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Rapid review

Executive summary

A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer

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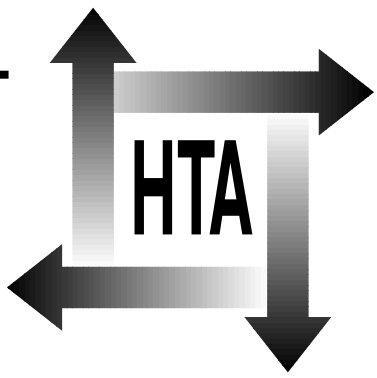

Executive summary

Research question

The aim of this systematic review was to bring together the most recent reliable data to elucidate the following areas of uncertainty: (1) the use of paclitaxel (Taxol®) and docetaxel (Taxotere®) as first- and second-line treatment of advanced breast cancer; and (2) the use of paclitaxel as first-line treatment of ovarian cancer. Adjuvant chemotherapy was not considered in this review.

Methods

This systematic review was conducted in accordance with the NHS Centre for Reviews and Dissemination's Guidelines for Conducting Systematic Reviews. All randomised controlled trials (RCTs) and economic evaluations on the effectiveness of paclitaxel and docetaxel as first- or second-line treatments for breast cancer, or paclitaxel as first-line treatment for ovarian cancer, were considered. The main outcomes were progression-free survival, overall survival, quality of life and economic evaluation.

The body of evidence

The searches identified 2250 articles relating to the taxanes. After independent assessment against the inclusion criteria by two reviewers, it was agreed that 213 references were to be obtained. Of these: 100 were trials listed in the National Research Register, the authors of which were contacted; 13 were reviews and background information; 32 appeared to be economic assessments; and the remaining 68 appeared to be reports of RCTs. Many were duplicate publications. On examination of the obtained papers and reports, those selected for review were as shown in *Table A*.

Results

There was considerable heterogeneity in the populations investigated, intervention and control regimens, and outcomes assessed. Some studies were available only as conference abstracts or presentations, limiting the amount of information that could be extracted.

Breast cancer

First-line treatment

Paclitaxel Four randomised controlled Phase III trials were identified: EORTC, TITGANZ, E1193 and CA139-278. A total of 1974 patients were included. Of these, the EORTC, E1193 and TITGANZ trials evaluated single-agent paclitaxel, and the E1193 and CA139-278 trials evaluated combination paclitaxel/anthracycline. There were no economic evaluations for first-line treatment of breast cancer. Information about the EORTC trial has been removed from this

TABLE A *The body of evidence reviewed*

Review question			No. RCTs (no. patients)	No. economic evaluations
Cancer	**Level of treatment**	**Chemotherapy**		
Breast	First-line	Paclitaxel	4[a] (1545)	0
		Docetaxel	1[b] (429)	0
	Second-line	Paclitaxel	1 (81)	7[c]
		Docetaxel	4 (1092)	6
Ovarian	First-line	Paclitaxel	4[a] (3746)	13[c]

[a] *Data from published papers substituted for original data from manufacturer's confidential submission (1 study)*
[b] *Phase III trial that does not specifically mention randomisation*
[c] *One study not presented in this report at request of manufacturer*

document because it was obtained from a paper that has been submitted for publication and is not yet available for public comment (expected publication date February 2000). Where possible, consistent information from an interim report and meeting abstracts has been substituted.

Quality of trials The TITGANZ trial was analysed on an intention to treat basis and gave details on length of follow-up: 26 months. The EORTC and E1193 trials allowed cross-over to alternate treatment and the TITGANZ trial recommended treatment with epirubicin on progression. Patients crossing over in this way were violating the randomisation; however, no details were given concerning whether or not such patients were censored.

Median progression-free survival:

- Single-agent paclitaxel: The median progression-free survival in the paclitaxel arm ranged from 4 months (EORTC) to 5.9 months (E1193). In no trial was this greater than the control arm. In the EORTC trial, the anthracycline group had significantly longer progression-free survival (7.5 months versus 4.0 months, $p = 0.0001$).
- Combination paclitaxel/anthracycline: The median progression-free survival in the paclitaxel plus anthracycline arms ranged from 8 months (E1193) to 8.3 months (CA139-278). In both trials this was significantly greater than the control arm (E1193: 8 months versus 6 months, $p = 0.003$; CA139-278 8.3 months versus 6.2 months, $p = 0.034$).

Median overall survival:

- Single-agent paclitaxel: The median length of overall survival in the paclitaxel arm ranged from 17.3 months (TITGANZ) to 22.2 months (E1193). In no trial was this significantly different to control.
- Combination paclitaxel/anthracycline: The median length of overall survival for patients in the paclitaxel/anthracycline combination arm ranged from 22 months (E1193) to 22.7 months (CA139-278). Patients in the paclitaxel/anthracycline arm survived for significantly longer than control (22.7 months versus 18.3 months, $p = 0.02$) in one trial (CA139-278) but not in the other (E1193) (22 versus 18.9 months, $p = 0.24$), although the difference was comparable.
- E1193 trial: Survival in the single-agent paclitaxel and the combined paclitaxel/ anthracycline arms was similar (22.2 versus 22 months).

