USE OF TAXANES FOR ADJUVANT AND NEO-ADJUVANT TREATMENT OF EARLY AND LOCALLY ADVANCED BREAST CANCER

In 2003 the National Breast Cancer Centre commissioned a systematic review to clarify the role of taxanes in early and locally advanced breast cancer with a view to providing evidence to support the information needs of clinicians and policy makers. A summary of the systematic review is provided below. To access the full review click on the following link www.nbcc.org.au/bestpractice/treatment/index.html

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The aim of neo-adjuvant therapy in breast cancer is to reduce the size of the cancer prior to surgery. The aim of adjuvant therapy in breast cancer is to prevent systemic recurrence and improve overall survival. Options for neo-adjuvant and adjuvant therapy in women with breast cancer include radiotherapy, cytotoxic chemotherapy and hormonal therapy (ovarian ablation, ovarian suppression and anti-oestrogen therapy).

What are taxanes?

Taxanes (paclitaxel and docetaxel) are antimicrotubule agents that prevent cell division. They are amongst the most active chemotherapeutic agents in metastatic breast cancer.¹²

Current use of taxanes

The use of taxanes in neo-adjuvant and adjuvant settings for metastatic breast cancer is increasing.

There are few mature trials of taxanes for early breast cancer, and there is uncertainty about the optimal role of these agents for this indication outside clinical trials.
In Australia, paclitaxel is authorised by the Therapeutic Goods Administration (TGA) for ‘treatment of node-positive, oestrogen receptor-negative breast cancer administered sequentially to doxorubicin hydrochloride and cyclophosphamide’. Its use is subsidised by the Pharmaceutical Benefits Scheme (PBS) for this indication (authority required). Docetaxel is neither approved nor subsidised for adjuvant therapy in early breast cancer. Neither paclitaxel nor docetaxel is approved or subsidised as neo-adjuvant therapy for early breast cancer.

**Systematic review**

The methodology, search criteria and quality appraisal methods for the systematic review are outlined in the full report. The systematic review focused on properly randomised trials of adjuvant or neo-adjuvant systemic therapy comparing a taxane-containing arm with a non-taxane-containing comparator arm in women with early and locally advanced breast cancer.

Reports of 10 trials were located and summarised:

- five assessed neo-adjuvant therapy\(^3\)–\(^7\)
- four assessed adjuvant therapy\(^8\)–\(^{11,13,14}\)
- one assessed both adjuvant and neo-adjuvant therapy\(^12\)

Information was available as a published conference abstract for six trials\(^3\)–\(^5,8\)–\(^{10,13,14}\) and as full journal articles for four trials\(^6,7,11,12\) The trials include a total of 12,217 women. Both neo-adjuvant and adjuvant treatments were heterogeneous, with differences in both the taxane-containing arm (paclitaxel\(^3,6,8,11–13\) and docetaxel\(^4,5,7,9,10,14\)) and in the comparator regimens studied.

**Results of neo-adjuvant trials (Five trials, 2799 women)**

Four of the five neo-adjuvant trials, including 2523 women, reported pathological complete response (pCR) rates\(^3,4,6,7\). Absolute increases of 9–25% in pCR were seen in the taxane-containing arm (not significant). There was no indirect evidence supporting superiority of one taxane over the other in inducing pCR.

Clinical response rates (complete response + partial response) were 1–37% higher in the taxane-containing arms. The difference was statistically significant in one trial, in which four cycles of docetaxel (100mg/m\(^2\) q21d) were added to four cycles of cyclophosphamide (600mg/m\(^2\) q21d) and doxorubicin (60mg/m\(^2\) q21d) pre-operatively (p=0.001).\(^4\)
None of the trials reported overall survival or disease-free survival as an endpoint during the period of this review.

One aim of neo-adjuvant therapy is to downstage locoregional disease, and the data suggest that regimens with taxanes achieve this aim at least as often as regimens without taxanes.

Results of adjuvant trials (Five trials, 9211 women)

All five adjuvant trials showed improvements in disease-free survival with taxanes. The improvements were statistically significant in the three trials confined to women with node-positive disease. The risk reductions in the remaining two trials were similar in magnitude, but there were too few events to establish whether differences of this size were beyond the play of chance. Interestingly, the benefits in terms of disease-free survival were not dependent on oestrogen receptor (ER) status. Current TGA approval for the use of paclitaxel in early breast cancer is restricted to women with ER-negative (ER–) disease. This approval was last amended in 2001 and reflects the data available at that time suggesting greater benefit in women with ER– disease. Further investigation of the possibility that benefits may be independent of ER status is warranted.

Fewer deaths were reported with taxanes than without taxanes in all five adjuvant trials, but the difference was statistically significant in only one trial, in which four cycles of paclitaxel (175mg/m² over 3 hours q21d) were added to four cycles of cyclophosphamide (600mg/m² q21d) and doxorubicin (60, 75 or 90mg/m² q21d) (p=0.001).

Toxicity and quality of life

Toxicity was not reported uniformly in these trials. Side effects reported included:

- febrile neutropenia myalgia and fatigue – generally reported more commonly with taxanes than without

- peripheral neuropathy – generally higher with paclitaxel.

Treatment-related mortality was not higher with taxanes in any trial and rates of cardiac failure were low when reported, with no clear differences between treatment with or without taxanes. Longer follow-up is needed for reliable assessment of late side effects, such as leukaemia and cardiac failure.
Quality of life has not been reported in any of these trials and it is not possible to tell from the current publications whether quality of life data are being collected.

**Conclusions**

**Neo-adjuvant treatment**

These results suggest that taxane-containing regimens are a reasonable option if neo-adjuvant chemotherapy is to be used, but do not warrant their adoption as standard best practice. The follow-up period in these trials was short, and limited information has been reported so this conclusion may change with longer follow-up.

**Adjuvant treatment**

These results provide moderate support for the use of adjuvant taxanes in women with early and locally advanced breast cancer. The strongest support is for the addition of four cycles of paclitaxel to four cycles of doxorubicin and cyclophosphamide. However, firm guidelines based on these outcomes are precluded by substantial differences in the treatments, populations, settings and extent of follow-up.

There are 14 unreported trials including over 14,000 women addressing related questions. Longer follow-up of all the trials is needed to clarify the role of taxanes in the treatment of early and locally advanced breast cancer.

The conclusions of this systematic review are based on evidence available to November 2003. New data are constantly emerging. The conclusions of this systematic review are likely to change with longer follow-up periods and in light of evidence from other trials.

**Note**

Since the completion of this review, follow-up data from two of the trials have been reported showing a significant increase in overall survival associated with docetaxel.¹⁵,¹⁶
References


