and New Evidence

The new search (October 2006 to August 2010) yielded 16 relevant publications (nine abstracts and five full text publications) from 13 RCTs. Initial publications of two randomized controlled trials (RCTs) were already included in the original document. Brief results of these publications are shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports the existing recommendations but the current recommendations do not cover all relevant subjects. The newly identified evidence introduces targeted therapies in combination with chemotherapy (e.g., bevacizumab and platinum). Hence, the Breast Cancer DSG decided that the 2007 recommendations on the role of gemcitabine in the management of metastatic breast cancer require an UPDATE.
Evidence-based Series 1-12: Section 1

The Role of Gemcitabine in the Management of Metastatic Breast Cancer:
A Clinical Practice Guideline

S. Dent, H. Messersmith, M. Trudeau, and the Breast Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Please see the EBS 1-12 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2006 and 2010.

Report Date: January 22, 2007

Question

- What is the role of gemcitabine, alone or in combination, as first-line chemotherapy in women with metastatic breast cancer?
- What is 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.

Recommendations and Key Evidence

The combination of gemcitabine and docetaxel may be considered as an alternative to capecitabine and docetaxel for first- or second-line chemotherapy in patients where the toxicity of the capecitabine and docetaxel regimen is a concern.

- One randomized phase III study reported by Chan et al in abstract form (1,2) found no significant difference between the combination of gemcitabine (1000 mg/m² on days one and eight) and docetaxel (75 mg/m² on day one) every 21 days and the combination of capecitabine (1250 mg/m² 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.
Qualifying Statements

- The efficacy of capecitabine and docetaxel over docetaxel alone was demonstrated in a trial by O'Shaughnessy et al (3) but the clinical utility of this regimen has been hampered by significant toxicities, especially hand-foot syndrome and mucositis.

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.

- A randomized controlled trial reported at the 2003 and 2004 American Society of Clinical Oncology (ASCO) meetings (4-9) compared the combination of gemcitabine (1250 mg/m² on days one and eight) and paclitaxel (175 mg/m² 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.

Qualifying Statements

- Patients who received the combination regimen experienced a higher rate of neutropenia (48% versus 11%) over those treated with paclitaxel alone.
- The clinical relevance of this regimen in Ontario is questionable as docetaxel has been the standard taxane used in the metastatic setting.

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.

- One randomized phase III study reported by Feher et al in (10) compared epirubicin (35 mg/m² on days one, eight, and 15) with gemcitabine (1200 mg/m² on days one, eight, and 15) every 28 days in postmenopausal patients aged 60 or older. No significant differences were found between the treatment arms in terms of time to response and duration of response. Epirubicin was significantly better than gemcitabine in terms of ORR (40.3% versus 16.4%, p<0.0001), TTP (6.1 months versus 3.4 months, p=0.0001), and overall survival (19.1 months versus 11.8 months, p=0.004).
- A randomized controlled trial reported by Zielinski et al (11) compared the combination of gemcitabine (1000 mg/m² on days one and four), epirubicin (90 mg/m² on day one), and paclitaxel (175 mg/m² on day one), with the combination of 5-fluorouracil (500 mg/m²), epirubicin (90 mg/m²), and cyclophosphamide (500 mg/m²), all on day one. Both combinations used a 21-day cycle. Patients were required to have had one prior non-anthracycline adjuvant chemotherapy. That trial found no significant differences in terms of ORR, TTP, or overall survival and found significantly higher haematological toxicities, polyneuropathy, and mucositis in the gemcitabine-containing arm.

Qualifying Statements

- 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.
Funding
The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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For information about the PEBC and the most current version of all reports, please visit the CCO at http://www.cancercare.on.ca/ or contact the PEBC office at:
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REFERENCES


The Role of Gemcitabine in the Management of Metastatic Breast Cancer: A Systematic Review

S. Dent, H. Messersmith, M. Trudeau, and the Breast Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Please see the EBS 1-12 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2006 and 2010.

Report Date: January 22, 2007

QUESTIONS
- What is the role of gemcitabine, alone or in combination, as first-line chemotherapy in women with metastatic breast cancer?
- What is the role of gemcitabine, alone or in combination, as second-line or greater chemotherapy in women with metastatic breast cancer?

INTRODUCTION
Breast Cancer is the most common malignancy of women in developed countries and is the second most common cause of cancer-related death in women in Canada (1). Despite the improvements in breast cancer prevention, early detection, and adjuvant therapy, many women develop metastatic breast cancer that is considered incurable, with a median survival of 2-3 years.

The anthracyclines have been considered one of the most active classes of chemotherapy agents in the treatment of advanced breast cancer. Over the last 10 years, the widespread adoption of anthracyclines in the treatment of early-stage breast cancer has led to a shift in the first line treatment of women with metastatic breast cancer. The anthracyclines remain an option for women who are chemotherapy naive. The taxanes (docetaxel/paclitaxel), alone or in combination, are now offered as a standard of care in first-line treatment for women with metastatic breast cancer; however, this is likely to change. Several studies have investigated the impact of the combination of anthracyclines and taxanes, given either sequentially (2-4) or in combination (5) in women with early-stage disease. The favourable results of those studies have led to the increasing use of taxanes in the treatment of women with early-stage breast cancer and diminishing use in women with advanced breast cancer. Several other cytotoxic chemotherapy agents, alone or in...
combination, have been shown to have activity in women with metastatic breast cancer, including capecitabine, vinorelbine, platinums (cisplatin, carboplatin), mitoxantrone, and targeted therapies such as trastuzumab (in patients who overexpress HER-2).

There is no single standard systemic therapy for the treatment of women with metastatic breast cancer. Gemcitabine (Gemzar) is a pyrimidine antimetabolite that interferes with DNA synthesis. Gemcitabine has shown promising activity as a single agent and in combination in the treatment of metastatic breast cancer with minimal toxicity. Consequently, the Breast Cancer Disease Site Group (DSG) undertook a systematic review of the evidence for the role of gemcitabine in the treatment of women with metastatic breast cancer.

METHODS
This systematic review was developed by Cancer Care Ontario’s Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by two members (MT and SD) of the PEBC Breast Cancer DSG and one methodologist (HM). This review is a convenient and up-to-date source of the best available evidence on the role of gemcitabine in the management of metastatic breast cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trials and phase II trial data. That evidence forms the basis of a clinical practice guideline developed by the Breast Cancer DSG and published as Section 1 of this evidence-based series. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is funded by, but editorially independent of, Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy
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/ac/1,1003,12-002095,00.asp; 1999-2006) and the San Antonio Breast Cancer Symposium (http://www.sabcs.org/SymposiumOnline/index.asp#abstracts; 2001-2005) were also searched. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines 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.

Synthesizing 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.

RESULTS

Literature Search Results

Eighty-three studies were identified (7-99). Of those, four were phase III randomized clinical studies, one was a randomized phase II clinical trial, and the remainder were single-arm phase II clinical trials. Thirty-nine of the studies were reported solely in abstract form. The following were eligible for inclusion in the systematic review of the evidence:

Table 1. Studies included in this systematic review.

