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Capecitabine in Stage IV Breast Cancer Practice Guideline Report #1-16 Version 2.2003

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(This practice guideline report replaces a evidence summary originally published in 2000)

SUMMARY

Guideline Questions

1. What is the role of capecitabine as second-, third-, or fourth-line chemotherapy in stage IV (metastatic) breast cancer?
 - What is its role in anthracycline failure?
 - What is its role in taxane failure?
2. What is the role of capecitabine as first-line chemotherapy in stage IV (metastatic) breast cancer?

Target Population

These recommendations apply to women with stage IV (metastatic) breast cancer who are anthracycline-resistant or who have previously received an anthracycline as adjuvant therapy.

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/m² twice daily of capecitabine (75% of full dose) on days 1 to 14 plus docetaxel 75 mg/m² intravenously on day 1 of a 21-day cycle.
- In patients who have been pretreated with anthracyclines and/or taxanes, capecitabine alone (1250 mg/m² twice daily, on days 1 to 14 of a 21-day cycle) is a reasonable treatment option.
- There is insufficient evidence for the use of capecitabine as 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 1900 mg/m² for patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min). Patients with mild renal impairment should be closely monitored.

Qualifying Statements

- 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.

Methods

Entries to MEDLINE (through May 2003), the Cochrane Library (2003, Issue 1), conference proceedings, and the Physician Data Query Clinical Trials Database were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative Breast Cancer Disease Site Group. This practice guideline report was reviewed and approved by the Breast Cancer Disease Site Group, which is comprised of surgeons, medical oncologists, radiation oncologists, epidemiologists, pathologists, a medical sociologist, and a patient representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report will be obtained from the Practice Guidelines Coordinating Committee. The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Evidence

- Five trials (one phase III randomized controlled trial and four phase II studies) form the basis of evidence for this report.
- 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).
- 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 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 CMF 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 >2100 mg/m².

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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FULL REPORT

I. QUESTIONS

1. What is the role of capecitabine as second-, third-, or fourth-line chemotherapy in stage IV (metastatic) breast cancer?
 - What is its role in anthracycline failure?
 - What is its role in taxane failure?
2. What is the role of capecitabine as first-line chemotherapy in stage IV (metastatic) breast cancer?

II. CHOICE OF TOPIC AND RATIONALE

Capecitabine (Xeloda™) is a new and relatively expensive drug that has been approved by the Canadian Health Protection Branch for the treatment of patients with advanced or metastatic breast cancer after failure of standard therapy (including a taxane, unless therapy with a taxane is clinically contraindicated). It is the first oral chemotherapy option approved for patients with advanced or metastatic breast cancer who do not respond to standard chemotherapy or for whom standard chemotherapy has failed. A critical examination of the clinical evidence is required to help inform decisions by clinicians and policy makers in Ontario.

Capecitabine is a novel, selectively tumour-activated fluoropyrimidine carbamate. The parent compound is inactive; however, after gastrointestinal absorption, capecitabine is hydrolyzed in the liver by carboxylesterase to produce 5'-deoxy-5-fluorocytidine. This moiety is then deaminated on its pyrimidine ring to produce 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, an enzyme primarily located in hepatic and neoplastic tissue. The final enzymatic step, selective tumour activation of 5'-DFUR to 5-fluorouracil (FU), is catalyzed by thymidine phosphorylase, an enzyme typically found in higher concentrations in solid tumours than in corresponding normal tissue. This phenomenon, coupled with the unique activation pathway of capecitabine, results in intra-tumoural concentrations of 5-FU that are significantly higher than plasma and normal tissue levels. Thus, it is hypothesized that the tumour-selective generation of 5-FU with low systemic exposure provides an improved therapeutic ratio for capecitabine.

III. METHODS

This guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (1). Evidence was selected and reviewed by two members of the PGI's Breast Cancer Disease Site Group (DSG). Members of the Breast Cancer DSG disclosed potential conflict of interest information.

