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The Role of the Taxanes in the Management of Metastatic Breast Cancer

Practice Guideline Report # 1-3

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SUMMARY

Guideline Question
What is the role of the taxanes in the management of metastatic breast cancer?

Target Population
These recommendations apply to women with metastatic breast cancer for whom first- or greater-line chemotherapy is being considered outside the context of a clinical trial.

Recommendations

- In ***anthracycline-naive patients,*** who would ordinarily be offered treatment with a single-agent anthracycline (doxorubicin or epirubicin) or an anthracycline in a standard combination, the following options are also reasonable:
  - Treatment with single-agent docetaxel 100 mg/m^2 over one hour every three weeks.
  - Docetaxel or paclitaxel in combination with doxorubicin.

- In ***anthracycline-naive patients for whom anthracyclines are contraindicated:***
  - Treatment with single-agent docetaxel 100 mg/m^2 over one hour every three weeks is recommended.

- In ***anthracycline-resistant patients or patients who have previously received an anthracycline as adjuvant therapy:***
  - Either docetaxel (100 mg/m^2 over one hour every three weeks) or paclitaxel (175 mg/m^2 over three hours every three weeks) may be considered as a treatment option after failure of prior anthracycline treatment or in women whose disease is resistant to anthracyclines. The evidence supporting the use of single-agent docetaxel is more consistent, and is based on a larger number of trials and patients, than the evidence for paclitaxel.
  - In selected patients, the combination of docetaxel and capecitabine is a therapeutic option. Due to the toxicity of the combination, patient selection for good performance status or younger age is recommended. It is recommended that capecitabine in the docetaxel/capecitabine combination be given at 75% of full dose.

Qualifying Statements

- Patients should be fully informed of all the treatment options and should be aware of the risks and benefits associated with each of them.
- There is generally little difference in overall survival between chemotherapeutic agents in the treatment of metastatic breast cancer. Treatment in this setting should be based on clinical considerations and patient preferences, with a focus on palliation and quality of life.
- There is no evidence that initial combination therapy with anthracyclines and taxanes in the metastatic setting provides a survival advantage over the usual sequence of treatments conventionally employed in patients with metastatic breast cancer (e.g., an anthracycline followed by a taxane followed by capecitabine).
- The combination of paclitaxel (infused over three hours) and doxorubicin in rapid sequence should not exceed doses of doxorubicin >360 mg/m^2 due to the high incidence of congestive heart failure.
- Although few trials have compared weekly to three-weekly taxane therapy, the toxicities observed with weekly taxane therapy appear to be lower than those observed with the conventional three-weekly regimen. Weekly therapy could be considered for selected patients (elderly, low performance status, or women who wish to avoid some of the toxicities associated with the three-weekly taxane therapy).
- Women should be encouraged to enter clinical trials assessing novel treatments in the setting of metastatic breast cancer.

Methods

The literature was searched using MEDLINE (through July 2002), the Cochrane Library (Issue 2, 2002), the Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the European Society for Medical Oncology.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Breast Cancer Disease Site Group and methodologists. This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which is comprised of surgeons, medical oncologists, radiation oncologists, epidemiologists, a pathologist, 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 was 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 process consists of periodic review and evaluation of the scientific literature and where appropriate, integration of this literature with the original guideline information.

Key Evidence

There is evidence from 17 randomized trials (9 published reports and 8 reports in abstract form) that compared paclitaxel or docetaxel, as single agents or in combination with other chemotherapeutic agents, as first- or second-line chemotherapy for the treatment of metastatic breast cancer.

Anthracycline-naive patients

- Seven randomized trials assessed the use of paclitaxel in anthracycline-naïve patients and four randomized trials investigated the use of docetaxel in this setting.
- One randomized trial evaluated the use of single agent docetaxel versus doxorubicin. The trial reported a higher response rate and less febrile neutropenia, stomatitis, and nausea/vomiting with docetaxel than with doxorubicin monotherapy.

- Evidence from the three randomized trials of single-agent paclitaxel versus doxorubicin-based chemotherapy was conflicting.
- Paclitaxel or docetaxel, in combination with doxorubicin, was associated with higher response rates compared to standard anthracycline combinations in three randomized trials and longer time to disease progression and survival in one trial. Such therapy, however, was associated with higher rates of grade 3/4 neutropenia and neuropathy compared to standard anthracycline regimens.

Anthracycline-resistant patients

- Four randomized trials evaluated the use of docetaxel for anthracycline-resistant metastatic breast cancer and two small randomized trials investigated the use of paclitaxel in this setting.
- One of two small randomized trials detected improved time to progression with paclitaxel compared to non-taxane-containing chemotherapy. The other trial reported no significant difference in time to progression.
- Two of three randomized trials that compared docetaxel with non-taxane-containing chemotherapy detected improved response rates and time to progression with docetaxel, while the third reported no significant difference for these outcome measures. One trial also detected a significant survival advantage with docetaxel compared to mitomycin/vinblastine. The other trial that reported survival data did not detect a significant survival difference.
- The taxanes were associated with higher rates of grade 3/4 neutropenia and neuropathy than mitomycin plus vinblastine.
- One randomized trial that compared docetaxel plus capecitabine to docetaxel alone demonstrated a superior response rate, time to progression, and survival rate for the combination, with high rates of toxicity in both treatment arms.

Treatment Alternatives

Common treatment alternatives include single-agent doxorubicin, single-agent epirubicin, combinations of 5-fluorouracil and cyclophosphamide with doxorubicin (FAC) or with epirubicin (FEC) or with methotrexate (CMF), capecitabine, trastuzumab (Herceptin), mitomycin, vinblastine, and vinorelbine.

Related Practice Guidelines Initiative Guidelines and Evidence Summaries (available at http://www.cancercare.on.ca/ccopgi/):

- #1-6: *Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer*
- #1-4: *Use of Vinorelbine in Stage IV Breast Cancer*
- #1-15: *Use of Trastuzumab (Herceptin) in Metastatic Breast Cancer*
- #1-16: *Use of Capecitabine in Stage IV Breast Cancer*

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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 (PEBC). 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 (PGCC), whose membership includes oncologists, other health providers, patient representatives and CCO executives. Formal approval of a practice guideline by the PGCC 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 in consultation 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

What is the role of the taxanes in the management of metastatic breast cancer?

- In patients with no previous anthracycline exposure, where anthracyclines would ordinarily be considered, what is the role of paclitaxel or docetaxel delivered as monotherapy or in combination with other chemotherapeutic agents?
- In patients with prior anthracycline exposure, what is the role of single-agent paclitaxel or docetaxel?

II. CHOICE OF TOPIC AND RATIONALE

During the year 2000, close to one million women were diagnosed with breast cancer worldwide. In Canada alone, there were almost 20,000 new cases and approximately 7,500 deaths from this disease (1). Despite many advances in the diagnosis and treatment of early breast cancer, up to 50% of newly diagnosed patients may eventually develop metastases. The prognosis for women who develop metastatic disease is poor, and such patients are usually considered incurable (2-7). The goals of therapy are to control the disease, relieve symptoms with as few side-effects as possible, and maintain or improve quality of life.

Several options now exist for the treatment of women who develop metastatic breast cancer, including endocrine and cytotoxic therapies. In general, it is accepted practice to consider chemotherapy for patients who have estrogen-insensitive disease (defined as estrogen-receptor-negative disease or disease which has demonstrated clinical resistance to hormonal manipulation) or for patients who have rapidly progressive (aggressive), symptomatic, or potentially life-threatening visceral disease.

Among the novel chemotherapeutic agents introduced in the past decade (taxanes, vinorelbine, gemcitabine, capecitabine, etc.), the taxanes have emerged as the most powerful single agents for the management of breast cancer. Paclitaxel (Taxol®, Bristol-Myers Squibb) was initially isolated from the bark of the Pacific yew, *taxus brevifolia* in 1971. Docetaxel (Taxotere®, Aventis), a semi-synthetic analogue of paclitaxel, was subsequently synthesized from the needles of the European yew, *taxus baccata.* Both drugs demonstrated *in vitro* and *in vivo* activity in breast cancer, which prompted extensive phase I, II, and III clinical trials.

A number of single-institution and multicentre phase II studies have evaluated single-agent paclitaxel or docetaxel. Many of these studies were reviewed as part of the practice guidelines on the use of paclitaxel and docetaxel in the treatment of metastatic breast cancer developed by the Breast Cancer Disease Site Group (DSG) in 1997. These trials were generally performed in populations of patients where treatment with a taxane was offered as *first-line treatment* (i.e., initial chemotherapy treatment) for metastatic disease or as *second-line treatment* in patients who had received prior anthracyclines in the adjuvant or metastatic setting.

Previous practice guidelines from the Breast Cancer DSG suggested that it was a reasonable option to use a taxane in patients with symptomatic or rapidly progressing metastatic breast cancer who had failed first-line anthracycline-containing chemotherapy or who had anthracycline-resistant disease. Since the development of the original guidelines, additional evidence, including results from randomized trials, has been published. This new information merits further examination to answer the contemporary clinical questions identified by the Breast Cancer DSG.

III. BACKGROUND ON DOSE AND INFUSION TIME: PHASE I AND II TRIALS

Paclitaxel

Phase I trials with paclitaxel have evaluated schedules ranging from short daily infusions to longer infusions over 24, 96, or 120 hours every three weeks. Different maximum-tolerated doses were defined for each schedule. Neutropenia appeared to be the dose-limiting toxicity

that emerged in studies using longer infusion schedules and higher doses. Other adverse effects included neurotoxicity, mucositis, vomiting, alopecia, myalgia, arthralgia, skin reactions, and fatigue. Hypersensitivity reactions were also observed at an early point in these studies and led to the universal use of premedication with corticosteroids and histamine antagonists (8-20).