<table>
<thead>
<tr>
<th>Drug combination studied</th>
<th>1st Line plus other lines</th>
<th>1st Line only</th>
<th>2nd Line or greater</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RANDOMIZED TRIALS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G + D versus capecitabine + D</td>
<td>1 (6,7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G + T versus T</td>
<td>1 (8-13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G versus E</td>
<td>1 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G + E + T versus F + E + C</td>
<td>1 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G + T and G + D (Phase II)</td>
<td>1 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NON-RANDOMIZED TRIALS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine alone</td>
<td>2 (17,18)</td>
<td>2 (19,20)</td>
<td>7 (21-27)</td>
</tr>
<tr>
<td><strong>Doublet combinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G + anthracycline</td>
<td>3 (28-30)</td>
<td>3 (31-33)</td>
<td>1 (34)</td>
</tr>
<tr>
<td>G + taxane</td>
<td>3 (35-37)</td>
<td>6 (38-43)</td>
<td>4 (44-47)</td>
</tr>
<tr>
<td>G + platinum agents</td>
<td>2 (48,49)</td>
<td>2 (50,51)</td>
<td>11 (52-63)</td>
</tr>
<tr>
<td>G + Other agents</td>
<td>8 (64-71)</td>
<td>17 (72-88)</td>
<td></td>
</tr>
<tr>
<td><strong>Triplet combinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G + anthracycline</td>
<td>2 (89,90)</td>
<td>7 (91-97)</td>
<td>2 (98,99)</td>
</tr>
</tbody>
</table>

Abbreviations: C, cyclophosphamide; D, docetaxel; E, epirubicin; F, 5-fluorouracil; G, gemcitabine; T, paclitaxel; V, vinorelbine.
Critical Appraisal of Selected Studies
There were no notable deficiencies in trial design identified in any of the randomized trials included in this review, although the reporting of randomization details (sequence generation, allocation concealment, and implementation) were not completely reported in any of the trial reports. A summary of key trial characteristics can be found in Table 2.

A large number of phase II studies were identified for inclusion. The selected studies all had very similar inclusion and exclusion criteria for patients in the study, where those requirements were reported. With few exceptions, those criteria included the following: women with advanced or metastatic breast cancer; adequate bone marrow, renal, and hepatic function; either a Karnofsky performance scale rating of greater than sixty or an Eastern Cooperative Cancer Group (ECOG)/World Health Organization (WHO)/Zubrod performance scale rating of 0 to 2; no second malignancy other than cervical carcinoma or basal cell carcinoma of the skin (usually within five years); and no brain or central nervous system (CNS) metastases. In terms of patient characteristics, the studies are comparable. The dosing regimen of gemcitabine often differed between studies, which could account for differences in outcome measures between trials.

Outcomes
First-Line Therapy
Reports of non-randomized studies published prior to August 2005 of gemcitabine in first line or multiple lines of chemotherapy are described in the Appendix, Tables A1 and A2—the outcome information is described in Table A1, and the toxicity information is described in Table A2. Phase III randomized controlled trials are described in further detail in the text below. The results of each trial are summarized in Table 3, and toxicity results are summarized in Table 4.
Table 2. Gemcitabine alone or in combination in first-line therapy or greater for metastatic breast cancer - Characteristics of included randomized trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms</th>
<th>Pts</th>
<th>Type of Trial and Analysis</th>
<th>Treatment setting</th>
<th>Patient Characteristics</th>
<th>Expected Effect, Power, and Planned Sample Size(^a)</th>
<th>Intent to Treat Analysis?</th>
<th>Correction for Interim Analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al (6,7) [abstract]</td>
<td>GD XD</td>
<td>153</td>
<td>Multicentre Phase III, Final</td>
<td>First- or second-line</td>
<td>One prior anth.-containing (neo)adj. or first-line met. chemo., prior (neo)adj. taxane allowed if ≥ 6 months</td>
<td>PFS median 6 months versus 8.2 months, 80% power, ≥ 250 events (actual 259 events)</td>
<td>Yes</td>
<td>No interim analysis reported</td>
</tr>
<tr>
<td>O'Shaughnessy et al (8-13) [abstract]</td>
<td>GT T</td>
<td>267</td>
<td>Multicentre Phase III, Interim</td>
<td>First-line</td>
<td>Prior (neo)adj. anth.-containing chemo., unless contraindicated, no chemo. for met. disease</td>
<td>At final analysis, HR 0.75 for overall survival, 85% power, 440 events (actual 343 events)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Feher et al (14)</td>
<td>G E</td>
<td>198</td>
<td>Multicentre Phase III, Final</td>
<td>First-line</td>
<td>No prior anth. chemo., up to one prior adj. chemo. if ≥ 1 year before study, no prior chemo. for met. disease</td>
<td>TTP median 26 versus 35 weeks, 80% power, 440 patients (actual 397 patients)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zielinski et al (15)</td>
<td>GET FEC</td>
<td>124</td>
<td>Multicentre Phase III, Final</td>
<td>First-line</td>
<td>No prior anth. chemo., up to one prior adj. chemo. if relapsed ≥ 6 months after chemo., no prior chemo. for met. disease</td>
<td>TTP HR 1.50, 80% power, 260 patients (actual 259 patients)</td>
<td>No</td>
<td>No interim analysis reported</td>
</tr>
<tr>
<td>Khoo et al (16)</td>
<td>GT1(^b) GT2(^b) GD</td>
<td>72</td>
<td>Randomized Phase II</td>
<td>First-line or greater</td>
<td>Prior anth. chemo., either adjuvant or metastatic. Prior taxane therapy allowed if ≥ 12 months</td>
<td>Rule out response rate of 40% or lower given a true response rate of 60%, 89% power, 70 patients per arm</td>
<td>NR</td>
<td>No interim analysis reported</td>
</tr>
</tbody>
</table>

Note: See text for complete dosage and schedule information, except as indicated below.
\(^a\) Significant level 0.05.
\(^b\) GT1 was 1250 mg/m\(^2\) gemcitabine plus 175 mg/m\(^2\) paclitaxel. GT2 was 1000 mg/m\(^2\) gemcitabine and 100 mg/m\(^2\) paclitaxel.
Abbreviations: anth., anthracycline; adj., adjuvant; C, cyclophosphamide; chemo., chemotherapy; D, docetaxel; E, epirubicin; F, 5-fluorouracil; G, gemcitabine; HR, hazard ratio; met., metastatic; NR, not reported; PFS, progression-free survival; Pts, number of patients; T, paclitaxel; TTP, time-to-progression; X, capecitabine.
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Table 3. Gemcitabine alone or in combination in first-line therapy or greater for metastatic breast cancer - Efficacy results of randomized trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms (Pts)</th>
<th>Rate</th>
<th>ORR Comp.</th>
<th>Median (months)</th>
<th>Median (months)</th>
<th>Median (months)</th>
<th>Median (months)</th>
<th>Median (months)</th>
<th>Median (months)</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al (6,7)</td>
<td>GD (153) XD (152)</td>
<td>32%</td>
<td>32%</td>
<td>p=0.93</td>
<td>4.75</td>
<td>4.5</td>
<td>p=0.51</td>
<td>8.75A</td>
<td>p=0.29</td>
<td>9</td>
</tr>
<tr>
<td>O'Shaughnessy et al</td>
<td>GT (267) T (262)</td>
<td>40.8%</td>
<td>22.1%</td>
<td>p&lt;0.0001</td>
<td>5.2</td>
<td>2.9</td>
<td>p&lt;0.0001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Feher et al (14)</td>
<td>G (198) E (199)</td>
<td>16.4%</td>
<td>40.3%</td>
<td>p&lt;0.0001</td>
<td>3.4</td>
<td>6.1</td>
<td>p&lt;0.0001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zielinski et al (15)</td>
<td>GET (124) FEC (135)</td>
<td>62.3%</td>
<td>51.2%</td>
<td>p=0.093</td>
<td>9.1</td>
<td>9.0</td>
<td>p=0.557</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Khoo et al (16)</td>
<td>GT1 (72) GT2 (67)</td>
<td>48.6%</td>
<td>52.2%</td>
<td>NR</td>
<td>7.5</td>
<td>7.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GD (65)</td>
<td>52.3%</td>
<td>NR</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Note: See text for complete dosage and schedule information, except as indicated below. Statistically significant comparisons are in bold text.

A Originally in weeks, converted at 4 weeks per month for comparability.
B HR (GT vs. T) 0.650 (95% CI 0.524 to 0.805).
C HR (GT vs. T) 0.775 (95% CI 0.627 to 0.959).
D GT1 was 1250 mg/m^2 gemcitabine plus 175 mg/m^2 paclitaxel, GT2 was 1000 mg/m^2 gemcitabine and 100 mg/m^2 paclitaxel.
E HR (GT1 vs. GT2) 0.96 (95% CI 0.65 to 1.42), HR (GT1 vs. GD) 0.97 (95% CI 0.65 to 1.44), HR (GT2 vs. GD) 1.01 (95% CI 0.68 to 1.51).

