

OPTIMAL USE OF TAXANES IN METASTATIC BREAST CANCER

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The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

In 2007, breast cancer is projected to be the second most commonly diagnosed cancer, and the third leading cause of cancer-related mortality in Canadian women.¹ Cancer was the leading cause of potential years of life lost in Canadian adults in 2003 and breast cancer accounted for 18.3% of cancer-related premature mortality in women.¹ Approximately 6% of women are diagnosed initially with metastatic disease.² This will account for just over 1300 new breast cancer diagnoses in Canadian women in 2007.^{1,2} Unfortunately, many women with early breast cancer will be diagnosed with a metastatic relapse in the years following local-regional and systemic adjuvant therapies. The goals of treatment in metastatic breast cancer include prolongation of survival, symptom control and maintenance of quality of life.

In Alberta, chemotherapy for breast cancer is prescribed at tertiary, associate and community cancer clinics, which are all affiliated with the Alberta Cancer Board. The literature on taxanes and breast cancer has been growing exponentially since the mid-1990's. In the absence of an evidence-based provincial guideline, it is expected then, that there is regional variability in taxane prescription. The objective of creating a provincial guideline on the optimal use of taxanes in the management of metastatic breast cancer is to promote evidence-based consistency in practice, and hence, equitable access for patients to appropriate therapies.

Guidelines for taxane use in the management of metastatic breast cancer have previously been published. The current effort will be to systematically adapt recommendations of others, and create de novo recommendations to account for recent evidence.

GUIDELINE GOALS AND OBJECTIVES

To outline the optimal clinical use of taxanes in the management of metastatic breast cancer

GUIDELINE QUESTIONS

1. What taxane regimens can be offered to anthracycline-naïve patients with metastatic breast cancer (where HER2 is not over-expressed)?
2. What taxane regimens can be offered to anthracycline-pre-treated/resistant patients with metastatic breast cancer (where HER2 is not over-expressed)?
3. What taxane regimens can be offered to patients with metastatic breast cancer where HER2 is over-expressed?
4. What are the benefits (time to progression, progression free survival, overall survival, quality of life)?
5. What are the potential toxicities?

DEVELOPMENT PANEL

This **guideline** was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. **Evidence** was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

SEARCH STRATEGY

A systematic search for relevant, existing practice guidelines and other evidence was conducted of: MEDLINE, Pub Med, CINAHL, EMBASE, CancerLit, the Cochrane Library, the Physician Data Query database, practice guideline INTERNET sites, and conference proceedings from the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SA). The following search terms were used Taxane* Exp., Taxanes Exp., metastatic breast cancer exp., metastases, breast tumour, breast tumor, Women exp., adding AND/OR Anthracycline exp., Anthracyclines exp.

The search for practice guidelines was conducted for the period January 1, 2000 to August 31, 2007. As the most up-to-date evidence-based practice guideline selected for the adaptation process was published in 2003, the search for other evidence was conducted for the period January 1, 2003 to August 5, 2009. Other evidence cited in bibliographies and brought forward during editing and review was collected as necessary.

DEVELOPMENT PROCESS

This guideline was developed by the Alberta Health Services – Cancer Corridor, Provincial Breast Tumour Group Guideline Panel using the ADAPTE process³ and some aspects of the Practice Guidelines Development Cycle.⁴ Panel members included four medical oncologists, one oncology pharmacist, one oncology nurse, and one methodologist. All panel members disclosed information on potential conflicts of interest before the development process started (none disclosed). The Alberta Health Services – Cancer Corridor, Provincial Breast Tumour Group Guideline Panel is editorially independent of the Alberta Health Services – Cancer Corridor.

Titles and abstracts (where possible) were assessed independently by two reviewers for relevance. A full copy of the publication or abstract (if only a conference proceeding) was obtained if either reviewer considered the literature to be relevant. These documents were assessed for inclusion and exclusion criteria as follows:

For practice guidelines:

1. Pertaining to individuals with metastatic (not locally advanced) breast cancer, anthracycline naïve or pre-treated.
2. Pertaining to palliative chemotherapy with reference to taxane or taxane-containing regimens (taxane = docetaxel, paclitaxel or nab-paclitaxel).
3. Published in the English language.
4. Recommendations clearly linked to the supporting literature. A comprehensive review of the existing, relevant evidence +/- meta-analyses of data where appropriate, is presented.

For other evidence:

1. Systematic reviews, randomized phase III clinical trials and randomized phase II clinical trials where data on time to progression, progression free survival, overall survival or quality of life (plus/minus data on response rates) was reported.
2. Pertaining to individuals with metastatic (not locally advanced) breast cancer, anthracycline naïve or pre-treated.

3. Pertaining to palliative chemotherapy where a taxane or taxane-containing regimen is compared with a non-taxane chemotherapy regimen or a different taxane chemotherapy regimen (taxane = docetaxel, paclitaxel or nab-paclitaxel).
4. Published in the English language.

Data synthesis

The Comprehensive Meta-analysis Package Version 2 was used for data pooling where deemed appropriate. Random effects models were used to obtain odds ratios or rate ratios.

External review

A draft report was distributed to other members of the Alberta Cancer Board Provincial Breast Tumour Group with representation from medical oncology, nursing and pharmacy for review. Reviewers were asked to read the guideline, complete a questionnaire (based on the questionnaire published in Elit et al)⁵ and provide other written comments.

TARGET POPULATION

This guideline is intended for use by chemotherapy-prescribing physicians, nurse practitioners, and pharmacists within Alberta Health Services – Cancer Care and the Alberta Health Services Pharmacy & Therapeutics Committee. The recommendations in this guideline are intended for individuals with metastatic breast cancer (anthracycline naïve or pre-treated/resistant) who are eligible for palliative chemotherapy (hormone refractory and/or rapidly progressive disease, adequate performance status and organ function).

