Complete Summary

GUIDELINE TITLE

Capecitabine in stage IV breast cancer.

BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. Tomiak E, Verma S, Trudeau M, Robinson P. Capecitabine in stage IV breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Nov 26 [online update]. 17 p. (Practice guideline report; no. 1-16). [31 references]

GUIDELINE STATUS

This is the current release of the guideline.

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

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

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SCOPE

DISEASE/CONDITION(S)

Stage IV breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide recommendations about the role of capecitabine as second-, third-, or fourth-line chemotherapy in stage IV (metastatic) breast cancer, specifically in anthracycline or taxane failure
- To provide recommendations about the role of capecitabine as first-line chemotherapy in stage IV (metastatic) breast cancer

TARGET POPULATION

Women with stage IV (metastatic) breast cancer who are anthracycline-resistant or who have previously received an anthracycline as adjuvant therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Capecitabine plus docetaxel in anthracycline-pretreated breast cancer
2. Capecitabine as a single agent after previous anthracycline treatment
3. Capecitabine as first-line therapy
4. Capecitabine as second-, third-, or fourth-line therapy

MAJOR OUTCOMES CONSIDERED

- Tumour response rates
- Time to progression
- Survival rates
- Quality of life
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

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

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Medline (Ovid) database was searched from January 1995 to May 2003 using disease-specific text words and subject headings (breast, mammary, cancer, carcinoma, neoplasm[s]), treatment-specific terms (capecitabine, xeloda), and design-specific terms (clinical trial[s] as an exploded Medical Subject Heading [MeSH] term and publication type). The searches were not restricted by language. Issue 1 (2003) of the Cochrane Library, the Physician Data Query (PDQ®) database (www.cancer.gov/search/clinical_trials), conference proceedings from the American Society of Clinical Oncology (ASCO) (1998-2002) and the San Antonio Breast Cancer Symposium (2000, 2001), and bibliographies were also searched. The Canadian Medical Association (CMA) Infobase (www.cma.ca/cpgs/index.asp), the National Guideline Clearinghouse™ (www.guideline.gov), and other web sites were searched for existing evidence-based practice guidelines.

Eligibility Criteria

Studies were eligible for inclusion in the practice guideline report if they included patients with stage IV breast cancer and reported tumour response rate, time to progression, or duration of survival after treatment with capecitabine, administered alone or in combination with other agents. Randomized controlled trials of capecitabine were of primary interest, but reports of uncontrolled phase II studies were eligible where evidence from randomized trials was not available.

NUMBER OF SOURCE DOCUMENTS

One randomized phase III trial, two randomized phase II trials, and two non-comparative phase II trials were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Results from the three randomized trials included in this overview were not pooled because of differences in the interventions evaluated. One trial compared capecitabine as a single agent to cyclophosphamide/methotrexate/fluorouracil (CMF), the second compared capecitabine as a single agent to paclitaxel, and the third compared capecitabine plus docetaxel to docetaxel alone.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Breast Cancer Disease Site Group (DSG) discussed the evidence about capecitabine in the context of three clinical scenarios:

- **Patients with metastatic breast cancer whose tumours are refractory to anthracyclines and for whom a taxane-based chemotherapy regimen is being considered.** Based on their review of a randomized trial of capecitabine plus docetaxel versus docetaxel alone, the DSG decided to formulate a recommendation for the use of capecitabine with docetaxel in selected patients (i.e., those with good performance status or younger age).
- **Patients considering capecitabine as first-line chemotherapy for metastatic breast cancer.** The Breast Cancer DSG recognized the appeal of an oral outpatient regimen with an acceptable toxicity profile to women with metastatic breast cancer but felt that the limited data currently available do not support a recommendation at this time for capecitabine's use as a single agent in the first-line setting.
- **Patients with metastatic breast cancer who have already received anthracycline- and taxane-containing chemotherapy (either in the adjuvant or metastatic settings) and whose tumours are felt to be refractory to these classes of agents.** In this clinical situation, if second-, third- or fourth-line chemotherapy is considered to be an appropriate treatment option, the Breast Cancer DSG agreed that capecitabine would be a reasonable treatment choice. The DSG recognized that, at the current time, no standard regimen has been defined for these patients and encouraged further trials evaluating capecitabine's place among other available agents (vinorelbine, Herceptin, 5-fluorouracil (5FU)-based regimens).

