OPTIMAL USE OF TAXANES IN METASTATIC BREAST CANCER (MBC)

Effective Date: September, 2013

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

An estimated 186,400 new cases of cancer and 75,700 deaths from cancer were projected to occur in Canada in 2012. Breast cancer is the most commonly diagnosed cancer in women, representing 26% of all newly diagnosed cancers and ranking second in mortality, at 14%. In 2012, 22,700 new cases were expected. Approximately 30% of women initially diagnosed with earlier stages of breast cancer eventually develop recurrent or metastatic disease. Therapy of MBC has improved over the last decades probably due to sequential systemic chemotherapy treatment. Anthracyline and taxane-based treatment regimens are standard first-line therapies for MBC. The goals of treatment in MBC include prolonged survival, symptom control and maintenance of quality of life.

The literature on taxanes and breast cancer has been growing exponentially since the mid-1990s. Thus, in the absence of an evidence-based provincial guideline regional variability in taxane prescription is expected. The objective of this guideline is to promote evidence-based consistency in practice, and hence, equitable access for women with MBC to appropriate therapies.

GUIDELINE QUESTIONS

What taxanes regimens can be offered to the following types of women with MBC?

- Anthracycline-naïve, tumours do not overexpress human epidermal growth factor receptor (HER)2
- Anthracycline-pre-treated/resistant, tumours do not overexpress HER2
- Anthracycline naïve or pretreated/resistant, tumours overexpress HER2
- Anthracycline naïve or pretreated/resistant AND paclitaxel or docetaxel intolerance

DEVELOPMENT AND REVISION HISTORY

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 Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in December, 2007 using the ADAPTE process and some aspects of the Practice Guidelines Development Cycle. 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) or rate ratios. This guideline was revised in December, 2009 and September, 2013.

SEARCH STRATEGY

Original search strategy. A systematic search for relevant clinical practice guidelines and peer-reviewed medical literature was conducted using prominent developer’s websites and databases, MEDLINE, PubMed, CINAHL, EMBASE, CancerLit, Cochrane Database of Systematic Reviews, Physician Data Query, as well as conference proceedings from the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium. Search terms included: Taxane* Exp., Taxanes Exp.,

Updated search strategy. A systematic search for relevant clinical practice guidelines published since 2009 was conducted using prominent developer’s websites, National Guideline Clearinghouse and the Standards and Guidelines Evidence (SAGE) database. MEDLINE, PubMed, and Cochrane Database of Systematic Reviews was used to identify peer-reviewed literature using similar search terms listed above, for the period 2009 to May 8, 2013.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with MBC who are anthracycline naïve or pre-treated/resistant.

RECOMMENDATIONS

The following taxanes regimens are recommend for women with

1. Anthracycline naïve, tumours do not overexpress HER2

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.

- An every 3 week (q3w) regimen of docetaxel 100 mg/m² is recommended
- The following weekly taxane regimens are reasonable options if reduced risk of toxicities is desired:
  - Docetaxel 35 - 40 mg/m² weekly, x3 q4w or weekly, x6 q8w
  - Paclitaxel 80 - 90 mg/m² weekly

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 (PFS), but have not been shown to improve overall survival (OS). Additionally, an OS 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.

2. Anthracycline pretreated/resistant, tumours do not overexpress HER2

If single-agent chemotherapy is preferred, a taxane regimen is recommended. Single-agent taxanes appear to improve OS and response compared with non-taxane/non-anthracycline regimens.

- An every 3 week regimen of docetaxel 100 mg/m² is recommended
- The following weekly taxane regimens are reasonable options if reduced risk of toxicities is desired:
  - Docetaxel 35 - 40 mg/m² weekly, x3 q4w or weekly, x6 q8w
  - Paclitaxel 80 - 90 mg/m² weekly
If combination chemotherapy is preferred, taxane/non-anthracycline regimens are recommended. Taxane/non-anthracycline regimens are superior with respect to OS 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, twice daily (b.i.d), for 14 consecutive days, q3w
  - Docetaxel 75 mg/m² day 1 + gemcitabine 1000 mg/m² days 1 and 8, q3w
  - Paclitaxel 175 mg/m² day 1 + gemcitabine 1250 mg/m² days 1 and 8, q3w

3. Anthracycline naïve or pretreated/resistant with HER2 over-expression

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

The strongest evidence is for the following single-agent taxane regimens plus weekly trastuzumab:
- Docetaxel 100 mg/m² q3w
- Paclitaxel 175 mg/m² q3w

