

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal



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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of docetaxel for the adjuvant treatment of early node-positive breast cancer based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The manufacturer's scope restricts the intervention to docetaxel in combination with doxorubicin and cyclophosphamide (TAC), and the comparator to anthracycline-based chemotherapy. Based on the BCIRG 001 trial, the submitted evidence shows that TAC is associated with superior disease-free and overall survival at 5 years compared with the anthracycline-based regimen FAC. The absolute risk reduction in patients treated with TAC compared with those treated with FAC was 7% for disease-free survival and 6% for overall survival. However, TAC was associated with significantly greater toxicity than FAC. There is also evidence that docetaxel, in an unlicensed sequential regimen FEC100-T, is associated with superior disease-free and overall survival at 5 years compared with FEC100. An economic model was developed by the manufacturer based on the BCIRG 001 trial. This generated central estimates of the cost per life-year gained and cost per quality-adjusted life-year (QALY) gained of TAC compared with FAC of £7900 and £9800 respectively. The manufacturer's submission predicts a cost-effectiveness of £15,000–£20,000 per QALY gained for TAC compared with E-CMF (epirubicin in sequential therapy with cyclophosphamide, methotrexate, and

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fluorouracil), and estimates the cost-effectiveness of FEC100-T to be £8200 per QALY compared with FEC100. Taking into account a number of issues identified by the ERG this may generate higher estimates of cost-effectiveness, but these are unlikely to exceed £35,000 per QALY gained. Importantly, FAC is not commonly used in clinical practice in the UK and, therefore, the submitted evidence does not indicate whether TAC is superior to the anthracycline-based regimens that are in common use (FEC or E-CMF). The indirect comparisons presented suggest that the economic case for TAC in comparison to current UK practice may not be proven. The manufacturer's submission failed to record evidence of three serious adverse events in patients receiving docetaxel with doxorubicin or to mention the concern of the European Medicines Agency regarding TAC's long-term adverse events. The guidance issued by NICE in June 2006 as a result of the STA states that docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen), is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of docetaxel for the adjuvant treatment of early node-positive breast cancer.²

Description of the underlying health problem

Breast cancer is the most common cancer among women in England and Wales. Around one in nine women will be diagnosed with breast cancer at some time in their lives. In 2002, 37,134 new cases of breast cancer were diagnosed in women in England and Wales.³ The risk of breast cancer increases with age; over 80% of cases occur in women aged over 50.³

In breast cancer, prognosis is related to a number of factors, including the extent of disease progression identified at diagnosis or initial surgery.

Scope of the decision problem

The scope of the manufacturer's submission was limited to docetaxel in combination with doxorubicin and cyclophosphamide (TAC) for the adjuvant treatment of women diagnosed with operable node-positive breast cancer (i.e. the relevant licensed application), compared with anthracycline-based chemotherapy. It thus excludes women with high-risk node-negative cancers. Such women, who are at intermediate risk of recurrence, would, in clinical practice, be considered for adjuvant chemotherapy. The scope also excludes docetaxel used in sequential therapy (i.e. following or preceding several cycles of other cytotoxic drugs), although current clinical opinion appears to favour such regimens rather than combination regimens such as TAC. The anthracycline-based regimens in common use in the UK at the time of the assessment were FEC and E-CMF. The limitation of the comparators to anthracycline-based regimens excludes paclitaxel, another taxane, which, like docetaxel, is licensed for use in the UK as adjuvant therapy for operable node-positive breast cancer in sequential therapy following treatment with doxorubicin and cyclophosphamide.

Methods

The ERG report comprised a critical review of the evidence for the clinical and cost-effectiveness of the technology, based upon the manufacturer's/sponsor's initial submission to NICE and subsequent clarification of issues raised by the ERG early in the STA process. A narrative critique of the

submitted evidence was presented. The economic model submitted by the manufacturer was analysed to investigate the impact of different assumptions regarding potential indirect comparisons with UK comparator therapies.