Abbreviations: C, cyclophosphamide; CI, confidence interval; Comp., comparison; D, docetaxel; E, epirubicin; F, 5-fluorouracil; G, gemcitabine; HR, hazard ratio; NR, not reported; ORR, Objective Response Rate; PFS, progression-free survival; Pts, number of patients; T, paclitaxel; TTF, time-to-treatment-failure; TTP, time-to-progression; X, capecitabine.

Table 4. Gemcitabine alone or in combination in first-line therapy or greater for metastatic breast cancer - Toxicity results of randomized trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms (Pts)</th>
<th>Anemia</th>
<th>Leukopenia</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Rate of Grade 3/4 Toxicity</th>
<th>Diarrhea</th>
<th>Mucositis</th>
<th>Polyneuropathy</th>
<th>Hand-foot Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al (6,7)</td>
<td>GD</td>
<td>7%</td>
<td>85%</td>
<td>25.3%</td>
<td>11%</td>
<td>8%</td>
<td>-8%</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>XD</td>
<td>-3%</td>
<td>22.1%</td>
<td>19.7%</td>
<td>3%</td>
<td>9%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>O'Shaughnessy et al</td>
<td>GT</td>
<td>7%</td>
<td>48%</td>
<td>25.3%</td>
<td>11%</td>
<td>8%</td>
<td>-8%</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>-3%</td>
<td>11%</td>
<td>15.9%</td>
<td>3%</td>
<td>9%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Feher et al (14)</td>
<td>G</td>
<td>5.3%</td>
<td>43.0%</td>
<td>17.9%</td>
<td>11.1%</td>
<td>8%</td>
<td>-8%</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>5.7%</td>
<td>63.9%</td>
<td>26.7%</td>
<td>15.8%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Zielinski et al (15)</td>
<td>GET</td>
<td>21.1%</td>
<td>74.8%</td>
<td>92.7%</td>
<td>25.8%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>FEC</td>
<td>7.7%</td>
<td>83.8%</td>
<td>73.3%</td>
<td>36.8%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Khoo et al (16)</td>
<td>GT1</td>
<td>10.3%</td>
<td>50.0%</td>
<td>17.9%</td>
<td>14.7%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>GT2</td>
<td>23.5%</td>
<td>58.8%</td>
<td>67.2%</td>
<td>22.1%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>GD</td>
<td>23.5%</td>
<td>58.8%</td>
<td>67.2%</td>
<td>22.1%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Note: See text for complete dosage and schedule information, except as indicated below. Statistically significant comparisons are in bold text. There were no statistical test results reported for comparisons in italics.

A Originally in weeks, converted at 4 weeks per month for comparability.
B Specific p-values were not reported, but comparisons were reported as statistically significant.
C GT1 was 1250 mg/m^2 gemcitabine plus 175 mg/m^2 paclitaxel.

Abbreviations: C, cyclophosphamide; D, docetaxel; E, epirubicin; F, 5-fluorouracil; G, gemcitabine; NR, not reported; T, paclitaxel; X, capecitabine.
Gemcitabine and docetaxel
One study (6,7) reported by Chan et al as an abstract and oral presentation at the 2005 ASCO meeting, was a randomized phase III trial of gemcitabine and docetaxel versus capecitabine and docetaxel as first- or second-line therapy for women with metastatic breast cancer. These same results have since been summarized elsewhere (100,101) but without any new analysis. In one arm, women received gemcitabine 1000 mg/m² days one and eight and docetaxel 75 mg/m² day one every 21 days; in the other, women received capecitabine 1250 mg/m² twice per day for 14 days and docetaxel 75 mg/m² day one every 21 days. All patients had received anthracycline-containing chemotherapy in either the (neo)adjuvant or metastatic setting. That trial found no significant difference between the gemcitabine-based and capecitabine-based arms in terms of ORR, TTP, PFS, or response duration but did find significantly lower rates of grade 3/4 hand-foot syndrome, mucositis, and diarrhea in patients treated with the gemcitabine combination.

An additional abstract and slide presentation has been presented from this trial at the 2006 ASCO Annual Meeting (102,103) that reports on an exploratory analysis of toxicity and quality of life. The Rotterdam Symptom Checklist (RSCCL) was used to assess quality of life at baseline and every cycle of chemotherapy in patients included in the trial. Of the randomized patients, 267 had completed checklists and were available for analysis. Over the first six cycles of chemotherapy, 79% to 88% of checklists were completed. No significant differences in quality of life scores were measured at baseline or in any cycle or therapy. However, attrition due to toxicity was higher in the capecitabine and docetaxel arm, with 28% discontinuing therapy due to serious adverse events versus 13% in the gemcitabine and docetaxel arm.

Gemcitabine and paclitaxel
One study (8-13), reported by O’Shaughnessy et al, Albain et al, and Moinpour et al in both abstract and oral presentation at the 2003 and 2004 ASCO meetings, was a randomized phase III clinical trial in which treatment with paclitaxel alone was compared to treatment with the combination of gemcitabine and paclitaxel in first-line therapy. Those reports were of two different interim analyses of the trial. The first (10-13) was a planned interim analysis of TTP, PFS, ORR, and toxicity, as well as quality of life. The second (8,9) was an unplanned interim analysis done as part of the United States (US) Food and Drug Administration approval process. Women in one arm received 1250 mg/m² of gemcitabine on days one and eight and 175 mg/m² paclitaxel on day one every 21 days. In the other arm, women received the same dosage of paclitaxel on day one every 21 days. All patients must have received prior adjuvant or neoadjuvant anthracycline therapy. The combination of gemcitabine plus paclitaxel produced significantly better outcomes for ORR, TTP, and overall survival. There was a statistically significant (p-value not reported) interaction between mean global quality-of-life scores compared to baseline on the Rotterdam Symptom Checklist (RSCCL) instrument and time, with patients receiving the gemcitabine combination reporting higher scores near the end of treatment (cycles 5 and 6) than those patients receiving paclitaxel alone (10,11). The overall survival benefit at the unplanned interim analysis, while significant (p=0.018), did not meet the planned stopping rule (p<0.0001).

Gemcitabine versus epirubicin
One randomized phase III study (14), reported by Feher et al in 2005, compared gemcitabine versus epirubicin in elderly females with metastatic breast cancer. All patients were post-menopausal and age greater than 60 years. That study compared epirubicin (35 mg/m² on days one, eight, and 15) with gemcitabine (1200 mg/m² on days one, eight, and 15) every 28
days. Epirubicin was found to be superior to gemcitabine in terms of objective response rate, median TTP and median overall survival.

**Gemcitabine plus an anthracycline and a taxane**
The randomized phase III trial (15) reported in 2005 by Zielinski et al had two treatment arms. Both arms used a 21-day cycle regimen and planned eight cycles of therapy. In the gemcitabine plus epirubicin plus paclitaxel (GET) arm, patients received 90 mg/m² of epirubicin and 175 mg/m² of paclitaxel on day one, and 1000 mg/m² of gemcitabine on days one and four. In the 5-fluorouracil plus epirubicin plus cyclophosphamide (FEC) arm, patients received 90 mg/m² of epirubicin, 500 mg/m² of 5-fluorouracil, and 500 mg/m² of cyclophosphamide, all on day one. Patients were required to have had one prior non-anthracycline adjuvant chemotherapy. There were no significant differences in any of the reported outcomes between the two arms, but there were significantly greater rates of multiple grade 3 and 4 toxicities in the GET arm.