Paclitaxel as a single agent, given as a three-hour infusion at doses from 135-250 mg/m^2, was evaluated in nine phase II studies involving 496 patients. The observed response rates ranged between 6% and 94% (21-29). Responses to first-line paclitaxel ranged from 32% to 94% (21-26). Three trials that included only patients who had been heavily pre-treated and were anthracycline-resistant detected response rates between 6% and 22%, using doses of 135-250 mg/m^2 in a three-hour infusion (27-29).

Seven phase II studies have also investigated longer infusion schedules (30-36). Doses of 135 or 250 mg/m^2 given over 24 hours as first-line treatment were associated with response rates of 32%-62% in three trials (30-32). In patients with prior anthracycline exposure, the 24-hour regimen produced responses in 23%-33% of patients, using doses of paclitaxel between 135 and 250 mg/m^2 as second-, third- or greater-line therapy (33,34). A 96-hour infusion in anthracycline-exposed patients was administered in two small studies (20 and 33 patients) with observed response rates of 30% and 48%, respectively (35,36).

More recently the issue of dose and schedule for paclitaxel has been addressed in five randomized studies (Table 1).

Table 1. Efficacy data from randomized phase II and III studies comparing doses and schedules of paclitaxel.

Study	# of patients	Paclitaxel Dose Allocation	Duration of Infusion (hours)	Response Rate (%)	Median Time to Progression (months)	Median Survival (months)
Nabholtz (37)	234	135 mg/m^2	3	22%*	3.0	10.5
	236	175 mg/m^2	3	29%*	4.2**	11.7
Winer (38)	475	175 mg/m^2	3	21%	3.8	9.8
[abstract]	total	210 mg/m^2	3	28%	4.1	11.1
		250 mg/m^2	3	22%	4.8**	11.9
Holmes (39)	90	250 mg/m^2	3	23%	3	11
[abstract]	92	140 mg/m^2	96	29%	4	10
Smith (40)	279	250 mg/m^2	3	44%	NR	NR
	284	250 mg/m^2	24	54%**	NR	NR
Peretz (41)	521	175 mg/m^2	3	29%	3.8	9.8
[abstract]	total	175 mg/m^2	24	32%	4.6**	13.4**

* complete response rates were 2% with 135 mg/m^2 and 5% with 175 mg/m^2; complete response data were not available for the other trials.
** Indicates significant differences of $p<0.05$ between treatment groups.
NR, not reported.

The first two trials (Nabholtz and Winer) listed in Table 1 compared different doses given over three hours and detected significantly longer times to progression with higher doses of paclitaxel (37,38). However, these two studies indicate that there is no response or survival advantage with a dose that is higher or lower than 175 mg/m^2 when paclitaxel is given as a three-hour infusion.

Three prospective randomized studies (two phase II, one phase III) examining the influence of a longer duration of infusion (24 hours or 96 hours) versus a three-hour infusion have been reported (39-41), two in abstract form (39,41). Two of these trials compared the same dose given over long and short infusion times (40,41). In the trial by Peretz et al, a statistically significant increase in median time to progression with the 24-hour infusion (175 mg/m^2), compared with the three-hour infusion, was accompanied by a significant increase in the duration of survival (41). Survival data were not reported for the trial by Smith et al, but they did

report that the overall response rate was significantly higher with the 24-hour infusion (250 mg/m^2) than with the three-hour infusion (40). In a smaller study, Holmes et al did not detect any significant difference in response or survival when they compared 250 mg/m^2 over three hours with 140 mg/m^2 over 96 hours (39).

In these randomized trials, higher doses were associated with more hematologic toxicity than lower doses, and longer infusion times were associated with less neurosensory toxicity than short infusion times (Table 2). Nabholtz et al reported that the 175 mg/m^2 dose was associated with a higher incidence of grade 3/4 neutropenia than the 135 mg/m^2 dose (67% vs. 50%, $p<0.001$) (37). Grade 4 hematologic toxicity was also more common in the high- and moderate-dose arms of the Winer et al trial, compared to the low-dose arm (57% with 250 mg/m^2 vs. 54% with 210 mg/m^2 vs. 33% with 175 mg/m^2) (38). Peretz et al found more grade 4 neutropenia (79% vs. 30%, $p<0.001$), febrile neutropenia (17% vs. 1%, $p<0.001$), mucositis (45% vs. 22%, $p<0.001$), and diarrhea (41% vs. 25%, $p<0.001$) with an infusion time of 24 hours vs. three hours, but the three-hour infusion resulted in significantly more peripheral neuropathy (78% vs. 65%, $p<0.001$) (41).

Table 2. Toxicity data from randomized phase II and III studies comparing doses and schedules of paclitaxel.

Study	# of patients	Paclitaxel Dose Allocation	Duration of Infusion (hours)	% of patients with adverse effects		
				Febrile Neutropenia	Infection	Grade 3/4 Neurosensory Toxicity
Nabholtz (37)	234 236	135 mg/m^2 175 mg/m^2	3 3	2% 4%	14% 23%	3% 7%
Winer (38) [abstract]	475 total	175 mg/m^2 210 mg/m^2 250 mg/m^2	3 3 3	NR	NR	6% 13% 26%
Holmes (39) [abstract]	90 92	250 mg/m^2 140 mg/m^2	3 96	7% 11%	15% 11%	33% 3%
Smith (40)	279 284	250 mg/m^2 250 mg/m^2	3 24	5% 18%	7% 12%	22% 13%
Peretz (41) [abstract]	521 total	175 mg/m^2 175 mg/m^2	3 24	1% 17%	NR	78% 65%

NR, not reported.

Docetaxel

Based on results from phase I trials of docetaxel, there was general consensus among investigators that a dose of 100 mg/m^2 be chosen for subsequent studies involving docetaxel monotherapy. At this dose, the dose-limiting toxicities were mainly neutropenia and mucositis (42,43). As with paclitaxel, hypersensitivity was also witnessed and subsequently led to the use of steroid premedication (44).

With dose and scheduling issues resolved, 18 phase II trials (45-62) documenting the activity of docetaxel in metastatic breast cancer were conducted in three settings: *1) first-line therapy, 2) second-line therapy, and 3) in patients known to be resistant to anthracyclines.* In the *first-line* setting, docetaxel at a dose of 75-100 mg/m^2 produced response rates between 52% and 68% (45,46,48-50). In the *second-line* setting with a total of 606 evaluable patients in nine trials, doses of 60-100 mg/m^2 produced responses in 44%-58% of women (47,51-58). Finally, in four studies in patients known to be *resistant to anthracyclines*, response rates of 29%-50% were observed with a dose of 100 mg/m^2 (59-62).

Adverse effects associated with docetaxel monotherapy have generally consisted of alopecia, neutropenia, fatigue, nail and skin changes, and fluid retention (usually reduced with

steroid prophylaxis). Allergic reactions were rare because of appropriate premedication with steroids.

IV. METHODS

Guideline Development

This guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care using methods of the Practice Guidelines Development Cycle (63). Evidence was selected and reviewed by members of the PGI's Breast Cancer DSG and methodologists. Members of the Breast Cancer DSG disclosed information on potential conflict of interest before discussing this practice guideline.

The guideline is a convenient and up-to-date source of the best available evidence on the taxanes in the management of metastatic breast cancer, developed through systematic review, 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. The practice guideline 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 was 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.

Practice guidelines on paclitaxel and docetaxel were originally developed by the Breast Cancer DSG in 1997. The DSG has summarized the current evidence on both paclitaxel and docetaxel in this practice guideline report, which replaces the 1997 reports, and has formulated new recommendations on the taxanes for metastatic breast cancer.

Literature Search Strategy

A MEDLINE search was conducted for the period from 1966 to June 2001 using disease-specific terms [(breast neoplasms/ or breast cancer.tw. or mammary neoplasms/) and (neoplasm metastasis/ or metast:.tw. or advanced.tw.)] with treatment-specific terms (taxane:.tw. or paclitaxel/ or paclitaxel.tw. or taxol.tw. or docetaxel.tw. or taxotere.tw.) and design-specific terms (meta-analysis.pt,sh,tw. or randomized controlled trial:.sh,pt,tw. or random:.tw.). The search was updated in July 2002. Issue 2 (2002) of the Cochrane Library, the Physician Data Query database (http://cnetdb.nci.nih.gov/trialsrch.shtml), clinical trial and practice guideline Internet sites, conference proceedings from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology, article bibliographies, and personal files were also searched up to July 2002.

Inclusion Criteria

Published reports or abstracts were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Randomized controlled trials (RCTs) on the use of paclitaxel or docetaxel as single agents or in combination with other chemotherapeutic agents, as first- or second-line chemotherapy, for metastatic breast cancer.
- Reported results for at least one of the outcomes of interest: quality of life, survival, time to disease progression, tumour response, and adverse effects.

Evidence-based clinical practice guidelines from guideline-development groups were also reviewed.

Exclusion Criteria
Letters and editorials were not eligible.

Synthesizing the Evidence
Because of the heterogeneity in dose, schedule, and drug combinations used in the experimental (i.e., taxane) and control arms of the trials reviewed, the guideline authors decided not to pool the results of the randomized trials.

V. RESULTS

Literature Search Results
The following were eligible for inclusion in the systematic review of the evidence: 14 randomized phase III trials and three randomized phase II trials on the use of paclitaxel or docetaxel as single agents or in combination with other chemotherapeutic agents as first- or greater-line chemotherapy in metastatic breast cancer (64-81). Table 3 provides a list of the studies summarized in this practice guideline report.

One evidence-based practice guideline from another guideline-development group was found by the literature search and is described below (82).

Table 3. Randomized trials included in this practice guideline report.

