Cyclophosphamide-methotrexate 'metronomic' chemotherapy for the palliative treatment of metastatic breast cancer: comparative pharmacoeconomic evaluation


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Oral low-dose cyclophosphamide-methotrexate "metronomic" chemotherapy (methotrexate 2.5 mg twice daily on days 1 and 2, and cyclophosphamide 50 mg every day) was compared with the following novel, maximum tolerated dose (MTD) chemotherapy strategies.

Intervention 1 was oral capecitabine, 2,510 mg/m2 per day given for 2 weeks, followed by a 1-week rest period.

Intervention 2 was oral estramustine phosphate, 10 mg/kg administered daily.

Intervention 3 was intravenous vinorelbine, 30 mg/m2 per week.

Intervention 4 was intravenous vinorelbine, 8 mg/m2 on day 1 then 8 mg/m2 on days 1 to 4 in a continuous infusion, at home.

Intervention 5 was docetaxel, 85 mg/m2 as a 1-hour infusion followed immediately by 5-fluorouracil (5-FU) 750 mg/m2 as a continuous infusion for 5 days.

Intervention 6 was oxaliplatin 85 mg/m2 as a 2-hour infusion, leucovorin 200 mg/m2 daily as a 2-hour infusion, followed by a bolus of 5-FU 400 mg/m2 day and a 22-hour infusion of 5-FU 600 mg/m2 daily repeated for 2 consecutive days. Treatment was repeated every 3 weeks.

Intervention 7 was docetaxel 40 mg/m2, administered as a 30-minute intravenous infusion for 6 consecutive weeks, followed by 2 weeks without treatment.

Intervention 8 was intravenous vinorelbine 25 mg/m2 and docetaxel 60 mg/m2; cycles 14 days.

Intervention 9 was docetaxel 75 mg/m2 as a 1-hour intravenous infusion followed by carboplatin AUC 6 mg/mL x minutes as a 30-minute intravenous infusion; cycles 3 week.

Intervention 10 was gemcitabine 1,200 mg/m2 30-minute intravenous infusion on days 1, 8 and 15 of a 28-day cycle.

Intervention 11 was trastuzumab 4 mg/kg intravenous loading dose plus 2 mg/kg intravenously per week; paclitaxel 60/90 per m2 intravenously per week.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with histologically confirmed metastatic breast carcinoma that had either progressed or not progressed after first-line chemotherapy for metastatic disease.

**Setting**
The study setting was secondary care. The economic study was carried out in Italy.

**Dates to which data relate**
The effectiveness and resource use data were derived from studies published between 1999 and 2004. The unit costs would appear to relate to 2003. The price year was 2003.

**Source of effectiveness data**
The effectiveness data were derived from a review of published studies.

**Outcomes assessed in the review**
The outcomes assessed were progression-free life-years (PFLYs) and the overall tumour response rate (i.e. complete plus partial response to chemotherapy administration and stable disease). PFLYs were calculated as the percentage of days free from disease progression in a year.

**Study designs and other criteria for inclusion in the review**
Only published Phase II clinical trials of metastatic breast cancer, performed in Western countries, were included in the review.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Twelve Phase II trials were included in the review.

**Methods of combining primary studies**
Not relevant as the effectiveness of each drug was evaluated from a single study (i.e. each of the 12 studies evaluated the outcomes of one of the drugs being compared).

**Investigation of differences between primary studies**
The authors did not report whether differences between primary studies used to compare each intervention head to head were investigated. For example, the authors did not report the age of the patient sample in each study used.

**Results of the review**
The PFLYs for each intervention under study were as follows:

23 (95% confidence interval, CI: 17.3 to 48.5) with cyclophosphamide/methotrexate;

25.5 (95% CI not reported in the study) with intervention 1;

intervention 2, outcome not reported in the study;

intervention 3, outcome not reported in the study;

19.7 (95% CI: 15 to 24.4) with intervention 4;

43.56 (95% CI: 4.11 to 157.81) with intervention 5;

55 (95% CI: 42.5 to 70.68) with intervention 6;

69 (95% CI: 48.85 to 92) with intervention 7;

90.4 (95% CI: 70.7 to 110.9) with intervention 8;

82.2 (95% CI: 16.4 to 135.6) with intervention 9;

66.57 (95% CI: 20.55 to 225.2) with intervention 10; and

70.7 (95% CI: 20.5 to 199) with intervention 11.