The guideline is a convenient and up-to-date source of the best available evidence on the use of capecitabine in patients with metastatic breast cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. It is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the guideline report will be obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

An evidence summary on this topic was originally completed in January 2000 and published

in *Current Oncology* 2000;7:84-90. At that time, only abstract reports of two randomized phase II trials of capecitabine were available (2,3). These two studies have since been published in full (4,5). When evidence from three meeting abstracts reporting results from a large randomized phase III trial became available in 2001 (6-8), the DSG updated the evidence summary to include the new evidence from this trial of capecitabine plus docetaxel versus docetaxel alone and added a statement that the combination of docetaxel and capecitabine may represent an appropriate therapeutic option in selected patients. In June 2002, the Breast Cancer DSG reviewed a full report of the phase III trial, which had recently been published in the *Journal of Clinical Oncology* (9), and decided to draft a practice guideline with recommendations on the use of capecitabine with docetaxel.

Literature Search Strategy

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 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 (http://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 (<http://www.cma.ca/cpgs/index.asp>), the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>), 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.

Pooling Trial Results

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) (4), the second compared capecitabine as a single agent to paclitaxel (5), and the third compared capecitabine plus docetaxel to docetaxel alone (9).

IV. RESULTS

Literature Search Results

Evidence is available from one randomized phase III trial of capecitabine plus docetaxel versus docetaxel alone in patients who had prior anthracycline-containing chemotherapy (9). There are also two relevant randomized phase II trials: one of capecitabine versus CMF in patients receiving first-line chemotherapy for metastatic disease (4) and one of capecitabine versus paclitaxel following prior anthracycline therapy (5). There are two non-comparative phase II trials evaluating the activity of capecitabine in women with heavily pretreated, paclitaxel- or docetaxel-refractory metastatic breast cancer (10,11).

One single-cohort phase II trial (N=22), published in Chinese, was not included in the systematic review of the evidence because resources were not available for translation (12).

Tumour Response, Disease Progression, and Survival

Addition of Capecitabine to Docetaxel in Anthracycline-pretreated Breast Cancer

In a phase III trial by O'Shaughnessy et al, 511 women with locally advanced or metastatic breast cancer were randomized to docetaxel (75 mg/m² every 21 days) plus capecitabine (1250 mg/m² twice daily on days 1-14 of every 21-day cycle) or docetaxel alone (100 mg/m² every 21 days) (9). Thirty-three percent of participants received study medication as first-line chemotherapy for advanced disease, 50% as second-line chemotherapy, and the remaining 17% as third- or fourth-line chemotherapy. One half had received endocrine therapy for metastatic disease.

All patients had been previously treated with anthracyclines in the neoadjuvant, adjuvant, or metastatic setting. Anthracycline failure was defined as:

- progression while receiving anthracycline-based chemotherapy, without any transient improvement,
- no response after four or more cycles of anthracycline-based chemotherapy,
- relapse within two years of completing adjuvant or neoadjuvant anthracycline-based chemotherapy, or
- a brief objective response to anthracycline-based chemotherapy with subsequent progression while receiving the same therapy or within 12 months after the last dose.

The proportion of patients in each of the anthracycline-failure categories did not differ between the two groups. The response criteria above are considered by the Breast Cancer DSG as clinically credible. There were significantly more objective tumour responses with combination therapy (42% versus [vs.] 30% with docetaxel alone, p=0.006). After a minimum of 15 months of follow-up, median survival was 14.5 months with docetaxel/capecitabine and 11.5 months with docetaxel alone (mortality hazard ratio [HR], 0.775; 95% confidence interval [CI], 0.63 to 0.95; p=0.0126). Median time to progression was 6.1 months with combination therapy and 4.2 months with monotherapy (HR, 0.652; 95% CI, 0.54 to 0.78; p=0.0001).

Capecitabine, as a Single Agent, after Previous Anthracycline Treatment

One randomized phase II trial compared capecitabine with paclitaxel in women (mean age, 52 years) who had previously received anthracycline-based chemotherapy (5).

Forty-four percent were anthracycline resistant, defined as:

- relapse within six months of completing adjuvant therapy,
- initial response followed by disease progression while on the same therapy, or
- disease progression on therapy without evidence of objective response;

and 56% were anthracycline failures, defined as:

- stable disease after four or more cycles of anthracycline-based chemotherapy,
- response followed by disease progression within 12 months of treatment, or
- relapse within six to 12 months after anthracycline-based adjuvant chemotherapy.