Authors, Year	Comparisons*	Reference
	The taxanes in anthracycline-naive patients	
Paridaens et al, 2000	Paclitaxel vs. doxorubicin	64
Bishop et al, 1999	Paclitaxel vs. CMFP	65
Sledge et al, 1997	Paclitaxel vs. doxorubicin vs. paclitaxel/doxorubicin	66 [abstract]
Jassem et al, 2001	Paclitaxel/doxorubicin vs. FAC	67
Carmichael, 2001	Paclitaxel/epirubicin vs. epirubicin/cyclophosphamide	68 [abstract]
Luck et al, 2000	Paclitaxel/epirubicin vs. epirubicin/cyclophosphamide	69 [abstract]
Chan et al, 1999	Docetaxel vs. doxorubicin	71
Nabholtz et al, 1999	Doxorubicin/docetaxel vs. doxorubicin/cyclophosphamide	72 [abstract]
Nabholtz et al, 2001**	Doxorubicin/docetaxel/cyclophosphamide vs. FAC	73 [abstract]
Bonneterre et al, 2001	Epirubicin/docetaxel vs. FEC (phase II)	74 [abstract]
Biganzoli et al, 2002	Paclitaxel/doxorubicin vs. doxorubicin/cyclophosphamide	70
	The taxanes in anthracycline-resistant patients	
Dieras et al, 1995	Paclitaxel vs. mitomycin (phase II)	75
O'Reilly et al, 1998	Paclitaxel vs. capecitabine (phase II)	76 [abstract]
Nabholtz et al, 1999	Docetaxel vs. mitomycin/vinblastine	77
Sjostrom et al, 1999	Docetaxel vs. methotrexate/5-fluorouracil	78, 79
Bonneterre et al, 1997	Docetaxel vs. 5-fluorouracil/vinorelbine	80 [abstract]
O'Shaughnessy et al, 2002	Docetaxel vs. docetaxel/capecitabine	81

* See Appendix 1 for complete information on regimen, schedule and dosing.
** Addendum, June 2002: Further results were presented at ASCO 2002 (116)
These were consistent with the results presented in 2001.
CMFP, cyclophosphamide/methotraxate/fluorouracil/prednisone; FAC, fluorouracil/doxorubicin(Adriamycin)/cyclophosphamide; FEC, fluorouracil/epirubicin/cyclophosphamide.

Results of Randomized Trials
Data on response rate, time to progression, and survival from randomized trials of paclitaxel and docetaxel are presented in Table 4. Please see Appendix 1 for complete information on the

doses and schedules of administration used in these trials. The evidence for patients with and without prior anthracycline exposure is discussed separately in the text below.

Table 4. Efficacy data from randomized trials of the taxanes for the treatment of metastatic breast cancer.

Author (Reference)	Treatment allocation	# of patients	Paclitaxel/ docetaxel dose – infusion time	Response rates (%)		Median time to progression (months)	Median survival (months)
				Complete response	Overall response		
Anthracycline-naive patients							
Paclitaxel							
Paridaens (64)	paclitaxel doxorubicin	166 165	200 mg/m^2 – 3hr	2% 6%	25% 41%*	3.9 7.5*	15.6 18.3
Bishop (65)	paclitaxel CMFP	107 102	200 mg/m^2 – 3 hr	2% 6%	29% 35%	5.3 6.4	17.3 13.9
Sledge (66) [abstract]	paclitaxel doxorubicin paclitaxel/doxorubicin	245 248 245	175 mg/m^2 – 24 hr 150 mg/m^2 – 24 hr	NR NR NR	33% 34% 46%*	5.9 6.2 8.0*	22.2 20.1 22.2
Jassem (67)	paclitaxel/doxorubicin FAC	134 133	220 mg/m^2 – 24 hr	19% 8%	68%* 55%	8.3* 6.2	23.3* 18.3
Carmichael (68) [abstract]	paclitaxel/epirubicin EC	705	200 mg/m^2	NR NR	56% 67%	NR NR	13.8 13.7
Luck (69) [abstract]	paclitaxel/epirubicin EC	429	175 mg/m^2 – 3 hr	9% 6%	46% 41%	NR NR	NR NR
Biganzoli (70)	paclitaxel/doxorubicin AC	275	175-200mg/m^2 – 3hr	7% 3%	58% 54%	5.9 6.0	20.6 20.5
Docetaxel							
Chan (71)	docetaxel doxorubicin	161 165	100 mg/m^2 – 1 hr 75 mg/m^2	7% 5%	48%* 33%	6.5 5.3	15 14
Nabholtz (72) [abstract]	docetaxel/doxorubicin AC	215 214	75 mg/m^2 – 1 hr	11% 8%	60%* 47%	NR NR	NR NR
Nabholtz (73) [abstract]	docetaxel/dox/cyclo FAC	238 237	75 mg/m^2 – 1 hr	8% 5%	54%* 43%	NR NR	NR NR
Bonneterre (74) [abstract]	docetaxel/epirubicin FEC	51 54	75 mg/m^2	NR NR	65% 37%	8.4 7.4	NR NR
Anthracycline-resistant patients							
Paclitaxel							
Dieras (75)	paclitaxel mitomycin	41 40	175 mg/m^2 – 3hr	0% 0%	17% 6%	3.5* 1.6	12.7 8.4
O'Reilly (76) [abstract]	paclitaxel capecitabine	20 22	175 mg/ m^2 – 3 hr	0% 14%	21% 36%	3.4 3.3	NR NR
Docetaxel							
Nabholtz (77)	docetaxel mitomycin/vinblastine	203 189	100 mg/m^2 – 1 hr	4% 1%	30%* 12%	4.8* 2.8	11* 9
Sjostrom (78)	docetaxel methotextrate/5-FU	143 140	100 mg/m^2 – 1 hr	9% 3%	42%* 21%	6* 3	10.4 11
Bonneterre (80) [abstract]	docetaxel 5-FU/vinorelbine	46 45	100 mg/m^2 – 1 hr	NR NR	54% 44%	7 5	NR NR
O'Shaughnessy (81)	docetaxel docetaxel/capecitabine	255 256	100 mg/m^2 – 1 hr 75 mg/m^2 – 1 hr	4% 5%	30% 42%*	4.2 6.1*	11.5 14.5*

* Indicates statistically significant differences ($p < 0.05$) between treatment groups.
5-FU, 5-fluorouracil; AC, doxorubicin(Adriamycin)/cyclophosphamide;
CMFP, cyclophosphamide/methotraxate/fluorouracil/prednisone; cyclo, cyclophosphamide;
EC, epirubicin/cyclophosphamide; FAC, fluorouracil/doxorubicin(Adriamycin)/cyclophosphamide;
FEC, fluorouracil/epirubicin/cyclophosphamide; NR = not reported

Paclitaxel in Patients with No Prior Anthracycline Exposure

Eight comparisons between paclitaxel and other regimens were made in seven randomized trials in anthracycline-naive patient populations (64-70). Results of four trials were published in full (64,65,67,70) and three were presented in abstract form (66,68,69). Paclitaxel was used as a single agent in three trials and in combination with doxorubicin or epirubicin in five (Table 4).

Women were eligible for inclusion in the trials by Paridaens et al (64), Jassem et al (67), and Biganzoli et al (70) if they had no prior chemotherapy for metastatic disease and were anthracycline- and taxane-naive. Bishop et al included women with recurrent, locally advanced or metastatic disease and no prior chemotherapy for advanced disease (65). Barring progression or undue toxicity, treatment consisted of seven courses in the Paridaens trial, and patients who progressed within the seven cycles were crossed over to the alternate drug.

Fewer details about eligibility criteria and treatment crossover after disease progression were provided for the trials reported only in abstract form (66,68,69). Fourteen percent of participants in the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) trial reported by Carmichael had received adjuvant anthracyclines (68). In a trial by Sledge et al (66), patients who received paclitaxel or doxorubicin as a single agent were crossed over at the time of progression; 20% of patients responded who crossed from doxorubicin to paclitaxel, compared with 14% who crossed from paclitaxel to doxorubicin (p=0.06).

Six of seven RCTs assessed survival (64-70), but only one detected a statistically significant improvement with paclitaxel versus control (67). In the trial by Jassem et al, patients treated with paclitaxel plus doxorubicin experienced longer survival times than those treated with the combination of 5-fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide (FAC) (p=0.013). This survival difference was accompanied by an improvement in time to progression (p=0.034). Two additional trials detected significant differences between regimens in time to progression (64,66). Paridaens reported longer progression-free survival with doxorubicin, compared with paclitaxel (p=0.0001) (64). Sledge et al did not find a significant difference between paclitaxel and doxorubicin in terms of time to treatment failure but did detect a significant prolongation of time to treatment failure when paclitaxel and doxorubicin were used in combination (paclitaxel vs. paclitaxel/doxorubicin, p=0.009; doxorubicin vs. paclitaxel/doxorubicin, p=0.003) (66). All three trials found parallel differences in response rates, which were statistically significant (64,66,67). A multivariate analysis by Bishop et al showed a survival benefit for paclitaxel over cyclophosphamide/methotraxate/fluorouracil/prednisone (p=0.025) but only after adjustment for the prognostic factors performance status, visceral disease, and years since diagnosis (65).

Luck et al reported response rates but no survival or time-to-progression data (69). There was no significant difference in response rate between epirubicin plus paclitaxel and epirubicin plus cyclophosphamide. The UKCCCR trial, described in an abstract for ASCO 2001 by Carmichael, did not detect a significant difference between these two regimens in response rate or duration of survival (68).

After completion of the draft guideline report for external review, results of an additional trial were published. In the trial by Biganzoli et al (70), there were no significant differences in response rate, time to progression, or survival between the two treatment arms. In this trial, 80% of the study population had visceral involvement, and 25% of patients had more than three sites of disease. However, these poor prognostic factors were equally distributed between the two treatment groups. Only 54% of patients in the paclitaxel arm received a relative dose intensity >90% of doxorubicin, compared with 67% of patients in the doxorubicin/cyclophosphamide group. The median cumulative dose of doxorubicin in the paclitaxel arm was also lower (299 mg/m^2 vs. 353 mg/m^2).

