Impact of uncertainty on cost-effectiveness analysis of medical strategies: the case of high-dose chemotherapy for breast cancer patients

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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
The use of high-dose chemotherapy (HDC) for breast cancer patients. The treatment consisted of four cycles of FEC 100 (fluorouracil, epirubicin, cyclophosphamide) followed by one course of CMA (cyclophosphamide, mitoxantrone, Alkeran). Peripheral blood stem cells were collected during FEC 100 cycles under 5 +/- g/kg filgrastim stimulation and reinfused after intensification.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 to 60 years old with a histologically confirmed nonmetastatic breast cancer with axillary lymph node invasion (8 positive nodes), and with a World Health Organization performance status of lower than 2.

Setting
The setting was a hospital. The economic study was carried out in France.

Dates to which data relate
The effectiveness data and most resource use data were gathered from 1994 and 1998. Other resource use data were derived from a study published in 1999. The price year was not explicitly reported, but it appears to have been 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing, with the exception on data on relapse, was carried out prospectively on the same sample of patients as that included in the clinical study.

Study sample
Limited information on the sample selection and characteristics were reported because the data referred to a prior study. However, it was unclear whether this study had been published. A total of 314 patients were enrolled into the trial. Data were not available for 14 patients who were initially included in the intensive arm but did not receive HDC.
There were 155 patients in the conventional treatment group and 145 patients in the intensive treatment group. No details of the patients' characteristics were given.

**Study design**
This was a randomised clinical trial. It was not stated whether it was performed in different hospitals. The median follow-up was 61.2 months. Data on loss to follow-up were not reported.

**Analysis of effectiveness**
The two primary outcome measures used in the analysis of effectiveness were overall survival (OS) and DFS. Details of the baseline comparability of the study groups were not reported, nor were other methods used to analyse clinical end points. However, the randomised design should ensure the comparability of the two study groups.

**Effectiveness results**
DFS was 49.49 (+/- 2.81) months (95% confidence interval, CI: 44.1 - 54.8) in the conventional treatment group and 61.1 (+/- 2.60) months (95% CI: 56.1 - 65.8) in the intensive treatment group. The difference was 11.61 (+/- 0.31) months, (p<0.01). The 5-year DFS rates were 40.7% (conventional treatment) and 60% (intensive treatment), respectively. These represented 65 relapses for the conventional arm versus 44 for the intensive arm.

OS was 70.27 (+/- 2.48) months (95% CI: 65.47 - 75.08) in the conventional treatment group and 71.78 (+/- 2.13) months (95% CI: 67.83 - 75.73) in the intensive treatment group, but the difference (1.51 +/- 3.26 months) did not reach statistical significance. At the time of analysis, 91 patients had died (50 in the standard arm and 41 in the intensive arm).

**Clinical conclusions**
The effectiveness analysis showed that HDC improved DFS in comparison with conventional chemotherapy in breast cancer patients, while estimates of OS were comparable.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were DFS and OS. These were derived directly from the effectiveness analysis. No discounting was reported.

**Direct costs**
The cost analysis was performed from the perspective of a French hospital. The health services included in the economic analysis were hospital stays (length of inpatient stays and number of day-clinic visits), pharmacy (quantities of drugs administered), blood products (number of transfusion episodes), laboratory (clinical protocol-specified tests and medical examinations, plus additional tests due to febrile events), surgical procedures (mastectomy or breast-conserving surgery). The costs associated with radiotherapy were excluded since modalities of irradiation were identical in both treatment groups. The unit costs were not presented separately from the quantities of resources used. Resource use was estimated on the basis of data collected prospectively alongside the clinical trial.

Only data on the costs and resource use associated with relapse were derived from another published study. The hospital costs were derived from one centre (Institut Paoli-Calmettes) using real costs rather than charges. Such costs included consumable supplies, staff, food, depreciation of equipment and overheads. The overhead costs were estimated using the step-down methodology. Drug prices represented the purchase prices nationally negotiated by the Federation of French Cancer Hospitals. Prices of blood products were derived from official 1999 prices. The costs of laboratory tests, diagnostic examinations and surgical interventions were determined using the official tariffs of the French National Health Service. The costs of the peripheral stem-cell collection procedure (including the costs of labour, supplies, equipment and laboratory tests) were obtained from a parallel French study. Discounting was not relevant since 6-month costs were assessed. The price year was not reported, but it might have been 1999.
Statistical analysis of costs
Parametric and non-parametric bootstrap tests were used to test the difference in mean costs between treatments.

Indirect Costs
The indirect costs were not included because they were not consistent with the perspective adopted in the study.

Currency
Euros (Euro).