RECOMMENDATIONS

Anthracycline Naïve Patients

1. If single agent chemotherapy is preferred, sequential anthracycline followed by taxane at the time of disease progression, or vice versa, are acceptable alternatives. A survival benefit has not been shown for starting with a taxane.
 - a. The following q3 weekly regimen is recommended: Docetaxel 100 mg/m² every 3 weeks.
 - b. Weekly taxane regimens are also reasonable options if minimization of risk for certain toxicities associated with docetaxel every 3 weeks is desired:
 - i. Docetaxel 35 - 40 mg/m² weekly x3 q4 weeks or weekly x6 q8 weeks.
 - ii. Paclitaxel 80 - 90 mg/m² weekly.
2. If combination chemotherapy is preferred, non-taxane/anthracycline and taxane/anthracycline regimens are acceptable alternatives. Taxane/anthracycline combinations are superior with respect to overall response and progression free survival, but have not been shown to improve overall survival. Additionally, an overall survival benefit for using a taxane/anthracycline combination over planned sequential single agent anthracycline followed by single agent taxane (before disease progression), or at the time of disease progression, has not been shown.

Regarding possible taxane/anthracycline regimens, doublet docetaxel or paclitaxel plus doxorubicin or epirubicin, and triplet docetaxel + doxorubicin + cyclophosphamide have been studied.

Anthracycline Pretreated/Resistant Patients

3. If single agent chemotherapy is preferred, a taxane regimen is recommended. Single agent taxanes appear to improve overall survival and response compared with non-taxane/non-anthracycline regimens.
 - a. The following q3 weekly regimen is recommended: Docetaxel 100 mg/m² every 3 weeks.
 - b. Weekly taxane regimens are also reasonable options if minimization of risk for certain toxicities associated with docetaxel every 3 weeks is desired:
 - i. Docetaxel 35 - 40 mg/m² weekly x3 q4 weeks or weekly x6 q8 weeks.
 - ii. Paclitaxel 80 - 90 mg/m² weekly.
4. If combination chemotherapy is preferred, taxane/non-anthracycline regimens are recommended. Taxane/non-anthracycline regimens are superior with respect to overall survival and response compared with single agent taxanes. Definitive survival data with taxane/non-anthracycline combinations compared with sequential single agent taxane followed by single agent non-taxane/non-anthracycline (at progression) is not available.

The following taxane/non-anthracycline regimens should be options:

- Docetaxel 75 mg/m² day 1 + capecitabine 1250 mg/m² BID days 1-14, q3 weeks.
- Docetaxel 75 mg/m² day 1 + gemcitabine 1000 mg/m² days 1 & 8, q3 weeks.
- Paclitaxel 175 mg/m² day 1 + gemcitabine 1250 mg/m² days 1 & 8, q3 weeks.

Anthracycline naïve or pretreated/resistant patients with paclitaxel or docetaxel intolerance

5. In the setting of an intolerance to paclitaxel or docetaxel (severe infusion reaction considered to be due to the vehicle of the taxanes or severe toxicity from previous administration of a taxane, including corticosteroid intolerance) the following single agent nab-paclitaxel regimens should be options where docetaxel or paclitaxel would otherwise be prescribed:
 - a. Nab-paclitaxel 260-300 mg/m² q3 weeks.
 - b. Nab-paclitaxel 100 - 150 mg/m² weekly x3 q4 weeks.

Anthracycline naïve or pretreated/resistant patients where HER2 is over-expressed

6. A taxane/trastuzumab combination is recommended up front. The addition of trastuzumab to a taxane has been shown to improve overall survival and response. Although the addition of trastuzumab to anthracycline regimens has also been shown to improve overall survival and response, the incidence of cardiac failure is unacceptable. The addition of carboplatin to taxane/trastuzumab combinations has not yet been shown to improve overall survival or consistently increase response.

The strongest evidence is for the following single agent taxane regimens plus weekly trastuzumab:

- Docetaxel 100 mg/m² q3 weeks.
- Paclitaxel 175 mg/m² q3 weeks.

DISCUSSION

Recommendation #1

Recommendations from existing guidelines

The CCO guideline recommends that patients who would be offered treatment with a single agent anthracycline could also be offered single agent docetaxel 100 mg/m² every 3 weeks.⁶ The NICE guideline does not give guidance with respect to single agent taxanes in anthracycline naïve patients.⁷

The BCCA and CECOG statements do not recommend a single agent taxane as initial therapy in a patient who is anthracycline naïve and who has metastatic breast cancer where HER2 is not over-expressed.^{9, 11} The NCCN does not differentiate anthracycline-naïve and pre-treated/resistant patients but suggests that a variety of single agent taxane regimens can be considered.¹⁰

Other evidence considered by this panel

Two meta-analyses have looked at the question of single agent taxanes versus single agent anthracyclines. The meta-analysis by Piccart et al pooled individual patient data (n = 919) from three randomized trials.¹² The hazard ratios for the taxane compared with the anthracycline were 1.01 (CI 0.97-1.26) for death and 1.19 (CI 1.04 – 1.36) for progression. Response rates were similar: 38% for the single agent taxane and 33% for the single agent anthracycline. Piccart et al¹² point out that there was significant heterogeneity with respect to the finding of improved progression free survival for the anthracycline compared with the taxane, and that this result was largely driven by the EORTC trial¹⁴ that compared paclitaxel 175 mg/m² every 3 weeks with doxorubicin 75 mg/m² every 3 weeks. The meta-analysis by Ghersi et al extracted data from published trials.¹³ In their analysis of the same three trials examined by Piccart et al,¹² similar results were found. Ghersi et al,¹³ however, looked at time to progression and did not find a difference between the taxane and anthracycline arms.