Docetaxel in Patients with No Prior Anthracycline Exposure

One published randomized trial (71) compared single-agent docetaxel to doxorubicin, and three trials, reported as abstracts, compared docetaxel plus doxorubicin or epirubicin to other multi-agent chemotherapy regimens in anthracycline-naive patients (72-74) (Table 4).

Participants in the trial by Chan et al were required to have prior alkylating-agent chemotherapy, to have received no more than one line of chemotherapy for advanced or metastatic disease, and to be anthracycline- and taxane-naive (71). Patients were eligible for inclusion in the studies by Nabholtz et al and Bonneterre et al if they had received no prior chemotherapy for metastatic disease (72-74).

Survival data were reported only for the randomized trial of docetaxel versus doxorubicin by Chan et al (71). Median survival times were very similar for these two single-agent treatments. Two trials reported time-to-progression, but neither detected a significant difference between regimens with and without docetaxel (71,74). Four trials evaluated tumour response, and three of these detected significantly higher response rates with docetaxel-containing regimes (71-73). The negative study was a randomized phase II trial with a relatively small sample size (74).

Paclitaxel in Patients with Prior Anthracycline Exposure

Paclitaxel has been compared to mitomycin and to capecitabine in two phase II randomized trials (75,76), both of which involved fewer than 100 patients (Table 4).

All of the women in the trial by Dieras et al had received prior chemotherapy for metastatic disease, and 98% had been treated with anthracyclines as part of adjuvant or first-line chemotherapy (75). Crossover to the alternate arm was allowed upon progression. Of the 21 patients who crossed over from mitomycin to paclitaxel after progression, 24% achieved an objective response; no patients were crossed over to mitomycin. There were no significant differences between paclitaxel and mitomycin in terms of response rate or overall survival, but patients in the paclitaxel arm had longer time to progression (p=0.026).

The trial by O'Reilly et al, comparing paclitaxel to capecitabine, was prematurely terminated after 42 patients were randomized, because of problems with recruitment (76). There was no statistically significant difference between paclitaxel and capecitabine in terms of response rate or time to progression.

Docetaxel in Patients with Prior Anthracycline Exposure

Three randomized trials (two published and one abstract) compared single-agent docetaxel with combination chemotherapy in anthracycline-resistant patients (77,78,80). A fourth trial compared docetaxel alone with docetaxel plus capecitabine (81). Results from all four trials are summarized in Table 4.

Participation in these trials was restricted to women who had received prior anthracycline-containing chemotherapy, in either the adjuvant or metastatic setting. Women with more than one line of chemotherapy for advanced or metastatic disease, or with prior mitomycin, vinca alkaloid, or taxane exposure, were excluded from the Nabholtz trial (77). Patients were eligible for inclusion in the Sjostrom study if they had no more than one prior chemotherapy regimen for advanced disease and no prior taxane exposure (78). O'Shaughnessy et al required that patients have had no prior docetaxel-containing therapy (79).

Two trials of docetaxel versus non-docetaxel containing chemotherapy reported data on survival (77,78). One detected a longer duration of survival with docetaxel than with mitomycin/vinblastine (p=0.0097) (77), and the other did not detect a statistically significant difference between docetaxel and methotraxate/5-fluorouracil (78). Two of three trials detected significantly longer times to disease progression and higher response rates with docetaxel than with multi-agent chemotherapy (77,78). Although the observed effects were similar to those from the other two studies, Bonneterre et al failed to detect a significant benefit for docetaxel

over 5-fluorouracil/vinorelbine (80), but the data presented in Table 4 for this study are based on an abstract report of preliminary data assembled before recruitment to the trial was complete.

O'Shaughnessy et al reported that the duration of survival and time to progression were significantly longer and that the response rate was higher when capecitabine was added to docetaxel (p=0.0126 for survival, p=0.0001 for progression-free survival, p=0.006 for response), compared with docetaxel alone (81). Both groups were to receive continuous treatment until progression or undue toxicity. Analysis was on an intent-to-treat basis, and no formal crossover provisions were made.

Quality of Life

Nine RCTs included an assessment of quality of life at baseline and during chemotherapy (Table 5) (64-68,71,77-79,81). Eight of the trials did not detect statistically significant differences between treatment groups on changes from baseline in measures of quality of life. The exception was the trial by Jassem et al (67). A comparison between treatment groups for "longitudinal differences between baseline and subsequent study periods" found that patients in the FAC arm had better scores for physical and sexual functioning (p=0.039 and p=0.015, respectively) and worse scores for pain (p=0.014), fatigue (p=0.008), insomnia (p=0.007), and diarrhea (p=0.02), compared with the paclitaxel/doxorubicin group. Patients in the paclitaxel/doxorubicin arm had worse scores for nausea and vomiting (p=0.01).

Table 5. Quality of life data from randomized trials of the taxanes for the treatment of metastatic breast cancer

Author (Reference)	Treatment comparison	% of those randomized with quality-of-life data	Time of assessment for quality of life (after baseline)	Assessment tools
Paclitaxel				
Paridaens (64)	paclitaxel doxorubicin	53%	after 3rd cycle of treatment	- EORTC QLQ-C30 - Rotterdam Symptom Checklist
Bishop (65)	paclitaxel CMFP	NR	averaged over measure taken after each cycle	- 6 linear-analog scales (patient) - Spitzer QOL index (physician)
Sledge (66) [abstract]	paclitaxel doxorubicin paclitaxel/doxorubicin	71%	at week 16	FACT-B (Functional Assessment of Cancer Therapy Breast)
Jassem (67)	paclitaxel/doxorubicin FAC	79%	before each cycle, longitudinal analysis	EORTC QLQ-C30 with Breast Cancer Module BR-23
Carmichael (68) [abstract]	paclitaxel/epirubicin EC	NR	"during treatment"	FACT-B
Docetaxel				
Chan (71)	docetaxel doxorubicin	87%	averaged over first 4 cycles	EORTC QLQ-C30
Nabholtz (77)	docetaxel mitomycin/vinblastine	70%	at cycle 2	EORTC QLQ-C30
Sjostrom* (78,79)	docetaxel methotextrate/5-FU	82%	at cycle 6	EORTC QLQ-C30
O'Shaughnessy (81)	docetaxel docetaxel/capecitabine	89%	at start of each cycle	EORTC QLQ-C30 with Breast Cancer Module BR-23

5-FU, 5-fluorouracil; CMFP, cyclophosphamide/methotraxate/fluorouracil/prednisone; EC, epirubicin/cyclophosphamide; EORTC, European Organisation for Research and Treatment of Cancer; FAC, fluorouracil/doxorubicin(Adriamycin)/cyclophosphamide; NR = not reported; QLQ, quality-of-life questionnaire; QOL, quality of life.

* from paper by Hakamies-Blomqvist et al (79), reporting quality-of-life data from the trial by Sjostrom et al (78).

Adverse Effects

Clinical studies of epirubicin with either docetaxel or paclitaxel have not detected any significant incidence of congestive heart failure. In pharmacokinetic studies of epirubicin and the taxanes, no significant negative interactions between epirubicin and either taxane were detected but increased area under the concentration curves of epirubicinol and 7-deoxydoxorubicin were noted. However, these metabolites are either less active or inactive when compared to the parent compound and cardiotoxicity was not observed (83).

An early study had detected reduced clearance of doxorubicin, when given in combination with paclitaxel, which resulted in high rates of clinical congestive heart failure (84). Strategies used to decrease the risk of congestive heart failure seen with the doxorubicin-paclitaxel combination have included: add dexrazoxane (85), substitute epirubicin or liposomal doxorubicin (86) for doxorubicin, use docetaxel rather than paclitaxel if a doxorubicin combination is considered, limit the total dose of doxorubicin administered ($\leq$360 mg/m^2) (87), change the schedule of infusion of doxorubicin (66), or separate doxorubicin and paclitaxel administration by 16-24 hours (66,67).

Data on serious hematologic, gastrointestinal, and neurological adverse effects from the randomized trials summarized above appear in Table 6. Data on congestive heart failure and toxic death are presented in Table 7.

O'Shaughnessy et al noted a decreased tolerance to the combination of docetaxel and capecitabine in women $\geq$60 years of age (81). 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.

Table 6. Toxicity data from randomized trials of the taxanes for the treatment of metastatic breast cancer - 4ates of grade 3 & 4 adverse events.

