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Economic evaluation of chemotherapy

Review of cost–effectiveness assessments of chemotherapy in adjuvant and advanced breast cancer

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Economic assessments of treatment alternatives in breast cancer have been predominantly ones addressing the role and type of adjuvant therapy. These assessments have shown that the effectiveness of the intervention drives the cost–effectiveness results. Other key factors were the relative risk of recurrence, the time frame considered and only minimally the costs of the intervention. Assessments in advanced breast cancer are few in parallel with the limited number of phase III trials. Future assessments should address neoadjuvant therapy, high-dose adjuvant therapy and agents that alter disease associated complications agents such as biphosphonates. [© 1998 Lippincott Williams & Wilkins.]

Key words: Breast neoplasm, cost–benefit analysis, costs, decision modeling, review.

Introduction

As other papers in this special issue have noted, the inability to contain the costs of health care and curtail its growth is a major public policy issue in all Western societies. As Eisenberg has stated, "to suggest that medical decision making can be divorced from consideration of cost denigrates the complexity of patient care".[1] In the US, oncology services have been a particular focus of attention since they consume an increasingly relative amount of hospital resources, is an area with a diverse set of recent advances due to biotechnology innovations, a reluctance to stop 'active therapy', and a blurriness of the line between established and investigational therapy. Tools are available to aid health planners in the assessment of alternative allocation of limited health care resources. The application of economic principles to medicine only addresses how to do so more effectively, not the absolute size of total revenues consumed or allocated. The tools of meta-analysis, decision analysis and cost-effectiveness analyses are each quantitative methods used to combine information to arrive at a summary conclusion, and have been essential to our research.[2] Although each method may appear intuitively easy, their proper conduct can be complex and rely on multi-faceted methodology. The skills required to do these types of analysis are also used in other areas of outcomes research and are cornerstone steps used in practice guideline development: extensive knowledge of research study design, practical skills and knowledge of the limitations and data collection, statistics, and critical appraisal of the published literature.

To date, the majority of our group's work in the assessment of the cost-effectiveness of oncologic interventions has focused on breast cancer. In this short review, we will revisit the findings of our past work, discuss selected work done by others and highlight areas in breast cancer ripe for future assessments.

Assessments of adjuvant therapies

Breast cancer readily leads itself to such assessments since it is the area with the most randomized controlled trials and meta-analyses. Adjuvant therapy is a classic set-up for decision analysis since the toxicities, costs and inconvenience of the adjuvant therapy occur immediately while the potential benefits

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will occur, if they occur, in the future. The scientific evaluation of adjuvant therapy after primary surgical treatment for early breast cancer has evolved gradually over the last two decades (see Table 1). The landmark 1988 meta-analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) confirmed the effectiveness of chemotherapy for node-positive pre-menopausal woman and tamoxifen especially for post-menopausal woman.[3] Despite over 23 000 women from 61 trials being assessed in the meta-analyses, controversies persisted for many reasons including the limited long-term follow-up, the larger relative effectiveness in disease-free survival compared to overall survival and the size of the benefit in absolute when compared to relative effect.