With respect to toxicities reported in the trials included in the meta-analyses, there was more sensory peripheral neuropathy in the taxane arms, but more febrile neutropenia, mucositis, nausea/vomiting, cardiac failure and toxic deaths in the anthracycline arms.¹⁴⁻¹⁶ Quality of life was analyzed in all three of the trials and there was no significant difference in the treatment groups with respect to physical, social and emotional functioning, and relationship with physician.¹⁴⁻¹⁶ In one of the trials, the toxicities of doxorubicin were offset by better symptom control.¹⁴

In the systematic reviews, the taxanes have not been compared in subgroup analyses. In the EORTC trial¹⁴ included in the meta-analyses, overall survival was inferior in the paclitaxel group (15.6 versus 18.3 months). One phase III trial randomized patients with anthracycline-pre-treated metastatic breast cancer to receive either docetaxel 100 mg/m² or paclitaxel 175 mg/m² every three weeks.¹⁷ Overall survival and time to progression was significantly better for the docetaxel arm at the expense of greater hematologic and non-hematologic toxicities.

The current panel agreed to include weekly taxane regimens as options. The evidence and rationale is largely drawn from the anthracycline pre-treated setting and is discussed under Recommendation #3.

Summary Statement

The CCO recommendation was adapted. The current panel acknowledged the results of 2 meta-analyses, the individual trial data included in the meta-analyses, one study of docetaxel versus paclitaxel q3 weekly (from the anthracycline pre-treated setting) in support of this recommendation. Including weekly taxane regimens as options was a de novo addition.

Recommendation #2

Recommendations from existing guidelines

The CCO guideline states docetaxel or paclitaxel in combination with doxorubicin can be considered as options.⁶ This is in contrast to the NICE guideline. The NICE guideline only evaluated data for docetaxel/anthracycline combinations. It recommends against such combination therapy for the reason that the effectiveness of sequential therapy was unknown.⁷

The NCCN statement lists docetaxel or paclitaxel in combination with doxorubicin as options.¹⁰ The BCCA and CECOG statements do not consider taxane/anthracycline combinations as options for anthracycline naïve patients.^{9,11}

Other evidence considered by this panel

The Piccart and Gherzi meta-analyses have also addressed the issue of taxane/anthracycline regimens versus non-taxane/anthracycline combination therapy.^{12,13} Piccart et al included individual patient data from 8 randomized trials. Docetaxel was the taxane in 4 of the trials, and paclitaxel was the taxane in the other 4 trials. The hazard ratios for the taxane/anthracycline regimen compared with the non-taxane/anthracycline combination were 0.95 (CI 0.88 - 1.03) for death and 0.92 (CI 0.85 – 0.99) for progression. Response rates significantly favoured the taxane/anthracycline regimens (57 versus 46%). The authors postulated that patients with worse prognosis (visceral or ER-negative disease) would benefit from taxane/anthracycline regimens but this hypothesis was not supported in subgroup analyses. Gherzi et al¹³ identified 9 potentially eligible studies for this question but only 3 studies had reported time-to-event data. Docetaxel was the taxane in 1 of the trials and paclitaxel was the taxane in the other 2 trials. The hazard ratios for the taxane/anthracycline regimens compared with the anthracycline combinations were 0.88 (CI 0.76 - 1.02) for death and 0.81 (CI 0.70 – 0.94) for progression. Five trials reported information on response. The odds ratio for response for the taxane/anthracycline regimens compared with the non-taxane/anthracycline combinations was 1.7 (CI 1.39 – 2.08). Four studies provided adequate data on toxicity. The taxane/anthracycline regimens were associated with significantly more leukopenia and neurotoxicity, but less nausea and vomiting. There was no difference in quality of life.

Again the systematic reviews have not compared the taxanes in subgroup analyses. One phase III trial compared docetaxel + doxorubicin with paclitaxel + doxorubicin has been published.¹⁸ Outcomes were not significantly different in terms of median overall survival (22.6 versus 24.1 months) and response (40 versus 42%). More peripheral neuropathy was observed in the paclitaxel group. There was no difference between the groups with respect to quality of life although some sub-scores favoured the docetaxel/doxorubicin group.

The current panel was also interested in the issue of taxane/anthracycline combinations versus sequencing of single agent anthracycline to single agent taxane. Two trials have examined planned

sequential anthracycline followed by taxane (before progression).^{19, 20} Alba et al randomized women with metastatic breast cancer to docetaxel 75 mg/m² + doxorubicin 50 mg/m² q3 weeks x6 or doxorubicin 75 mg/m² q3 weeks x3 followed by docetaxel 100 mg/m² q3 weeks x3.¹⁹ Women who were anthracycline pretreated and randomized to the combination arm, received 3 cycles of docetaxel + doxorubicin followed by 3 cycles of docetaxel 100 mg/m² q3 weeks. There were no significant differences for median overall survival (21.8 versus 22.3 months), median time to progression (9.2 versus 10.5 months) or overall response (51 versus 61%). Conte et al randomized participants to paclitaxel 200 mg/m² + epirubicin 90 mg/m² q3 weeks x8 or epirubicin 120 mg/m² q3 weeks x4 followed by paclitaxel 250 mg/m² q3 weeks x4.²⁰ There were no significant differences for median overall survival (20 versus 26 months), median progression free survival (10.8 versus 11 months) or overall response (58.5 versus 57.6%). Quality of life assessment suggested better functioning and symptom control for the combination arm. Sledge et al¹⁶ were able to examine the issue of taxane/anthracycline combination versus sequencing of single agents at progression. The three arms in this trial were as follows: paclitaxel 150 mg/m² + doxorubicin 50 mg/m² q3 weeks, paclitaxel 175 mg/m² q3 weeks followed by doxorubicin 60 mg/m² q3 weeks at progression, and doxorubicin 60 mg/m² q3 weeks followed by paclitaxel 175 mg/m² q3 weeks at progression.¹⁶ Just over half of participants in the single agent arms actually did cross over to the alternate single agent at progression. No significant differences were found for median overall survival between the combination arm and either sequential single agent arm (22 versus 22 versus 18.9 months). Time to failure was significantly longer and response rate was significantly higher for the combination arm compared to either sequential single agent arm.

