Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group

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
First-line chemotherapy alternatives for patients with advanced breast cancer were assessed. The alternatives were:

- six cycles of epirubicin (EPI) at a dose of 80 mg/m2 followed by paclitaxel (Taxol; Bristol-Myers Squibb) 175 mg/m2 in a 3-hour infusion (EPI-PAC); and

- six cycles of paclitaxel 175 mg/m2 in a 3-hour infusion, followed immediately by carboplatin (Cp) at an area under the curve of 6 mg x min/mL in 500 mL normal saline in a 30-minute infusion (PAC-Cp).

The cycles were delivered every 3 weeks.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women aged 18 years or older who had histologically proven advanced breast cancer, a life expectancy of more than 12 weeks, and a performance status of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale. They also had to have adequate bone marrow, hepatic and renal function, and a left ventricular ejection fraction of 50% or more, measured either by multi-gated scan or ultrasonography. Patients with osseous metastases as the only metastatic site and receptor-positive status were eligible only if they progressed after at least one hormonal manipulation.

The exclusion criteria were symptomatic brain metastases, history of other malignancy (except curatively resected non-melanoma skin cancer or in situ cervical cancer), myocardial infarction within the last 6 months, or any other serious illness that would impair the ability of the patient to receive protocol treatment. Previous chemotherapy for advanced disease was not allowed. However, patients pre-treated with hormonal therapy or radiation, either in the adjuvant setting or for metastatic disease, were eligible provided that any treatment was stopped at least 4 weeks before study entry.

Setting
The setting was secondary care. The economic analysis was carried out in Greece.

Dates to which data relate
The effectiveness and resource use data were gathered between January 1999 and April 2002. The price year was not
Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
The authors estimated that to detect a +/- 15% difference in a survival rate of 50% at 20 months in the EPI-PAC group, 320 patients were needed for the study to have 80% power at the 5% significance level. Considering a 2% withdrawal rate, the total number of patients was increased to 327. The post-hoc power to detect a +/- 15% difference according to the study design, based on the total events observed, was 82%.

From January 1999 to April 2002, 332 patients entered the study. Five patients were excluded from the analysis because of inadvertent randomisation (1 patient), missing medical records (2 patients) and non eligibility (2 patients, one with a performance status of 3 and the other an initial low platelet count). Of the remaining 327 patients, 163 were randomised to group A (EPI-PAC) and 164 to group B (PAC-Cp). One patient in group A and 4 patients in group B never started chemotherapy. These 5 patients were excluded only from the analysis of treatment characteristics and toxicity. The median age was 59 years in group A (range: 30 - 78) and 59 years in group B (range: 27 - 78).

Study design
This was a randomised controlled trial. The study appears to have been a multi-centre trial, although the authors did not report the number of centres taking part in the study. The patients were randomised centrally and stratified according to the history of previous adjuvant chemotherapy and risk category. The risk categories were based on the following criteria: free interval from initial radical surgery to first recurrence more than 5 years with only osseous or with only loco regional metastases; free interval 1 to 5 years and absence of visceral metastases; and all others. The groups were followed for a median of 23.5 months (range: 0.1 - 49.5). The authors reported that 5 patients in group A and 2 patients in group B were lost to follow-up. The authors also provided the number of patients who withdrew (voluntarily or not). It was unclear whether these patients should be included in the number of patients lost to follow-up.

Analysis of effectiveness
The clinical study was conducted on an intention to treat basis. The primary health outcome was survival. The secondary outcomes included the overall (complete plus partial) response rate, the time to treatment failure (TTF), compliance with treatment and severe toxic effects. In the case of a complete response, the duration of response was calculated from the date when complete response was documented until the date of progression; in the case of a partial response, the duration was calculated from the initiation of chemotherapy until the date of progression. The TTF was calculated from a randomisation date to the date when progression of the disease was documented. Survival was calculated from the randomisation date to the date of the last contact or to the date of death. Quality of life was also assessed using the Greek version of the EORTC QLQ-C30, both at baseline and at the end of the study. Major patient and tumour characteristics were generally equally distributed in the two groups of patients. The exception was the rate of osseous metastases, which was significantly higher in group B (44% versus 57%; p=0.02).