Author (Reference)	Treatment allocation	Grade 3/4 adverse effects (% of patients)				
		Hematological		Gastrointestinal		Neurological
		FN	N	Stomatitis/ mucositis	Nausea/ vomiting	Neurosensory/ PNS
Anthracycline-naive patients						
Paclitaxel						
Paridaens (64)	paclitaxel doxorubicin	7% 20%*	40% 80%*	1% 15%*	2% 13%*	9%* 0%
Bishop (65)	paclitaxel CMFP	NR NR	67% 73%	3% 6%*	1% 8%*	10%* 0%
Jassem (67)	paclitaxel/doxorubicin FAC	8% 5%	89%* 65%	1% 1%	8% 19%*	12%* 0%
UKCCCR (68)	paclitaxel/epirubicin EC	NR NR	NR NR	6% 2%	NR NR	5% 1%
Luck (69)	paclitaxel/epirubicin EC	2% 2%	34% 45%	NR NR	NR NR	NR NR
Biganzoli (70)	Paclitaxel/doxorubicin AC	32% 9%	89% 81%	10% 9%	7% 18%	3% 0%
Docetaxel						
Chan (71)	docetaxel doxorubicin	6% 12%*	94% 89%	3% 12%*	6% 26%*	5% 0%
Nabholtz (72)	docetaxel/doxorubicin AC	6% 2%	82% 69%	1% 1%	NR NR	0% 0%
Nabholtz (73)	docetaxel/dox/cyclo FAC	30% 4%	94% 81%	8% 3%	NR NR	NR NR
Bonneterre (74)	docetaxel/epirubicin FEC	25% 0%	68% 59%	0% 5%	17% 19%	3% 0%
Anthracycline-resistant patients						
Paclitaxel						
Dieras (75)	paclitaxel mitomycin	3% 0%	61%* 3%	3% NR	3% NR	11% NR
O'Reilly (76)	paclitaxel capecitabine	NR NR	68% 18%	NR NR	NR NR	NR NR
Docetaxel						
Nabholtz (77)	docetaxel mitomycin/vinblastine	9%* <1%	93%* 63%	9%* <1%	7% 5%	5%* <1%
Sjostrom (78)	docetaxel methotextrate/5-FU	NR NR	NR NR	9% 5%	6% 11%	5% 1%
Bonneterre (80)	docetaxel 5-FU/vinorelbine	9% 9%	78% 65%	NR NR	NR NR	NR NR
O'Shaughnessy (81)	docetaxel docetaxel/capecitabine	21% 16%	15% 16%	5% 17%	2% 6%	NR NR

* Indicates significant differences of $p < 0.05$ between treatment groups.
5-FU, 5-fluorouracil; AC, doxorubicin(Adriamycin)/cyclophosphamide;
CMFP, cyclophosphamide/methotraxate/fluorouracil/prednisone; cyclo, cyclophosphamide; dox, doxorubicin;
EC, epirubicin/cyclophosphamide; FAC, fluorouracil/doxorubicin(Adriamycin)/cyclophosphamide;
FEC, fluorouracil/epirubicin/cyclophosphamide; FN, febrile neutropenia; N, neutropenia; NR, not reported;
PNS, toxicity to the peripheral nervous system.

Table 7. Data on congestive heart failure and toxic death from randomized trials of the taxanes for the treatment of metastatic breast cancer

Author (Reference)	Treatment allocation	Congestive heart failure n	Congestive heart failure (% of patients)	Toxic death n	Toxic death (% of patients)
Paclitaxel - Anthracycline-naive patients					
Paridaens (64)	Paclitaxel	0		0	
	Doxorubicin	6	3.6%	3	1.8%
Sledge (66) [abstract]	paclitaxel	NR		2	0.8%
	doxorubicin	NR		6	2.4%
	paclitaxel/doxorubicin	NR		4	1.6%
Jassem (67)	paclitaxel/doxorubicin	2	1.5%	1	0.8%
	FAC	1	0.8%	1	0.8%
Biganzoli (70)	paclitaxel/doxorubicin	3	2.2%	0	0
	AC	1	0.7%	1	0.7%
Docetaxel - Anthracycline-naive patients					
Chan (71)	docetaxel	0		2	1.2%
	doxorubicin	6	3.6%	5	3.0%
Nabholtz (72) [abstract]	docetaxel/doxorubicin	2%		1	0.5%
	AC	4%		3	1.4%
Nabholtz (73) [abstract]	docetaxel/dox/cyclo	2%		5	2.1%
	FAC	1%		2	0.8%
Bonneterre (74) [abstract]	docetaxel/epirubicin	NR		1	1.9%
	FEC	NR		0	
Docetaxel - Anthracycline-resistant patients					
Nabholtz (77)	docetaxel	NR		4	2.0%
	mitomycin/vinblastine	NR		3	1.6%
Sjostrom (78)	docetaxel	NR		3	2.1%
	methotextrate/5-FU	NR		1	0.7%
Bonneterre (80) [abstract]	docetaxel	NR		1	2.1%
	5-FU/vinorelbine	NR		2	4.4%

5-FU, 5-fluorouracil; AC, doxorubicin(Adriamycin)/cyclophosphamide;
FAC, fluorouracil/doxorubicin(Adriamycin)/cyclophosphamide; FEC, fluorouracil/epirubicin/cyclophosphamide;
NR, not reported.

Of note are several trials that found statistically significant differences between treatment regimens in the rates of grade 3 and 4 adverse events. These are summarized in the text below.

Single-agent paclitaxel or docetaxel versus doxorubicin

Patients in the paclitaxel arm of the trial by Paridaens et al (64) experienced less grade 4 neutropenia ($p<0.001$), febrile neutropenia ($p<0.001$), vomiting ($p<0.001$), and stomatitis ($p<0.001$) but more arthralgia/myalgia (4% vs. 0%, $p<0.015$) and sensory neurotoxicity ($p<0.001$) than those on doxorubicin (Table 6). Chan et al found similar results in a trial of docetaxel versus doxorubicin (71). Patients in the docetaxel group had significantly less febrile neutropenia ($p\leq0.05$), grade 3/4 anemia (4.4% vs. 16.1%, $p\leq0.05$), grade 4 thrombocytopenia (1.3% vs. 7.5%, $p\leq0.05$), and fewer transfusions of red blood cells (6.9% vs. 20.9%, $p\leq0.05$). Women in the docetaxel group also had less severe nausea/vomiting ($p\leq0.05$) and stomatitis ($p\leq0.05$) but more problems with diarrhea (10.7% vs. 1.2%, $p\leq0.05$).

Single-agent paclitaxel or docetaxel versus combination chemotherapy

Bishop et al (65) reported that paclitaxel resulted in significantly less overall leukopenia ($p<0.0001$), thrombocytopenia ($p<0.0001$), nausea/vomiting ($p=0.0032$), mucositis ($p=0.0002$), infection ($p=0.0006$), and fever without infection ($p=0.0069$), while CMFP resulted in significantly

less overall peripheral neuropathy ($p<0.0001$) and myalgia/arthralgia (1% vs. 20% with paclitaxel, $p<0.0001$).

Patients in the docetaxel group of the trial by Nabholtz et al had significantly more febrile neutropenia ($p<0.05$), grade 3/4 neutropenia ($p<0.05$), and severe infection (11.0% vs. 1.1%, $p<0.05$) but less severe thrombocytopenia (4.1% vs. 12%, $p<0.05$) than those on mitomycin/vinblastine (77). They also experienced significantly more severe nausea/vomiting, stomatitis, diarrhea, skin toxicity, asthenia, nail disorder, and neurosensory toxicity (all $p<0.05$).

Taxane/doxorubicin versus other combination chemotherapy

In the study by Jassem et al (67), grade 3/4 adverse effects in the paclitaxel plus doxorubicin group were higher than in the FAC group in terms of neutropenia ($p<0.001$), arthralgia/myalgia (10% vs. 0%, $p<0.001$), and peripheral neuropathy ($p<0.001$) but lower in terms of nausea and vomiting ($p =0.028$). Similar observations have been documented in the study by Biganzoli et al (70).

In the trial by Nabholtz et al of docetaxel/doxorubicin/cyclophosphamide versus FAC, clinical congestive heart failure occurred in 2% of the docetaxel group and 1% of the FAC group (73). Although these rates are not particularly high, they do merit consideration and monitoring when anthracycline/taxane combinations are considered in this population.

Practice Guideline from another Guideline-development Group

In June 2000, the National Institute for Clinical Excellence (NICE) in the United Kingdom issued a guidance document on taxane use in the treatment of patients with advanced breast cancer, based on a systematic review of the evidence developed by the National Health Service Health Technology Assessment Programme. The document was updated in September 2001 (82). The review included published and unpublished data from 11 randomized trials that compared either paclitaxel or docetaxel, as single agents or as part of multi-agent regimens, to other chemotherapeutic agents for the treatment of advanced breast cancer; seven of the data sources used for this PGI guideline report were included in the NICE overview (64,66,67,69,70,78,80). The guidance document stated that:

- The use of docetaxel in combination with an anthracycline in first-line treatment of advanced breast cancer is not currently recommended. As paclitaxel is not licensed for first-line use with anthracycline, its use has not been considered in this indication.
- Docetaxel and paclitaxel are recommended as an option for the treatment of advanced breast cancer where initial cytotoxic chemotherapy (including an anthracycline) has failed or is inappropriate (82).

The recommendations from the NICE guideline were considered by the Breast Cancer DSG in its deliberations. For anthracycline-resistant patients, the NICE recommendations are consistent with those of the Breast Cancer DSG. However, as outlined in the interpretive summary section below, the Breast Cancer DSG felt that in first-line therapy, taxane-anthracycline combinations could be considered for anthracycline-naive patients.

VI. INTERPRETIVE SUMMARY

Initially, phase II trials with paclitaxel or docetaxel detected clinically meaningful activity of these drugs in patients with metastatic breast cancer who had or had not been exposed to prior anthracyclines. Preliminary review of these data by the clinical community, who were somewhat desperate for additional therapeutic options to offer women with metastatic breast cancer, led to the early adoption of both taxanes as “acceptable” treatment in those patients who had symptomatic, progressing disease and who had failed prior anthracyclines. Anthracycline failure was defined as: i) progression while on an anthracycline-containing regimen, ii) relapse within 12 months of discontinuing anthracycline-containing adjuvant therapy, or iii) inability to receive

further anthracycline-containing treatment because of toxicity, including potential cardiotoxicity. Additional data from well-conducted randomized clinical trials comparing docetaxel or paclitaxel (alone or in combination with other agents) to acceptable standard treatments permit more conclusive recommendations, particularly with regard to the choice of taxane and the relevant patient subsets (anthracycline–naive or anthracycline–resistant) in whom such treatments are applicable.

Anthracycline-naive Patients

Paclitaxel

Evidence is available from eight comparisons from seven randomized controlled trials, involving a total of 2954 patients, comparing paclitaxel (alone or in combination with doxorubicin or epirubicin) with standard treatments (64-70).