The overall tumour response rate was:

31.7% (95% CI: 20.6 to 44.7) with cyclophosphamide/methotrexate;

20% (95% CI: 14 to 28) with intervention 1;

17.5% (95% CI: 6 to 30) with intervention 2;

25% (95% CI: 13 to 41) with intervention 3;

19% (95% CI: 7.88 to 42.94) with intervention 4;

34% (95% CI: 21 to 49) with intervention 5;

70% (95% CI: 53.6 to 86.4) with intervention 6;

34% (95% CI: 19 to 50) with intervention 7;

45% (95% CI: 31 to 60) with intervention 8;

61% (95% CI: 45.2 to 77.0) with intervention 9;

29% (95% CI: 16 to 46) with intervention 10; and

56% (95% CI: 36.5 to 75.5) with intervention 11.

Measure of benefits used in the economic analysis

The measures of benefits used were PFLYs and the overall tumour response rate. These measures were derived directly from the studies included in the review.
Direct costs
The direct costs to the health care system were included in the analysis. Such costs covered chemotherapy acquisition and administration, hospitalisation, visits to health professionals, use of concomitant medications and clinical examinations. The resource use data were derived from the clinical studies included in the review of effectiveness. The costs of chemotherapy and other medications were derived from the Italian National Formulary, while hospitalisation costs were from the current Italian Reference Costs. Chemotherapy administrative and health professional costs were taken from the current Italian-based sources of unit costs in health care. The time period over which the costs were incurred was not clear, thus it was unclear if discounting was actually necessary. The authors do not appear to have used discounting. The price year was 2003. The study reported the median costs per patient.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included.

Currency
Euros (EUR).

Sensitivity analysis
The authors performed a series of one-way sensitivity analyses. Where 95% CIs were available (i.e. for outcome measures), these were used to explore variation in treatment costs. At baseline, the median costs associated with hospitalisation, concomitant medication, chemotherapy administration and drug treatment costs were used. In the sensitivity analyses, these parameters were varied by up to 50% in each direction.

Estimated benefits used in the economic analysis
See the 'Results of the Review' section.

Cost results
The median cost for each of the interventions under study was:

- EUR 3,524 for cyclophosphamide/methotrexate:
- EUR 18,656 for intervention 1;
- EUR 9,048 for intervention 2;
- EUR 28,887 for intervention 3;
- EUR 10,691 for intervention 4;
- EUR 26,157 for intervention 5;
- EUR 23,146 for intervention 6;
- EUR 27,226 for intervention 7;
- EUR 19,770 for intervention 8;
- EUR 21,155 for intervention 9;
EUR 11,100 for intervention 10; and
EUR 67,688 for intervention 11.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the incremental cost per additional PFLY or per overall tumour response gained).

Compared with cyclophosphamide/methotrexate, the additional cost per PFLY was:

- EUR 605,280 with intervention 1;
- not available for intervention 2 as the study did not quote PFLY as an outcome;
- not available for intervention 3 as the study did not quote PFLY as an outcome;
- EUR 217,182 with intervention 4;
- EUR 70,728 with intervention 5;
- EUR 95,438 with intervention 6;
- EUR 51,526 with intervention 7;
- EUR 19,157 with intervention 8;
- EUR 29,782 with intervention 9;
- EUR 17,388 with intervention 10; and
- EUR 134,516 with intervention 11.