Our group developed a decision analysis model that addressed the incremental benefits and cost-effectiveness of chemotherapy that was originally used for node-negative breast cancer and has subsequently been extended to other settings of early breast cancer.[4–6] The impetus for this work was the 1988 National Cancer Institute Clinical Alert to all physicians recommending that all node-negative breast cancer patients should be considered for treatment with adjuvant chemotherapy.[7] The thrust of this controversy focussed on the difference on the relative versus absolute benefit since women with node-negative disease have a relatively low risk of subsequent systemic recurrence and the number of events in the three trials on which the Clinical Alert was based were few. This model used a Markov process to calculate the cumulative outcomes of women who receive adjuvant therapy or not. The model described nine different health states possible after diagnosis from wellness to death. Simultaneously, all women experience anxiety about their potential future survival, may experience the adverse effects of chemotherapy if given, incur the costs of treatment and the majority will experience no increase in their survival. The model used the conceptual framework outlined in Table 2. The model addresses the question from a societal perspective using hypothetical cohorts of women who are subsequently followed using a mathematical Markov process to assess their lifetime survival and risk of recurrence. The efficacy of one group receiving chemotherapy was based on treatment efficacy derived from reported randomized clinical trials. The initial study used a relative risk reduction of 30% that was subsequently confirmed by the 1992 meta-analysis.[3,8] Two additional features of the efficacy of therapy were correctly modeled: the relative risk reduction is constant for a high or low risk of recurrence, therefore the absolute benefit will be greatest in those at greatest risk. In addition, the benefit of any form of adjuvant therapy appears to plateau after 5 years. After that, the recurrence curves are nearly parallel.

The model considered only direct health care costs based on a retrospective cost analyses of individuals at one academic health center. These estimates were based on a tracking fee for service patients charges and then adjusting these to estimate actual costs, drug purchasing costs and published estimates for treating disease recurrence. The model was done with and

Table 2. Conceptual framework used in cost–effectiveness assessments decision of adjuvant therapies in breast cancer[4–6]

Hypothetical cohorts
Societal perspective
Lifetime perspective estimating cost–effectiveness and cost–utility
Efficacy derived from published randomized trials or meta-analysis
Direct health care costs
Retrospective cost based on chart review and published estimates
Quality of life when included based on results obtained from surrogates using a linear analog scale
No specific co-morbidities considered or excluded

Table 1. Adjuvant therapies options

	Pre-menopausal	Post-menopausal	Elderly
Node-negative, ER−	chemotherapy versus Ø	chemotherapy versus Ø	Ø versus chemotherapy
Node-negative, ER+	chemotherapy versus tamoxifen	tamoxifen versus chemotherapy+tamoxifen	tamoxifen versus Ø
Node-positive, ER−	chemotherapy	chemotherapy	chemotherapy versus Ø
Node-positive, ER+	tamoxifen+chemotherapy versus chemotherapy	chemotherapy+tamoxifen versus tamoxifen	tamoxifen

The more commonly used strategy in the US is shown to the left. Additional prognostic factors such as S phase, ploidy and Heu-2 have been excluded.
Note: to date, no economic assessments of ovarian ablation are available.

without quality of life adjustments based on the use of a linear analog scale of surrogates. Since this was a hypothetical cohort—no specific co-morbidities were considered or patients were excluded.

The model showed that the benefit of adjuvant chemotherapy was highly dependent on the likelihood of disease recurrence that varied with patient age and biological features of the tumor. For example, an average 45-year-old women with an estimated recurrence risk of 4% would have survival benefit of an increase in quality-adjusted life expectancy of about 5 months. However, for older women with smaller cancers the benefit would decrease to less than 1 month. In contrast, in women with an 8% annual probability of recurrence, such as those with a large, estrogen receptor-negative tumor, the treatment would increase quality-adjusted survival by approximately 8 months.

Models translating the results of the meta-analysis into units that are more intuitively accessible to patients, physicians and policy makers have been used to tailor recommendations to individual patients and guide policy development. What remains a distressing finding is that many surveys have repeatedly shown that the perception that oncologists and woman have of the therapeutic gain from use of adjuvant chemotherapy markedly overestimates the actual benefit.[9,10] A variety of tools to aid patients in their decision making build upon these analyses: Levine's decision board, Ravdin's computer program Adjuvant! and the Foundation for Shared Decision Making Video series.[11,12] In many ways, to American oncologists showing that for most women at average or high risk for subsequent recurrence the incremental cost-effectiveness is less than $30 000 per quality-adjusted life-year was 'icing on the cake' since they were already extensively giving chemotherapy. To many it was surprising that the estimated costs of chemotherapy (or tamoxifen) were not a particularly sensitive factor. Our local tracking of drugs costs, preparation, delivery, physician fees, laboratory monitoring and potential anti-emetics assuming no hospitalizations for six cycles of cyclophosphamide+methotrexate+fluorouracil (CMF) or four cycles of adriamycin+cyclophosphamide in standard doses were each about $6000. Messori in his retrospective economic analysis of CMF used only $1595 per patient.[13,14]