Participants had received one or two previous regimens for metastatic disease. Two schedules of oral capecitabine were studied: 2510 mg/m²/day, divided into two doses, on days 1 to 14 of each three-week cycle (intermittent schedule), or 1331 mg/m²/day, divided into two doses, daily (continuous schedule), but the continuous-schedule arm was discontinued early. The entire study was stopped after a total of 44 patients were randomized. The reason given by the authors for premature closure of the study was refusal by patients to be randomized because of a strong preference for one or the other of the treatments under investigation; however, it is possible that the decision to stop the study early was biased in some way, particularly since the criteria for early closure were not defined a priori.

The analysis of intermittent capecitabine versus paclitaxel is based on 41 patients. In this small group of patients, capecitabine appeared to have comparable efficacy to paclitaxel: responses were seen in eight of 22 patients (36%; 95% CI, 17% to 59%) receiving capecitabine

(including three complete responses) and five of 19 patients (26%; 95% CI, 9% to 51%) receiving paclitaxel (no complete responses observed). Time to progression and survival were similar for the two treatment arms. Median time to progression was 3.0 months (95% CI, 1.4 to 6.6) with capecitabine versus 3.1 months (95% CI, 2.5 to 6.5) with paclitaxel, and median survival was 7.6 (95% CI, 3.5 to 13.5) and 9.4 months (95% CI, 6.1 to 10.2), respectively. Given the early closure of the study and the lack of power to detect differences that would be clinically meaningful between groups, the claims of equivalence between the two drugs are premature.

Capecitabine as First-line Therapy for Metastatic Disease

One randomized phase II trial compared capecitabine (2510 mg/m²/day on days 1 to 14 of every three-week cycle) to CMF (600/40/600 mg/m² I.V. every three weeks) in women aged 55 years or older receiving first-line treatment for metastatic disease (4). Ninety-five patients were enrolled in this trial; 62 were randomized to capecitabine and 33 to CMF in order to achieve a 2:1 allocation ratio. (The use of unequal allocation to treatment or placebo groups is supported by the International Conference on Harmonization [ICH] guidelines, as unbalanced randomization may enhance the safety data base and may also make the study more attractive to patients and/or investigators (13)). Overall tumour response rates were 30% (95% CI, 19% to 43%) with capecitabine and 16% (95% CI, 5% to 33%) with CMF. Median time-to-progression was 4.1 months (95% CI, 3.2 to 6.5) versus 3.0 months (95% CI, 2.4 to 4.8), and median survival was 19.6 months versus 17.2 months for the capecitabine and CMF arms, respectively.

Capecitabine as Second-, Third- or Fourth-line Therapy

Two multicentre phase II trials evaluated the safety and efficacy of twice-daily oral capecitabine, at 2510 mg/m²/day on days 1 to 14 every three weeks in women with taxane-refractory metastatic breast cancer (10,11). Drug resistance was strictly defined as: disease relapse within six months of completing adjuvant therapy, objective response to therapy followed by disease progression while on therapy, or disease progression on therapy without improvement, and drug failure as: disease relapse within six to 12 months of completing adjuvant therapy, objective response to therapy followed by disease progression within 12 months of last dose, or stable disease while on therapy for a minimum of four cycles. The first trial enrolled 162 paclitaxel-refractory patients (10) and the second, 74 patients, 47 with prior paclitaxel and 27 with prior docetaxel (11). Patients were heavily pretreated, and 92% had received an anthracycline.

The primary endpoint for these studies was response rate. Objective tumour responses were observed in 20% of patients (95% CI, 14% to 28%) in the first trial (10) and 26% (95% CI, 16% to 36%) in the second (11). Of particular interest was the demonstration of a 29% response rate in 42 patients considered to be resistant to both anthracycline and paclitaxel in the first trial (10). In the second trial, response rates were 27% in the paclitaxel-pretreated patients and 20% in the docetaxel pretreated patients (11). Median time to disease progression was three months in both trials, and median survival was 12 months.

