Is adjuvant therapy for older patients with node (-) early breast cancer cost-effective

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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 present study compared five treatment options for node negative (-) breast cancer in elderly women:

cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) x6 chemotherapy;
adriamycin, cyclophosphamide (AC) x4 chemotherapy;
tamoxifen hormone therapy (HRT) x5 years;
tamoxifen HRT+CMF; and
tamoxifen HRT+AC.

All strategies were compared with the reference strategy of giving no adjuvant therapy.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The authors evaluated the strategies for six hypothetical cohorts of node (-) women: all combinations of (1) 65, 75, 85 years old and (2) oestrogen-receptor positive or negative (ER+ and ER-, respectively).

Setting
The setting was tertiary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence was obtained from studies dating from 1999 to 2002. The resource use data were derived from published guidelines and research studies, and practising physicians were consulted, but no dates were reported. The price year was 2001.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on expert opinions.

Modelling
Decision analysis modelling, using life tables, integrated the cost of treatment in dollars and impact in length and quality
of life. The time horizon was 10 years. Several assumptions were used in the model. It was estimated that 10% of patients would require daily granulocyte colony stimulating factor (G-CSF) for 10 days each cycle, after the first cycle of chemotherapy, to treat low white blood counts. It was estimated that 3% would require hospitalisation for fever and neutropenia (low blood counts). For models on tamoxifen therapy, the percentage patients dying in the first 5 years on therapy in life expectancy models was used to calculate both the costs and disutility of treatment. Finally, the 10-survival benefit from chemotherapy was divided equally over all the years.

Outcomes assessed in the review
The outcomes assessed were mortality rates for breast cancer and odds ratios reductions in 10-year mortality.

Study designs and other criteria for inclusion in the review
No inclusion criteria for the review were reported. However, the study designs used by the authors included meta-analyses of clinical trials and randomised controlled trials (RCTs).

Sources searched to identify primary studies
The primary data sources on the benefits of adjuvant therapy were meta-analyses conducted by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). In addition, the 2000 to 2002 Proceedings of the American Society of Clinical Oncology online abstracts were searched for RCTs pertinent to the analysis.

Criteria used to ensure the validity of primary studies
No criteria were reported to ensure the validity of the primary studies, but the EBCTCG has undertaken systemic overviews every 5 years since 1984/85, using rigorous methods for trial identification, data checking and meta-analysis.

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

Number of primary studies included
The authors reported that 27 primary studies provided effectiveness evidence.

Methods of combining primary studies
A narrative method was used to combine the studies.

Investigation of differences between primary studies
Not reported.

Results of the review
This analysis used initial 10-year breast cancer mortality rates of 20%, which roughly corresponded to the natural history of younger women with node-negative diseases.

For HRT x5 years, the odds reduction (+/- standard deviation, SD) in 10-year mortality was 0.32 (+/- 0.10) for 45-year-old women, 0.33 (+/- 0.06) for 65-year-old women and 0.34 (+/- 0.13) for 75-year-old women.

For intravenous CMF, the odds reduction (+/- SD) in 10-year mortality was 0.34 (+/- 0.07) for 45-year-old women and 0.08 (+/- 0.04) for 65-year-old women.

For intravenous AC, the odds reduction (+/- SD) in 10-year mortality was 0.38 (+/- 0.09) for 45-year-old women and
0.11 (+/- 0.06) for 65-year-old women.

For HRT+CMF, the odds reduction (+/- SD) in 10-year mortality was 0.57 (+/- 0.17) for 45-year-old women and 0.44 (+/- 0.11) for 65-year-old women.

For HRT+AC, the odds reduction in 10-year mortality was 0.60 (SD not available) for 45-year-old women and 0.46 (SD not available) for 65-year-old women.

**Methods used to derive estimates of effectiveness**
The study was based on published data, experts' opinions and authors' assumptions. As prognosis data were unavailable for the older cohorts, some assumptions were made.

**Estimates of effectiveness and key assumptions**
The following survival benefit values were assumed:

- HRT x5 years, 0.25 (range: 0.20 - 0.36) for 85-year-old women;
- intravenous CMF, 0.02 (range: 0 - 0.08) for both 75- and 85-year-old women;
- intravenous AC, 0.033 (range: 0 - 0.11) for both 75- and 85-year-old women;
- HRT+CMF, 0.36 (range: 0.30 - 0.44) for 75-year-old women and 0.25 (range: 0.20 - 0.44) for 85-year-old women; and
- HRT+AC, 0.38 (range: 0.30 - 0.46) for 75-year-old women and 0.27 (range: 0.20 - 0.46).