Three randomized trials assessed single-agent paclitaxel and none demonstrated its superiority over control in terms of survival (64-66). In one trial, differences in response rates and median time to progression favoured doxorubicin over paclitaxel, but adverse effects were significantly more frequent with doxorubicin (64). The dose of doxorubicin used in this study (75mg/m^2) is higher than the conventionally accepted standard (60mg/m^2) and may explain the higher toxicity observed. In another trial, peripheral neuropathy, myalgia, and arthralgia were significantly more common in patients treated with paclitaxel than in those receiving CMFP (65). Although CMFP is not ordinarily considered a "standard" treatment in anthracycline-naive patients, it is of interest to note that in the Bishop study more women in the CMFP group survived progression-free at six months and more women in the paclitaxel group were alive at two years (65). Although there are differences in the dose and schedule of paclitaxel administered in these studies and questions regarding the suitability of the control arms, on the whole, <u>these data provide little evidence that single-agent paclitaxel is superior to standard treatment (doxorubicin) in terms of response, time to progression, or overall survival in anthracycline-naive patients.</u>

Five randomized trials have evaluated the effectiveness of paclitaxel combined with doxorubicin or epirubicin versus doxorubicin alone or in combination with other agents (66-70). Response rates and times to progression were statistically superior to control for the paclitaxel/doxorubicin combination in two trials (66,67), but not for the paclitaxel/epirubicin combination (68,69). One trial detected a significant survival advantage for the combination of paclitaxel plus doxorubicin over FAC (67). Data on toxicity are scant, but as expected, significantly higher rates of neutropenia were observed with paclitaxel/doxorubicin than with FAC (67). The combination of paclitaxel/doxorubicin was also associated with significantly higher rates of neurotoxicity than FAC (67). <u>Based on these data, it would seem reasonable to offer paclitaxel/doxorubicin polychemotherapy to patients for whom therapy with anthracyclines is being considered.</u>

Docetaxel

Data on docetaxel in this patient population are somewhat more sparse but more consistent than those from trials of paclitaxel. Randomized trials of docetaxel were generally well conducted. Three of four trials evaluating docetaxel alone or in combination with anthracyclines detected significantly higher response rates with docetaxel than with control (71-73). No significant differences were detected in time to progression, or survival. One trial reported significantly more serious adverse effects with doxorubicin than with docetaxel, when both were used as single agents (71). Although the papers did not report that the differences were statistically significant, it is important to note that more patients treated with docetaxel and an anthracycline in combination experienced febrile neutropenia and neutropenia, compared to cyclophosphamide and an anthracycline with or without fluorouracil (72-74). <u>Based on the</u>

observed response rates and time-to-progression data, it is reasonable to offer docetaxel, alone or in combination with doxorubicin, to anthracycline-naive patients.

Anthracycline-resistant Patients

Paclitaxel

Two randomized trials addressed the role of paclitaxel in this group of patients (75,76). Unfortunately, the trial by O'Reilly et al was terminated early and lacked the power to draw any meaningful conclusions (75). The phase II randomized trial by Dieras et al demonstrated the superiority of paclitaxel over mitomycin C in terms of the duration of disease control (76). Interestingly, most patients in the mitomycin arm crossed over to the paclitaxel arm (only two initially responded), making survival differences difficult to assess. Nonetheless, this trial provides weak evidence that paclitaxel is effective in anthracycline-resistant metastatic breast cancer and is likely more effective than previously used, older, non-taxane-containing regimens.

Docetaxel

Three randomized trials compared docetaxel, as a single agent, to accepted standard treatments (77,78,80) but one of these was still accruing patients when results were reported in a meeting abstract (80). Two trials detected a significantly higher response rate and longer time to progression with docetaxel than with control (77,78). One trial detected a statistically superior overall survival with docetaxel (11 months vs. 9 months with mitomycin/vinblastine) (77). These trials provide evidence that docetaxel is an effective treatment in anthracycline-resistant metastatic breast cancer. Although docetaxel was associated with higher rates of adverse events, toxicity appeared manageable, with more patients remaining on treatment in the docetaxel arm than the control arm (77).

Recently, O'Shaughnessy et al reported the results of a randomized trial comparing docetaxel/capecitabine with single-agent docetaxel in women with anthracycline-resistant metastatic breast cancer (81). These indicate a significant superiority of the combination over single-agent docetaxel in response rate, time to progression and survival. Capecitabine-specific toxicity was higher in the combination arm, and further review of the data indicate that toxicity can be reduced, with no apparent loss in effectiveness of the regimen, by initiating therapy at 75% of full dose capecitabine. This is the first trial to demonstrate the superiority of a taxane combination over a taxane as a single agent in this population.

Docetaxel versus Paclitaxel

No data from direct comparisons of docetaxel with paclitaxel are available. However, an overview of the trials discussed above reveals some consistent findings from indirect comparisons across trials, which show higher response rates with single-agent docetaxel than with paclitaxel. While this observation might support the preferential use of docetaxel as a single agent in anthracycline-treated/resistant patients, the lack of evidence from randomized trials that directly compare the two agents in this setting makes it difficult to recommend one drug over the other.

The Taxanes in Combination with Anthracyclines

Despite the observation in certain randomized trials of the superiority of taxane combinations in anthracycline-naive and -resistant patients, there is still some reluctance on the part of oncologists to readily embrace such treatment. Part of this concern relates to the small magnitude of benefit. Although the differences observed in clinical trials were statistically significant, time to progression was prolonged by approximately two months on average. Although higher response rates have been observed in the taxane arms of many of these trials, there is scant information on "time to response". Such data would be helpful if one were trying to select treatment for patients with rapidly progressing, symptomatic disease. Additionally, except

for one trial (Sledge et al), none of the trials have provided information on crossover responses between non-taxane and taxane-containing regimens, adding to the therapeutic dilemma. Finally, there is no evidence on whether initial combination therapy with taxanes in either setting provides an advantage over the usual sequence of treatments conventionally employed in patients with metastatic breast cancer (e.g., an anthracycline followed by a taxane followed by capecitabine).

Nonetheless, in patients with aggressive disease and poor prognosis (early relapse after adjuvant therapy, multiple sites of involvement, bulky visceral involvement), initial combination therapies that produce a higher response rate may benefit a proportion of women who might not benefit from the progressively lower response rates induced by subsequent, sequential therapy.

VII. ONGOING DEVELOPMENTS IN TAXANE THERAPY

Table 8 summarizes data from several phase II studies (88-110), primarily reported in abstract form, on the safety and efficacy of weekly taxane administration. Based on these preliminary data, overall response rates range from 21% to 86% for paclitaxel and 11% to 54% for docetaxel. On average, adverse effects associated with weekly taxane administration are minimal, and such programs are becoming popular with oncologists, as they are thought to be "less toxic". Until randomized trials comparing weekly to three-weekly regimens are completed, only selected patients (elderly, low performance status, or those who do not accept conventional taxane toxicity) should be considered for such therapy.

Addendum, June 2002: Preliminary results of a phase II randomized trial of weekly (40 mg/m^2) versus three-weekly (100 mg/m^2) docetaxel for metastatic breast cancer were reported in an abstract for ASCO 2002 (115). Data were available from 35 patients. The response rate was 40% in both treatment groups, but the toxicity profiles were different for the two schedules of administration. There were more nail problems, fatigue, and anorexia with the weekly regimen, compared with treatment every three weeks. There was more stomatitis, neurosensory toxicity, and edema on the three-weekly schedule.

Ongoing Trials

Docetaxel versus Paclitaxel

- RP-56976-TAX-311, NCI-V95-0680 (111): A randomized trial comparing paclitaxel and docetaxel in anthracycline-resistant patients with metastatic or locally advanced breast cancer. Target Accrual is 400 patients.

Randomized Comparisons of Different Doses and Schedules for Administering Docetaxel or Paclitaxel

- CLB-9840 (112): Phase III randomized study of paclitaxel via one-hour infusion every week versus three-hour infusion every three weeks with or without trastuzumab (Herceptin) in patients with inoperable, recurrent, or metastatic breast cancer with or without overexpression of HER2-Neu. Target Accrual is 340 patients.
- FRE-GERCOR-TAXMAX-SOO-1, EU-20029 (113): Phase II randomized study of two different schedules of docetaxel or paclitaxel in women with unresectable locally advanced or metastatic breast cancer.

Table 8. Phase II studies of weekly chemotherapy with taxanes.