4. Anthracycline naïve or pretreated/resistant AND paclitaxel or docetaxel intolerance

For patients with intolerance to paclitaxel or docetaxel caused by a severe infusion reaction or severe toxicity from previous administration of a taxane, including corticosteroid intolerance, the following single-agent nab-paclitaxel regimens should be options:
- Nab-paclitaxel 260 - 300 mg/m² q3w
- Nab-paclitaxel 100 - 150 mg/m² weekly, x3 q4w

DISCUSSION

For women with MBC, if single-agent chemotherapy is preferred, what taxane regimens can be offered if she is anthracycline-naïve and her tumour does not overexpress HER2?

Guidelines: The now archived Cancer Care Ontario (CCO) guideline about the role of taxanes in the management of MBC states that in anthracycline-naïve patients who would ordinarily be offered treatment with a single-agent anthracycline (doxorubicin or epirubicin) or an anthracycline in a standard combination, treatment with single-agent docetaxel 100 mg/m² over one hour q3w is a reasonable option. The National Comprehensive Cancer Network (NCCN) guideline lists paclitaxel (175 mg/m² [intravenous] IV day 1, q21d or 80 mg/m² IV day 1 weekly) as the preferred single agent taxane for MBC, albeit not specifically stated for women who are anthracycline-naïve.

Evidence: 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 from three randomized trials. The hazard ratios for the taxane compared with the anthracycline were 1.01 (Confidence interval
[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. The authors point highlight that there was significant heterogeneity with respect to the finding of improved PFS for the anthracycline compared with the taxane, and that this result was largely driven by the European Organization for Research and Treatment of Cancer (EORTC) trial\(^8\) that compared paclitaxel 175 mg/m\(^2\) q3w with doxorubicin 75 mg/m\(^2\) q3w.\(^8\) The meta-analysis by Ghersi et al. extracted data from published trials.\(^9\) Similar results were found in their analysis of the same three trials examined by Piccart et al.,\(^6\). However, Ghersi et al. looked at time to progression (TTP) and did not find a difference between the taxane and anthracycline arms.

With respect to toxicities reported in the trials included in the two 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.\(^9,11,12\) Quality of life was analyzed in all three of the trials and there was no significant difference in the treatment arms with respect to physical, social and emotional functioning, or relationship with physician.\(^9,11,12\) In one of the trials, the toxicities of doxorubicin were offset by better symptom control.\(^9\)

In the systematic reviews, the taxanes have not been compared in subgroup analyses. In the EORTC trial included in the meta-analyses, OS was inferior in the paclitaxel arm (15.6 v18.3 months).\(^9\) In a phase III trial in which patients with anthracycline-pre-treated MBC were randomized to receive docetaxel (100 mg/m\(^2\)) or paclitaxel (175 mg/m\(^2\)) q3w, OS and TTP were significantly better for the docetaxel arm at the expense of greater hematologic and non-hematologic toxicities.\(^13\)

**For women with MBC, if combination chemotherapy is preferred, what taxane regimens can be offered if she is anthracycline-naïve and her tumour does not overexpress HER2?**

**Guidelines:** The now archived CCO guideline about the role of taxanes in the management of MBC states that in anthracycline-naïve patients who would ordinarily be offered treatment with a single-agent anthracycline (doxorubicin or epirubicin) or an anthracycline in a standard combination, treatment with docetaxel or paclitaxel in combination with doxorubicin are reasonable options.\(^6\) The NCCN guidelines list docetaxel (75 mg/m\(^2\) IV day 1) plus capcitabine (950 mg/m\(^2\) PO BID day 1,2,3 and 4) cycled q21d, gemcitabine (1250 mg/m\(^2\) IV days 1 and 8 [following paclitaxel on day 1]) plus paclitaxel (175 mg/m\(^2\) IV day 1), and paclitaxel (90 mg/m\(^2\) by 1 hour IV day 1, 8 and 15) plus bevacizumab (10 mg/kg IV day 1 and 15) cycled q28d, as possible chemotherapy combinations for MBC, albeit not specifically stated for women who are anthracycline-naïve.\(^7\)

**Evidence:** The Piccart et al. and Ghersi et al. meta-analyses also addressed the issue of taxane/anthracycline regimens versus non-taxane/anthracycline combination therapy.\(^8,10\) Piccart et al. included individual patient data from eight randomized trials. Docetaxel was used as the taxane in four of the trials, while paclitaxel used in the other four 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% vs 46%). The authors hypothesized that patients with worse prognosis (visceral or estrogen-receptor [ER] negative disease) would benefit from taxane/anthracycline regimens but this hypothesis was not supported in subgroup analyses. Ghersi et al. identified nine potentially eligible studies to address this question, but only three studies reported time-to-event data. Docetaxel was used as the taxane in one of the trials, while paclitaxel was used in the other two 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.