**Gemcitabine plus taxane**
A randomized phase II trial by Khoo et al (16) trial evaluated three schedules of gemcitabine combined with taxanes: 1250 mg/m² gemcitabine and 175 mg/m² paclitaxel (GP1), 1000 mg/m² gemcitabine and 100 mg/m² paclitaxel (GP2), and 1000 mg/m² gemcitabine and 40 mg/m² docetaxel (GD). All regimens were given every 21 days. All relevant data from this trial can be found in Tables 3 and 4.

**Second-Line Therapy or Greater**
Reports of non-randomized trials published prior to August 2005 of gemcitabine as second-line or greater chemotherapy are described in the Appendix, Tables A3 and A4. The outcome information is described in Table A3, and the toxicity information is described in Table A4. There were no randomized trials identified that compared gemcitabine-based second-line chemotherapy with other forms of chemotherapy.

**DISCUSSION**
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 (6,7) 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 (104), 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 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 (8-13), 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 (105) 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 (16) 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 Zielinski et al (15) demonstrated equal efficacy with significantly higher hematological toxicity in patients treated with a gemcitabine/taxane triplet (GET) over those treated with FEC chemotherapy. Patients receiving GET 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.

ONGOING TRIALS

A search was made of the National Cancer Institute’s clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) for ongoing randomized clinical trials of gemcitabine alone or in combination in metastatic breast cancer. Three were identified: NCT00236899, comparing two different schedules of the combination of gemcitabine with a taxane (106); NCT00191243, comparing docetaxel to docetaxel plus gemcitabine (107); and NCT00294385, comparing concurrent docetaxel and gemcitabine with sequential docetaxel followed by gemcitabine (108). A search of the Cochrane Central Register of Controlled Trials did not identify any additional ongoing trials. In addition, a preliminary report of a randomized trial comparing the combination of vinorelbine and gemcitabine against capecitabine in patients with advanced breast cancer pretreated with taxane and anthracycline chemotherapy was published at the 2006 ASCO Annual Meeting (109).
CONCLUSIONS
Four randomized phase III trials have been conducted evaluating gemcitabine, alone or in combination, as chemotherapy for metastatic breast cancer. Two found some benefit to gemcitabine-based chemotherapy in terms of efficacy or toxicity. Two found it inferior, again based on efficacy or toxicity. Gemcitabine, alone or in combination, has also been evaluated by a large number of phase II trials, with few combinations showing results compelling enough to warrant additional randomized trials. It is unlikely that further randomized trials of gemcitabine, alone or in combination, will identify a broader role for this agent in this patient population.

CONFLICT 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.

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For a complete list of the Breast Cancer Disease Site Group, please visit the CCO Web site at http://www.cancercare.on.ca/.