Results

Summary of submitted clinical evidence

There is evidence from a randomised controlled trial (RCT) that, compared with the anthracycline-based regimen FAC, TAC is associated with superior disease-free and overall survival at 5 years (HR 0.72, 95% CI 0.59–0.88, $p = 0.001$ versus HR 0.70, 95% CI 0.53–0.91, $p = 0.008$).⁴ The absolute risk reduction at 5 years in patients treated with TAC compared with those treated with FAC was 7% for disease-free survival and 6% for overall survival, and the number of patients who had to be treated with TAC rather than FAC for one additional patient to benefit was 14 for disease-free survival and 17 for overall survival. However, TAC was associated with significantly greater toxicity than FAC.

There is also RCT evidence that a sequential regimen, FEC100-T, in which docetaxel is used after the anthracycline-based regimen FEC100, is associated with superior disease-free and overall survival at 5 years (adjusted HR 0.83, 95% CI 0.69–0.99, $p = 0.041$ versus HR 0.77, 95% CI 0.59–1.00, $p = 0.05$) compared with FEC100.⁵ The estimated absolute risk reduction at 5 years in patients treated with FEC100-T compared with those treated with FEC100 was 5.1% for disease-free survival and 4.0% for overall survival, and the number of patients who had to be treated with FEC100-T rather than FEC100 for one additional patient to benefit was 20 for disease-free survival and 25 for overall survival.

Summary of submitted cost-effectiveness evidence

An economic model was developed by the manufacturer, based primarily on the single trial BCIRG 001.⁴ This submission model generates central estimates of the cost per life-year gained and cost per quality-adjusted life-year (QALY) gained of TAC compared with FAC of £7900 and £9800 respectively.

The manufacturer's submission predicts a cost-effectiveness of £15,000–£20,000 per QALY

gained for TAC compared with E-CMF (epirubicin in sequential therapy with cyclophosphamide, methotrexate, and fluorouracil). This estimate was based upon an indirect comparison of absolute disease-free survival rates.

Based upon the RCT of FEC100-T compared with FEC100, the manufacturer's submission estimates the cost-effectiveness of FEC100-T to be £8200 (£3500–£56,000) per QALY compared with FEC100. Only four of the six potentially relevant studies reported overall survival and/or disease-free survival (*Table 1*).

Commentary on the robustness of submitted evidence

The ERG identified four other potentially relevant studies that do not meet the inclusion criteria in full, which were missed by the manufacturer in their literature search. These are the ECOG 2197,⁶ GEICAM 9805,⁷ USO 9735⁸ and RAPP 01⁹ studies.

The submitted clinical evidence depends primarily on an interim analysis from one trial, BCIRG 001, which uses docetaxel in its licensed regimen (TAC).⁴ This is a large study carried out in a population that appears to be representative of the population for whom adjuvant docetaxel is licensed and who are expected to be eligible to receive it. However, there is no evidence that the study outcome assessors were blinded to treatment allocation, although the US Food and Drug Administration (FDA) recommends such blinding when disease-free survival is measured and considers it necessary to minimise bias in the assessment of drug toxicity. FAC, the anthracycline-based regimen used as the comparator in the trial, is not in common use in the UK, where FEC and E-CMF predominate. The submitted evidence does not therefore indicate whether TAC is superior to the anthracycline-based regimens that are in common use.

No evidence of systematic bias has been found in the primary economic analysis of TAC compared with FAC presented within the manufacturer's submission. It is the ERG's opinion that a revised model taking into account a number of modelling issues identified by the ERG may generate higher estimates of cost-effectiveness (*Table 2*), but it is unlikely that these estimates would exceed £35,000 per QALY gained. The manufacturer's submission presents a probabilistic sensitivity analysis of uncertainty in the economic estimates; the certainty in the cost-effectiveness estimates is overestimated.

