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Economic evaluation of chemotherapy

Economic evaluation of endocrine therapy in the treatment of breast cancer

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Endocrine therapy has become an integral part of the management of breast cancer and its different clinical applications raise different economic issues. The low toxicity, good response and relatively low cost of agents makes endocrine therapy an attractive treatment option for breast cancer patients at different stages of their disease. The method, hypotheses and expectations from economic analysis of endocrine therapy depend on the objectives of treatment (preventive, curative or palliative), the therapies being compared, the population being treated and the clinical benefits expected. The economic and quality of life literature has focused mainly on the analysis of endocrine therapy in the adjuvant setting. As budgets continue to shrink and treatment guidelines become challenged by new therapeutic and preventive approaches, decision analysis in breast cancer management is likely to become more explicit. Economic analysis can be a useful tool to guide clinical decisions in the management of this complex and chronic disease. Ultimately, the positioning of endocrine therapy with respect to other complementary or alternative treatment modalities will depend on the level of expected effectiveness, and on finding the best therapeutic solution to meet the breast cancer patient's clinical situation, expectations and needs. [© 1998 Lippincott Williams & Wilkins.]

Key words: Breast cancer, economic analysis, endocrine therapy, quality of life.

Introduction

Of all the oncological indications, breast cancer has received the greatest attention from economists and public health researchers over the past 15 years. Breast cancer is one of the most prevalent cancers in the industrialized world, with approximately 1 in every 10 women being affected during the course of her lifetime.[1] However, screening programmes and therapeutic advances have had a tangible impact on prognosis for breast cancer. Breast cancer patients often traverse several stages of disease and treatment, with recurrences sometimes occurring up to 10 years after the initial tumor is diagnosed, lending breast cancer a chronicity untypical of other cancer types. For example, whereas the prevalence and incidence of breast cancer in the UK are in the order of 105 000 and 25 000 cases, respectively, these figures are 40 000 and 26 000 for lung cancer and 27 000 and 56 000 for colorectal cancer.[2] This high prevalence-to-incidence ratio has important economic implications, i.e. (i) breast cancer is accounting for an ever-growing share of health care resources, and (ii) analysis of any therapeutic strategy for breast cancer warrants a life-long model which encompasses costs and effects over the full course of illness. Alternatively, treatments can be examined within each phase of breast cancer management, with clinical and cost components restricted to the period concerned (pre-operative, adjuvant, advanced disease, palliative, etc.).

Endocrine therapy can be defined as the chemical or surgical interference with estrogen synthesis to slow or inhibit tumor growth.[3] The era of endocine therapy began over 100 years ago in 1895 when Beatson discovered the clinical benefit in removing the ovaries of a 33-year-old patient with advanced breast cancer.[4] The discovery of tamoxifen marked another milestone in the development of hormonal therapy and several new classes of agents have been introduced since then. Today, endocrine therapy is an integral part of established treatment guidelines, the most recent being the 1995 St Gallen recommendations on the treatment of primary breast cancer[5] and the 1990 NIH guidelines on adjuvant treatment of breast cancer.[6] On-going research efforts continue to explore new opportunities for the use of endocrine therapy either in addition or as a substitute to surgery, radiotherapy, chemotherapy

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or supportive care at various stages of the disease and in different subsets of patients.[3,7-10]

The purpose of economic evaluation is to compare the relative value of alternative therapies in terms of resources used and clinical benefits expected. The economic merits of endocrine therapy are contingent upon several factors: (i) the objectives of treatment, (ii) the treatments being compared, (iii) the population being treated and (iv) clinical benefit. The purpose of this paper is to present the issues governing the economic evaluation of endocrine therapies, to discuss results published in the literature, and to highlight priority areas for future research and its applications.