The systematic reviews have not compared the taxanes in subgroup analyses. In a phase III trial comparing docetaxel plus doxorubicin with paclitaxel plus doxorubicin, outcomes were not significantly different in terms of median OS (22.6 v 24.1 months) and response (40 v 42%). However, more peripheral neuropathy was observed in the paclitaxel arm. There was no difference between the arms with respect to quality of life although some sub-scores favoured the docetaxel plus doxorubicin arm.

Two trials have examined planned sequential anthracycline followed by taxane (before progression). Alba et al. randomized women with MBC to docetaxel (75 mg/m²) plus doxorubicin (50 mg/m²) q3w x6 or doxorubicin (75 mg/m²) q3w x3 followed by docetaxel (100 mg/m²) q3w x3. Women who were anthracycline pretreated and randomized to the combination arm, received 3 cycles of docetaxel plus doxorubicin followed by 3 cycles of docetaxel (100 mg/m²) q3w. There were no significant differences for median OS (21.8 v 22.3 months), median TTP (9.2 v 10.5 months) or overall response (51% v 61%). Conte et al. randomized participants to paclitaxel (200 mg/m²) plus epirubicin (90 mg/m²) q3w x8 or epirubicin (120 mg/m²) q3w x4 followed by paclitaxel (250 mg/m²) q3w x4. There were no significant differences for median OS (20 v 26 months), median PFS (10.8 v 11 months) or overall response (58.5% v 57.6%). Quality of life assessment suggested better functioning and symptom control for the combination arm.

Sledge et al. examined the issue of taxane/anthracycline combination versus sequencing of single-agents at progression. The three arms in this trial included paclitaxel (150 mg/m²) plus doxorubicin (50 mg/m²) q3w, paclitaxel (175 mg/m²) q3w followed by doxorubicin (60 mg/m²) q3w at progression, and doxorubicin (65 mg/m²) q3w followed by paclitaxel (175 mg/m²) q3w at progression. Just over half of participants in the single-agent arms crossed over to the alternate single-agent at progression. No significant differences were found for median OS between the combination arm and either of the sequential single-agent arms (22 v 22 v 18.9 months). Time to failure was significantly longer and response rate was significantly higher for the combination arm compared to either of the sequential single-agent arms.

For women with MBC, if single-agent chemotherapy is preferred, what taxane regimen can be offered if she is anthracycline pretreated/resistant and her tumour does not overexpress HER2?

Guidelines: The now archived CCO guideline about the role of taxanes in the management of MBC states that either docetaxel (100 mg/m² over one hour q3w) or paclitaxel (175 mg/m² over 3 hours q3w) may be considered as a treatment option after failure of prior anthracycline treatment or in women whose disease is resistant to anthracyclines. NICE also recommends first-line treatment with single-agent docetaxel for patients with advanced breast cancer who are not suitable for anthracycline. Again, the NCCN guideline lists paclitaxel as the preferred single agent taxanes for MBC, albeit not specifically stated for women who are anthracycline pretreated/resistant.