Summary statement

The CCO recommendation was adapted. The current panel has acknowledged the results of 2 meta-analyses and one trial of docetaxel + doxorubicin versus paclitaxel + doxorubicin in support of this recommendation. Data on taxane/anthracycline combinations versus sequential single agents was also considered.

Recommendation #3

Recommendations from existing guidelines

The CCO⁶ and NICE⁷ guidelines both suggest that single agent docetaxel and paclitaxel are options. The CCO⁶ guideline takes the stance that the evidence for using docetaxel q3 weeks is more consistent and based on larger trials than the evidence for using paclitaxel q3 weeks. The CCO⁶ suggests reserving weekly taxane regimens (options not specified) for those who are elderly, have a low performance status or would prefer avoiding some of the toxicities associated with taxanes q3 weeks. The NICE guideline is non-directive in terms of which single agent regimens can be considered.

It was noted that the recent BCCA,⁹ NCCN¹⁰ and CECOG¹¹ statements also suggest that single agent taxanes are options. BCCA⁹ considers docetaxel q3 weeks and weekly, plus paclitaxel q3 weeks. NCCN¹⁰ considers both docetaxel and paclitaxel q3 weeks and weekly, plus nab-paclitaxel q3 weeks. CECOG¹¹ is non-directive in terms of which single agent regimens can be considered.

Other evidence considered by this panel

Compared with non-taxane/non-anthracycline regimens, single agent taxanes appear to improve overall survival and response. It was possible to pool overall survival data from 4 of the 5 studies outlined in Table 1.²¹⁻²⁵ Figure 1 shows that the odds ratio (OR) for death was 0.68 (95% CI 0.36 – 1.3) using a random effects model with a trend favouring the single agent taxane. Overall response rate data from all 5 studies in Table 1 was pooled. Figure 2 shows that the rate ratio for overall response was 2.23 (95% CI 1.43 – 3.49) using a random effects model, favouring the single agent taxane.

Paclitaxel 175 mg/m² q3 weeks was not included as an option by the panel. Firstly, three of the five studies included in Table 1 were of docetaxel versus a non-taxane/non-anthracycline regimen. The three docetaxel studies were much larger in comparison to the two paclitaxel studies. Secondly, one randomized phase III trial of docetaxel 100 mg/m² versus paclitaxel 175 mg/m² both q3 weeks showed significantly longer median survival in the docetaxel group (15.4 versus 12.7 months) and significantly longer median time to progression (5.7 versus 3.6 months) [17]. The benefit of docetaxel was however, at the cost of more hematologic and non-hematologic toxicity: febrile neutropenia (14.9 versus 1.8%), stomatitis/mucositis (10.8 versus 0%), nausea/vomiting (8.6 versus 2.7%) and sensory peripheral neuropathy (7.2 versus 4.1%). Quality of life scores were not significantly different.

Evidence for the effectiveness, and perhaps more favourable toxicity profiles, associated with weekly taxane regimens is mounting.

Weekly docetaxel: One phase III trial compared docetaxel 35-40 mg/m² weekly x3 q4 weeks with docetaxel 75-100 mg/m² q3 weeks.^[26, abstract] There was no significant difference with respect to median overall survival (18.6 versus 18.3 months) or median progression free survival (5.5 versus 5.7 months). Overall response, however, in the weekly group was lower (20.3 versus 35.6%). In the weekly group, there was less febrile neutropenia (3 versus 10%), myalgias (3 versus 27%), and fatigue (13.5 versus 25%). A randomized phase II trial of docetaxel 40 mg/m² weekly x6 q8 weeks versus docetaxel 100 mg/m² q3 weeks has been published.²⁷ This study suggested a longer median overall survival for the weekly group (29.1 versus 20.1 months) but similar median time to progression (5.7 versus 5.3 months) and overall response rates (34.1 versus 33.3%). However, there appeared to be less febrile neutropenia (4.9 versus 19.5%), nausea/vomiting (12.2 versus 14.6%), stomatitis/mucositis (7.3 versus 17.1%) and sensory peripheral neuropathy (2.4 versus 17.1%). In this study, there appeared to be slightly more asthenia/fatigue with the weekly compared with the q3 weekly regimen (14.6 versus 12.2%), and more anorexia (4.9 versus 0%). Where reported, phase II studies of weekly docetaxel suggest quite a variable incidence of asthenia/fatigue ranging from 7 – 47% as summarized in the CCO⁶ guideline.

Weekly paclitaxel: Two randomized trials have compared weekly versus q3 weekly paclitaxel. Seidman et al²⁸ compared paclitaxel 80 mg/m² weekly versus paclitaxel 175 mg/m² q3 weeks.^[28, abstract] Of note, participants with HER2 negative disease were also randomized to receive trastuzumab or not, and all participants with HER2 positive disease received trastuzumab. For the entire study population, there was a trend to longer median overall survival in the weekly group (24 versus 16 months) but this result was not statistically significant. Time to progression for the weekly regimen was significantly longer (9 versus 5 months), and overall response was significantly higher (40 versus 28%). The incidence of febrile neutropenia (3.0 versus 4.0%), nausea/vomiting (both arms < 5%), and stomatitis/mucositis (both arms < 5%) was similar for the treatment groups. These rates for these important toxicities are acceptably low. The incidence of sensory peripheral neuropathy was, however, higher in the weekly group (23 versus 12%). In cases where HER2 was not over-expressed, global quality of life and cancer symptom control

were significantly better in the weekly group [29, abstract]. Verrill et al.³⁰ compared paclitaxel 90 mg/m² weekly x12 and paclitaxel 175 mg/m² q3 weeks x6.^[30, abstract] No difference was detected with respect to overall survival. There was a trend for longer median time to progression in the weekly group (6 versus 5.5 months) and response rate was significantly higher in the weekly group (43 versus 27%). Toxicity profiles of the two arms were similar.