Endocrine therapy

The rationale for endocrine therapy is to reduce the estrogenic stimulus to tumor growth, either by removing sites of estrogen synthesis, removing the source of or inhibiting gonadotrophins, blocking estrogenic action, antagonizing estrogens with androgens or progestogens, or inhibiting estrogen synthesis.[3] There is some discrepancy in the categorization of endocrine therapies; however, the major categories remain unchallenged. They include: ovarian ablation, anti-estrogens, aromatase inhibitors, progestins, anti-progestins, gonadotrophin releasing hormonal agents and luteinizing hormone releasing hormonal analog.[1,7] Somastostatin analog, vitamin D analog and retinoids can also be considered endocrine therapies; however, few clinical data are available on the use of these products in breast cancer.[1] They will not be covered in this article.

Tamoxifen is the recognized treatment of choice in endocrine therapy and is the *de facto* comparator for any endocrine agent seeking acceptance as first-line therapy in most breast cancer indications. Tamoxifen has demonstrated high response rates in specific subgroups of women with breast cancer. Long-term use of tamoxifen has been associated with a decrease in the occurrence of contralateral cancers, osteoporosis and cardiovascular disease, mainly due to the lowering of blood lipid levels. However, data have also suggested an increased risk of endometrial carcinoma, thrombosis and secondary cancers in the gastrointestinal tract.[1,9] The thrust of endocrine research has thus been driven by the search for a highly effective, non-toxic therapy which can replicate the positive effects of tamoxifen without any impending long-term toxicity.[1] Aromatase inhibitors and some progestins, i.e. toremifene,[11] have demonstrated equivalent response rates and efficacy to tamoxifen in advanced breast cancer,[1] while trials in the adjuvant and pre-operative setting are ongoing for several agents. Non-steroidal anti-estrogens have a similar toxicity profile to tamoxifen,[1] whereas steroidal anti-estrogens and selective aromatase inhibitors are most promising as they produce neither carcinogenic effects on the endometrium nor thrombosis.[1,12] Evidence of positive skeletal, cardiovascular and lipid effects of sustained endocrine therapy exists for some agents but needs to be confirmed by more substantial data.[1]

Table 1. Treatment guidelines for early stage breast cancer (adapted from Dess and Davidson[35] based on Goldhirsch *et al.*[5])

Patient group	Receptor status	Tumor characteristics (risk)	Treatment
Treatment guidelines for node-negative patients			
Premenopausal	positive	minimal to moderate	none or tamoxifen
		high	chemotherapy ± tamoxifen
	negative	minimal	none
		high	chemotherapy
Postmenopausal	positive	minimal to moderate	none or tamoxifen
		high	tamoxifen ± chemotherapy
	negative	minimal	none
		high	chemotherapy (if tolerated) ± tamoxifen
Treatment guidelines for node-positive patients			
Premenopausal	positive		chemotherapy ± tamoxifen
			ovarian ablation ± tamoxifen
	negative		chemotherapy
Postmenopausal	positive		tamoxifen ± chemotherapy
	negative		chemotherapy

Clinical expectations

The positioning of endocrine therapy within the management of breast cancer depends on the timing of introduction and on the prognostic group being targeted. In the adjuvant setting, in which endocrine therapy is given after surgery, the intent is to cure, by both delaying and preventing relapse and ultimately improving survival. In the metastatic breast cancer patient, therapy may be expected to increase response rates and duration of response, thereby postponing disease progression; however, no curative or survival effect may be expected. In the preventive setting, morbidity and mortality should both be reduced and even prevented altogether in specific subsets of women. The merits of combined endocrine and chemotherapy, i.e. the addition of chemotherapy to tamoxifen in post-menopausal, estrogen receptor-positve (ER+) women, or tamoxifen to chemotherapy in premenopausal women, are still debated in the clinical literature.[13] Confounding variables to the evaluation of chemoendocrine trials are the interactions between chemotherapy and endocrine therapeutic agents, as well as the scheduling of different treatments.[13]

Detailed guidelines have been elaborated for the management of early (non-metastatic) breast cancer disease.[5,6] Summary recommendations are presented