Compared with cyclophosphamide/methotrexate, the additional cost per overall tumour response gained was:

- EUR 129,334 with intervention 1;
- EUR 38,901 with intervention 2;
- EUR 378,552 with intervention 3;
- EUR 56,433 with intervention 4;
- EUR 59,094 with intervention 5;
- EUR 853,130 with intervention 6;
- EUR 1,030,522 with intervention 7;
- EUR 97,083 with intervention 8;
- EUR 60,174 with intervention 9;
- EUR 280,592 with intervention 10; and
- EUR 264,049 with intervention 11.
The results of the sensitivity analyses were reported to be robust to variations in key parameters with few exceptions.

**Authors’ conclusions**

Metronomic cyclophosphamide-methotrexate was significantly cost-effective.

**CRD COMMENTARY - Selection of comparators**

A justification was given for the comparators used. They represented novel chemotherapy strategies in metastatic breast cancer. You should decide if the comparators represent current practice in your own settings.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature had been undertaken to identify all relevant research and minimise biases. The authors reported the entry criteria for inclusion in the review (mainly Phase II trials undertaken in Western countries). For each of the twelve drugs under study, the outcomes of each were derived from a separate study. However, the authors do not appear to have compared any potential differences in the study populations and samples of each study, nor did they assess the validity of the studies included. Therefore, differences in treatment outcomes could be due to differences in study participants (i.e. age, disease severity, deprivation, etc.) rather than treatment effectiveness.

**Validity of estimate of measure of benefit**

The estimation of benefits was obtained directly from the effectiveness studies. The choice of estimate was not justified. As the authors acknowledged, tumour responses should be interpreted cautiously as an outcome of metastatic breast cancer therapy. A more general measure of health benefit, such as the number of quality-adjusted life-years gained, would facilitate comparisons of the study results with those from different interventions.

**Validity of estimate of costs**

All the categories of cost relevant to the health care system perspective adopted appear to have been included in the analysis, although the costs of antibacterial chemotherapy associated with the risk of infectious complications might have been omitted from the analysis since the authors mentioned that their incidence was considered to be minor. The costs and resource use were not reported separately (which would hinder reflation exercises in other settings), but the authors did report costs according to resource use category. Resource use was derived from the same studies as those used in the review of effectiveness. As before, for each of the twelve drugs under study, resource use was derived from a separate study. However, the authors do not appear to have compared any potential differences in the study populations and samples of each study. Therefore, differences in resource use could be due to differences in study participants (i.e. age, disease severity, deprivation, etc.) rather than the resource use requirements of each treatment.

The unit costs were derived from published sources. Appropriate one-way sensitivity analyses were undertaken. The authors reported median costs which, although valuable when dealing with skewed data, do not convey the average cost for each patient; this might be important for policy-makers when estimating the potential cost of their decisions. The price year was appropriately reported, which will aid any possible inflation exercises. The authors do not appear to have used discounting, although it is unclear whether it was necessary since the time horizon considered for the cost estimation was not clear.

**Other issues**

The authors reported that there were no prior examples of pharmacoeconomic studies involving metastatic breast cancer treated with cyclophosphamide-containing regimens. The issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors highlighted another issue related to the generalisability, which arose from the fact that not all patients are eligible for MTD regimens and a considerable number of them will refuse chemotherapy if they consider it highly toxic. The authors do not appear to have presented their results selectively, but their conclusions did not reflect the findings of their analysis. The authors concluded that metronomic...
cyclophosphamide-methotrexate was significantly cost-effective. However, they did not derive a cost-effectiveness threshold (i.e. additional cost per PFLY or overall tumour response gained) above which the additional cost for an additional outcome would not be warranted. As the analysis stands, it is unclear how much a country, society, or decision-makers would be willing to pay for an additional PFLY or gain in overall tumour response.

The authors reported a number of further limitations to their study. First, the generalisability of the analyses, which were based on costs and outcomes from published trials. Second, they did not compare cyclophosphamide plus methotrexate with other novel anti-cancer approaches such as those involving targeted therapies.

Implications of the study
The authors reported that further comparisons between other novel anti-cancer approaches will be needed if the cost-effectiveness of the metronomic regimen is to be fully evaluated.

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