Evidence: Compared with non-taxane/non-anthracycline regimens, single-agent taxanes appear to improve OS and response. Table 1 in the appendix shows key outcomes for clinical trials comparing single-agent taxanes to non-taxane/non-anthracycline regimens. Three of the five studies compared docetaxel to a non-taxane/non-anthracycline regimen, while the other two studies used paclitaxel as the comparator. The three docetaxel studies were much larger in comparison to the two paclitaxel studies. In
addition, a randomized phase III trial of docetaxel (100 mg/m²) versus paclitaxel (175 mg/m²) q3w showed significantly longer median survival in the docetaxel arm (15.4 v 12.7 months) and significantly longer median TTP (5.7 v 3.6 months). However, the benefit of docetaxel was at the cost of more hematologic and non-hematologic toxicity, including: febrile neutropenia (14.9% v 1.8%), stomatitis/mucositis (10.8% v 0%), nausea/vomiting (8.6% v 2.7%), and sensory peripheral neuropathy (7.2 v 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. A phase III clinical trial was conducted in patients with MBC who were treated with docetaxel either q3w or once weekly to determine and compare response rate and duration, TTP, PFS, OS, and toxicity. Patients were randomized to receive docetaxel at a starting dose of 75 mg/m² q3w or 35 mg/m² weekly, x3 followed by 1 week of rest. There was no significant difference between the q3w and the weekly treatment arms with regard to with respect to median PFS (5.7 v 5.5; p=0.46) months) or OS (18.3 v 19.6 months; p=0.34). However, the response rate in the weekly arm was lower (20.3 v 35.6%). In the weekly arm, there was less neutropenic fever (3% v 10%), myalgia (3% v 27%), and fatigue (13 v 25%). Findings from a randomized phase II trial of docetaxel (40 mg/m² weekly) x6 q8w versus docetaxel (100 mg/m²) q3w showed a longer median OS for the weekly arm (29.1 v 20.1 months) but a similar median TTP (5.7 v 5.3 months) and ORR (34.1% v 33.3%). Although less febrile neutropenia (4.9% v 19.5%), nausea/vomiting (12.2% v 14.6%), stomatitis/mucositis (7.3% v 17.1%), and sensory peripheral neuropathy (2.4% v 17.1%) were reported in the weekly arm, slightly more asthenia/fatigue (14.6% v 12.2%), and more anorexia (4.9% v 0%) were noted.

Weekly paclitaxel. Two randomized trials have compared weekly versus q3w paclitaxel. Seidman et al. compared paclitaxel (80 mg/m²) weekly versus paclitaxel (175 mg/m²) q3w. In this study, participants with HER2 negative disease were randomized to receive trastuzumab or not, while all participants with HER2 positive disease were given trastuzumab. For the entire study population, there was a trend to longer median OS in the weekly arm (24 v 16 months), but this result was not statistically significant. TTP for the weekly regimen was significantly longer (9 v 5 months), and overall response was significantly higher (40% v 28%). The incidence of febrile neutropenia (3.0% v 4.0%), nausea/vomiting (both arms < 5%), and stomatitis/mucositis (both arms < 5%) was similar for the treatment arms. However, the incidence of sensory peripheral neuropathy was higher in the weekly arm (23% v 12%). In cases where HER2 was not over-expressed, global quality of life and cancer symptom control were significantly better in the weekly arm.

Verrill et al. compared paclitaxel (90 mg/m²) weekly x12 and paclitaxel (175 mg/m²) q3w x6. Although no difference was detected with respect to OS, a trend for longer median TTP in the weekly arm (6 v 5.5 months) was reported. In addition, response rate was significantly higher in the weekly arm (43% v 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 q3w regimen. In the neoadjuvant setting, Green et al. examined weekly versus q3w paclitaxel regimens. Results for the primary outcome, clinical complete response, were not statistically different. For the weekly regimen, pathologic complete response was significantly better (28.2% v 15.7%), as was the breast conservation rate (47% v 38%). However, neurotoxicity was worse with the weekly regimen. In women with resected high risk node negative or node positive breast cancer, the Eastern Cooperative Oncology Group (ECOG) 1199 trial explored various taxane schedules (paclitaxel given either weekly or q3w, or docetaxel given either weekly or q3w) following treatment with doxorubicin and cyclophosphamide. No disease-free survival (DFS) differences emerged in the overall study population.
In an exploratory analysis of patients with ER negative disease, both the weekly paclitaxel and q3w docetaxel arms proved superior to q3w paclitaxel in terms of DFS (81.5% and 81.2% vs 76.9% respectively). The weekly paclitaxel regimen was superior to q3w paclitaxel in terms of OS (89.7% vs 86.5%). This study also demonstrated a favourable safety profile for weekly paclitaxel compared with docetaxel q3w.

For women with MBC, if combination chemotherapy is preferred, what taxane regimen can be offered if she is anthracycline pretreated/resistant and her tumour does not overexpress HER2?