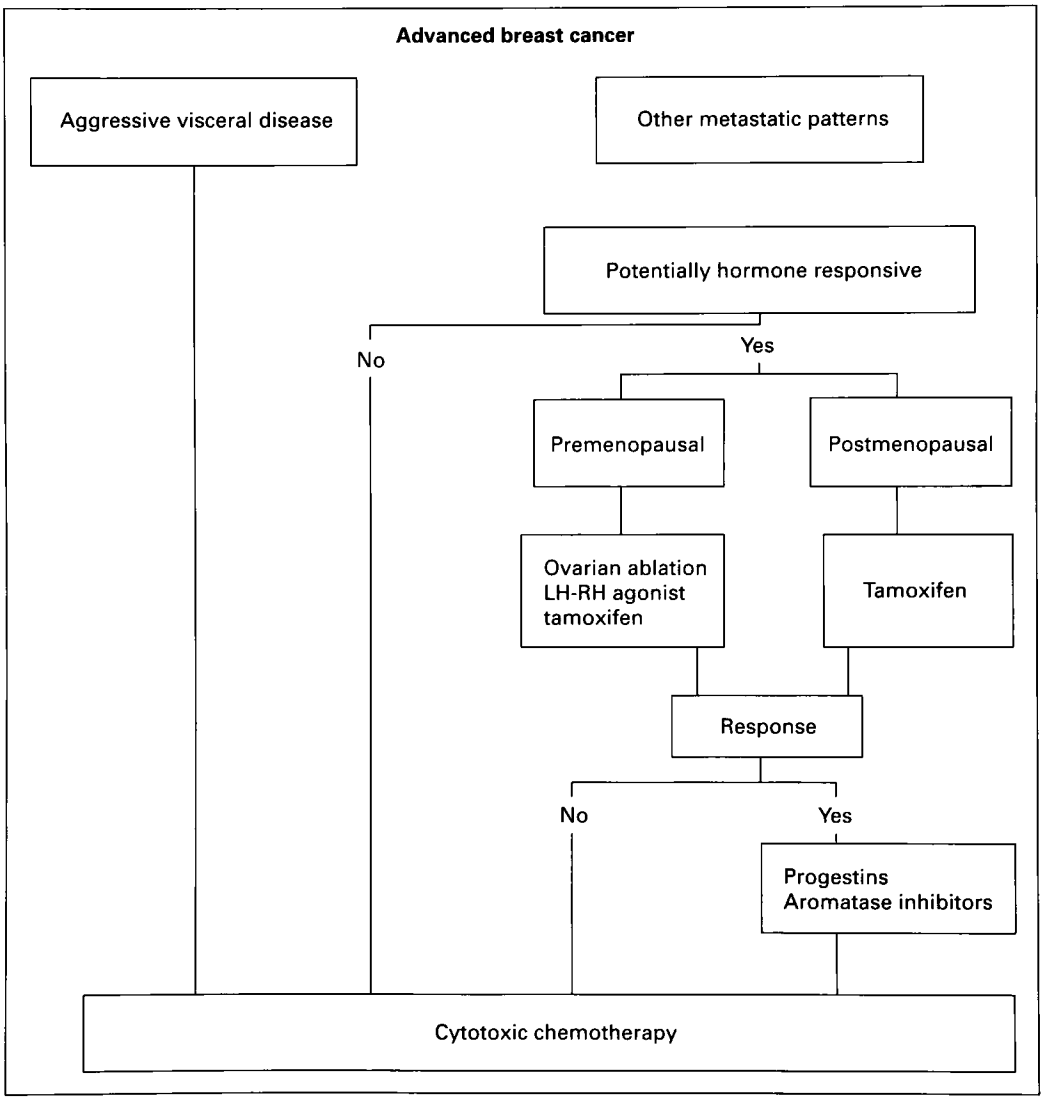

Figure 1. Decision tree for the use of palliative systemic therapy in advanced breast cancer (adapted from Rubens[3]). LH-RH, luteinizing hormone releasing hormone.