The common key factors for this and subsequent analyses were the size of the relative reduction in risk with treatment, the relative risk of recurrence and the time frame considered. Our assessment of the role of tamoxifen in pre-menopausal women shows that for estrogen receptor-positive woman, tamoxifen should always be given since it provides meaningful increases in survival at a modest cost. This is particularly true in countries were tamoxifen is now available as a generic drug with typical costs of less than 25 cents per day. The larger controversy is whether tamoxifen alone is sufficient or if it should be combined with chemotherapy. Our results show that chemotherapy for higher risk pre-menopausal woman provides additional benefit at a modest incremental cost ($14 800–33 100) per life-year gained. What is surprising, is that many US oncologist only use chemotherapy and do not follow it with tamoxifen. In addition, the just published 1998 update from the EBCTCG found the relative efficacy of tamoxifen if used for 5 years to be 50% compared to our analyses estimate of 19%.[15] It is likely that combination therapy is actually cost-saving based on this efficacy estimate!

In absolute terms, the largest groups of woman facing the adjuvant therapy decision are woman between the ages of 51 and 65 who have zero or one axillary node involved and have estrogen receptor-positive primary tumors. For these women, the worldwide standard of care is tamoxifen for 5 years. Whether adding chemotherapy to tamoxifen provides any additional benefit remains uncertain, and is the source of much of the discordance in the patterns of adjuvant care between the US, Canada and Western Europe. The 1992 EBCTCG meta-analyses reported on indirect comparisons of these treatments suggesting that the combined therapy provided about an additional 20% relative risk reduction. This was markedly lower than that seen in NSABP B-16 that at 3 years of follow-up had about a 50% relative risk reduction and a 17% absolute risk reduction.[16] Our group modified our model and reported in abstract form only our results using a 19% relative risk reduction.[17] We found cost-utility ratios of combination therapy compared to tamoxifen alone added 0.23 years to overall survival, 0.12 quality-adjusted years at an incremental cost of $58 000 per quality-adjusted year. We are eagerly awaiting the publication of the next round of the EBCTCG meta-analyses that includes direct comparisons of these strategies, longer follow-up for survival effects, and comparisons between anthracycline and non-anthracycline combinations. Meanwhile, it should be humbling to the chemotherapy advocates to see the results of the Gelber Q-TWiST analysis from nine trials involving over 3900 patients.[18] With 7 years of follow-up the modest benefit of increased relapse-free and overall survival for patients who received chemotherapy just balanced the costs in terms of acute toxic side effects. They found that chemotherapy-treated patients gained an average of 5.4 months of relapse-free and 2 months of overall survival. No values of preference

weights for time spent undergoing chemotherapy and time after relapse gave significantly more Q-TWiST with chemotherapy plus tamoxifen than with tamoxifen alone.

Assessments in advanced breast cancer

In contrast to the adjuvant setting, there are few comparative randomized controlled trials, particularly for second-line therapy, that support a specific form of chemotherapy. Paclitaxel and docetaxel were each approved in the US for treatment of metastatic breast cancer based on open-label phase II trials. We are unaware of any published cost-effectiveness comparisons of alternative chemotherapy regiments outside bone marrow transplantation.

Since the onset of its use, the debate about the role of high-dose chemotherapy with autologous bone marrow transplantation (ABMT) has been as much about the costs of the procedures as its efficacy. Although marked improvements in supportive care with cytokines, peripheral stem cells and anti-infectives have lowered the morbidity and mortality of ABMT, the procedure remains very expensive with costs hovering at 3- to 10-fold those associated with conventional therapy.[19] Despite the costs, its use has continued to grow since many women believe that ABMT is the only reasonable approach in an otherwise hopeless situation and attempts to restrict its use by contract or 'experimental' exclusion have been found illegal. Currently, breast cancer is the most common indication for ABMT in North America.