Author (Reference)	Patients			Dose & schedule		Response rates (%)		Grade 3/4 adverse effects			
Weekly paclitaxel											
Study	**#**	**% prior A**	**% prior T**	**Dose per week (mg/m^2)**	**Schedule (weeks)**	**Complete response**	**Objective response**	**FN**	**N**	**PNS**	**Anemia**
Seidman (88)	16	63%	0%	100	Continuous	6%	40%	0%	14%	NR	NR
Waintraub (89) [abstract]	13	100%	54%	90	Continuous	0%	54%	NR	NR	NR	NR
Mickiewicz (90) [abstract]	49	100%	73%	100 or 80	Continuous /3 on, 1 off	16%	61%	NR	NR	NR	6%
Perez (91) [abstract]	130	NR	35%	80	Continuous	5%	21%	NR	NR	8%	NR
Asbury (92) [abstract]	21	NR	NR	50-100	3 on, 1 off	0%	62%	NR	14%	NR	10%
Breier (93) [abstract]	24	NR	NR	80	Continuous	8%	50%	0%	NR	0%	NR
Sikov (94) [abstract]	14	NR	NR	131	6 on, 2 off	7%	86%	13%	47%	20%	NR
Scuderi (95) [abstract]	22	72%	0%	60-90	NR	0%	45%	0%	0%	NR	NR
Madrueno (96) [abstract]	23	65%	NR	80	NR	NR	NR	0%	NR	NR	NR
Weekly docetaxel											
Study	**#**	**% prior A**	**% prior T**	**Dose per week (mg/m^2)**	**Schedule (weeks)**	**Complete response (%)**	**Objective response (%)**	**FN**	**N**	**Asthenia/ fatigue**	**Nausea/ vomiting**
Jackisch (97) [abstract]	60	43%	0%	35-40	Continuous	7%	33%	NR	3% (cycles)	NR	0.8% (cycles)
Kim (98) [abstract]	36	33%	0%	40	3 on, 1 off	3%	39%	NR	16%	NR	0%
Ramos (99) [abstract]	29	100%	NR	40-36	6 on, 2 off	7%	48%	0%	24%	7%	7%
Stemmler (100) [abstract]	33	NR	NR	35	6 on, 2 off	6%	36%	0%	3% (cycles)	NR	NR
Burstein (101)	29	31%	NR	40	6 on, 2 off	0%	41%	0%	14%	14%	3%
Loeffler (102) [abstract]	41	61%	15%	40	6 on, 2 off	12%	48%	0%	12%*	0%	NR
Climent (103) [abstract]	14	43%	NR	35	Continuous	0%	36%	0%	NR	0%	0%
Roscigno (104) [abstract]	18	35%	NR	40	6 on, 3 off	0%	40%	0%	33%	22%	0%
Adami (105) [abstract]	15	73%	NR	35	6 on, 2 off	0%	17%	0%	7%*	47%	NR
Mey (106) [abstract]	9	100%	NR	40	3 on, 1 off	0%	11%	0%	11%*	NR	NR
Malik (107) [abstract]	16	NR	NR	33	Continuous	0%	25%	NR	NR	NR	NR
Miranda (108) [abstract]	8	NR	NR	36	6 on, 2 off	0%	38%	NR	NR	NR	NR
Krapfl-Gast (109) [abstract]	25	>80%	0%	32	6 on, 2 off	4%	52%	NR	22%	NR	0%
Koshizuka (110) [abstract]	13	NR	NR	22-33	6 on, 2 off	0%	54%	NR	NR	NR	NR

* indicates hematological adverse effects other than neutropenia;
A, anthracycline; FN, febrile neutropenia; N, neutropenia; NR, not reported; PNS, toxicity to the peripheral nervous system; T, taxane.

VIII. DISEASE SITE GROUP CONSENSUS PROCESS

In the context of current clinical practice, the Breast Cancer DSG discussed the evidence surrounding the role of the taxanes in the treatment of women with metastatic breast cancer.

The DSG agreed that the primary goal for treatment in this population is to achieve the longest survival with the best quality of life, using a treatment with acceptable toxicity. There is very little reported difference in overall survival among the standard chemotherapeutic drugs available for patients with metastatic breast cancer. While there is some variability, it is now conventional practice to commence therapy with an anthracycline-containing regimen, followed by a taxane as a single agent as second-line treatment. Third-line treatment usually consists of capecitabine or vinorelbine. As they have in the past, members of the DSG acknowledge that there is a role for innovative treatments and investigational agents at each point in this treatment algorithm, including the introduction of investigational new drugs in patients who are chemotherapy-naive.

The DSG considered the evidence regarding the use of a taxane (either alone or in combination with other agents) in the first-line setting, where anthracycline-based chemotherapy would ordinarily be considered. Members of the DSG acknowledged that a survival advantage for a taxane-based regimen over a standard anthracycline-based regimen has not yet been demonstrated. However, it was also pointed out that significant increases in response rates and time to progression have been demonstrated in this setting, when a taxane is used alone or in combination with an anthracycline. In particular patients, those with aggressive, symptomatic disease, a taxane-based combination in the first-line setting might offer a *higher probability* of response, and by inference, a relief of symptoms. In patients with particularly aggressive, rapidly progressing disease, a taxane-based treatment in the first-line setting might be the preferred choice to provoke a more rapid response. However, this argument could not be resolved with the currently available data, because time to response is rarely reported in trial results. After considering these issues, the DSG members agreed that in the first-line setting, either paclitaxel or docetaxel could be considered as reasonable treatment options for patients with metastatic breast cancer who receive multi-agent chemotherapy. The DSG members recommended that the choice should be offered to patients who are fully informed about the harms and benefits associated with each drug or drug combination, especially as cardiotoxicity and febrile neutropenia remain of concern.

The DSG also considered the evidence regarding the effectiveness of docetaxel over paclitaxel. Docetaxel appears to be more effective than paclitaxel, based on indirect comparisons, but published results of an ongoing trial directly comparing the two drugs are not yet available.

IX. IMPLICATIONS FOR POLICY

There are no published economic evaluations based on randomized trials of the taxanes in metastatic breast cancer. The Breast Cancer DSG is aware of one Canadian cost-utility analysis conducted at the Princess Margaret Hospital in Ontario, which is based on total resource consumption by a cohort of 88 patients treated with paclitaxel (n=34), docetaxel (n=29), or vinorelbine (n=25) for anthracycline-resistant metastatic breast cancer (114). However, comparisons based on non-randomized studies must be interpreted with caution.

X. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Practice Guideline

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

Target Population

These recommendations apply to women with metastatic breast cancer for whom first- or greater-line chemotherapy is being considered.

Draft Recommendations

- In ***anthracycline-naive patients,*** who would ordinarily be offered treatment with a single-agent anthracycline (doxorubicin or epirubicin) or an anthracycline in a standard combination***, or in patients in whom anthracyclines are contraindicated***, the following options are also reasonable:
  - Treatment with single-agent docetaxel 100 mg/m^2 over one hour every three weeks.
  - Paclitaxel or docetaxel in combination with doxorubicin.

- In ***anthracycline-resistant patients or patients who have previously received an anthracycline as adjuvant therapy:***
  - Either paclitaxel or docetaxel may be considered as treatment options after failure of prior anthracycline treatment or in women whose disease is resistant to anthracyclines.
  - In selected patients, the combination of docetaxel and capecitabine may represent an appropriate therapeutic option.

Qualifying Statements

- Patients should be fully informed of all the treatment options and should be aware of the risks and benefits associated with each of them.
- There is generally little difference in overall survival between chemotherapeutic agents in the treatment of metastatic breast cancer. Treatment in this setting should be based on clinical considerations and patient preferences, with a focus on palliation and quality of life.
- There is no evidence that initial combination therapy with anthracyclines and taxanes in the metastatic setting provides an advantage over the usual sequence of treatments conventionally employed in patients with metastatic breast cancer (e.g., an anthracycline followed by a taxane followed by capecitabine).
- The combination of paclitaxel (infused over three hours) in rapid sequence should not exceed doses of doxorubicin >360 mg/m^2 due to the high incidence of congestive heart failure.
- It is recommended that capecitabine in the docetaxel/capecitabine combination be given at 75% of full dose. Due to the toxicity of the combination, patient selection for better performance or younger age is recommended.
- Until randomized trials comparing weekly to three-weekly regimens are completed, only selected patients (elderly, low performance status, or those who do not accept conventional taxane toxicity) should be considered for such therapy.

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 83 medical oncologists in Ontario. The survey consisted of 21 questions about the quality of the practice-guideline-in-progress (PGIP) report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The guideline report and questionnaire were mailed on April 18th, 2002. Follow-up reminders were sent two weeks (post card) and four weeks (complete package mailed again) later. The Breast Cancer DSG reviewed the results of the survey.

Results
Fifty-six responses were received out of the 83 surveys sent (68% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 46 indicated that the report was relevant to their clinical practice, and they completed the questionnaire. Key results of the practitioner feedback survey are summarized in Table 9.

Table 9. 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 "*Choice of Topic*" section of the report, is clear.	45 (98%)	1 (2%)	0
There is a need for a clinical practice guideline on this topic.	42 (91%)	2 (4%)*	1 (2%)
The literature search is relevant and complete.	44 (96%)	2 (4%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	43 (94%)	3 (6%)	0
The draft recommendations in this report are clear.	43 (94%)	2 (4%)	1 (2%)
I agree with the draft recommendations as stated.	40 (87%)	2 (4%)	4 (9%)
This PGIP report should be approved as a practice guideline.	38 (83%)	4 (9%)	4 (9%)
If this PGIP 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**
	40 (87%)	2 (4%)*	3 (6%)

* plus 1 (2%) missing

Summary of written comments

Fourteen respondents (30%) provided written comments. The main points contained in the written comments were:

1. Practitioners commented on the relative risks and benefits of the taxanes and on the relative value of increased time to progression and response in the absence of survival data. There were concerns that gains from increased response rates and time to progression with the taxanes may be negated by increased toxicity. Practitioners commented that there appears to be no superiority of the taxanes over other chemotherapeutic regimens with respect to quality of life and that the survival data from trials are inconsistent in both the anthracycline-exposed and anthracycline-naïve patient populations.
2. Despite the lack of evidence from randomized trials, practitioners' experience leads them to feel that docetaxel may be more effective and less toxic than paclitaxel. They asked why, if the DSG concluded that "docetaxel appears more effective than paclitaxel", the draft guideline recommended that practitioners consider paclitaxel in anthracycline-resistant/pretreated patients? Practitioners suggested that indirect results could be used to be more definite in recommending docetaxel over paclitaxel.
3. It was pointed out that the first set of draft recommendations ("*In anthracycline-naive patients,. . . or in patients in whom anthracyclines are contraindicated"*) were confusing. There should be a separate bullet for patients for whom anthracyclines are contraindicated, which would not include the combination of paclitaxel or docetaxel with doxorubicin.

Modifications/Actions

The DSG discussed the issues described above and responded as follows

1. The small increases in response rates, time to progression and survival in some trials have been acknowledged. Treatment with taxanes (particularly in combination) are also noted to be associated with increased toxicity and hence such therapies are presented as <u>options</u>.
2. Recommendations have been qualified to address the use of taxanes in anthracycline-resistant patients, and it has been acknowledged that evidence supporting the use of docetaxel is more consistent.
3. A separate bullet concerning patients for whom anthracyclines are contra-indicated has been included in the recommendations.