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

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

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 86 medical oncologists in Ontario. 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 practitioner feedback survey was mailed out on February 18, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer Disease Site Group (DSG) reviewed the results of the survey.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Breast Cancer Disease Site Group and has been approved by the Practice Guidelines Coordinating Committee (PGCC).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- In selected patients (e.g., those with good performance status, less than 70 years of age, and with no other major comorbidities) who are anthracycline-resistant or who have previously received an anthracycline as adjuvant therapy, the combination of docetaxel and capecitabine is an appropriate therapeutic option.
- If docetaxel and capecitabine are used in combination, the recommended starting dose for most patients is 950 mg/m^2 twice daily of capecitabine (75% of full dose) on days 1 to 14 plus docetaxel 75 mg/m^2 intravenously on day 1 of a 21-day cycle.
- In patients who have been pretreated with anthracyclines and/or taxanes, capecitabine alone (1,250 mg/m^2 twice daily, for 21 days) is a reasonable treatment option.
- There is insufficient evidence for the use of capecitabine as a first-line chemotherapy in metastatic breast cancer.
- Warnings:
    - Patients receiving concomitant capecitabine and coumarin-derivative therapy should have their anticoagulant response monitored, as coagulant response time is significantly increased in patients stabilized on anticoagulants at the time of capecitabine introduction.
    - In patients with renal impairment, capecitabine therapy can increase systemic exposure to alpha-fluoro-beta-alanine (FBAL) and 5´-deoxy-5-fluorouridine (5´- DFUR). Specifically, capecitabine is contraindicated in patients with severe renal impairment (calculated creatinine clearance <30 mL/min) and should be reduced to a starting daily dose of 1,900 mg/m2 for patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min). Patients with mild renal impairment should be closely monitored.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The references are supported by phase II and III randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized phase III trial that compared docetaxel plus capecitabine to docetaxel alone detected superior response, time to progression, and survival for the combination, with high rates of toxicity from both treatments and no differences in measures of quality of life (N=511).
- Two randomized phase II trials evaluated capecitabine as a single agent. One trial compared capecitabine with intravenous cyclophosphamide/methotrexate/fluorouracil (CMF) in patients receiving first-line chemotherapy for metastatic breast cancer (N=93) and the second trial compared capecitabine to paclitaxel following anthracycline therapy (N=41). Both studies failed to demonstrate any significant difference in response, time-to-progression, or survival when capecitabine was compared to CMF as first-line treatment or with paclitaxel as second- or third-line treatment. However, it must be noted that both trials were small and underpowered to detect significant differences in outcomes between the respective treatment arms. Thus, it is not possible to draw meaningful conclusions from these trials.
- Two multicentre uncontrolled phase II trials that evaluated the efficacy of capecitabine in heavily pretreated patients with taxane-refractory metastatic breast cancer reported response rates of 20% and 26%, median time to progression of 3 months, and median survival of 12 months (N=162, N=74).

POTENTIAL HARMS

In randomized trials, grade 3 or 4 gastrointestinal adverse effects and hand-foot syndrome were more common with capecitabine plus docetaxel than with docetaxel alone and with capecitabine as a single agent than with cyclophosphamide/methotrexate/fluorouracil (CMF); serious clinical adverse effects were less common with capecitabine than with paclitaxel. Grade 3 or 4 neutropenia was less common with capecitabine than with either cyclophosphamide/methotrexate/fluorouracil or paclitaxel. Outside of clinical trials, 74% of patients treated with capecitabine experienced hand-foot syndrome, 44% diarrhea, 37% stomatitis, and 47% nausea and vomiting; grade 3 or 4 adverse events were more common at doses of capecitabine >2,100 mg/m^2.

CONTRAINDICATIONS

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In patients with renal impairment, capecitabine therapy can increase systemic exposure to alpha-fluoro-beta-alanine (FBAL) and 5´-deoxy-5-fluorouridine (5´-DFUR). Specifically, capecitabine is contraindicated in patients with severe renal impairment (calculated creatinine clearance <30 mL/min) and should be reduced to a starting daily dose of 1,900 mg/m^2 for patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min). Patients with mild renal impairment should be closely monitored.

QUALIFYING STATEMENTS

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- In patients who have been heavily pretreated, a reduction in the starting dose of single-agent capecitabine (75% of full dose) may be considered.
- Available data are limited and do not allow a firm clinical recommendation to be made for capecitabine's optimal use in metastatic breast cancer. Further studies are needed to evaluate its role in combination and sequential therapies.
- Capecitabine needs to be further evaluated as an alternative to paclitaxel or docetaxel in patients whose tumour has progressed on an anthracycline-based regimen, and in selected women, as first-line therapy as an alternative to more toxic standard combination chemotherapy regimens.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

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

DATE RELEASED

2003 Nov 26

GUIDELINE DEVELOPER(S)

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

GUIDELINE DEVELOPER COMMENT

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

SOURCE(S) OF FUNDING

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

GUIDELINE COMMITTEE

Breast Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Breast Cancer Disease Site Group disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

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

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Capecitabine in stage IV breast cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2003 Nov. Electronic copies: Available from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 19, 2004. The information was verified by the guideline developer on April 29, 2004.

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