Quality of Life during Capecitabine Treatment

Quality of life was measured for 454 participants in the randomized trial of docetaxel/capecitabine versus docetaxel alone using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 Items (QLQ-C30) questionnaire. No statistically significant differences between treatment groups were found with respect to changes in any of the domains of quality of life over 48 weeks.

The effect of capecitabine on tumour-associated symptoms in patients with taxane-refractory disease was studied in the non-comparative phase II trials reported by Blum et al (10,11). Clinical benefit was assessed using a novel measure, the clinical benefit response (CBR) rate, which incorporated improvements in pain intensity, analgesic consumption, and performance status. Positive CBR was defined as an improvement that was maintained for at least four

weeks in one or more of the following measures, with no deterioration in the other two measures:

- an improvement of 50% or more in pain intensity score for patients with baseline pain scores greater than 20 mm,
- a reduction of 50% or more in analgesic consumption for patients with baseline analgesic consumption of at least 70 morphine equivalents per week,
- an improvement of at least 20 points in Karnofsky Performance Status.

Overall CBR could be evaluated in 201 of 236 patients. Twenty percent of patients in the first trial and 15% in the second had a positive CBR, as defined above; 31% and 41%, respectively, were judged to have a stable CBR. In the first trial, improvements in patients with positive responses lasted for over 18 weeks (10), but this information was not reported for the second trial (11).

Toxicity of Capecitabine

In the randomized trial by O'Shaughnessy et al, treatment-related adverse events were reported by 98% of patients on the combination of capecitabine and docetaxel versus 94% on docetaxel alone (9). There was more grade 3 or 4 stomatitis (17% vs. 5%), diarrhea (14% vs. 5%), and hand-foot syndrome (24% vs. 1%) with capecitabine plus docetaxel than with docetaxel alone. Neutropenic fever (16% vs. 21%), myalgia, and arthralgia were more common with single agent docetaxel. The incidence of treatment-related hospitalization was similar in the two arms (28% with capecitabine vs. 26% without). Deaths on study classified as probably, possibly, or remotely related to study treatment occurred in three patients in the combination arm (1.2%) and one patient (0.4%) in the single-agent arm. The investigators noted a decreased tolerance to the combination of docetaxel and capecitabine in women ≥ 60 years of age. They suggested that a 25% reduction in the starting dose of capecitabine should be considered for these patients, as well as for patients with compromised performance status or comorbidity.

Toxicity data were available from two randomized phase II trials and two non-comparative phase II trials of capecitabine as a single agent (4,5,10,11). O'Shaughnessy et al observed less grade 3 or 4 neutropenia with capecitabine than with CMF (8% vs. 41%) but more grade 3 or 4 diarrhea, stomatitis, and fatigue (4). Forty-three percent of patients on capecitabine had hand-foot syndrome, including 15% rated as grade 3. Talbot et al reported less grade 3 or 4 neutropenia with capecitabine than with paclitaxel (9% vs. 53%) and fewer treatment-related grade 3 clinical adverse events (23% versus 58%) (5). Grade 4 clinical adverse events were rare. Eighteen percent of the capecitabine group had hand-foot syndrome, including 9% rated as grade 3. In the multicentre phase II trials by Blum et al, grade 3 and 4 adverse effects included: diarrhea (11%, 19%), hand-foot syndrome (10%, 22%), fatigue (7%, 8%), stomatitis (3%, 12%), nausea (4%, 10%), and vomiting (4%, 5%) (10,11).

A retrospective analysis of data from 107 women who were treated with capecitabine outside of clinical trials found that 74% experienced hand-foot syndrome, 44% diarrhea, 37% stomatitis, and 47% nausea and vomiting (14). Grade 3 or 4 adverse events were more common at doses of capecitabine >2100 mg/m². The median time to progression was 11.9 weeks among 49 patients who received starting doses of 2375-2625 mg/m², 19.9 weeks among 15 who received starting doses of 2101-2374 mg/m², and 15.1 weeks among 41 who received starting doses ≤ 2100 mg/m².