Guidelines: The now archived CCO guideline about the role of taxanes in the management of MBC states that in select patients, those with good performance status or younger age, the combination of docetaxel and capecitabine is a therapeutic option, but capecitabine in this combination should only be given at 75% of full dose. In a more recent CCO guideline (in review as of November 19, 2010) about the role of gemcitabine in the management of MBC, it states that the combination of gemcitabine and docetaxel may be considered as an alternative to capecitabine and docetaxel for first- or second-line chemotherapy in patients where the toxicity of the capecitabine and docetaxel regimen is a concern. In addition, for patients with MBC who have received prior (neo)adjuvant anthracycline therapy, the combination of gemcitabine plus paclitaxel is superior compared to paclitaxel alone as first-line chemotherapy. NICE guidelines state that gemcitabine in combination with paclitaxel, within its licensed indication, is an option for the treatment of MBC when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. Again, the NCCN guidelines list docetaxel plus capecitabine, gemcitabine plus paclitaxel, and paclitaxel plus bevacizumab as possible chemotherapy combinations for MBC, albeit not specifically stated for women who are anthracycline pretreated/resistant.

Evidence: In a large phase III trial of docetaxel plus capecitabine versus docetaxel alone, the combination regimen was found to be superior with respect to several endpoints, including median OS (14.5 v 11.5 months), median TTP (6.1 v 4.2 months) and ORR (42 v 30%). The incidence of febrile neutropenia was similar (13 v 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 phase III global study comparing gemcitabine plus paclitaxel versus paclitaxel alone in patients with advanced breast cancer, median survival was 18.6 v 15.8 months, respectively (log-rank p = 0.0489) and median TTP was 6.14 v 3.98 months, respectively (log-rank p=0.0002). More grade 3 to 4 neutropenia was reported in the gemcitabine plus paclitaxel arm. In addition, grade 2 to 4 fatigue and neuropathy were slightly more prevalent in the gemcitabine plus paclitaxel arm.

A phase III study compared the efficacy and safety of gemcitabine (1000 mg/m² days 1 and 8) plus docetaxel (75 mg/m² day 1) versus capecitabine (1250 mg/m² BID days 1-14) plus docetaxel (75 mg/m² day 1). Median PFS was 8.05 months versus 7.98 months (log-rank p=0.121) in the gemcitabine plus docetaxel versus capecitabine plus docetaxel arms. ORR was 32% in both arms, and OS was not different between arms (p=0.983). Hematologic toxicity was similar in both arms, except for grades 3 to 4 leukopenia (78% v 66%; p=0.025) and transfusions (17% vs. 7%; p=0.0051), which were higher in the gemcitabine plus docetaxel arm. Grades 3 to 4 diarrhea, mucositis, and hand-and-foot syndrome were significantly higher in the capecitabine plus docetaxel arms. The results of a randomized phase II study showed similar outcomes for docetaxel plus gemcitabine, paclitaxel q3w plus gemcitabine and paclitaxel weekly (days 1 + 8) plus gemcitabine. Median TTP was 7.4 versus 7.5 versus 7.0 months and ORR was 50.3% versus 48.6% versus 52.3%. OS data has not yet been reported. The incidence of febrile neutropenia appeared to be highest in the docetaxel plus gemcitabine arm (11.8% v 0% v 4.4%).
Therefore, docetaxel plus gemcitabine cannot yet be recommended over docetaxel plus capecitabine or paclitaxel plus gemcitabine with respect to effectiveness. However, docetaxel plus gemcitabine could be offered in place of docetaxel plus capecitabine if there was a preference to avoid capecitabine-related toxicities. In addition, paclitaxel weekly plus gemcitabine cannot yet be recommended over paclitaxel q3w plus gemcitabine and docetaxel plus capecitabine have not directly been compared with paclitaxel plus gemcitabine.

In the docetaxel plus capecitabine versus docetaxel, and the paclitaxel plus gemcitabine versus paclitaxel studies, cross-over from the single-agent taxane to the single-agent non-taxane/non-anthracycline at the time of progression was not planned. A phase II trial was designed to determine whether capecitabine plus docetaxel is better than sequential docetaxel followed by capecitabine in first-line MBC. Patients were randomized to receive 3-weekly cycles of either capecitabine (1250 mg/m² BID 14 consecutive days) plus docetaxel (75 mg/m² day 1) or docetaxel (100 mg/m² day 1) followed after progression by capecitabine (1250 mg/m² BID 14 consecutive days). In terms of ORR (68% v 40%; p=0.004), median TTP (9.3 v 7.7 months; p=0.001) and median OS (22.0 v 19 months; p=0.006), the combination arm showed significant advantages over the sequential arm.