Data from the neoadjuvant and adjuvant settings also suggests that weekly paclitaxel may be more effective than the q3 weekly regimen. In the neoadjuvant setting, Green et al. examined weekly versus q3weekly paclitaxel regimens.³¹ Results for the primary outcome (clinical complete response) were not statistically different. For the weekly regimen, pathologic complete response was significantly better (28.2 vs. 15.7%), as was the breast conservation rate (47 vs. 38%). Again neurotoxicity was worse with the weekly regimen. In women with resected high risk node negative or node positive breast cancer, ECOG 1199 explored various taxane schedules (weekly versus q3weekly paclitaxel and docetaxel) following a backbone of adriamycin and cyclophosphamide.^[32, abstract] No disease free survival differences emerged in the overall study population. In an exploratory analysis of patients with ER negative disease, both the weekly paclitaxel and q3weekly docetaxel arms proved superior to q3weekly paclitaxel in terms of disease free survival (81.5%/81.2% vs. 76.9% respectively). The weekly paclitaxel regimen was superior to q3 weekly paclitaxel in terms of overall survival (89.7% vs. 86.5%). This study also demonstrated a favourable safety profile for weekly paclitaxel compared with docetaxel every 3 weeks.

Summary statement

The CCO and NICE recommendations for use of single agent taxanes were adapted. More current evidence in support of recommending docetaxel over paclitaxel q3 weeks, and further evidence in support of weekly taxane regimens was available.

Recommendation #4

Recommendations from existing guidelines

The CCO guideline includes docetaxel + capecitabine as an option in younger patients with good performance status [6]. Assessment of the other regimens by the CCO guideline examined, and all taxane/non-anthracycline regimens by NICE, was not possible due to lack of data at the time.

The CCO has, however, updated a recent guideline specifically on the role of gemcitabine in the management of metastatic breast cancer.³³ In this guideline they conclude that docetaxel + gemcitabine can be considered as an alternative to docetaxel + capecitabine based on a trial that the current panel has also examined. This guideline also concludes that paclitaxel + gemcitabine is an option but the clinical relevance questionable given that docetaxel has been the preferred taxane for use in metastatic breast cancer in Ontario.

It was noted that the BCCA,⁹ NCCN¹⁰ and CECOG¹¹ statements also include taxane/non-anthracycline regimens as options. BCCA considers docetaxel + capecitabine or paclitaxel + gemcitabine in the setting of an aggressive relapse in a fit patient. The NCCN considers the same two options. CECOG states that a taxane in combination with either capecitabine or gemcitabine can be considered.

Other evidence considered by this panel

In a large phase III trial of docetaxel + capecitabine versus docetaxel alone, the combination regimen was found to be superior with respect to several endpoints: median overall survival (14.5 versus 11.5 months), median time to progression (6.1 versus 4.2 months) and overall response rate (42 versus 30%).³⁴ The incidence of febrile neutropenia was similar (13 versus 16%). As expected, the combination regimen was associated with higher incidence of capecitabine-related toxicities. No differences between the arms were found with respect to quality of life.

In a large phase III trial of paclitaxel + gemcitabine versus paclitaxel alone, the combination regimen was found to be superior in terms of median overall survival (18.5 versus 15.8 months) and median time to progression (5.2 versus 2.9 months).^[35, abstract] With the combination regimen, overall response rate appeared to be superior (40.8 versus 22.1%) but this finding was not statistically significant. Clinically relevant reported toxicities appeared to be similar between the two groups: febrile neutropenia (5 versus 1%), nausea/vomiting (2 versus 2%) and sensory peripheral neuropathy (5 versus 4%). Global quality of life was significantly better for the combination arm.

One phase III study has compared docetaxel + gemcitabine versus docetaxel + capecitabine.^[36, abstract] Overall survival data has not been presented but no differences were observed with respect to median progression free survival (35 versus 35 weeks) or overall response rate (32 versus 32%). There was a trend for less febrile neutropenia in the docetaxel + gemcitabine arm (8 versus 13%). As expected, there was significantly less mucositis, diarrhea and hand-foot syndrome in the docetaxel + gemcitabine arm. One randomized phase II study suggests similar outcomes for docetaxel + gemcitabine, paclitaxel q3 weeks + gemcitabine and paclitaxel weekly (days 1 + 8) + gemcitabine: median time to progression (7.4 versus 7.5 versus 7.0 months) and overall response rate (50.3 versus 48.6 versus 52.3%).³⁷ Overall survival data has not yet been reported. The incidence of febrile neutropenia appeared to be highest in the docetaxel + gemcitabine group (11.8 versus 0 versus 4.4%). Hence, docetaxel + gemcitabine cannot yet be recommended over docetaxel + capecitabine or paclitaxel + gemcitabine with respect to effectiveness. Docetaxel + gemcitabine could be offered in place of docetaxel + capecitabine if there was a preference to avoid capecitabine-related toxicities. Paclitaxel weekly + gemcitabine cannot yet be recommended over paclitaxel q3 weeks + gemcitabine. Docetaxel + capecitabine have not directly been compared with paclitaxel + gemcitabine.