In December 2000, Hoffmann-La Roche issued a bulletin to clinicians warning about toxicity in patients with renal impairment (10). Based on a clinical pharmacology study and data in their clinical database, Hoffmann-La Roche modified the labelling for Xeloda to state that capecitabine is contraindicated in patients with severe renal impairment (calculated creatinine clearance <30 mL/min). They also recommended that the starting daily dose of capecitabine be reduced to 1900 mg/m² for patients with moderate renal impairment (calculated creatinine

clearance 30-50 mL/min) and that patients with mild renal impairment should receive close monitoring.

In September 2001, the American Federal Drug Administration and Hoffman-La Roche added a warning and strengthened the precautions section in the label for Xeloda™ to alert practitioners to a clinically important drug interaction between capecitabine and warfarin. This warning was based on data from a clinical pharmacology trial and reports of clinically significant increases in prothrombin time and International Normalized Ratio (INR) in patients who were stabilized on anticoagulants when treatment with capecitabine was started. The warning advised that patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently (15,16).

V. INTERPRETIVE SUMMARY

Addition of Capecitabine to Docetaxel

The open-label randomized trial by O'Shaughnessy et al detected a significant superiority for the combination of capecitabine and docetaxel over single-agent docetaxel in response rate, time to progression, and survival (9). The lack of a cross-over design in this trial, however, makes it difficult to comment on the superiority of combination versus sequential therapy. Capecitabine-specific toxicity was higher in the combination arm, and further review of the data indicate that toxicity can be reduced, with no loss in effectiveness of the regimen, by initiating therapy at 75% of full-dose capecitabine.

Capecitabine Alone as First-line Treatment

Evidence from one small phase II randomized trial suggests that, upon further investigation, capecitabine may become an attractive alternative regimen to consider for the palliation of metastatic disease in the elderly population or in women who wish to avoid the alopecia and myelosuppression associated with traditional CMF regimens (4). However, in randomized trials completed to date, classical CMF regimens (17) and anthracycline-based regimens (18-20) have produced response rates that were higher than those observed in the trial of capecitabine versus CMF as first-line treatment (4). Confirmatory studies, particularly those assessing quality of life, are needed before capecitabine is considered as an option for first-line treatment.

Capecitabine Alone as Second-, Third- or Fourth-line Treatment

Two non-comparative phase II studies demonstrated a promising level of activity (20-26% overall response rate) in heavily pretreated patients with anthracycline- and taxane-refractory metastatic breast cancer (10,11). This level of activity, and the associated time to progression (median=3 months) and survival (median=12 months), compare favourably with data available for other single agents currently considered in the clinic for this difficult-to-treat patient subgroup (21-27). The superiority of one drug over another remains to be established through well-designed randomized trials that should evaluate not only response rate, time to progression, and overall survival, but also toxicity, quality-of-life and cost-effectiveness parameters. If third- or fourth-line chemotherapy is to be considered in this clinical situation, capecitabine appears to be a reasonable treatment option.

Results from a small, prematurely closed trial appeared to suggest that capecitabine may be a reasonable alternative to paclitaxel for patients in whom anthracycline-based treatment has failed (5). However, due to insufficient power and the possibility that the decision to close the study early may have been biased, these results must be interpreted with caution. A larger randomized trial with a strict definition of anthracycline resistance and a quality-of-life assessment is required to definitively demonstrate equivalence between capecitabine and paclitaxel for patients in whom anthracycline-based treatment has failed. In addition, the

performance of capecitabine compared with other drugs used in this setting must be evaluated in phase III randomized controlled trials.

VI. ONGOING TRIALS

Two relevant randomized trials of capecitabine are open to recruitment:

ROCHE-PHARMATECH-XEL-154

Phase II Randomized Pilot Study of Capecitabine in Women with Advanced or Metastatic Breast Cancer.

This trial compares objective response rates, duration of response, time-to-progression, time-to-treatment failure, survival, incidence of adverse events, and time-to-onset of the adverse experience, and quality of life in patients treated with two dose levels of capecitabine. Target accrual is 120 patients within nine months of study commencement. Summary was last updated in December, 2001.

EORTC-10001, EORTC-16001O, IDBBC-EORTC-10001

Phase II/III Randomized Study of Capecitabine versus Vinorelbine in Women with Metastatic Breast Cancer Previously Treated with Taxanes with or without Anthracyclines.