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


Table A1. Gemcitabine alone or in combination in first-line or greater therapy for metastatic breast cancer - Range of patient outcome measures reported by included non-randomized trials.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Number of patients</th>
<th>ORR, percent of patients [median]</th>
<th>Median duration of response, in months [median]</th>
<th>Median TTF/TTP/PFS, in months [median]</th>
<th>Median OS, in months [median]</th>
</tr>
</thead>
<tbody>
<tr>
<td>G alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1st-line only (19,20)</td>
<td>77</td>
<td>14.3 - 37.1</td>
<td>5.6 - 8.8</td>
<td>5.1 - 5.6</td>
<td>15.2 - 21.1</td>
</tr>
<tr>
<td>- 1st-line and greater</td>
<td>60</td>
<td>25 - 25 (17,18)</td>
<td>13.5 (17)</td>
<td>6.3 (18)</td>
<td>11.5 - 51.9 (17,18)</td>
</tr>
<tr>
<td>G + anthracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + A (1st line)</td>
<td>123</td>
<td>52 - 57 [55 (31-33)]</td>
<td>5.6 - 12 (32,33)</td>
<td>4.5 - 23 [11.5 (31-33)]</td>
<td>16.1 - 27 (32,33)</td>
</tr>
<tr>
<td>- G + A (1st line and greater) (28)</td>
<td>21</td>
<td>47.6</td>
<td>6</td>
<td>5.8</td>
<td>NR</td>
</tr>
<tr>
<td>- G + E (1st line and greater)</td>
<td>49</td>
<td>28.6 - 60 (29,30)</td>
<td>11.2 (30)</td>
<td>5.8 (30)</td>
<td>17.1 (30)</td>
</tr>
<tr>
<td>G + taxanes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + D (1st line only)</td>
<td>194</td>
<td>59 - 71 [64.3 (36,38-40)]</td>
<td>6.1 (39)</td>
<td>8.5 - 13.6 [10 (36,38-40)]</td>
<td>&gt;15, 22.10 (36,40)</td>
</tr>
<tr>
<td>- G + D (1st line or greater)</td>
<td>79</td>
<td>36 - 79 (25,37)</td>
<td>10.3 (35)</td>
<td>7 (35)</td>
<td>12.7 - 24.5 (35,37)</td>
</tr>
<tr>
<td>- G + T (1st line only)</td>
<td>123</td>
<td>41.6 - 71 [66.7 (41-45)]</td>
<td>11.5 - 18 [13.4 (41-45)]</td>
<td>7.5 - 16.6 [11 (41-45)]</td>
<td>19 (41)</td>
</tr>
<tr>
<td>G + platinum agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + cisplatin (1st line only) (30,51)</td>
<td>61</td>
<td>76.7 - 80</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>- G + cisplatin (1st line and greater)</td>
<td>36, 58</td>
<td>29 - 44.4 (48,49)</td>
<td>NR</td>
<td>4.4 (49)</td>
<td>9.7 (49)</td>
</tr>
<tr>
<td>G + other agents</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>- G + V (1st line only)</td>
<td>45</td>
<td>55.5 (64)</td>
<td>10.8 (64)</td>
<td>9.5 (64)</td>
<td>NR</td>
</tr>
<tr>
<td>- G + V (1st line or greater)</td>
<td>214</td>
<td>24 - 48 [43.8 (65-69)]</td>
<td>5.3 - 12 [6.2 (65-67,69)]</td>
<td>4.3 - 5.0 (65,67,69)</td>
<td>14 - 20 (66,69)</td>
</tr>
<tr>
<td>- G + erlotinib (1st line or greater) (70)</td>
<td>59</td>
<td>14</td>
<td>4.6</td>
<td>2.8</td>
<td>NR</td>
</tr>
<tr>
<td>- G + pemetrexed (1st line and greater) (71)</td>
<td>59</td>
<td>24</td>
<td>5</td>
<td>3.8</td>
<td>10.3</td>
</tr>
<tr>
<td>G + anthracycline + taxane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + E + T (1st line only)</td>
<td>84</td>
<td>71 - 92 (91,92)</td>
<td>10.3 (91)</td>
<td>10.5 - 21 (91,92)</td>
<td>25.9 (91)</td>
</tr>
<tr>
<td>- G + A + T (1st line only) (92)</td>
<td>41</td>
<td>82.9</td>
<td>14.1</td>
<td>13.9</td>
<td>26.2</td>
</tr>
<tr>
<td>- G + A + C (1st line only) (94)</td>
<td>20</td>
<td>80</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>G + T + H (1st line or greater) (96)</td>
<td>27</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G + T + H (1st line only)</td>
<td>82</td>
<td>52.5 - 67 (89,95)</td>
<td>14 (89)</td>
<td>9 - 13.7 (89,95)</td>
<td>-27 (95)</td>
</tr>
<tr>
<td>G + D + H (1st line only) (97)</td>
<td>34</td>
<td>56</td>
<td>12</td>
<td>14.6</td>
<td>NR</td>
</tr>
<tr>
<td>G + F + Leucovorin (1st line or greater) (90)</td>
<td>27</td>
<td>22</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Notes: Median of reported outcome is only provided if at least three studies reported that outcome. If references are provided in the “Combination” column, then all reports provided all listed outcomes; otherwise, references are provided by outcome and unlisted references did not provide that outcome. Abbreviations: A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; G, gemcitabine; H, trastuzumab; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T, paclitaxel; TTF, time-to-treatment-failure; TTP, time-to-progression; V, vinorelbine.
<table>
<thead>
<tr>
<th>Combination</th>
<th>Neutropenia</th>
<th>Febrile Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Nausea/Vomiting</th>
<th>Stomatitis/Mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gemcitabine alone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G (1st line only)</td>
<td>11.9 - 30.3</td>
<td>0</td>
<td>4.8 - 6.3</td>
<td>0 - 9.1</td>
<td>10.3 - 14.6</td>
<td>0</td>
</tr>
<tr>
<td>- G (1st line and greater)</td>
<td>15 - 30.3</td>
<td>0 (18)</td>
<td>0 - 2 (17,18)</td>
<td>0 - 2 (17,18)</td>
<td>10 - 27.3 (17,18)</td>
<td>0 (17)</td>
</tr>
<tr>
<td><strong>G + anthracycline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + A (1st line)</td>
<td>66.6 - 74 (32,33)</td>
<td>0 - 2.0 (31,33)</td>
<td>16.7 - 27.5</td>
<td>0 - 12.7 [2,4]</td>
<td>5.7 - 10.6 [7,3]</td>
<td>8.5 - 9.8 (32,33)</td>
</tr>
<tr>
<td>- G + A (1st line and greater)</td>
<td>39</td>
<td>3.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>11</td>
</tr>
<tr>
<td>- G + E (1st line and greater)</td>
<td>51.5 - 64 (29,30)</td>
<td>26.7 (29)</td>
<td>6 - 11 (29,30)</td>
<td>5.8 (30)</td>
<td>6 - 11.4 (29,30)</td>
<td>2.9 - 11 (29,30)</td>
</tr>
<tr>
<td><strong>G + taxanes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + D (1st line)</td>
<td>13.8 - 44 (33)</td>
<td>0 - 6 (4)</td>
<td>6, 6.9 (39,42)</td>
<td>3.4 - 4</td>
<td>1.7 - 8.3 [2]</td>
<td>2 - 3.4 (39,42)</td>
</tr>
<tr>
<td>- G + D (1st line or greater)</td>
<td>29 - 100 (49,0)</td>
<td>7.7 (37)</td>
<td>0 - 5.0 (2.6)</td>
<td>2 - 10.0 [5.1]</td>
<td>5.1 - 8.0 [6]</td>
<td>0 - 5.1 (45-37)</td>
</tr>
<tr>
<td>- G + T (1st line only)</td>
<td>13.3, 29 (41,42)</td>
<td>2 (42)</td>
<td>4, 13.3 (41,42)</td>
<td>0, 0 (41)</td>
<td>0 (42)</td>
<td>4, 15.5 (41,42)</td>
</tr>
<tr>
<td><strong>G + platinum agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + cisplatin (1st line only)</td>
<td>20 - 20 (51,51)</td>
<td>NR</td>
<td>1.7 (51)</td>
<td>2.9 (51)</td>
<td>3.3 - 16.9 (51,51)</td>
<td>NR</td>
</tr>
<tr>
<td>- G + cisplatin (1st line or greater)</td>
<td>10.2 - 43 (48,49)</td>
<td>NR</td>
<td>35.8 - 38 (48,49)</td>
<td>5.1 (48)</td>
<td>10 - 30.8 (48,49)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>G + other agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + V (1st line or greater)</td>
<td>0 - 52 (37) (64-67,69)</td>
<td>6.3 (67)</td>
<td>0 - 20 (7.9) (64-69)</td>
<td>0 - 15.1 [3.8] (64-66,68,69)</td>
<td>0 - 12 [5] (64-67,69)</td>
<td>0 - 4 [0] (64-65,69)</td>
</tr>
<tr>
<td>- G + erlotinib (1st line or greater)</td>
<td>35</td>
<td>NR</td>
<td>9</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>- G + pemetrexed (1st line or greater)</td>
<td>81</td>
<td>12</td>
<td>25</td>
<td>NR</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td><strong>G + anthracycline + taxane</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- G + E + T (1st line only)</td>
<td>92 (92)</td>
<td>11.1 (92)</td>
<td>28 (92)</td>
<td>20 (92)</td>
<td>2 - 8 (91,92)</td>
<td>17 - 31 (91,92)</td>
</tr>
<tr>
<td>- G + A + T (1st line only)</td>
<td>43.9</td>
<td>2.4</td>
<td>7.2</td>
<td>12.3</td>
<td>14.6</td>
<td>1.9</td>
</tr>
<tr>
<td>- G + T + H (1st line or greater)</td>
<td>33</td>
<td>0</td>
<td>2</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- G + T + H (1st line only)</td>
<td>25 - 66.7 (89,95)</td>
<td>NR</td>
<td>12.5 - 20 (89,95)</td>
<td>5 - 8.9 (89,95)</td>
<td>8.9 (85)</td>
<td>2.5 (89)</td>
</tr>
<tr>
<td>- G + D + H (1st line only)</td>
<td>64</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>- G + F + Leucovorin (1st line or greater)</td>
<td>27</td>
<td>NR</td>
<td>17</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Notes: Median of reported toxicities is only provided if at least three studies reported that toxicity. If references are provided in the “Combination” column, then all reports provided all listed toxicities; otherwise, references are provided by toxicity and unlisted references did not provide that outcome.
Abbreviations: A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; G, gemcitabine; NR, not reported; T, paclitaxel; V, vinorelbine.
Table A3. Gemcitabine alone or in combination in second-line or greater therapy for metastatic breast cancer – Range of patient outcome measures reported by included non-randomized trials.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Number of patients</th>
<th>ORR, percent of patients [median]</th>
<th>Median duration of response, in months [median]</th>
<th>Median TTF/TTP/PFS, in months [median]</th>
<th>Median OS, in months [median]</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>186</td>
<td>0, 16, 17, 20, 22.6, 29, 42</td>
<td>8.5 - 9 (22,23)</td>
<td>1.9 - 3.6 [3] (21,23,24)</td>
<td>6.8, 7.8, 8.1, 9.5,11, 18.6 (21-23,27)</td>
</tr>
<tr>
<td>G + A (54)</td>
<td>31</td>
<td>29</td>
<td>NR</td>
<td>7.0</td>
<td>&gt;11</td>
</tr>
<tr>
<td>G + D</td>
<td>234</td>
<td>43 - 54 [52.3]</td>
<td>3.6 - 7.8 [6.1] (44-46,110)</td>
<td>6.6 - 8 [7.5] (36,44-46,110)</td>
<td>15 - 16.5 (44,45)</td>
</tr>
<tr>
<td>G + T</td>
<td>169</td>
<td>48 - 55 [52.2]</td>
<td>8 - 8.3 [8.2] (47,110)</td>
<td>7.0 - 7.5 [110]</td>
<td>12 (47)</td>
</tr>
<tr>
<td>G + carboplatin</td>
<td>93</td>
<td>21.5 - 69.2 [30] (52-56)</td>
<td>8.6 (56)</td>
<td>4.8 - 5 [53,56]</td>
<td>7.2 (52)</td>
</tr>
<tr>
<td>G + V</td>
<td>270</td>
<td>10 - 54 [31.3]</td>
<td>4 - 7.4 [6] (64,72-75,77-79)</td>
<td>3 - 8.3 [6] (64,72-75,77-79)</td>
<td>9.5 - 17.8 [11.5] (72,74,75,77-79)</td>
</tr>
<tr>
<td>G + V + H (99)</td>
<td>23</td>
<td>39.1</td>
<td>NR</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>G + H</td>
<td>89</td>
<td>36 - 38 [80,81]</td>
<td>5.8 (80)</td>
<td>5.8 - 7.8 [80,81]</td>
<td>14.7 - 18.7 [80,81]</td>
</tr>
<tr>
<td>G + C (84)</td>
<td>12</td>
<td>8</td>
<td>NR</td>
<td>6</td>
<td>NR</td>
</tr>
<tr>
<td>G + capecitabine</td>
<td>73</td>
<td>21.4 - 52 [33.3] (83-85)</td>
<td>4.3 [84]</td>
<td>4.2, - 10.5 [8.8] (83-85)</td>
<td>12.0 - 17 [83-85]</td>
</tr>
<tr>
<td>G + irinotecan (86)</td>
<td>38</td>
<td>18</td>
<td>5</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>G + mitoxantrone (87,88)</td>
<td>86</td>
<td>24 - 30</td>
<td>4.4 - 5.1</td>
<td>9.8 - 13.3</td>
<td></td>
</tr>
<tr>
<td>G + F + C + leucovorin (98)</td>
<td>69</td>
<td>38</td>
<td>NR</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

Notes: Median of reported outcome is only provided if at least three studies reported that outcome. If references are provided in the “Combination” column, then all reports provided all listed outcomes; otherwise, references are provided by outcome and unlisted references did not provide that outcome.