Other key assumptions were also made. Tamoxifen and chemotherapy were assumed to have no impact on the non-cancer mortality rate. Node-negative patients were assumed to have a 20% chance of dying in 10 years after surgical resection for breast cancer. It was also assumed that there were no long-term effects of adjuvant therapy.

**Measure of benefits used in the economic analysis**
The measure of benefits was quality-adjusted life-years (QALYs). The utility weights were mostly derived from the literature and expert opinion. Health state valuations were based on a time trade-off of the number of days of healthy life a patient would give up to avoid the side effects of adjuvant therapy. The baseline health state assigned was 1.0, representing perfect health on a 0 to 1 scale. Values derived from other studies were used for the analysis. More specifically, treatment health state valuations of 0.99 of baseline for hormone therapy, 0.90 of baseline for minor toxicity with chemotherapy, and 0.80 of baseline for major toxicity with chemotherapy. The QALYs were discounted at an annual rate of 3%.

**Direct costs**
The medical direct costs were included in the analysis. These were for the initial consultation, chemotherapy administration, drugs, biweekly laboratory testing and biweekly follow-up visits.

To calculate costs, published guidelines, research studies and practising physicians were consulted. The cost estimates were based on the cost of health services in 2001 Medicare-allowed charges. For drug costs, 2001 Average Wholesale Prices and the proportion paid by the Public Health Service were used. The costs were discounted at a rate of 3%. The authors did not report the quantities and the costs separately. The estimations of the quantities and the total costs were derived through modelling.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.
Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
The authors investigated areas of uncertainty related to variability in the data through sensitivity and scenario analyses. The ranges selected were derived from published literature or authors’ assumptions. The parameters investigated were the baseline health states (0.8 and 0.6), discount rate (0, 5 and 25%) and drug costs (0 and 5%, and Public Health Service pricing). In addition, the authors determined the degree of efficacy needed for chemotherapy and combined therapy to be cost-effective using two cut-off points for cost-effectiveness ($50,000/QALY and $100,000/QALY).

Estimated benefits used in the economic analysis
Compared with the reference strategy of no adjuvant therapy (0 benefit), the highest gains of adjuvant treatments for women with node (-) breast cancer were 0.89 years for 65-year-old women, 0.42 years for 75-year-old women and 0.13 years for 85-year-old women. In older women aged 75 and 85, these gains reflected the most optimistic assumptions of treatment efficacy, with a response equivalent to that of a 65-year-old woman.

Cost results
Compared with the reference strategy of no adjuvant therapy (0 cost), the discounted costs of adjuvant treatment were:

- $4,568 for CMF x6;
- $5,965 for AC x4;
- $6,320 for HRT x5 years;
- $10,923 for HRT(5)+CMF; and
- $12,320 for HRT(5)+AC.

In addition, the authors reported the health costs in days rounded to the nearest full day and representing toxicity of chemotherapy:

- 17 days for CMF x6;
- 11 days for AC x4;
- 17 days for HRT x5 years;
- 35 days for HRT(5)+CMF; and
- 28 days for HRT(5)+AC.

Synthesis of costs and benefits
In a 65-year-old woman with node (-) ER+ disease, HRT was more cost-effective ($10,194/QALY) than CMF or AC chemotherapy. Although CMF was less expensive than HRT, treating half of the women with no adjuvant therapy and half with HRT cost less and bought more years of life than treating all women with CMF or AC. HRT had an "extended dominance" over CMF and AC in ER+ women. The combined therapy HRT+AC was also efficient since the incremental cost-effectiveness ratio was $22,220/QALY over HRT. In women who were node (-) ER-, the incremental
cost-effectiveness ratio of chemotherapy was $30,451/QALY for CMF over no treatment and $46,572/QALY for AC compared with CMF.

In a 75-year-old woman with node (-) ER+ disease, 5 years of hormone therapy (at $19,530/QALY) dominated all other adjuvant therapy options unless chemotherapy was assumed to be as efficacious as in 65-year-old women. In that case, adding chemotherapy in node (-) patients bought QALYs for $54,530/QALY using HRT(5)+AC. If the effect of adding chemotherapy declines with age, the gains would be much smaller and it would cost over $280,000/QALY at the mid bound for chemotherapy efficacy, and it would not cost-effective. In a patient who is ER-, assuming a high bound for the efficacy of chemotherapy, AC dominated CMF and cost $75,559/QALY when compared with no adjuvant treatment.