The phase II component of this trial will compare the response rates and duration of response in women treated with capecitabine versus vinorelbine. The phase III component will compare overall survival, progression-free survival, time-to-treatment failure, overall safety, quality of life, and clinical benefit response in women treated with these drugs. Target accrual is 72 women for the phase II component and 406 to 452 for the phase III component. Accrual will be met within 18.5 months of study commencement. Summary was last updated in November, 2002.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Breast Cancer 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 the randomized trial of capecitabine plus docetaxel versus docetaxel alone by O'Shaughnessy et al (9), 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, 5FU-based regimens).

VIII. PRESCRIBING CAPECITABINE

Capecitabine is administered daily for two weeks, followed by a one-week rest period, given as three-week cycles. The daily dose is given orally in two divided doses (approximately 12 hours apart) 30 minutes after the end of a meal. Tablets should be swallowed with water.

Two retrospective studies examining the impact of dose reduction in patients treated with capecitabine have been reported in ASCO abstracts (14,28). Although the quality of the evidence is not high, these studies support the use of a lower dose of capecitabine (2000 mg/m²/day) than the manufacturer's recommended dose of 2500 mg/m². Reducing the dose to 2000 mg/m²/day reduced toxicity without an apparent effect on efficacy. Researchers and clinicians familiar with the use of capecitabine in heavily pre-treated patients with advanced breast cancer have suggested, anecdotally, that the incidence of both severe diarrhea and hand-foot syndrome in this population of patients may be reduced if patients are started at a dose of 2000 mg/m²/day rather than the dose of 2500 mg/m²/day used in the trials described above. Additionally, treating patients over the age of 70 with a dose of 2000 mg/m²/day has been suggested. (personal communication, Dr. Patricia LoRusso).

In the randomized phase III trial by O'Shaughnessy, 130 of the 255 patients in the capecitabine plus docetaxel arm required a dose reduction of capecitabine (9). The median time to first dose reduction was 1.5 months (range 0.2 to 10.4). A retrospective analysis of the data from this trial suggested that a reduction to 75% of the starting dose of capecitabine does not seem to impair the efficacy of the combination of capecitabine and docetaxel. **The DSG recommends that, when it is given in combination with docetaxel, the dose of capecitabine be reduced to 75% of the full dose: 1900 mg/m² daily** (full dose = 2500 mg/m² daily). Suggestions for dosing, supplied by the manufacturer, are given in Appendix 1.

There are concerns about the safety of capecitabine in patients with impaired renal function. In patients with severe renal impairment (creatinine clearance <30 mL/minute), capecitabine is contraindicated. A higher incidence of treatment-related grade 3 or 4 adverse events has been observed in patients with moderate renal impairment (creatinine clearance 30-50 mL/minute). In these patients, a dose reduction to 75% of the normal starting dose has now been recommended by the manufacturer (Roche); careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event (15,16).

Patients should be carefully monitored for diarrhea, hand-foot syndrome, mucositis, and nausea/vomiting. If grade 2 or greater adverse effects appear, treatment should be interrupted until the toxicity resolves, and the dosage should be adjusted for the next cycle. (The grading of hand-foot toxicity and suggested dose modifications are provided in Appendices 2 and 3). Patients receiving concomitant capecitabine and oral coumarin-derivative-anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly.

Studies suggest that the use of pyridoxine (Vitamin B6) at a dose of 50 mg t.i.d. may attenuate or alleviate the incidence of hand/foot syndrome (29,30). While the impact of the addition of Vitamin B6 on the incidence or severity of hand/foot syndrome and the efficacy of capecitabine has not been formally assessed, clinicians should take this into consideration when prescribing capecitabine.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE

Draft Practice Guideline

Based on the evidence described above, the Breast Cancer DSG drafted the following recommendations:

Target Population

These recommendations apply to women with stage IV (metastatic) breast cancer who are anthracycline-resistant or who have previously received an anthracycline as adjuvant therapy.