Abbreviations: A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; G, gemcitabine; H, trastuzumab; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T, paclitaxel; TTF, time-to-treatment-failure; TTP, time-to-progression; V, vinorelbine.
### Table A4. Gemcitabine alone or in combination in second-line or greater therapy for metastatic breast cancer - Range of grade 3 and 4 toxicities (percent of patients) reported by included non-randomized trials.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Neutropenia</th>
<th>Febrile Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Nausea/Vomiting</th>
<th>Stomatitis/Mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>G + A (54)</td>
<td>32</td>
<td>NR</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>G + T (110)</td>
<td>58 - 64</td>
<td>0 - 4</td>
<td>15 - 18</td>
<td>8 - 10</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>G + carboplatin</td>
<td>50 - 60 [50] (53,23,56)</td>
<td>3.6 - 10 (53,56)</td>
<td>21 - 40 [30] (53,20.56)</td>
<td>20 - 38.5 [27] (54-56)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>G + cisplatin</td>
<td>4.5 - 35 [22.0] (35-59,63)</td>
<td>0 (58)</td>
<td>0 - 19.5 [15] (58,59,63)</td>
<td>0 - 41.6 [6.0] (57-59)</td>
<td>0 - 21 [12.1] (57-59)</td>
<td>0 (58)</td>
</tr>
<tr>
<td>G + V</td>
<td>8.7 - 48 [12.5] (1/2-7/6,7/8,79)</td>
<td>0 (75,77)</td>
<td>0 - 6 [3] (1/2-7/6,7/8,79)</td>
<td>0 - 6.25 [3.5] (1/2-7/5,7/6,7/8,79)</td>
<td>0 - 5.9 [3.4] (1/2-7/3,7/5,7/8)</td>
<td>0 - 6 [2.2] (1/3-7/5,7/8,79)</td>
</tr>
<tr>
<td>G + V + H (99)</td>
<td>8.7</td>
<td>NR</td>
<td>4.3</td>
<td>4.3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>G + H</td>
<td>11 - 28 [80,81]</td>
<td>1.6 (80)</td>
<td>11 (81)</td>
<td>7 (81)</td>
<td>1.6 - 4 (80,81)</td>
<td>NR</td>
</tr>
<tr>
<td>G + C (82)</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>G + capecitabine</td>
<td>4.3 - 59 [29] (85-85)</td>
<td>NR</td>
<td>0 - 4.3 (85,85)</td>
<td>3 - 8.7 (85,85)</td>
<td>2.4 (85)</td>
<td>4.3 (85)</td>
</tr>
<tr>
<td>G + irinotecan (86)</td>
<td>34</td>
<td>8</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>G + mitoxantrone</td>
<td>35 - 41 (87,88)</td>
<td>4 (87)</td>
<td>7.5 - 8.5 (87,88)</td>
<td>5 - 13 (87,88)</td>
<td>5 (88)</td>
<td></td>
</tr>
<tr>
<td>G + F + C + leucovorin (98)</td>
<td>38</td>
<td>NR</td>
<td>16</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: Median of reported toxicities is only provided if at least three studies reported that toxicity. If references are provided in the “Combination” column, then all reports provided all listed toxicities; otherwise, references are provided by toxicity and unlisted references did not provide that outcome.

Abbreviations: A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; G, gemcitabine; NR, not reported; T, paclitaxel; V, vinorelbine.
Evidence-based Series #1-12: Section 3

The Role of Gemcitabine in the Management of Metastatic Breast Cancer: Guideline Development and External Review: Methods and Results

S. Dent, H. Messersmith, M. Trudeau, and the Breast Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Developed by the Breast Cancer Disease Site Group

Please see the EBS 1-12 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2006 and 2010.

Report Date: January 22, 2007

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.
The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- **Section 1: Clinical Practice Guideline.** This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- **Section 3: Guideline Development and External Review: Methods and Results.** This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

**DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

**Development and Internal Review**

This evidence-based series was developed by the Breast Cancer Disease Site Group (DSG) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the role of gemcitabine in the management of metastatic breast cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

**Report Approval Panel Review**

Prior to submission of this Evidence-based Series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel were the following, with the actions taken in response to that feedback:

- *The questions addressed the issue of first-line versus second- or greater line therapy, but the recommendations did not address the line of therapy.* The wording of the recommendations was changed to specifically address the line of therapy evaluated by the randomized trials that supported the recommendation.
- *There was considerable redundancy between the Results and Conclusions sections.* The Discussion section was modified to reduce redundancy and concentrate on key issues of clinical importance.
- *No comment was made on the issue of whether one can have confidence in the trials reported to date only in abstract form on which several of the recommendations were based, particularly the gemcitabine plus paclitaxel versus paclitaxel trial.* The discussion was modified to explain the author’s rationale in basing recommendations on of those abstracts.

**External Review by Ontario Clinicians**

Following the review and discussion of Sections 1 and 2 of this evidence-based series and review and approval of the report by the PEBC Report Approval Panel, the Breast Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.
BOX 1: DRAFT RECOMMENDATIONS (approved for external review April 6, 2006)

Target Population
Women with metastatic breast cancer.

Recommendations and Key Evidence
The combination of gemcitabine and docetaxel may be considered as an alternative to capecitabine and docetaxel for first- or second-line chemotherapy in patients where the toxicity of the capecitabine and docetaxel regimen is a concern.

- One randomized phase III study reported by Chan et al in abstract form (3,4) found no significant difference between the combination of gemcitabine (1000 mg/m² on days one and eight) and docetaxel (75 mg/m² on day one) every 21 days and the combination of capecitabine (1250 mg/m² 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.

Qualifying Statements
- The efficacy of capecitabine and docetaxel over docetaxel alone was demonstrated in a trial by O’Shaughnessy et al (5) but the clinical utility of this regimen has been hampered by significant toxicities, especially hand-foot syndrome and mucositis.

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.

- A randomized controlled trial reported at the 2003 and 2004 American Society of Clinical Oncology (ASCO) meetings (6-11) compared the combination of gemcitabine (1250 mg/m² of on days one and eight) and paclitaxel (175 mg/m² 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.

Qualifying Statements
- Patients who received the combination regimen experienced a higher rate of neutropenia (48% versus 11%) over those treated with paclitaxel alone.
- The clinical relevance of this regimen in Ontario is questionable as docetaxel has been the standard taxane used in the metastatic setting.

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.

- One randomized phase III study reported by Feher et al in (12) compared epirubicin (35 mg/m² on days one, eight, and 15) with gemcitabine (1200 mg/m² on days one, eight, and 15) every 28 days in postmenopausal patients aged 60 or older. No significant differences were found between the treatment arms in terms of time to response and duration of response. Epirubicin was significantly better than gemcitabine in terms of ORR (40.3% versus 16.4%, p<0.0001), TTP (6.1 months versus 3.4 months, p=0.0001), and overall survival (19.1 months versus 11.8 months, p=0.004).