TABLE 1 Docetaxel in women with node-positive or high-risk node-negative breast cancer: studies reporting survival or disease recurrence

| Study Intervention/comparator | Population | Median follow-up | Number of patients | Outcome | Intervention | Comparator | Hazard ratio (95% CI) | Absolute risk reduction |
|---|---|------------------|--------------------|---|--------------|------------|--|-------------------------|
| BCIRG 001, six cycles of TAC, six cycles of FAC | Node-positive | 55 months | 1491 | Recurrence of breast cancer within 5 years | 19% | 26% | 0.72 (0.59–0.88), <i>p</i> = 0.001 | 7% |
| PACS 01, three cycles of FEC100 followed by three cycles of docetaxel, six cycles of FEC100 | Node-positive | 60 months | 1999 | Recurrence of breast cancer within 5 years | 22% | 27% | 0.83 (0.69–0.99), <i>p</i> = 0.041 | 5% |
| ECOG 2197, four cycles of AT, four cycles of AC | Node-positive and high-risk node negative | 53 months | 2952 | 4-year disease-free survival 4-year overall survival | 87% | 87% | 1.08 (0.89–1.31), <i>p</i> = 0.43 1.09 (0.84–1.43), <i>p</i> = 0.48 | 0% |
| USO 9735, four cycles of TC, four cycles of AC | Node-positive and high-risk node-negative | 66 months | 1016 | Estimated 5-year disease-free survival Estimated 5-year overall survival | 86% | 80% | 0.67 (0.50–0.94), <i>p</i> = 0.015 0.76, <i>p</i> = 0.131 | 6% |

AC, doxorubicin and cyclophosphamide; AT, doxorubicin and docetaxel; FAC, fluorouracil, doxorubicin and cyclophosphamide; FEC100, fluorouracil, epirubicin 100 mg/m² and cyclophosphamide; TAC, docetaxel, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide.

TABLE 2 Economic results for TAC compared with FAC from an adjusted model**(a) Estimates of costs and outcomes**

| | TAC | FAC | Incremental |
|--|------------|------------|--------------------|
| Costs (deterministic mean per patient) | | | |
| Cost of chemotherapy and administration | £7173 | £1263 | £5910 |
| Cost of supportive G-CSF | £963 | £353 | £609 |
| Cost of managing adverse events | £1521 | £749 | £772 |
| Monitoring cost for patients in remission | £769 | £737 | £32 |
| Cost of treatment for relapsing patients | £5482 | £6042 | –£561 |
| Total expected cost | £15,908 | £9145 | £6763 |
| Outcomes (deterministic) | | | |
| Patients discontinuing because of adverse events (%) | 6.04 | 1.07 | 4.97 |
| Life-years (mean per patient) | 11.238 | 10.501 | 0.736 |
| QALYs (mean per patient) | 8.798 | 8.223 | 0.575 |

FAC, fluorouracil, doxorubicin and cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; QALYs, quality-adjusted life-years; TAC, docetaxel with doxorubicin and cyclophosphamide.

(b) Incremental cost-effectiveness ratio (ICER) estimates

| | Point estimate of mean | | 95% Confidence interval | |
|-----------------------|-------------------------------|----------------------------------|--------------------------------|--------------|
| | Deterministic | Probabilistic^a | Lower | Upper |
| Incremental cost/LYG | £9187 | £7932 | £7289 | £8641 |
| Incremental cost/QALY | £11,760 | £9760 | £7805 | £15,561 |

LYG, life-years gained; QALY, quality-adjusted life-year.

a The probabilistic results reflect the most recent run of the probabilistic simulation. If alternative analyses have been made without rerunning the probabilistic model they will not reflect the current analysis.

Conclusions

Docetaxel has been licensed for use in combination with doxorubicin and cyclophosphamide (TAC) for the adjuvant treatment of women diagnosed with operable node-positive breast cancer. Evidence from a large RCT demonstrates that TAC is superior to the anthracycline-based FAC regimen in terms of disease-free and overall survival at 5 years. However, the same evidence suggests that TAC is associated with significantly greater toxicity than FAC. Importantly, FAC is not commonly used in clinical practice in the UK. The most common adjuvant chemotherapy regimens currently in use in the UK are FEC, using an epirubicin dose of

75 mg/m² or greater, or E-CMF. FAC has not been demonstrated to be superior to these anthracycline regimens.