Draft Recommendations

- In selected patients (e.g., those with good performance status or younger age) 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 capecitabine 950 mg/m² twice daily on days 1 to 14 plus docetaxel 75 mg/m² IV on day 1.
- In heavily pretreated patients with anthracycline- and taxane-resistant metastatic breast cancer, capecitabine alone is a reasonable treatment alternative if third or fourth-line therapy is being considered.

Qualifying Statements

- 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.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

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 above 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 DSG reviewed the results of the survey.

Results

Fifty-two responses were received out of the 86 surveys sent (61% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 45 (87%) indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the “ <i>Choice of Topic</i> ” section of the report, is clear.	42 (93%)	3 (7%)	0
There is a need for a clinical practice guideline on this topic.	37 (82%)	7 (16%)	1 (2%)
The literature search is relevant and complete.	42 (93%)	3 (7%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	44 (98%)	1 (2%)	0
The draft recommendations in this report are clear.	42 (93%)	3 (7%)	0
I agree with the draft recommendations as stated.	38 (84%)	6 (13%)	1 (2%)
This report should be approved as a practice guideline.	38 (84%)	4 (9%)	3 (7%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	36 (80%)	5 (11%) [†]	1 (2%)

Percentages may not total 100% due to rounding

[†] Plus 3 (7%) missing

Summary of Written Comments

Eleven (24%) of the respondents provided written comments, the main points of which were:

1. Due to the lack of a cross-over design in the randomized phase III trial by O’Shaughnessy et al, it is difficult to comment on the superiority of combination therapy with capecitabine and docetaxel compared to sequential treatment.
2. Only limited evidence from retrospective, non-randomized comparisons is available to support the recommendation for an initial dose reduction of capecitabine, when capecitabine is used in combination with docetaxel.

Modifications/Actions

The DSG discussed the issues described above and responded as follows:

1. The DSG agreed the design of the phase III trial by O’Shaughnessy et al makes it difficult to comment on the benefit of combination versus sequential therapy. A statement to this effect was added to the interpretative summary.
2. The DSG acknowledged that only indirect evidence is available to support the recommendation for an initial dose reduction of capecitabine. However, given the potential toxicity of the combination, the DSG decided to maintain the recommendation as written. Information from the O’Shaughnessy phase III trial on the number of patients in the capecitabine/docetaxel arm who required a dose reduction of capecitabine was added to the “Prescribing Capecitabine” section.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Six of 14 members of the PGCC returned ballots. Two PGCC members approved the practice guideline report as written. Two members required modifications to the report as noted below, however, a written response by the Breast Cancer Disease Site Group was not required. One member approved the report conditional on the changes below (written response required). One member approved the report and offered suggestions for consideration by the Breast DSG.

The PGCC identified three methodological issues pertaining to the “Results” section. The first methodological issue required a change to the description of evidence for the addition of capecitabine to docetaxel in anthracycline-pretreated breast cancer (9). The PGCC wondered whether patients who were randomized were first stratified according to the category of anthracycline failure. They felt that since a lack of stratification would result in confounding bias, this issue should be addressed in the evidence. The second issue pertained to the evidence for capecitabine alone as second-, third- or fourth-line treatment. The PGCC noted that the premature discontinuation of one of the studies (5) was not adequately addressed in the “Results” section; specifically, the potential for bias in the decision to discontinue the study was questioned. The third methodological issue related to the first-line randomized phase II therapy trial of capecitabine versus CMF (4). The PGCC questioned the use of unbalanced randomization and felt that the rationale for this design should be described in the evidence.

In addition to the methodological issues, the PGCC felt that the recommendations should include: 1) warnings about the use of capecitabine in patients with renal failure and the potential for drug-interaction with warfarin; 2) the schedule of drug administration in addition to the doses of drugs; 3) the definition of “younger age” in the first recommendation; and 4) a response to the second guideline question, “what is the role of capecitabine as first-line chemotherapy in stage IV (metastatic) breast cancer?”.

Modifications/Actions

The Breast Cancer DSG agreed with the PGCC that the results section should be clearer regarding the potential for confounding bias. Since stratification according to anthracycline-resistance was performed in the trial in question (9), this statement was added to the evidence section. The Breast Cancer DSG also agreed that it was possible (though unlikely) that that bias could have influenced the decision to prematurely discontinue one of the studies (5). This qualification was added to the evidence section. It was felt that the qualifying statement already contextualized the recommendations so no further changes were made. With respect to the third methodological issue, the Breast Cancer DSG felt that the unbalanced randomization design used in one study was acceptable (4). A supporting explanation for the design was added to the results section.