- A randomized controlled trial reported by Zielinski et al (13) compared the combination of gemcitabine (1000 mg/m² on days one and four), epirubicin (90 mg/m² on day one), and paclitaxel (175 mg/m² on day one), with the combination of 5-fluorouracil (500 mg/m²), epirubicin (90 mg/m²), and cyclophosphamide (500 mg/m²), all on day one. Both combinations used a 21-day cycle. Patients were required to have had one prior non-anthracycline adjuvant chemotherapy. That trial found no significant differences in terms of ORR, TTP, or overall survival and found significantly higher hematological toxicities, polyneuropathy, and mucositis in the gemcitabine-containing arm.

Qualifying Statements
- 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.

Methods
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 DSG reviewed the results of the survey.

Results
Forty-one responses were received out of the 112 surveys sent (36.6% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 21 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.
Table 1. Responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a guideline, as stated in the “Introduction” section of the report, is clear.</td>
<td>20 (95.2%)</td>
<td>1 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>There is a need for a guideline on this topic.</td>
<td>18 (85.7%)</td>
<td>3 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>19 (90.5%)</td>
<td>1 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>19 (90.5%)</td>
<td>2 (9.5%)</td>
<td>0</td>
</tr>
<tr>
<td>The draft recommendations in the report are clear.</td>
<td>18 (85.7%)</td>
<td>2 (9.5%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>18 (90.0%) ^a</td>
<td>2 (10.0%) ^a</td>
<td>0 ^a</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>18 (85.7%)</td>
<td>3 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely</td>
<td>Unsure</td>
<td>Not at all likely or unlikely</td>
</tr>
</tbody>
</table>

Summary of Written Comments
Six respondents (28.6%) provided written comments. The main points contained in the written comments, with the response from the authors, were:

1. Several respondents commented that the recommendations would be difficult to implement without additional funding.
   The charge of the PEBC and the Breast Cancer DSG is to develop practice guidelines based on the best scientific evidence available. The Breast Cancer DSG does not address fiscal and policy issues in the context of an evidence-based series.

2. One respondent felt that the recommendation regarding gemcitabine plus docetaxel was not worded strongly enough, and should be more forceful in its support of that regimen.
   As the Chan et al (3,4) trial has not yet been published in a peer-reviewed journal, and as that trial was powered to detect superiority of the gemcitabine plus docetaxel combination over capecitabine plus docetaxel, not equivalence or noninferiority, the authors believe that the current wording of the recommendation is as strong as is warranted at this time.

3. One respondent felt that the role of single-agent gemcitabine should be addressed.
   Only one trial (12) of single-agent gemcitabine was identified as part of the systematic review. In the absence of additional trials, further discussion of the role of single-agent gemcitabine is premature.

4. One respondent felt that the role of HER2/neu over-expression or amplification with regard to gemcitabine/taxane combinations should be addressed.
   A separate guideline on HER2/neu and its relationship to the selection of systemic therapy agents is currently in development, and should be available by Fall, 2006.
Modifications/Actions
No modifications to the document were made in response to the practitioner feedback.

Implications for Policy
In September 2006 the PEBC submitted this evidence-based series to the Committee to Evaluate Drugs (CED) CCO subcommittee as part of the review process for the approval of the combination of gemcitabine and paclitaxel for funding as chemotherapy for metastatic breast cancer in Ontario.

2006 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.

For a complete list of the Breast Cancer Disease Site Group, please visit the CCO Web site at http://www.cancercare.on.ca/.

Funding
The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Disclaimer
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Contact Information
For further information about this series, please contact Dr. Maureen Trudeau, Co-Chair, Breast Cancer Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Ave, Toronto ON, M4N 3M5; (416) 480-5145; FAX (416) 480-6002.

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


### Document Assessment and Review Tool

| **Number and title of document under review** | 1-12 The role of gemcitabine in the management of metastatic breast cancer |
| **Date of current version** | 22 January 2007 |
| **Clinical reviewer** | Dr. Susan Dent |
| **Research coordinator** | Rovena Tey |
| **Date initiated** | 26 July 2010 |
| **Date and final results / outcomes** | 19 November 2010 (needs to be UPDATED) |

**Instructions.** Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. **Is there still a need for a guideline covering one or more of the topics in this document as is?** Answer Yes or No, and explain if necessary:  
   - **1. YES**  
     If No, then the document should be **ARCHIVED** with no further action; go to 11. If Yes, then go to 2.

2. **Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search?** Answer Yes or No, and explain if necessary:  
   - **2. NO** (not definitive or sufficient); 3.5 y elapsed  
     - a literature search needs to be conducted to review more current data  
     If Yes, the document can be **ENDORSED** with no further action; go to 11. If No, go to 3.

3. **Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?** Answer Yes or No, and explain if necessary, providing references of known evidence:  
   - **3. NO**  
     If Yes, the document should be taken off the Web site as soon as possible. A **WARNING** should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4.

4. **Do current resources allow for an updated literature search to be conducted at this time?** Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:  
   - **4. YES**  
     - there is a designated research co-ordinator at the PEBC to carry out the literature search  
     If No, a **DEFERRAL** should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5.

5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment and Review process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be **ARCHIVED** (i.e., go back to Q1 of this form and answer NO).

- No changes to the original questions

**Original Questions:**
What is the role of gemcitabine, alone or in combination, as first-line chemotherapy in women with metastatic breast cancer?
What is 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.

<table>
<thead>
<tr>
<th>5b. <strong>Inclusion and Exclusion criteria.</strong> List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No changes to the inclusion or exclusion criteria</td>
</tr>
<tr>
<td>• Both phase 2 and 3 RCTs should be included</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):</strong></td>
</tr>
</tbody>
</table>
| 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.

Search Period:
- October 2006 to 31 August 2010 (Medline + Embase)
- 2007 to 2010 (ASCO Annual Meeting)
- 2006 to 2009 (San Antonio Breast Cancer Symposium)