Quality of life Quality of life was evaluated in three of the studies: TITGANZ, E1193 and CA139-278. There were no significant differences between paclitaxel and control in any of the trials in terms of overall quality of life, although differences were apparent on some subscales. These did not appear to follow a consistent pattern across the trials.

Docetaxel One Phase III trial of docetaxel as a first-line treatment for advanced breast cancer was identified. This was available only as a conference abstract and randomisation was not specifically mentioned. Consequently, the results should be treated with caution. Although a combination of docetaxel and doxorubicin produced a greater overall response than doxorubicin and cyclophosphamide combined, there were no long-term results such as progression-free or overall survival.

Second-line treatment

Paclitaxel One randomised controlled Phase II trial was identified: CA139-047. A total of 81 patients were included. Patients had previously received chemotherapy. There were seven economic evaluations.

Quality of trial It is not clear whether this trial was analysed on an intention to treat basis and no details were given on length of follow-up. However, the authors stated that most of the patients were alive at the time of analysis. Only two patients responded in the mitomycin control arm. Cross-over to alternate treatment was allowed. More than half the patients in the control arm crossed over to the paclitaxel arm; none crossed the other way. No details were given about whether such patients were censored. In none of the economic evaluations was the estimation of benefits based on a direct clinical comparison.

Median progression-free survival The median progression-free survival in the paclitaxel arm was 3.5 months. This was significantly longer than the mitomycin control arm (1.6 months, $p = 0.026$).

Median overall survival The median length of overall survival in the paclitaxel arm was 12.7 months, compared with 8.4 months in the mitomycin arm.

Quality of life Quality of life was not reported.

Economic evaluation The only economic evaluation that compared paclitaxel with control (mitomycin) was submitted in confidence and has been removed from this report. Six economic evaluations involved

comparisons of paclitaxel and docetaxel, which are given below.

Docetaxel Four randomised controlled Phase III trials were identified: 303 Study, 304 Study, Scand and Bonneterre. A total of 1092 patients were included. One of these was a preliminary report of a study before completion of accrual (Bonneterre). Patients in the 303 Study had previously received chemotherapy involving alkylating agents; those in the other three had received anthracyclines. There were six economic evaluations on docetaxel.

Quality of trials The 303 and 304 Studies were analysed on an intention to treat basis; the Scand trial excluded a single patient. The length of follow-up ranged from 11 months (Scand) to 23 months (303 Study). At least two-thirds of the participants in these trials had died. The Scand study recommended cross-over to alternate treatment on objective signs of disease progression. Patients crossing over in this way were violating the randomisation; however, no details were given concerning whether or not such patients were censored. In the economic analyses, there were no direct comparisons for the estimation of benefits.

Median progression-free survival The median progression-free survival in the docetaxel arm ranged from 4.75 months (304 Study) to 7 months (Bonneterre). Patients in the docetaxel arms of the 304 and Scand studies had significantly longer progression-free survivals than controls (4.75 months versus 2.75 months, $p = 0.001$; 6.3 months versus 3 months, $p = 0.001$).

Median overall survival The median overall survival in the docetaxel arm ranged from 10.4 months (Scand) to 15 months (303 Study). Patients in the docetaxel arms of the 304 Study survived for significantly longer than the mitomycin plus vinblastine arm (11.4 months versus 8.7 months, $p = 0.03$).

Quality of life Quality of life was evaluated in two of the trials: the 303 and 304 Studies. There were no significant differences between docetaxel and control in either of these trials in terms of global health status, although differences were apparent on some subscales. These did not appear to follow a consistent pattern across the trials.

Economic evaluations All six of these involved comparisons of paclitaxel and docetaxel, where the range of cost–utility ratios for incremental quality-adjusted life-years (QALYs) gained was £1990–£2431. In addition, three analyses compared docetaxel and vinorelbine. The cost–utility ratio for incremental QALYs gained was £14,050 in the only one of these carried out in the UK.

Ovarian cancer

First-line treatment

Paclitaxel Four randomised controlled Phase III trials were identified: GOG111, GOG132, OV10 and ICON3. A total of 3746 patients were included. ICON3 evaluated the effectiveness of paclitaxel combined with carboplatin; the others evaluated a paclitaxel/cisplatin combination. There were 13 economic analyses, one of which was submitted in confidence and has been removed from this document.

Quality of trials All the studies were analysed on an intention to treat basis. The median length of follow-up ranged from 18 months (ICON3) to 37 months (GOG111). The ICON3 trial was reported only 6 months after accrual was completed, at which time over two-thirds of the patients were alive. All the studies allowed cross-over to alternate treatment. In the economic analyses, the estimation of benefits was based on a direct clinical comparison in only eight out of 13 studies.

Median progression-free survival The median progression-free survival in the paclitaxel/platinum arm ranged from 14.1 months (GOG132) to 18 months (GOG111). Patients in the GOG111 and OV10 trials had significantly greater median progression-free survivals with paclitaxel/platinum than controls (18 months versus 13 months, $p < 0.001$; 16.5 months versus 11.8 months, $p = 0.001$).