The Breast Cancer DSG agreed with and made the recommended changes to the practice guideline recommendations.

X. PRACTICE GUIDELINE

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 DSG and has been approved by the PGCC.

Target Population

These recommendations apply to women with stage IV (metastatic) breast cancer who are anthracycline-resistant or who have previously received an anthracycline as adjuvant therapy.

Recommendations

- In selected patients (e.g., those with good performance status, less than 70 years of age, and 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/m² twice daily of capecitabine (75% of full dose) on days 1 to 14 plus docetaxel 75 mg/m² IV on day 1 of a 21 day cycle.

- In patients who have been pretreated with anthracyclines and/or taxanes, capecitabine alone (1250 mg/m² twice daily, on days 1 to 14 of a 21-day cycle) is a reasonable treatment option.
- There is insufficient evidence for the use of capecitabine as 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 FBAL and 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 1900 mg/m² for patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min). Patients with mild renal impairment should be closely monitored.

Qualifying Statements

- 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.

XI. JOURNAL REFERENCE

E. Tomiak, S. Verma, M. Trudeau, P. Robinson, and members of the Breast Cancer Disease Site Group. Capecitabine in stage IV breast cancer. *Curr Oncol* 2003;10(3):180-90.

XII. ACKNOWLEDGEMENTS

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For a complete list of the Breast Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the Cancer Care Ontario Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1. Capecitabine (Xeloda™) dose calculation according to body surface area (31).

Dose level 2500 mg/m²/day		Number of tablets to be taken at each dose (morning and evening)	
Surface Area (m²)	Total Daily* Dose (mg)	150 mg	500 mg
≤1.25	3000	0	3
1.26 – 1.37	3300	1	3
1.38 – 1.51	3600	2	3
1.52 – 1.65	4000	0	4
1.66 – 1.77	4300	1	4
1.78 – 1.91	4600	2	4
1.92 – 2.05	5000	0	5
2.06 – 2.17	5300	1	5
≥2.18	5600	2	5

75% of Full Dose			
Dose level 1900 mg/m²/day		Number of tablets to be taken at each dose (morning and evening)	
Surface Area (m²)	Total Daily* Dose (mg)	150 mg	500 mg
≤1.25	2300	1	2
1.26 – 1.37	2600	2	2
1.38 – 1.51	2900	3	2
1.52 – 1.65	3000	0	3
1.66 – 1.77	3300	1	3
1.78 – 1.91	3600	2	3
1.92 – 2.05	3900	3	3
2.06 – 2.17	4000	0	4
≥2.18	4300	1	4

*Total Daily Dose is divided by 2 to allow equal morning and evening doses

Appendix 2. Grading system for hand-foot toxicity (10).

Grade	Clinical Domain	Functional Domain
1	Numbness, dysesthesia /paresthesia, tingling, painless swelling, or erythema	Discomfort which does not disrupt normal activities
2	Painful erythema with swelling	Discomfort which affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

Appendix 3. Recommended dose modifications (15).

Toxicity (NCIC Grade*)	During a course of therapy	Dose adjustment for next cycle (% of starting dose)
<i>Grade 1</i>	Maintain dose level	Maintain dose level
<i>Grade 2</i>		
- 1 st appearance	Interrupt until resolved to grade 0-1	100%
- 2 nd appearance	Interrupt until resolved to grade 0-1	75%
- 3 rd appearance	Interrupt until resolved to grade 0-1	50%
- 4 th appearance	Discontinue treatment permanently	
<i>Grade 3</i>		
- 1 st appearance	Interrupt until resolved to grade 0-1	75%
- 2 nd appearance	Interrupt until resolved to grade 0-1	50%
- 3 rd appearance	Discontinue treatment permanently	
<i>Grade 4</i>		
- 1 st appearance	Discontinue permanently <i>or</i> If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

* National Cancer Institute of Canada Common Toxicity Criteria