In the docetaxel + capecitabine³⁴ versus docetaxel, and the paclitaxel + gemcitabine versus paclitaxel^[35, abstract] studies, cross-over from the single agent taxane to the single agent non-taxane/non-anthracycline at the time of progression was not planned. One randomized phase II trial compared docetaxel 75 mg/m² + capecitabine 1250 mg/m² BID days 1-14, q3 weeks with docetaxel 100 mg/m² q3 weeks followed by capecitabine 1250 mg/m² BID days 1-14 q3 weeks at the time of disease progression^[35, abstract] Median time to progression was longer in the combination group (9.3 versus 7.7 months), and overall response rate was higher (68 versus 40%). No difference for median overall survival was found (22 versus 19 months).

Overall response rate data from the docetaxel + capecitabine versus docetaxel,³⁴ paclitaxel + gemcitabine versus paclitaxel^[35, abstract] and the docetaxel + capecitabine versus sequential docetaxel to capecitabine^[38, abstract] studies, as summarized in Table 2, was pooled. Figure 3 shows that the rate ratio for overall response was 1.69 (95% CI 1.26 – 2.11) using a random effects model, favouring taxane/non-anthracycline combinations. Given the heterogeneous trial designs (i.e. whether or not there was planned cross-over in the single agent arms), survival data was not pooled.

Summary statement

The CCO recommendation for docetaxel + capecitabine was adapted. More recent evidence for docetaxel + gemcitabine and paclitaxel + gemcitabine was considered by the current panel in order to create an updated recommendation on the role of taxane/non-anthracycline regimens.

Recommendation # 5

Recommendations from existing guidelines

The CCO guideline does not make recommendations regarding nab-paclitaxel due to lack of data available at the time of guideline publication. They did however publish a report specifically on the role of nab-paclitaxel in the treatment of metastatic breast cancer.³⁹ They conclude that women with metastatic breast cancer who are eligible for single agent paclitaxel could be offered nab-paclitaxel as an alternative. Specific regimens were not recommended.

The updated NCCN guideline version 1.2010 lists nab-paclitaxel as one of the preferred chemotherapy regimens for recurrent or metastatic breast cancer at 100 mg/m² or 150 mg/m² on D1, 8, and 15 of a 28 day cycle, or 260 mg/m² q3 weeks.¹⁰

The CECOG and NICE guidelines do not address the role of nab-paclitaxel.

BCCA has produced a protocol summary for palliative therapy for metastatic breast cancer using nab-paclitaxel at a dose of 260 mg/m² q3 weeks in patients with an intolerance to taxane or absolute contraindication to steroids, or a documented ethanol allergy.

Other evidence considered by this panel

The recommendation for the use of nab-paclitaxel has been updated to reflect the recommendations of the Alberta Health Services Outpatient Cancer Drug Benefit Program. Nab-paclitaxel should be available for patients who have had severe acute infusion reactions with paclitaxel or docetaxel (considered to be due to the vehicle of the taxanes), or in patients who have experienced severe toxicity from previous administration, including toxicity related to both the taxane and the premedications. Without corticosteroid or antihistamine pre-medication, nab-paclitaxel is associated with an incidence of hypersensitivity reactions under 1%.⁴⁰ In the absence of definitive data showing improved overall survival or significantly reduced toxicities for nab-paclitaxel in comparison to any of the solvent-based taxane regimens, the panel felt that it should not be offered as a routine, single-agent option.

One randomized phase II study has now been updated and published.^[41] This study compared three nab-paclitaxel arms (300 mg/m² q3 weeks, 100 mg/m² weekly x3 q4 weeks and 150 mg/m² weekly x3 q4 weeks) and one docetaxel arm (100 mg/m² q3 weeks).^[41] nab-paclitaxel 150 mg/m² weekly showed significantly longer PFS over the docetaxel arm by both independent radiologist and investigator assessment (12.9 vs 7.5 months, and 14.6 vs 7.8 months respectively). Both 150 mg/m² and 100 mg/m² demonstrated a higher ORR than docetaxel but this did not reach statistical significance. There was no statistical difference in ORR between nab-paclitaxel 300 mg/m² q 3 weeks versus docetaxel. The incidence of febrile neutropenia was 1% in all three nab-paclitaxel arms and 8% in the docetaxel arm. The incidence of sensory peripheral neuropathy was comparable in all arms but median time to improvement for grade 3 neuropathy was 19 to 22 days for the nab-paclitaxel arms and 37 days for the docetaxel arm.

Fatigue was more common in the docetaxel arm. In one phase III trial of nab-paclitaxel 260 mg/m² versus paclitaxel 175 mg/m², median time to progression was significantly longer in the nab-paclitaxel group (23 versus 16.9 months) and there was a trend for longer median overall survival in the nab-paclitaxel group (65 versus 55.7 weeks).⁴⁰ The incidence of sensory peripheral neuropathy in the nab-paclitaxel group was 10% and in the paclitaxel group was 2%.

Summary statement

The current panel largely considered the relevant trials of nab-paclitaxel versus the other taxanes in order to create a de novo recommendation.

Recommendation #6

Recommendations from existing guidelines

The CCO and NICE guidelines examined did not specifically make recommendations for patients with metastatic breast cancer where HER2 is over-expressed.

The CCO has published a separate guideline on the role of trastuzumab in the treatment of women with HER2 over-expressing metastatic breast cancer.⁴² Either docetaxel or paclitaxel every three weeks, plus trastuzumab, is recommended as first-line therapy.