In 1992, we reported a new Markov decision model that addressed this question.[20] A key assumption of the model, which has often been overlooked, was that ABMT was given only to women in whom the disease had responded to induction chemotherapy. We found ABMT was the preferred approach under almost all assumptions but the size of the benefit varied greatly with the period of interest. The incremental cost-effectiveness ratios were $115 800 per life-year using a 5 year time horizon and $28 600 if one assumed that disease-free women at 5 years are subsequently cured from their breast cancer. Unfortunately, in 1998 all members of the oncology community are still awaiting the results of the North American prospective randomized trials that should clarify but not settle the issue. An economic companion assessment to these trials is planned.

In addition to chemotherapy, Bates and colleagues have recently reported a model that addressed the role of a cardioprotective agent, dexrazoxane, in preventing anthracycline-induced caridiotoxicity.[21] The analysis attempted to abstract clinical events from the clinical trials assessing dexrazoxane. They found that therapy with dexrazoxane costs $5661 per cardiac event prevented. However, what remains problematic is that some studies found that the agent reduced the efficacy of chemotherapy that would like be deleterious to the cost-utility ratios.

Improved assessments and new issues in breast cancer

The previously described decision analysis models are based on hypothetical cohorts of patients. There are a few studies using a retrospective design assigning the community effectiveness of therapy. The most prominent breast cancer example is the British Columbia study of the effectiveness of adjuvant therapy.[22] However, retrospective assessments are limited by well-known flaws and plagued by incompleteness. The future of cost and outcomes assessments lies in the prospective assessment of cohorts in a randomized trial setting (efficacy) and/or cohorts within an integrated delivery (effectiveness). In the randomized trial settings doing an economic analysis within the clinical trial is being increasingly considered and

Table 3. Other current or potential situations in breast cancer amenable to pharmacoeconomic assessments

	Options
Neoadjuvant chemotherapy	pre- versus post-operative
High-risk stage II ($\geq$10 positive nodes)	standard chemotherapy versus high-dose chemotherapy with stem cell support
Limited stage metastatic breast cancer	high-dose chemotherapy versus standard chemotherapy
Taxanes versus anthracycline regimens as first-line therapy in hormone-resistant metastatic disease	numerous combinations
Biphosphonates in the prevention of metastatic bony complications	pamidronate versus Ø

occasionally incorporated into primary data collected with a specific trial. This topic was recently addressed at a conference sponsored by the National Cancer Institute.[23] Schulman and colleagues have been involved since the onset in the ECOG high-dose therapy adjuvant trial that should be reported in 1999. We are unaware of any current prospective economic assessments within the US in integrated health plans.

Table 3 lists some areas that I believe will be ripe for future cost-utility assessments in breast cancer. Each of these will likely be dependent on patient-specific utilities since substantial differences in survival are unlikely (with the possibly exception of high-dose adjuvant therapy).