The manufacturer's submission to NICE failed to record the premature termination of the French RAPP 01 trial following three fatal or life-threatening adverse events in patients receiving docetaxel with doxorubicin. Furthermore, the submission does not mention the concern of the European Medicines Agency (EMA) regarding TAC's long-term adverse events, as a result of which intensive monitoring for cardiotoxicity, secondary leukaemia and serious gastrointestinal toxicity is ongoing.

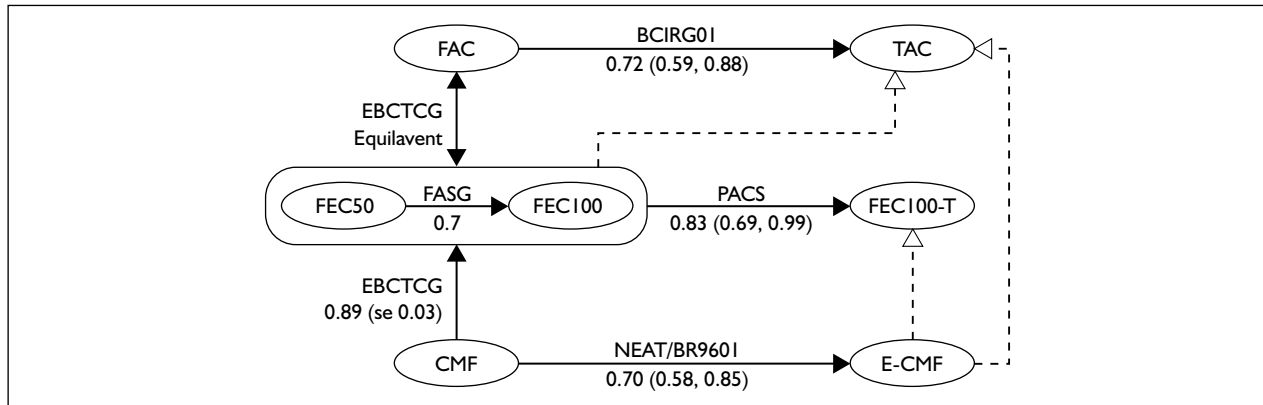


FIGURE 1 Indirect comparisons. CMF, cyclophosphamide, methotrexate and fluorouracil; E-CMF, epirubicin with cyclophosphamide, methotrexate and fluorouracil; FAC, fluorouracil, doxorubicin and cyclophosphamide; TAC, docetaxel with doxorubicin and cyclophosphamide.

There also exists RCT evidence that docetaxel, in an unlicensed sequential regimen FEC100-T, is associated with superior disease-free and overall survival at 5 years compared with FEC100.

The health economic model submitted by Sanofi-aventis estimates that TAC has a cost-effectiveness in the order of £10,000 per QALY gained compared with FAC. Indirect comparisons presented within this review (Figure 1) suggest that the economic case for TAC in comparison to current UK practice is not proven. As part of the unlicensed FEC100-T regimen, the manufacturer’s submission estimates that the cost-effectiveness for docetaxel is in the order of £10,000 per QALY gained compared with FEC100, a comparator that is currently used in the UK.

The relevance of the cost-effectiveness estimates put forward in the manufacturer’s submission depends on subjective judgments regarding the likely superiority of TAC over FEC75–100 or E-CMF (Table 3).

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in June 2006 states that:

Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) as per its licensed indication, is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.

TABLE 3 Relative risk of disease-free survival, TAC versus E-CMF, for a range of ICER/QALY values

| ICER threshold (£/QALY) | % Responders in E-CMF arm | Average relative monthly hazard of relapse over 5 years |
|-------------------------|---------------------------|---|
| £10,000 | 87.9 | 0.75 |
| £20,000 | 92.3 | 0.84 |
| £30,000 | 93.8 | 0.88 |
| £40,000 | 94.7 | 0.90 |
| £50,000 | 95.2 | 0.91 |
| £60,000 | 95.5 | 0.92 |
| £70,000 | 95.8 | 0.93 |
| £100,000 | 96.2 | 0.95 |
| E-CMF indirect estimate | | 0.92 |

E-CMF, epirubicin with cyclophosphamide, methotrexate and fluorouracil; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TAC, docetaxel with doxorubicin and cyclophosphamide.

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