In a recent phase III trial of the CECOG aimed to compare concomitant docetaxel plus gemcitabine with sequential docetaxel followed by gemcitabine, no difference in efficacy was observed between the arms in terms of TTP, ORR, and OS. However, the docetaxel followed by gemcitabine arm produced significantly more episodes of hematological toxicity due to the administration of docetaxel at 100 mg/m² without GCSF-support. Note that the trial was terminated after 100 of a pre-planned 430 patients due to poor recruitment. In another recent phase III trial, authors compared the efficacy of pegylated liposomal doxorubicin (PLD) plus docetaxel to docetaxel alone and concluded that the PLD plus docetaxel combination was more effective in women with MBC who had experienced relapse at least one year after prior adjuvant anthracycline therapy without an increase in cardiac toxicity. While the median TTP increase from 7.0 to 9.8 months in the PLD plus docetaxel arm (Hazard ratio [HR] 0.65, p=0.000001) the OS was similar between arms (HR 1.02, p=0.81). Symptomatic cardiac events were reported in 4% of patients in the docetaxel arm versus 5% of patients in the PLD plus docetaxel arm, including congestive heart failure in 1% of patients in both arms.

For women with MBC, what taxane regimen can be offered if she is anthracycline-naïve or pretreated/resistant and her tumour overexpresses HER2?

In CCO guideline about the role of trastuzumab in the treatment of women with HER2/neu-overexpressing MBC, it states that trastuzumab in combination with paclitaxel (175 mg/m² TIW, x6) or docetaxel (100 mg/m² TIW, x6) is recommended as a first-line therapy. The NCCN guideline lists pertuzumab (840 mg IV day 1 followed by 420 mg IV) plus trastuzumab (8 mg/kg IV day 1 followed by 6 mg/kg IV) plus doctaxel (75-100 mg/m² IV day 1) q21 days, or, pertuzumab (840 mg IV day 1 followed by 420 mg IV q21d) plus trastuzumab (4 mg/kg IV day 1 followed by 2 mg/kg IV weekly or 8 mg/kg IV day 1 followed by 6 mg/kg IV q21d) plus paclitaxel (80 mg/m² IV day 1 weekly) as first-line agents for HER2-positive disease. Neither guideline specifies that these recommendations are specifically for women who are also anthracycline-naïve or pretreated/resistant.

A randomized phase II study compared docetaxel (100 mg/m²) q3w plus weekly trastuzumab with docetaxel alone. Over half of participants had been exposed to an anthracycline in the adjuvant setting. The addition of trastuzumab improved median TTP (11.7 v 6.1 months), median OS (31.2 v 22.7 months), and ORR (61% v 34%). A large phase III study compared paclitaxel (175 mg/m²) q3w plus weekly...
trastuzumab with paclitaxel alone in the anthracycline pre-treated setting, and doxorubicin plus cyclophosphamide q3w plus weekly trastuzumab with doxorubicin plus cyclophosphamide alone in the anthracycline naïve setting. The addition of trastuzumab to paclitaxel improved median TTP (6.9 v 3.0 months), median OS (22.1 v 18.4 months), and ORR (49% v 17%). The addition of trastuzumab to doxorubicin plus cyclophosphamide also improved median OS (26.8 v 21.4 months) but the cardiac event rate was unacceptably high (28% v 9.6%). Finally, a randomized phase II study examined weekly paclitaxel (80 mg/ m²) plus or minus weekly trastuzumab. Women with advanced breast cancer and 2+ or 3+ over-expression of HER2 by immunohistochemistry (IHC) were included. For the subgroup of women with IHC 3+ (n = 84/124), median TTP was significantly longer (369 v 272 days) and response significantly higher (75% v 56.9%) for those who received paclitaxel plus trastuzumab.

The addition of carboplatin to taxane/trastuzumab doublets has not yet been shown to improve OS or consistently improve ORR. Preclinical findings of synergy between docetaxel, carboplatin, and trastuzumab prompted a phase III randomized trial comparing docetaxel, carboplatin, and trastuzumab with docetaxel plus trastuzumab in patients with HER2-amplified MBC. There was no significant difference between the two arms (doublet v triplet arms) in terms of the primary end point, TTP (medians of 11.1 v 10.4 months), ORR (72% for both arms), and OS (medians of 37.1 v 37.4 months) for the triplet arm. In a phase III trial comparing paclitaxel/trastuzumab plus carboplatin with paclitaxel/trastuzumab, median PFS was longer with the triplet arm (10.7 v 7.1 months), and ORR higher (52 v 36%). No difference was found for median OS (35.7 v 32.2 months).