References

1. Eisenberg JM. Clinical economics. A guide to the economic analysis of clinical practices. *J Am Med Ass* 1989; **262**: 2879-86.
2. Petitti DB. *Meta-analysis, decision analysis, and cost-effectiveness analysis*. New York: Oxford University Press 1994.
3. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. Early Breast Cancer Trialists' Collaborative Group. *N Engl J Med* 1988; **319**: 1681-92.
4. Hillner BE, Smith TJ. Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. A decision-analysis model. *N Engl J Med* 1991; **324**: 160-8.
5. Smith TJ, Hillner BE. The efficacy and cost-effectiveness of adjuvant therapy of early breast cancer in premenopausal women. *J Clin Oncol* 1993; **16**: 1-10.
6. Desch CE, Hillner BE, Smith TJ, Retchin SM. Should the elderly receive chemotherapy for node negative breast cancer? A cost-effectiveness analysis examining total and active life expectancy outcomes. *J Clin Oncol* 1993; **16**: 11-20.
7. National Cancer Institute. *Clinical Alert*. May 16-18. Bethesda, MD: National Cancer Institute 1988.
8. Early Breast Cancer Trialists' Collaborative group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1992; **339**: 1-15; 71-85.
9. Rajagopal S, Goodman PJ, Tannock IF. Adjuvant chemotherapy for breast cancer: discordance between physicians' perception of benefit and the results of clinical trials. *J Clin Oncol* 1994; **12**: 1296-304.
10. Ravdin PM, Siminoff IA, Harvey JA. Survey of breast cancer patients concerning their knowledge and expectations of adjuvant therapy. *J Clin Oncol* 1998; **16**: 515-21.
11. Levine MN, Gafni A, Markham B, Macfarlane D. A bedside decision instrument to elicit a patient's preference concerning adjuvant chemotherapy for breast cancer. *Ann Intern Med* 1992; **117**: 53-8.
12. Ravdin PM. A computer program to assist in making breast cancer adjuvant therapy decisions. *Semin Oncol* 1996; **23**: 43-50.
13. Trippoli S, Becagli P, Messori A. Adjuvant cyclophosphamide, methotrexate and fluorouracil for node-positive breast cancer: a lifetime cost-utility analysis based on a modified Q-TWiST method [letter]. *Eur J Clin Pharmacol* 1997; **53**: 281-2.
14. Messori A, Becagli P, Trippoli S, Tendi E. Cost-effectiveness of adjuvant chemotherapy with cyclophosphamide+methotrexate+fluorouracil in patients with node-positive breast cancer [published erratum appears in *Eur J Clin Pharmacol* 1997; **51**(5): 427]. *Eur J Clin Pharmacol* 1996; **51**: 111-6.
15. Early breast cancer trialists' collaborative group. Tamoxifen for early breast cancer: an overview of the randomized trials. *Lancet* 1998; **351**: 1451-67.
16. Fisher B, Redmond C, Legault-Poisson S, *et al*. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the National Surgical Adjuvant Breast and Bowel Project B-16. *J Clin Oncol* 1990; **8**: 1005-18.
17. Hillner BE, Smith TJ. Estimating the efficacy and cost-effectiveness of tamoxifen (TAM) versus TAM plus adjuvant chemotherapy in post-menopausal node-positive breast cancer. A decision analysis model. *Proc Am Soc Clin Oncol* 1992; **11**: 55 (abstr 46).
18. Gelber RD, Cole BF, Goldhirsch A, *et al*. Adjuvant chemotherapy plus tamoxifen compared with tamoxifen alone for postmenopausal breast cancer: meta-analysis of quality-adjusted survival. *Lancet* 1996; **347**: 1066-71.
19. Antman KH, Rowlings PA, Vaughan WP, *et al*. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol* 1997; **15**: 1870-9.
20. Hillner BE, Smith TJ, Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results. *J Am Med Ass* 1992; **267**: 2055-61.
21. Bates M, Lieu D, Zagari M, Spiers A, Williamson T. A pharmacoeconomic evaluation of the use of dexrazoxane in preventing anthracycline-induced cardiotoxicity in patients with stage IIIB or IV metastatic breast cancer. *Clin Ther* 1997; **19**: 167-84.
22. Olivotto IA, Bajdik CD, Plenderleith IH, *et al*. Adjuvant systemic therapy and survival after breast cancer. *N Engl J Med* 1994; **330**: 805-10.
23. National Cancer Institute Economic Conference. The integration of economic outcome measures into NCI-sponsored therapeutic trials. *Monogr Natl Cancer Inst* 1995; **19**: 1-84.