Sensitivity analysis
A sensitivity analysis was performed to assess the robustness of the cost estimates to variations in some parameters. In particular, the unit prices of the three main cost factors (hospitalisation, drugs and blood products), differences between the management of patients in a clinical trial and current clinical practice (i.e. decreases in hospitalisations), and length of hospitalisation. The authors appear to have set the alternative values. Further, the issue of uncertainty surrounding the cost-effectiveness estimates was addressed using the truncated Fieller's method to derive 95% CIs.

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

Cost results
The total 6-month costs per patient were Euro5,188 (+/- 1,920) (95% CI: 4,883 - 5,492) in the conventional treatment group and Euro17,837 (+/- 3,360) (95% CI: 17,286 - 18,389) in the intensive treatment group. The difference of Euro12,650, (p<0.001), was due mainly to the higher length of hospital stay and granulocyte colony-stimulating factor administration associated with intensive treatment.

However, including the cost of relapse, the difference between the mean costs of the two treatments decreased. The mean costs per patient were Euro28,262 for the intensive arm and Euro20,859 for the standard treatment, almost a 42% decrease in the cost-difference. This was due to a lower proportion of relapses with the intensive treatment.

The cost estimates were robust to variations carried out in the sensitivity analysis.

Synthesis of costs and benefits
When DFS was used as the summary benefit measure, an incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the two treatments. The incremental cost per disease-free life-year gained with intensive treatment over conventional chemotherapy was Euro13,074 (95% CI: 7,879 - 37,841).

When OS was used as the summary benefit measure, a cost-minimisation analysis was carried out because of the lack of statistically significant differences between the groups in terms of clinical end points. Thus, conventional treatment was the least costly strategy.

Authors' conclusions
For women with breast cancer, adding a single course of high-dose chemotherapy (HDC) led to a clinical benefit in terms of disease-free survival (DFS) for an additional cost that seems to have been acceptable from the perspective of a French hospital, although HDC was 3.4 times more expensive than standard-dose chemotherapy. However, handling uncertainty showed that the upper bound of the confidence interval (CI) for the cost-effectiveness ratio was around Euro38,000, which might be above society's willingness to pay for a disease-free life-year. If overall survival (OS) was used as the clinical benefit, then conventional treatment would be preferred.
CRD COMMENTARY - Selection of comparators
The selection of four cycles of FEC 100 as the comparator was appropriate as it represents the conventional chemotherapy approach for patients with breast cancer. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a clinical trial, but limited information on the design and other characteristics of the trial was provided. The size of the sample and the length of follow-up were reported, whereas the demographic and clinical characteristics of the two groups of patients were not. Further, the baseline comparability of the study groups was not reported. Details of the sample selection and randomisation procedures were not provided, nor was there any information on the loss to follow-up. Thus, it was difficult to assess the internal validity of the study, although a randomised, clinical trial is usually associated with a robust design.

Validity of estimate of measure of benefit
Two summary benefit measures were used. DFS was specific to the interventions considered in the study, while OS is a more generalisable measure and is thus comparable with the benefits of other health care interventions. Undiscounted survival was estimated. The authors stated that the use of DFS is particularly relevant in the context of treatments where quality of life is an important element of decision-making, such as cancer care.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective adopted in the study. A justification for excluding the costs of radiotherapy was provided. A breakdown of the cost items was reported, but the unit costs were not presented separately from the resource quantities. This limits the possibility of replicating the cost analysis in other settings. The source of the data for each item was reported. Statistical analyses were carried out because of the skewed distribution of the costs. The robustness of the cost estimates to variations in some key parameters was investigated in the sensitivity analysis. The authors emphasised that real costs rather than charges were used, which represents a strength of the analysis.

Other issues
The authors stated that their estimates of costs and benefits were consistent with those presented in other recently published studies. In terms of the generalisability of the study results to other settings, the authors noted that the results of the study depended strongly on treatment patterns, thus the conclusions of the analysis should be extrapolated only to contexts comparable with those observed in the current study. In fact, the development of outpatient treatment modalities would improve the cost-savings associated with the intensive chemotherapy protocol. The study referred to women with breast cancer and this was reflected in the authors’ conclusions.

Implications of the study
The study results suggested that caution is required when interpreting the results of the analysis in order to make a decision on the cost-effectiveness of HDC for women with breast cancer. The authors stated that an evaluation of toxicity, quality of life, and a quality-adjusted survival analysis of chemotherapy protocols is ongoing.

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Bibliographic details
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Antineoplastic Combined Chemotherapy Protocols /administration & dosage /economics; Breast Neoplasms /drug therapy /economics; Cost-Benefit Analysis; Cyclophosphamide /administration & dosage; Epirubicin /administration & dosage; Female; Filgrastim; Fluorouracil /administration & dosage; Granulocyte Colony-Stimulating Factor /administration & dosage; Health Services /utilization; Humans; Middle Aged; Mitoxantrone /administration & dosage; Recombinant Proteins; Stem Cell Transplantation; Uncertainty

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