Since the benefit of both hormone therapy and chemotherapy was even less clear in 85-year-old patients, the gains were smaller and more possibilities needed evaluation. If the efficacy of hormone therapy were age-sensitive at older ages, the incremental cost-effectiveness compared with no adjuvant treatment would be $100,533/QALY. In this scenario, combined therapy would be dominated.

There was a small difference in the rank order of treatment choice using 0, 5, 10 and 25% discount rates.

Authors' conclusions
Chemotherapy and combination therapy could still be cost-effective in older patients under certain conditions. Patient age impacted on the decision, both through the probable efficacy of treatment and from the potential years of life gained from cures. Even though age in these contexts most often referred to chronological age, physicians need to assess the older patient carefully to derive an estimate of a patient's physiological age. Also, given the fact that the costs and benefits of Adriamycin plus cyclophosphamide (AC) and cyclophosphamide, methotrexate and 5-fluorouracil (CMF) were relatively close, the decision as to the appropriate treatment must include non economic factors as well, such as tolerance and preference.

CRD COMMENTARY - Selection of comparators
The authors gave a justification for their choice of the comparators. The impact of chemotherapy for those women over the age of 70 and hormone therapy for those women over the age of 80 had not been analysed before because these subgroups represented a small percentage of the overall patients enrolled in clinical trials. You should judge whether these treatment strategies are relevant in your own setting, or whether other comparators from other drugs and treatments could also be relevant.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used. The authors used data from a high-quality meta-analysis when available, but one cannot be sure that all relevant literature was identified. The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources, experts' opinions and their own assumptions. The effectiveness evidence was derived from meta-analyses and randomised clinical trials, which are adequate sources to estimate effectiveness. The authors justified their own assumptions with reference to the medical literature. The estimates were investigated in sensitivity analyses, using ranges from the literature. The authors provided a justification for the ranges selected and reported.

Validity of estimate of measure of benefit
The authors used QALYs gained as a measure of benefits. This measure of benefit enables cross health technology comparisons. The authors stated that the utility weights used were mainly derived from the literature and health state valuations were based on the time trade-off method. Sensitivity analyses over adjusted QALYs were conducted, although they were not reported in full.
Validity of estimate of costs
The authors did not report the study perspective, although it seems to have been that of a health care payer. The medical direct costs were included but they were not reported in sufficient detail. The unit costs were taken from published sources. The quantities were not thoroughly reported, thus the analysis could not be easily reworked for other settings. In addition, the cost estimates were derived from Medicare-allowed charges; such charges do not reflect true opportunity costs (due to profit margin) and (in the absence of a cost-to-charge ratio) may limit the generalisability of the results beyond the authors' clinical setting. The total costs were reported only in discounted version. No statistical analysis of the costs was undertaken. Sensitivity analyses of the drug costs were conducted and reported. Discounting was appropriately carried out since the time horizon exceeded two years. The price year was reported, which will aid any future refutation exercise.

Other issues
The authors made comparisons of their findings with those from other studies, but they were not reported in full. According to the authors, the cost-effectiveness estimates from their model were different to those from previous models, which had demonstrated that the cost-effectiveness of chemotherapy was less than $50,000/QALY. These different results might be attributed primarily to the estimate of adjuvant therapy efficacy, a change in the cost of chemotherapy, and other assumptions about the costs of neutropenia and associated hospitalisations. The authors' conclusions reflected the scope of the analysis.

The authors did not explicitly address the generalisability of the results but they did consider other limitations. First, Medicare allowed charges were used to estimate the costs. Second, the same probability of neutropenia and resulting hospitalisation was used for all age groups. Third, the assumption of no impact of therapy on the non-cancer mortality rate. Finally, the preference weights used to estimate the health cost associated with the side effects of chemotherapy were based on aggregate data derived from limited studies. Many of the assumptions used would tend to increase the calculated value of adjuvant therapy.

Implications of the study
For women over 70 years old, who have traditionally been under-represented in clinical trials, there is a high degree of uncertainty in the expected benefit of therapies. This uncertainty is due, in part, to decreased longevity, to heterogeneity in older individuals in terms of co-morbidities and functional status, and to biological differences in the breast cancer itself. Focusing analytic and clinical research on older cancer patients would help ensure that high-quality cost-effective care could be provided in the next several decades, during which numbers of such cases will greatly increase. This study suggested that the cost-effectiveness of adjuvant therapy decreases with age. In 75-year-old ER+ patients, tamoxifen is especially cost-effective while chemotherapy is marginally cost-effective. In 85-year-old ER+ patients, hormone therapy was marginally cost-effective only if efficacy was age insensitive.

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