It was noted that the BCCA and NCCN statements recommended the addition of trastuzumab to either single agent docetaxel or paclitaxel, or to paclitaxel + carboplatin in this setting.^{9, 10} The CECOG statement recommended the addition of trastuzumab to a non-anthracycline regimen, which could include a taxane.¹¹

Other evidence considered by this panel

A randomized phase II study compared docetaxel 100 mg/m² q3 weeks + weekly trastuzumab with docetaxel alone.⁴³ Over half of participants had been exposed to an anthracycline in the adjuvant setting. The addition of trastuzumab improved median time to progression (11.7 versus 6.1 months), median overall survival (31.2 versus 22.7 months), and overall response rate (61 versus 34%). A large phase III study compared paclitaxel 175 mg/m² q3 weeks + weekly trastuzumab with paclitaxel alone in the anthracycline pre-treated setting, and doxorubicin + cyclophosphamide q3 weeks + weekly trastuzumab with doxorubicin + cyclophosphamide alone in the anthracycline naïve setting.⁴⁴ The addition of trastuzumab to paclitaxel improved median time to progression (6.9 versus 3.0 months), median overall survival (22.1 versus 18.4 months), overall response rate (49 versus 17%). The addition of trastuzumab to doxorubicin + cyclophosphamide also improved median overall survival (26.8 versus 21.4 months) but the cardiac event rate was unacceptably high (28 versus 9.6%). Finally, a randomized phase II study examined weekly paclitaxel 80 mg/m² plus or minus weekly trastuzumab.⁴⁵ Women with advanced breast cancer and 2+ or 3+ over-expression of HER2 by IHC were included. For the subgroup with IHC 3+ (n = 84/124), median time to progression was significantly longer (369 versus 272 days) and response significantly higher (75 versus 56.9%) for those who received paclitaxel plus trastuzumab.

The addition of carboplatin to taxane/trastuzumab doublets has not yet been shown to improve overall survival, or consistently improve overall response rates. One phase III trial compared docetaxel/trastuzumab + carboplatin with docetaxel/trastuzumab.^[46, abstract] Median time to progression was similar (10.4 versus 11.1 months), as was overall response rate (73 versus 73%). Median overall survival

was 41.7 months for the triplet arm but had not yet been reached in the doublet arm. One phase III trial compared paclitaxel/trastuzumab + carboplatin with paclitaxel/trastuzumab.⁴⁷ Median progression free survival was longer with the triplet arm (10.7 versus 7.1 months), and overall response rate higher (52 versus 36%). No difference was found for median overall survival (35.7 versus 32.2 months).

A Cochrane systematic review examining the efficacy of trastuzumab + other drug therapy, or trastuzumab alone in HER2 positive metastatic breast cancer is awaited.

Summary statement

The current panel largely considered the relevant trials of taxane regimens plus/minus trastuzumab in metastatic breast cancer where HER2 is over-expressed to create a de novo recommendation.

Limitations

The major limitation encountered in using the ADATPE process was that the two evidence-based guidelines selected, NICE⁷ and CCO⁶ were released in 2001 and 2003 respectively. A significant amount of more current evidence was reviewed to ensure up-to-date recommendations. In some instances, this required de novo recommendation development.

Implications for Alberta Health Services

Most regimens recommended or listed as options in this guideline were available through the Alberta Health Services – Cancer Care Drug Benefit Program as of July 2007 when the draft report was being sent for external review. Docetaxel and gemcitabine would require a formulary addition request to the Provincial Pharmacy and Therapeutics Committee (which takes into account cost implications). Nab-paclitaxel had recently been added to the Drug Benefit Program. In contrast to this guideline, criteria for use of nab-paclitaxel in the Drug Benefit Program includes: “demonstrated intolerance to solvent-based taxanes.”

IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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APPENDIX
Table 1: Single agent taxane vs. non-taxane/non-anthracycline regimens

Author, year	Phase	Treatment arms	N	mPFS (months)	mTTP (months)	mOS (months)	ORR (%)
Nabholtz, 1999	III	Docetaxel	203	16**	19**	11.4**	30**
		Mitomycin/vinblastine	189	10	11	8.7	11.6
Sjostrom, 1999	III	Docetaxel	143	NR	6.3**	10.4	42**
		Methotrexate/5FU	139	NR	3.0	11	21
Bonneterre, 1997	III	Docetaxel	86	NR	6.5	16	43
		Vinorelbine/5FU	90	NR	5.1	15	38.8
Dieras, 1995	II	Paclitaxel	36	9.1	3.5*	12.7	15
		Mitomycin	36	6.7	1.6	8.4	5
Talbot, 2002	II	Paclitaxel	19	NR	3.1	9.4	36
		Capecitabine	22	NR	3.0	7.6	26