Pertuzumab is a novel humanized monoclonal antibody that targets HER2. Results from the phase III Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trial, which treated patients not previously exposed to trastuzumab, showed a significant improvement in OS with pertuzumab, trastuzumab, and docetaxel compared to those receiving a placebo plus trastuzumab and docetaxel. A loading dose of 840 mg of pertuzumab administered intravenously and decreasing to 420 mg in subsequent cycles was given every three weeks. Median OS was 37.6 months for patients allocated to the placebo arm and it had not been reached for individuals assigned to the pertuzumab arm. Overall, adverse events were similar with respect to frequency, severity, and specificity. Note the use of pertuzumab in this setting is not funded in Alberta at the present time.

For women with MBC, what taxane regimens can be offered if she is anthracycline-naïve or pretreated/resistant and she has intolerance to paclitaxel or docetaxel?

Guidelines: In another now archived CCO guideline about the role of albumin-bound paclitaxel (nab-paclitaxel) in the treatment of women with MBC it states that for women with no previous taxanes chemotherapy who are candidates for first- or second-line single-agent paclitaxel could be offered nab-paclitaxel. The NCCN guideline lists nab-paclitaxel as an ‘other’ (i.e. not preferred) single agent chemotherapy regimen for MBC (100 mg/m² or 150 mg/m² days 1, 8 and 15 q 28 d, or, 260 mg/m² IV q21d), albeit not specifically stated for women who are anthracycline-naïve or pretreated/resistant and who have an intolerance to paclitaxel or docetaxel.

Evidence: Nab-paclitaxel should be available for patients who have had severe acute infusion reactions with paclitaxel or docetaxel considered by the treating physician to be due to the vehicle of the taxanes or in patients who have experienced severe toxicity from previous administration, including toxicity related to the taxane and premedication. Without corticosteroid or antihistamine premedication, nab-paclitaxel is associated with an incidence of hypersensitivity reactions under 1%. In the absence of definitive data
showing improved OS or significantly reduced toxicities for nab-paclitaxel in comparison to any of the solvent-based taxane regimens, it should not be offered as a routine, single-agent option.

A randomized phase II study compared three nab-paclitaxel arms (300 mg/m² q3w, 100 mg/m² weekly x3, q4w, and 150 mg/m² weekly x3, q4w) and one docetaxel arm (100 mg/m² q3w). Nab-paclitaxel 150 mg/m² weekly showed significantly longer PFS over the docetaxel arm by both independent radiologist and investigator assessment (12.9 v 7.5 months and 14.6 v 7.8 months respectively). Both the 150 mg/m² and 100 mg/m² regimens 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 q3w 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 a phase III trial of nab-paclitaxel 260 mg/m² versus paclitaxel 175 mg/m², median TTP was significantly longer in the nab-paclitaxel arm (23 v 16.9 months) and there was a trend for longer median OS in the nab-paclitaxel arm (65 v 55.7 weeks). The incidence of sensory peripheral neuropathy in the nab-paclitaxel arm was 10% versus 2% in the paclitaxel arm.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID</td>
<td>Twice daily</td>
</tr>
<tr>
<td>CCO</td>
<td>Cancer Care Ontario</td>
</tr>
<tr>
<td>CECOG</td>
<td>Central European Cooperative Oncology Group</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease-free survival</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>ER</td>
<td>Estrogen-receptor</td>
</tr>
<tr>
<td>GCSF</td>
<td>Granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>HER2</td>
<td>Human epidermal growth factor receptor 2</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>MBC</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Health and Clinical Excellence</td>
</tr>
<tr>
<td>ORR</td>
<td>Overall response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression free survival</td>
</tr>
<tr>
<td>q3w</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>PLD</td>
<td>Pegylated liposomal doxorubicin</td>
</tr>
<tr>
<td>PO</td>
<td>By mouth</td>
</tr>
<tr>
<td>SAGE</td>
<td>Standards and Guidelines Evidence</td>
</tr>
<tr>
<td>TIW</td>
<td>Three times a week</td>
</tr>
<tr>
<td>TTP</td>
<td>Time to progression</td>
</tr>
</tbody>
</table>
DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


## Table 1: Single-agent taxane v non-taxane/non-anthracycline regimens

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

* p-value <0.05  
** p-value <0.01