Effectiveness results
In total, 127 patients (78%) in group A and 135 (82%) in group B completed at least 6 cycles of treatment. Overall, 137 patients (66 patients in group A and 71 in group B) received maintenance hormonal therapy after treatment completion. Both regimens were well tolerated. In total, 39 patients (24%) in group A and 46 (29%) in group B suffered at least one severe side effect (Grade 3 or 4).
The overall response rate was 47% (95% confidence interval, CI: 38.8 - 54.6) in group A and 41% (95% CI: 33.25 - 48.8) in group B, (p=0.32).

The median duration of response was 8.98 months (range: 1.34 - 38+) in group A and 13.8 months (range: 3.6 - 41+) in group B, (p=0.01; when adjusting for maintenance hormonal treatment, p=0.006).

The median duration of complete response was 5.4 months (range: 1.34 - 35.05+) in group A, whereas in group B, it had not yet been reached (range: 3.6 - 27.7+ months).

The median time to achieve complete response was 4.2 months (range: 1.4 - 4.85) in group A and 4 months (range: 1.9 - 5.7) in group B.

The median TTF was 8.1 months (range: 0.1 - 42.7+; 95% CI: 7.0 - 9.2) in group A and 10.8 months (range: 0.1 - 40.7+; 95% CI: 8.9 - 12.6) in group B, (p = 0.04; when adjusting for maintenance hormonal treatment, p=0.02).

Median survival was 22.4 months (range: 0.1 - 42.7+; 95% CI: 17.8 - 27.0) in group A and 27.8 months (range: 0.26 - 49.5+; 95% CI: 20.8 - 34.9) in group B, (p=0.25; when adjusting for maintenance hormonal treatment, p=0.26).

Of the 322 patients, 98 (48 of group A and 50 of group B; 30%) had both baseline and end of study quality of life assessments. PAC-Cp (group B) was associated with significant improvements in the emotional functioning scale, (p=0.01) and sleep disturbance symptoms, (p=0.01) in comparison with EPI-PAC (group A). The result was non significant when using the appropriate Bonferroni adjustment.

**Clinical conclusions**
The study did not identify a significant difference in median survival when EPI was substituted by Cp, in combinations with PAC.

**Measure of benefits used in the economic analysis**
As the results of the trial indicated that there were no significant differences in median survival between the two treatment groups, a cost-minimisation analysis was carried out.

**Direct costs**
The direct costs included in the analysis were those of the Greek NHS. These were:

- chemotherapy, concomitant and other medications used in the case of adverse events;
- infusions in the outpatient setting;
- hormone therapy and consolidation radiotherapy after chemotherapy in selected cases;
- subsequent hospitalisations and visits to health professionals due to adverse events or follow-ups; and
- all laboratory imaging examinations carried out during the chemotherapy period, or for the treatment of adverse events associated with drug toxicity or patient health deterioration.

The costs and the quantities were not reported separately. The resource use data were obtained from the clinical study and were combined with unit cost data from Greek national sources and the database of the University General hospital of Patras. The time horizon of the economic analysis was the same as that used in the clinical study (approximately 2 years), hence discounting was not necessary and was not performed. The study reported the mean costs. The price year was not reported.

**Statistical analysis of costs**
Individual patient cost estimates were bootstrapped 2,500 times, and the mean of the bootstrapped means and its CIs used for comparisons. The authors reported that this was undertaken as economic data are often skewed by small numbers of very costly cases.

**Indirect Costs**
The indirect costs were not included.

**Currency**
Euros (Euro).

**Sensitivity analysis**
No sensitivity analyses were undertaken.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The mean cost per patient was Euro 17,058 (standard deviation, SD=8,688) in group A and Euro 17,681 (SD=8,701) in group B.