* *p-value <0.05*

** *p-value <0.01*

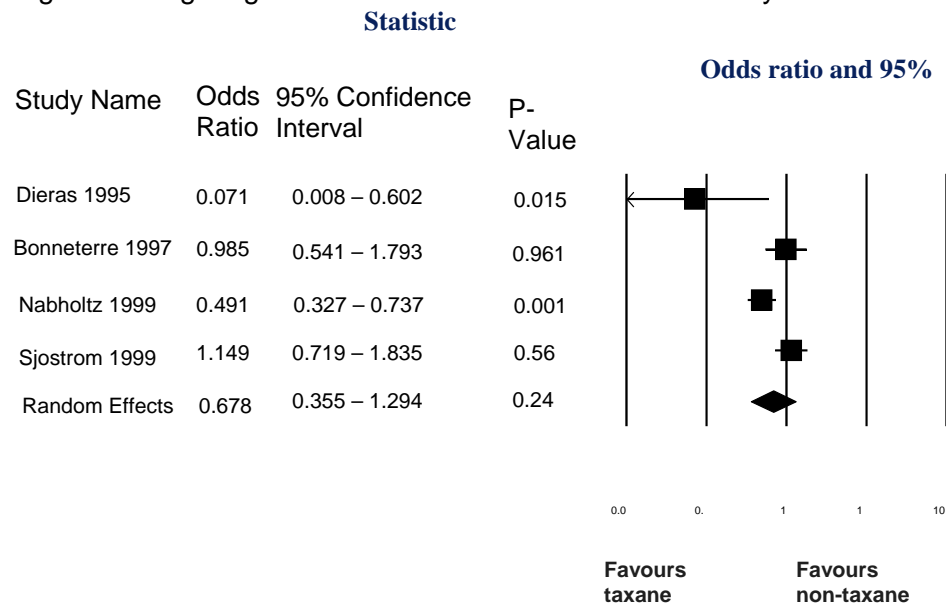
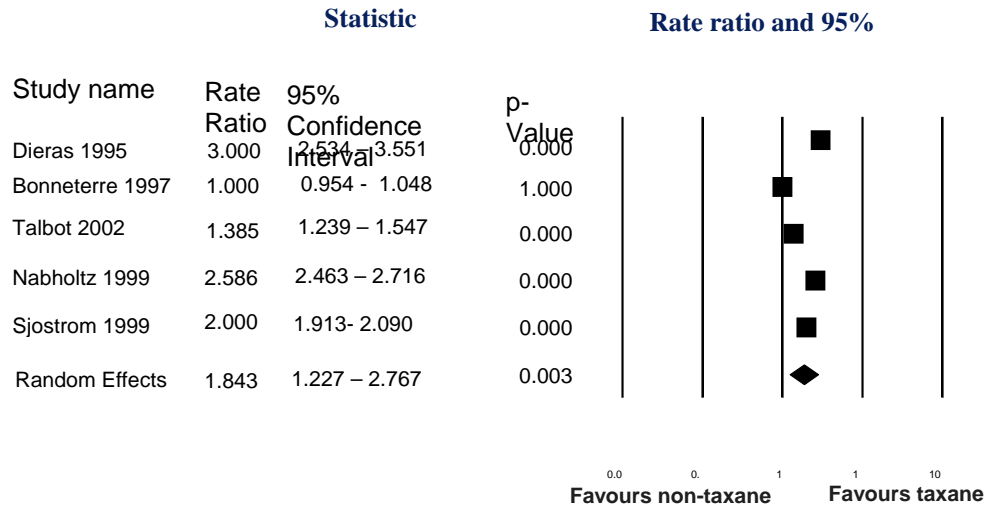
Figure 1: Single agent taxane vs. non-taxane/non-anthracycline: meta-analysis of overall survival


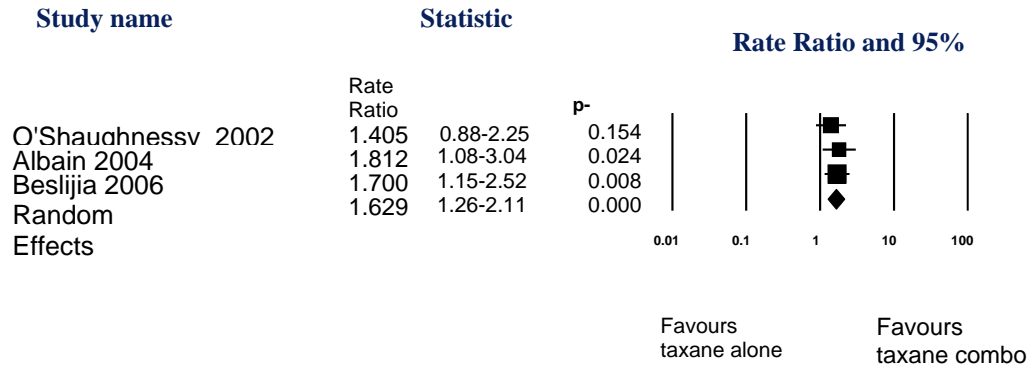
Figure 2: Single agent taxane vs. non-taxane/non-anthracycline: meta-analysis of overall response

Table 2: Taxane/non-anthracycline regimen vs. single agent taxane

Author, year	Phase	Treatment arms	N	mPFS (months)	mTTP (months)	mOS (months)	ORR (%)
O'Shaughnessy, 2002	III	Docetaxel + capecitabine	255	NR	6.1**	14.5*	42**
		Docetaxel	256	NR	4.2	11.5	30
Albain, 2004 [abstract]	III	Paclitaxel + gemcitabine	267	NR	5.2*	18.5*	40.8
		Paclitaxel	262	NR	2.9	15.8	22.1
Beslija, 2006 [abstract]	II	Docetaxel + capecitabine	50	NR	9.3*	22	68**
		Docetaxel to capecitabine at progression	50	NR	7.7	19	40

* *p-value <0.05*

** *p-value <0.01*

Figure 3: Taxane/non-anthracycline regimen vs. single agent taxane: meta-analysis of overall response



APPENDIX: External Review Questionnaire

Question	Response	Response Frequency
The guideline panel is credible.	Agree	1
	Strongly Agree	4
The guideline is unlikely to be influenced by vested interests.	Agree	2
	Strongly Agree	3
Rationale for developing the guideline is clear.	Agree	2
	Strongly Agree	3
There is a need for a provincial guideline on this topic.	Agree	2
	Strongly Agree	3
The literature search is relevant and complete.	Agree	1
	Strongly Agree	4
I agree with the methodology used for summarizing the evidence.	Agree	1
	Strongly Agree	4
The results are interpreted according to my understanding of data.	Agree	2
	Strongly Agree	3
The draft recommendations are clear.	Agree	1
	Strongly Agree	4
The draft recommendations are reasonable.	Agree	2
	Strongly Agree	3
When applied, the recommendations will produce more benefit than harm for patients.	Agree	1
	Strongly Agree	4
The recommendations are suitable for the intended patients.	Agree	2
	Strongly Agree	3
The draft report presents options will be acceptable to patients.	Agree	1
	Strongly Agree	4
When applied, the recommendations would result in better use of resources than current usual practice.	Neutral	1
	Agree	2
	Strongly Agree	2
Following the recommendations would not require reorganization of services in my practice setting.	Agree	2
	Strongly Agree	3
The draft recommendations are likely to be supported by most of my colleagues.	Agree	3
	Strongly Agree	2
The draft report should be approved as practice guideline.	Agree	3
	Strongly Agree	2