The role of the taxanes in the management of metastatic breast cancer

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CRD summary
The authors recommended the use of docetaxel with or without doxorubicin for women who have never previously received anthracyclines, and docetaxel or paclitaxel treatment for those with prior anthracycline use. The poor reporting of review methods and lack of a quality assessment make it difficult to assess the reliability of the authors’ conclusions.

Authors' objectives
To assess the role of taxanes in the management of metastatic breast cancer. In particular, to assess paclitaxel or docetaxel delivered as monotherapy, or in combination with other agents, in patients with no previous anthracycline exposure; and single-agent paclitaxel or docetaxel in patients with prior anthracycline exposure.

Searching
MEDLINE (1966 to July 2002), the Cochrane Library (2002), PDQ, and clinical trial and practice guideline internet sites were searched; the search terms were reported. Conference proceedings from the American Society of Clinical Oncology and the European Society for Medical Oncology, bibliographies and personal files were also searched up to July 2002.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Evidence-based clinical practice guidelines were also reviewed. Letters and editorials were excluded.

Specific interventions included in the review
Studies that evaluated paclitaxel or docetaxel either as single-agents or in combination with other chemotherapeutic agents, given as first- or second-line chemotherapy, were eligible for inclusion. The included studies assessed paclitaxel or docetaxel alone or in combination with at least one of the following: doxorubicin, epirubicin and cyclophosphamide. The comparator treatments were single agents or combinations of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, prednisone, fluorouracil (FU), mitomycin, vinblastine, vinorelbine, capecitabine and epirubicin. The doses and infusion times varied between studies.

Participants included in the review
Eligible participants were women with metastatic breast cancer.

Outcomes assessed in the review
The outcomes specified by the inclusion criteria were quality of life, survival, time to disease progression, tumour response and adverse events. The review specifically assessed grade 3 or 4 haematological, gastrointestinal and neurological toxicity.

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors stated that the evidence was 'reviewed' by two reviewers but reported no further details. Data on the
treatment schedules and relevant outcomes were extracted. Data extracted for each treatment arm included the percentage of women with complete and overall response to treatment the median number of months for survival and time to progression, and the percentage reporting specified adverse effects.

**Methods of synthesis**

**How were the studies combined?**
The studies were grouped by previous exposure to anthracycline and drug regimen and the results presented in a narrative synthesis.

**How were differences between studies investigated?**
Sources of heterogeneity due to drug schedules and doses were described in the results, but no formal statistical assessment of heterogeneity was undertaken.

**Results of the review**

Seventeen RCTs (n=5,689) were included.

In patients with no prior anthracycline exposure there were 7 RCTs of paclitaxel (n=2,954) and 4 RCTs of docetaxel (n=1,335). In patients with previous anthracycline exposure there were 2 RCTs of paclitaxel (n=123) and 4 RCTs of docetaxel (n=1,277).

Patients with no previous anthracycline exposure. Paclitaxel (7 RCTs).

Three RCTs assessed paclitaxel as a single agent (versus three different regimens) and none demonstrated any statistically significant benefits in terms of survival. One found significant benefits for time to progression and overall response for the control arm of doxorubicin, but there were more adverse events with doxorubicin. Five RCTs provided results for paclitaxel in combination with doxorubicin or epirubicin versus four different comparator regimens (one RCT had three arms, so was included in both the single and combined agent comparisons). Significant benefits of paclitaxel combined with doxorubicin for time to progression and response rates were found in 2 trials (versus fluorouracil-doxorubicin-cyclophosphamide (FAC) in one study and versus paclitaxel alone and doxorubicin alone in the other) and for survival in one trial (versus FAC). Higher rates of neutropenia and neurotoxicity were seen for the paclitaxel-doxorubicin combination.

Docetaxel (4 RCTs).