The bootstrapped mean cost per patient was Euro 17,054 (95% CI: 15,524 - 18,223) in group A versus Euro 17,366 (95% CI: 15,465 - 18,960) in group B.

**Synthesis of costs and benefits**
The costs and benefits were not combined.

**Authors' conclusions**
The study did not identify a significant difference in median survival when epirubicin (EPI) was substituted by carboplatin (Cp) in combinations with paclitaxel (PAC). In addition, no significant differences in overall response rate, quality of life, or cost were found between the two groups of patients. The authors also concluded that, as this study did not have sufficient power to detect small but meaningful differences in survival, the substitution of PAC-anthracycline regimens by the PAC-Cp combination could not be recommended as first-line chemotherapy in patients with advanced breast cancer on the basis of their findings.

**CRD COMMENTARY - Selection of comparators**
The authors based their choice of the two first-line chemotherapy alternatives on the results from earlier trials. However, they did not clearly justify their choice. Other commonly used regimens in first-line chemotherapy for advanced breast cancer, such as the combination of EPI (or doxorubicin) and cyclophosphamide with and without fluorouracil, could have been evaluated. You should decide if the comparators used represent current practice in your own setting, or whether other comparators from other therapeutic options could also have been relevant.

**Validity of estimate of measure of effectiveness**
The analysis was based on a randomised controlled trial (RCT). This was appropriate for the study question as well-conducted RCTs are considered the 'gold' standard study design when comparing health interventions. Further, the basis of the analysis was intention to treat. It was unclear if the study sample was representative of the study population, as the authors had very stringent eligibility criteria for entry into the study. The patient groups were shown to be
comparable at analysis in terms of major patient and tumour characteristics, but the rate of osseous metastases was significantly higher in group B (44% versus 57%; p=0.02). The authors performed appropriate statistical analyses to detect any statistically significant differences between the two groups. However, even though the study was powered to detect a +/- 15% difference in survival with 82% power, the authors acknowledged that the study was not powered to detect smaller, but meaningful differences in survival between the two groups.

**Validity of estimate of measure of benefit**
As the results of the trial indicated that there were no significant differences in median survival between the two treatment groups, a cost-minimisation analysis was carried out.

**Validity of estimate of costs**
All the categories of cost relevant to the health service perspective adopted were included in the analysis, and all relevant costs appear to have been included. Although the costs and the quantities were not reported separately, which will limit the generalisability of the authors' results, the authors did break down the mean costs per therapy group (i.e. the mean cost of chemotherapy, drugs, or hospitalisation per patient). The resource use data were derived from the clinical study, while the unit costs were derived from published sources and a University hospital. Appropriate statistical analyses, using bootstrap techniques, were undertaken to detect statistically significant differences in mean costs between the two groups. Since the costs were incurred during approximately 2 years, discounting was not relevant and was not performed. The price year was not reported, which will hamper any future inflation exercises.

**Other issues**
The authors reported that, to their knowledge, this was the first Phase III trial to compare the EPI-PAC combination with the PAC-Cp combination. The issue of generalisability to other settings was not addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported no further limitations to their study.

**Implications of the study**
The authors reported that more data from randomised studies are needed before one treatment strategy can be recommended over another. They also reported that their findings could stimulate additional studies that may eventually pave the way to an era of anthracycline-free chemotherapy.

**Source of funding**
Supported by a Hellenic Cooperative Oncology Group research grant, and by Bristol-Myers Squibb, Aventis and AstraZeneca.

**Bibliographic details**

**PubMedID**
15367413

**DOI**
10.1093/annonc/mdh395

**Other publications of related interest**


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Antineoplastic Combined Chemotherapy Protocols /adverse effects /therapeutic use; Breast Neoplasms /drug therapy /pathology; Carboplatin /administration & dosage; Epirubicin /administration & dosage; Female; Humans; Infusions, Intravenous; Middle Aged; Paclitaxel /administration & dosage; Survival Analysis; Treatment Outcome

AccessionNumber
22004001360

Date bibliographic record published
30/11/2005

Date abstract record published
30/11/2005