Median overall survival The median length of overall survival in the paclitaxel/platinum arm ranged from 26.6 months (GOG132) to 38 months (GOG111). Patients in the GOG111 and OV10 trials had significantly greater median overall survivals with paclitaxel/platinum than controls (38 months versus 24 months, $p < 0.001$; 35 months versus 25 months, $p = 0.001$).

Quality of life Quality of life was not reported.

Economic analysis Nine were cost-effectiveness and three were cost–utility analyses. The range of incremental costs per life-year gained (£7173–£12,417) found in two UK studies is within the range reported for all studies comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin

(£3960–£13,360). The two UK studies used carboplatin rather than cisplatin in their analyses. In the cost–utility analyses, the range of incremental cost per QALY gained was £5273–£11,269.

Summary of evidence on effectiveness

The ranges of median progression-free and overall survivals found in the RCTs are given in *Table B*.

Conclusions

For the first-line treatment of breast cancer, the evidence suggests a potential advantage of paclitaxel and anthracycline over control. However, this evidence is not robust. There are ongoing, multicentre randomised controlled Phase III trials, one comparing epirubicin and paclitaxel versus epirubicin and cyclophosphamide (ABO1) and another comparing doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide (EORTC) in the treatment of women with metastatic breast cancer. These trials should provide a clearer picture of the role of paclitaxel.

Both paclitaxel and docetaxel are licensed for use as second-line treatment for breast cancer. The evidence to support the use of paclitaxel in this context is not strong. There has been only one small trial and the cost-effectiveness of paclitaxel compared with mitomycin has not been proved.

There is a slightly greater body of evidence to support the use of docetaxel as a second-line treatment of advanced breast cancer, especially among women who are resistant to anthracyclines. In two trials there was an advantage in overall survival compared with control. However, there were no differences in quality of life. In addition, docetaxel was found to be of similar effectiveness to doxorubicin, so it may be useful in the treatment of women for whom anthracyclines are contra-indicated. In three studies comparing docetaxel to vinorelbine, the one UK study found the cost per QALY gained of docetaxel was £14,050. Docetaxel was found to have highly favourable cost-effectiveness ratios in comparison with paclitaxel (incremental cost per QALY gained £1990– £2431). These studies are weakened by the lack of direct comparison data.

Paclitaxel is licensed and recommended for use as first-line treatment for ovarian cancer. The best available evidence supports its use in combination with platinum in this context, with two trials showing significant improvement in overall survival. This treatment combination was also found to have potentially acceptable

TABLE B *Summary of effectiveness evidence*

	Review question		Range (mo) of median progression-free survival or median time to treatment failure (control)	Range (mo) of median overall survival (control)
Cancer	**Level of treatment**	**Chemotherapy**		
Breast	First-line	Paclitaxel	4.0–5.9[a] (6.0–7.5)	17.3–22.2 (13.9–18.9)
		Paclitaxel + anthracycline	8.0–8.3[b] (6.0–6.2)	22.0–22.7[c] (18.3–18.9)
	Second-line	Paclitaxel	3.5[d] (1.6)	12.7[e] (8.4)
		Docetaxel	4.7–7.0[f] (2.7–5.0)	10.4–15[g] (8.7–14)
Ovarian	First-line	Paclitaxel	14.1–18[h] (11.8–16.4)	26.6–38[h] (25–30.2)

[a] *Control significantly better than paclitaxel in 1/3 trials*
[b] *Paclitaxel plus anthracycline significantly better than control in 2/2 trials*
[c] *Paclitaxel plus anthracycline significantly better than control in 1/2 trials*
[d] *Paclitaxel significantly better than control in 1/1 trial*
[e] *Paclitaxel significantly better than control in 1/1 trial*
[f] *Docetaxel significantly better than control in 2/4 trials*
[g] *Docetaxel significantly better than control in 1/4 trials*
[h] *Paclitaxel plus platinum significantly better than control in 2/4 trials*

cost-effectiveness ratios (cost per QALY gained £5273–£11,269). As the results of the ICON3 trial mature, they may be able to demonstrate for which subgroups of women this treatment is more or less appropriate. The mature results of this trial will also add to our understanding of the comparative costs and benefits of cisplatin and carboplatin. In addition, when complete and mature, the SCOTROC Phase III comparison of paclitaxel/carboplatin versus docetaxel/carboplatin as first-line chemotherapy in ovarian cancer should provide information on the comparative merits of these two taxanes.

This review is based on currently available evidence, which favours docetaxel in the second-line treatment of advanced breast cancer and paclitaxel in the first-line treatment of ovarian cancer. However, the evidence is not robust for any indication. There are several relevant trials in progress, which will need to be taken into consideration once they are suitably mature. Further recommendations for primary research are premature before the final results of ongoing research are published in full. Updating this systematic review is the most pertinent recommendation at this stage.

Publication

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