One RCT of docetaxel alone and 2 RCTs of docetaxel combined with other agents (doxorubicin, epirubicin or doxorubicin-cyclophosphamide) found significantly higher overall response rates for docetaxel regimens compared with doxorubicin alone, doxorubicin-cyclophosphamide and FAC. One study reported no significant differences between docetaxel and doxorubicin for time to progression or survival; the other 2 RCTs did not report progression or survival. One trial reported significantly fewer serious adverse events with docetaxel compared with doxorubicin; in general, more patients treated with docetaxel and an anthracycline experienced neutropenia, but the trials did not report if these results were statistically significant or not.

Patients with previous anthracycline exposure.

Paclitaxel. Of the 2 RCTs assessing paclitaxel as a single agent, one was stopped early and did not demonstrate any significant results. The other was a phase II trial which showed a significant benefit for paclitaxel for time to progression compared with mitomycin.

Docetaxel.

Three RCTs assessed docetaxel as a single agent, although one was still ongoing at the time of this review. The other 2 trials both reported significant benefits of docetaxel with respect to overall response and time to progression (versus mitomycin-vinblastine and versus methotrexate-5FU), with one also showing a significant improvement in survival with docetaxel versus mitomycin-vinblastine. Higher rates of adverse events were seen with docetaxel, although more
patients remained on docetaxel compared with control treatment. One RCT assessed docetaxel and capecitabine in combination and reported significant benefits in response rate, time to progression and survival for the combination compared with docetaxel alone.

Docetaxel compared with paclitaxel.

No data directly comparing docetaxel with paclitaxel in either patient group were available. From observed indirect comparisons there appears to be higher response rates with single-agent docetaxel compared with paclitaxel.

Quality of life.

Eight of the 9 studies that presented quality-of-life measures reported no statistically significant differences between treatments. The one RCT reporting significant treatment differences reported improvements in scores with the experimental intervention for some domains, but a deterioration in scores for other domains.

Cost information

There are no published economic evaluations based on randomised trials of taxanes in metastatic breast cancer.

Authors’ conclusions

In patients without previous anthracycline exposure there is little evidence that single-agent paclitaxel is superior to doxorubicin. For patients who have already been treated with anthracycline, there is only weak evidence for paclitaxel but some evidence that docetaxel is an effective treatment in anthracycline-resistant metastatic breast cancer. There is a lack of evidence from direct comparisons, which makes it difficult to recommend one drug over the other.

CRD commentary

This was a systematic review used to inform the development of a practice guideline. The questions were clearly stated and the inclusion criteria specified the study design, treatments and outcomes of interest. The search strategy seemed appropriate, although it was unclear if any language restrictions were applied and around half of the included studies were abstracts only, which limits the interpretation of any trial results. Some aspects of the review methods were not reported clearly: it was unclear whether the study selection and data extraction processes were conducted in duplicate, which may lead to reviewer error and bias. There was no quality assessment, although some aspects of trial design and analysis were reported in the ‘Results’ section; this makes it difficult to assess the reliability of the information presented.

The narrative presentation of results was appropriate given the differences between the studies, although there was a lack of detail on the included participants and also the length of follow-up, which is important given that two of the main outcomes were based on time-to-event analyses. The lack of clear reporting of review methods, the lack of a quality assessment and the variation in comparator treatments make it difficult to assess the reliability of the authors’ conclusions.

Implications of the review for practice and research

Practice: The authors made the following recommendations. Women with metastatic breast cancer who have not previously received an anthracycline should be offered treatment with either single-agent docetaxel (100 mg/m² over 1 hour every 3 weeks) or docetaxel or paclitaxel in combination with doxorubicin. In those for whom anthracyclines are contraindicated, treatment with single-agent docetaxel, 100 mg/m² over 1 hour every 3 weeks, is recommended.

Women who have previously received an anthracycline, or who are anthracycline-resistant, should be given either docetaxel (100 mg/m² over 1 hour every 3 weeks) or paclitaxel (175 mg/m² over 3 hours every 3 weeks). The combination of docetaxel and capecitabine is an option for younger patients or those with good performance status, with capecitabine being given at 75% of the full dose.

Research: The authors did not state any recommendations for further research.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.