In addition to the changes noted above, the guideline report was modified to include new evidence found by an update search after the practitioner feedback survey. Data from the trial of docetaxel plus capecitabine versus docetaxel alone by O'Shaughnessy et al, previously available only in abstract form, was updated using the full report published in the *Journal of Clinical Oncology* in June 2002 (81). Preliminary results of a randomized trial of weekly versus three-weekly docetaxel, from the 2002 ASCO meeting (115), and results of a trial of paclitaxel/doxorubicin versus doxorubicin/cyclophosphamide, published by Bignazoli et al in July 2002 (70), were added to the guideline report.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to ten members of the Practice Guidelines Coordinating Committee (PGCC). Seven members of the PGCC returned ballots. Four PGCC members approved the practice guideline as written, with one member providing suggestions for consideration by the Breast Cancer DSG. Two members approved the guideline conditional on the DSG addressing specific concerns. One member had concerns regarding the appropriateness of the guideline process.

Two concerns expressed by members of the PGCC required a response from the Breast Cancer DSG. One PGCC member questioned why paclitaxel and doxorubicin is a reasonable option given that there is no survival advantage for the combination over the usual sequence

and no evidence is given for improved quality of life. One PGCC member asked whether the qualifying statement regarding the use of weekly taxane therapy should be less restrictive given that the guideline report states that an objective of chemotherapy in the setting of metastatic breast cancer is to improve quality of life.

Modifications/Actions

The DSG agreed with the PGCC comment regarding the use of weekly taxane therapy and modified the qualifying statement. No change was made to the recommendation regarding combination therapy. Although the qualifying statement indicates no survival advantage and no evidence for improved quality of life for the combination of paclitaxel and doxorubicin over the usual sequence, the rationale for considering combination therapy is, in the opinion of the DSG, clearly outlined in the interpretive summary. The DSG has indicated in its deliberations that in selected patients, where response is valued as a surrogate for the possible reduction of symptoms in patients with high tumour burden or rapidly progressive disease, the combination could be considered a reasonable option.

XIII. 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 the Practice Guidelines Coordinating Committee.

Target Population

These recommendations apply to women with metastatic breast cancer for whom first- or greater-line chemotherapy is being considered.

Practice Guideline

Recommendations

- In ***anthracycline-naive patients,*** who would ordinarily be offered treatment with a single-agent anthracycline (doxorubicin or epirubicin) or an anthracycline in a standard combination***,*** the following options are also reasonable:
  - Treatment with single-agent docetaxel 100 mg/m^2 over one hour every three weeks.
  - Docetaxel or paclitaxel in combination with doxorubicin.

- In ***anthracycline-naive patients for whom anthracyclines are contraindicated:***
  - Treatment with single-agent docetaxel 100 mg/m^2 over one hour every three weeks is recommended.

- In ***anthracycline-resistant patients or patients who have previously received an anthracycline as adjuvant therapy:***
  - Either docetaxel (100 mg/m^2 over one hour every three weeks) or paclitaxel (175 mg/m^2 over three hours every three weeks) may be considered as a treatment option after failure of prior anthracycline treatment or in women whose disease is resistant to anthracyclines. The evidence supporting the use of single-agent docetaxel is more consistent, and is based on a larger number of trials and patients, than the evidence for paclitaxel.
  - In selected patients, the combination of docetaxel and capecitabine is a therapeutic option. Due to the toxicity of the combination, patient selection for good performance status or younger age is recommended. It is recommended that capecitabine in the docetaxel/capecitabine combination be given at 75% of full dose.

Qualifying Statements

- Patients should be fully informed of all the treatment options and should be aware of the risks and benefits associated with each of them.
- There is generally little difference in overall survival between chemotherapeutic agents in the treatment of metastatic breast cancer. Treatment in this setting should be based on clinical considerations and patient preferences, with a focus on palliation and quality of life.
- There is no evidence that initial combination therapy with anthracyclines and taxanes in the metastatic setting provides a survival advantage over the usual sequence of treatments conventionally employed in patients with metastatic breast cancer (e.g., an anthracycline followed by a taxane followed by capecitabine).
- The combination of paclitaxel (infused over three hours) and doxorubicin in rapid sequence should not exceed doses of doxorubicin >360 mg/m^2 due to the high incidence of congestive heart failure.
- Although few trials have compared weekly to three-weekly taxane therapy, the toxicities observed with weekly taxane therapy appear to be lower than those observed with the conventional three-weekly regimen. Weekly therapy could be considered for selected patients (elderly, low performance status, or women who wish to avoid some of the toxicities associated with the three-weekly taxane therapy).
- Women should be encouraged to enter clinical trials assessing novel treatments in the setting of metastatic breast cancer.

XIV. JOURNAL REFERENCE

Verma S, Trudeau M, Pritchard K, Oliver T, Robinson P, and the Cancer Care Ontario Practice Guidelines Initiative Breast Cancer Disease Site Group. Role of taxanes in the management of metastatic breast cancer. *Curr Oncol* 2003;10(2):68-83.

XV. ACKNOWLEDGEMENTS

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Appendix 1. Dosages and schedules for studies summarized in this guideline report.

Author	Anthracycline-naïve Patients ***Paclitaxel***
Paridaens (64)	Paclitaxel every 3 weeks for 7 courses: 200 mg/m^2, 3 hour IV Doxorubicin every 3 weeks for 7 courses: 75 mg/m^2, IV bolus
Bishop (65)	Paclitaxel every 3 weeks for 8 courses: 200 mg/m^2, 3 hour IV CMFP every 4 weeks for 6 courses: cyclophosphamide 100 mg/m^2, orally days 1 to 14; methotrexate 40 mg/m^2, IV days 1 and 8; 5-flourouracil 600 mg/m^2, IV days 1 and 8; prednisone 40 mg/m^2, orally days 1 to 14
Sledge (66)	Paclitaxel every 3 weeks: 175 mg/m^2, 24 hour IV Doxorubicin every 3 weeks: 60 mg/m^2 Paclitaxel/Doxorubicin every 3 weeks: paclitaxel 150 mg/m^2, 24 hour IV; doxorubicin 60 mg/m^2
Jassem (67)	AT every 3 weeks for 8 courses: paclitaxel 220 mg/m^2, 24 hour IV; doxorubicin 50 mg/m^2 FAC every 3 weeks for 8 courses: 5-flourouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 100 mg/m^2
UKCCCR (68)	ET every 3 weeks for 6 courses: epirubicin 75mg/m^2 and paclitaxel 200mg/m^2 EC every 3 weeks for 6 courses: epirubicin 75mg/m^2 and cyclophosphamide 600mg/m^2
Luck (69)	ET every 3 weeks: epirubicin 60mg/m^2 and paclitaxel 175mg/m^2 EC every 3 weeks: epirubicin 60mg/m^2 and cyclophosphamide 600mg/m^2
Biganzoli (70)	AT every 3 weeks for 6 courses: paclitaxel 175 mg/m^2, 3-hour IV; doxorubicin 60 mg/m^2 AC for a maximum of 6 courses: doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2
	Docetaxel
Chan (71)	Docetaxel every 3 weeks for 7 courses: 100 mg/m^2 Doxorubicin every 3 weeks for 7 courses: 75 mg/m^2, IV
Nabholtz (72)	AT every 3 weeks for 8 courses: doxorubicin 50 mg/m^2, docetaxel 75 mg/m^2 AC every 3 weeks for 8 courses: doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2
Nabholtz (73)	TAC every 3 weeks for 8 courses: docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 FAC every 3 weeks for 8 courses: 5-flourouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2
Bonneterre (74)	ET every 3 weeks for 6 courses: epirubicin 75mg/m^2 and docetaxel 75mg/m^2 FEC every 3 weeks for 6 courses: 5-flourouracil, epirubicin 75mg/m^2 and cyclophosphamide
	Anthracycline-resistant Disease ***Paclitaxel***
Dieras (75)	Paclitaxel every 3 weeks: 175 mg/m^2, 3 hour IV Mitomycin every 6 weeks: 12 mg/m^2, slow bolus IV
O'Reilly (76)	Paclitaxel every 3 weeks: 175 mg/m^2, 3 hour IV Capecitabine every 3 weeks: 2510 mg/m^2 in 2 separate doses on day 1 and 14
	Docetaxel
Nabholtz (77)	Docetaxel every 3 weeks up to 10 courses: 100 mg/m^2, IV Mitomycin/Vinblastine every 3 weeks up to 10 courses: mitomycin 12 mg/m^2, IV every 6 weeks; vinblastine 6 mg/m^2, IV every 3 weeks
Sjostrom (78)	Docetaxel every 3 weeks: 100 mg/m^2, 1 hour IV Methotextrate/5FU every 3 weeks on days 1 and 8: methotrexate 200 mg/m^2, short IV; fluorouracil 600 mg/m^2, bolus IV 1 hour after methotrexate administration
Bonneterre (80)	Docetaxel every 3 weeks: 100 mg/m^2 5FU/Vinorelbine: 5-flourouracil 750 mg/m^2, continuous IV, days 1 to 5; vinorelbine 25 mg/m^2, days 1 and 5.
O'Shaughnessy (81)	Docetaxel every 3 weeks 75 mg/m^2, IV and capecitabine 1250 mg/m^2, oral administration twice daily on days 1 to 14 every 3 weeks, continuous treatment. Docetaxel every 3 weeks, continuous treatment: 100 mg/m^2, IV

AC = Adriamycin/cyclophosphamide
CMF = Cyclophosphamide/methotrexate/5-fluorouracil
EC = Epirubicin/cyclophosphamide
ET = epirubicin/paclitaxel
FAC = 5-fluorouracil/Adriamycin/cyclophosphamide