Brief Summary/Discussion of New Evidence:
Of 117 total hits from Medline + Embase; scanning 673 abstracts from ASCO and 17 hits from San Antonio conference abstract searches, 16 references representing 13 RCTs were found evaluating gemcitabine in metastatic breast cancer. The rows highlighted in grey represent 2 RCTs that were already mentioned in the existing guideline but these references are the full text publications of previous abstract presentations. The other 11 RCTs are potentially new studies, of which 5 had full text publications and 6 were abstract presentations.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Phase of RCT</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| gem + doc vs. cap + doc | 3 | Anthracycline-pretreated MBC | 1 = PFS  
2 = OS, ORR, TTF, DoR, QoL, toxicity | Grps did not differ for PFS, OS, ORR, TTF, QoL (p > 0.05)  
Gem grp had higher DoR (p = 0.047)  
Cap + doc was associated with diarrhea, mucositis, hand-foot syndrome | (Chan S et al. 2009)  
(Chan S et al. 2007) [abstract] |
| gem + doc vs. cap + doc | 3 | MBC | 1 = TTP  
2 = ORR, OS, DoR, toxicity | Grps did not differ for efficacy outcomes  
Cap grp had more mucositis, gastrointestinal toxicities, hand-foot syndrome | (Seidman A et al. 2009) [abstract] |
| gem + doc vs. doc | 3 | Anthracycline-pretreated advanced BC | 1 = TTP  
2 = ORR, O, DoR toxicity | Grps did not differ for efficacy outcomes  
Sequential gem led to more hematological toxicity | (Tomova A et al. 2010)  
(Tomova A et al. 2008) [abstract] |
| gem + doc vs. doc | 2 | Paclitaxel-pretreated MBC | 1 = ORR  
2 = TTP, OS, toxicity | Grps did not differ for ORR, OS, TTP  
Gem led to more grade 3/4 neutropenia | (Papadimitriou CA et al. 2009) |
| gem/doc (alternating) vs. doc | 2 | Advanced BC | 1 = TTF  
2 = TTP, OS, response rate, DoR, toxicity | Grps did not differ for efficacy outcomes  
Gem grp had less toxicity | (Joensuu H et al. 2010)  
(Joensuu H et al. 2008) [abstract] |
| gem + doc vs. pac + carb vs. pac | 3 | MBC | 1 = median survival  
2 = TTP, ORR, QoL, toxicity | For gem + doc vs. pac + carb vs. pac:  
Median survival = 27 mo vs. 30 mo vs. 41 mo  
Grps did not differ for ORR, TTP, QoL  
Gem led to more frequent myelotoxicity and mucositis | (Fountzilas G et al. 2009) |
| gem + pac vs. gem + doc | 2 | Previously treated LABC or MBC | 1 = CR, PR, ORR, disease control rate  
2 = toxicity | Grps did not differ for efficacy outcomes and had manageable grade 3/4 toxicity | (Boccia R et al. 2007) [abstract] |
| gem + pac vs. pac | 3 | Anthracycline-pretreated LABC or MBC | 1 = OS  
2 = TTP, RR, PFS, DoR, toxicity | For gem + pac vs. pac:  
Median OS = 19 mo vs. 16 mo  
TTP = 6 mo vs. 4 mo  
RR = 41% vs. 26%  
DoR = grps did not differ  
Gem led to more grade 3/4 neutropenia and grade 2/4 fatigue and neuropathy | (Albain KS et al. 2008) |
<table>
<thead>
<tr>
<th>Gem &amp; Paclitaxel vs. Gem &amp; Carb</th>
<th>Anthracycline-pretreated, stage 4 BC</th>
<th>1 = PR</th>
<th>2 = toxicity</th>
<th>This is a planned interim analysis. For gem+pac vs. gem+carb vs. gem+cis: PR = 19% vs. 20% vs. 8.7%</th>
<th>Grps had manageable toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem &amp; Carb + BSI-201 vs. Gem &amp; Carb</td>
<td>Previously treated triple-negative, negative MBC</td>
<td>1 = CBR</td>
<td>2 = ORR, PFS, OS, toxicity</td>
<td>For gem + carb + BSI vs. gem + carb: CBR = 62% vs. 21%</td>
<td>ORR = 48% vs. 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median PFS = 6.9 mo vs. 3.3 mo</td>
<td>Median OS = 9.2 mo vs. 5.7 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Toxicity = grps did not differ</td>
<td></td>
</tr>
<tr>
<td>Gem &amp; Pac + Bev vs. Pac + Bev</td>
<td>LABC or MBC</td>
<td>Toxicity</td>
<td>This is a planned interim safety analysis. Gem grp had more neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gem &amp; Vin vs. Gem &amp; Cis vs. Gem &amp; Cap</td>
<td>Anthracycline-pretreated, MBC</td>
<td>1 = ORR</td>
<td>2 = PFS, OS, toxicity</td>
<td>For gem + vin vs. gem + cis vs. gem + cap: ORR = 32% vs. 48% vs. 31%</td>
<td>PFS = 5.8 mo vs. 7.3 mo vs. 8.2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS = 18 mo vs. 13 mo vs. 20 mo</td>
<td>Grade 3/4 toxicity = grps did not differ</td>
</tr>
<tr>
<td>Gem &amp; Vin vs. Vin</td>
<td>Anthracycline- or taxane-pretreated MBC</td>
<td>1 = PFS</td>
<td>2 = ORR, DoR, OS, toxicity</td>
<td>For gem + vin vs. vin: Median PFS = 6 mo vs. 4 mo</td>
<td>Grps did not differ for OS, DoR, ORR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gem grp had more hematologic toxicity</td>
<td></td>
</tr>
</tbody>
</table>

**New References Identified (alphabetic order):**


**Literature Search Strategy:**

**Medline**

1. meta-Analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$ or quantitative overview).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embark or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinical$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp breast neoplasms/
39. (cancer? or carcinoma? or neoplasm? or tumour?).tw.
40. (breast? or mammary).tw.
41. 39 and 40
42. 38 or 41
43. (gemcitabine or gemzar).ti.
44. deoxycytidine/aa
45. 43 or 44
46. 42 and 45
47. 37 and 46
49. 47 and 48

**Embase**
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psychinfo or cinahl or cinhal or science citation index or sci search or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.
tw.
18. (clinical adj trial$1).tw.
19. (((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy))).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. limit 31 to human
33. exp breast neoplasms/
34. (cancer? or carcinoma? or neoplasm? or tumour?).tw.
35. (breast? or mammary).tw.
36. 34 and 35
37. 33 or 36
38. (gemcitabine or gemzar).ti.
39. deoxycytidine.tw.
40. 38 or 39
41. 37 and 40
42. 32 and 41
43. (200640: or 2007: or 2008: or 2009: or 2010:).ew.
44. 42 and 43

**ASCO Annual Meeting** - manually searched [www.asco.org](http://www.asco.org) from all abstracts in the section: Breast cancer - metastatic

**San Antonio Breast Cancer Symposium** - searched [www.sabcs.org](http://www.sabcs.org) with title keyword “gemcitabine”
<table>
<thead>
<tr>
<th>Go to 6.</th>
<th>6. NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?</td>
<td>If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 7.</td>
</tr>
</tbody>
</table>
| 7. On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary: | 7. YES  
- The newly identified evidence supports the existing recommendations, however,  
- the current recommendations do not cover all relevant subjects, because the newly identified evidence introduces targeted therapies in combination with chemotherapy (e.g., bevacizumab and platinum). |
| If Yes, the document can be ENDORSED. If No, go to 8. | 7. NO |
| 8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references: | 8. NO |
| If Yes, a WARNING note will be placed on the web site. If No, go to 9. | 8. NO |
| 9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary: | 9. NO |
| If Yes, the document update will be DEFERRED, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10. | 9. NO |
| 10. An update should be initiated as soon as possible. List the expected date of completion of the update: | 10. YES  
- Guideline 1-12 should be UPDATED to include additional recommendations based on the new studies with targeted agents.  
- The expected date to start production of the updated document for guideline 1-12 will be determined by the Breast DSG.  
An UPDATE will be posted on the website, indicating an update is in progress. |
| 11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review. | }
DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Outcomes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEP 1: Initiation of the Document Assessment &amp; Review process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEP 2: First teleconference to determine:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- the clinical relevance of the guideline,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- if a new literature search is needed, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- if Yes, the search criteria.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#1. Is there still a NEED for a guideline covering one or more of the topics in this document?  

No → Archive^1

Yes → #2

#2. Are all the current recommendations based on the current questions definitive\(^\ast\) or sufficient\(^5\), and have less than 5 years elapsed since the latest search?  

No → Deferral^3

Yes → Endorse^2

#3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?  

No → Warning^3

Yes → Teleconference with the reviewer(s) will focus the discussion on #5: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria

#4. Do current resources allow for an updated literature search to be conducted at this time?  

No → New search

Yes → RC conducts new search

#5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

STEP 3: A new literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date

Please note: No teleconference needed, IF the answers lead to one of these outcomes, PLUS the reviewer(s) complete & return the form with the answers & explanations.

RC emails DSG reviewer(s) the protocol

Discuss questions #1-5

^1 Archive

^2 Endorse

^3 Warning

^4 Deferral

^5 New search
### FLOW CHART (cont.)

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Outcomes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 4:</strong> Second teleconference to determine the ultimate status of the document</td>
<td></td>
<td><strong>Review questions #6-9</strong></td>
</tr>
</tbody>
</table>

#### #6. Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?

- **Yes** → Archive
- **No** → #7

#### #7. Does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?

- **Yes** to all → Endorse

#### #8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?

- **Yes** → Warning

#### #9. Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?

- **Yes** → Deferral

- **No** → #10

#### #10. An update should be initiated as soon as possible. List the expected date of completion of the update.

- **Yes** → Update

### STEP 5: Final outcome approval; Document Assessment & Review questions #11

#### #11. Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.

- **Yes** → RC emails draft for DSG approval
DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

*DEFINITIVE RECOMMENDATIONS* - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the , and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool (Appendix 2).

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.