Table 2. Economic expectations of endocrine therapy in different indications

Indication	Current clinical practice (comparator)	Clinical expectations	Economic expectations			
			Costs avoided/benefits	Costs incurred	Quality of life	Cost–effectiveness
Prevention of breast cancer in at-risk populations	no standard chemoprevention; mammography screening if used, surveillance for at-risk populations	prevention of breast cancer, associated morbidity and mortality	• treatment of breast cancer cases prevented • associated morbidity and loss of productivity • costs of avoided morbidity due to systemic effects of drug (e.g. skeletal effects, cardiovascular, etc.)	• long-term endocrine therapy • associated drug toxicity • regular endometrial surveillance (if needed) negative systemic effects of treatment (endometrial or secondary carcinoma, thrombosis, etc.)	• overall positive effect expected: avoidance of disease and disability • avoidance of anticancer toxicity • reduction of anxiety or fear of disease	favorable if large proportion of poor prognosis cases are prevented and no added toxicity is incurred in drug-receiving population
Primary systemic treatment of locally advanced disease (pre-operative)	tamoxifen used in many centers	↑response rate, tumor shrinkage before surgery, ↓need for radical surgery ↓relapse	• incremental morbidity from successful tumor shrinkage (long-term) • costs of avoided radical surgery • costs of recurrent or metastatic disease • costs of avoided morbidity due to systemic effects of drug (e.g. skeletal effects, cardiovascular, etc.)	• drug costs • associated drug toxicities • costs of more conservative surgery • endometrial surveillance • negative systemic effects of treatment (endometrial or secondary carcinoma, thrombosis, etc.)	• long-term effects of reducing need for radical surgery and improving outcome; differences only expected if significant differences observed with respect to tamoxifen	if significant benefit of new drug versus tamoxifen: added costs of drug offset by high benefit and lowered long-term costs; if similar: higher incremental cost–effectiveness ratio due to high drug acquisition costs

continued

Table 2. *Continued*

Indication	Current clinical practice (comparator)	Clinical expectations	Economic expectations			
			Costs avoided/benefits	Costs incurred	Quality of life	Cost–effectiveness
Adjuvant treatment (post surgery)	tamoxifen, chemotherapy or combined therapy, depending on the prognostic variables	↑response rate ↓relapse ↑disease-free survival? ↑overall survival?	• incremental morbidity from avoidance of metastatic disease • costs of recurrent disease and morbidity • costs of avoided morbidity due to systemic effects of drug (e.g. skeletal effects, cardiovascular, etc.) • adverse events associated with alternative therapies (e.g. chemotherapy)	• drug costs • associated drug toxicities • incremental differences in treatment costs • negative systemic effects of treatment (endometrial or secondary carcinoma, thrombosis, etc.)	• long-term effects of avoiding metastatic disease; differences only expected if significant differences observed with respect to tamoxifen	if significant benefit of new drug versus tamoxifen: added costs of drug offset by high benefit and lowered long-term costs; if similar: higher incremental cost–effectiveness ratio due to high drug acquisition costs
Metastatic disease	tamoxifen used in first line in ER+, postmenopausal women; if second line: aromatase inhibitor or progestin is relavant comparator	↑response rate ↑duration of response ↓disease progression ↑time to treatment failure ↑disease-free survival ↓toxicity	• relative drug toxicities, adverse events	• drug costs • associated drug toxicities	• differences related to toxicity profile and postponement of treatment failure	incremental cost–effectiveness (no survival benefit) expected; cost–effectiveness ratio highly sensitive to comparative drug prices

Table 3. Cost–utility for adjuvant endocrine therapy (adapted from Corry and Lonning[8])

Type of breast cancer	Cost per QALY (1989 US$)	
	ER–	ER+
Premenopausal node-negative	214000	1440
Premenopausal node-positive	57800	4330
Postmenopausal node-negative	NA	NA
Postmenopausal node-positive	NA	6000

in Table 1. For metastatic breast cancer, less formalized treatment decision guidelines have been defined; however, the sequencing of different agents for first- second- and third- line therapy has been pathed (Figure 1).[3] To our knowledge, treatment guidelines for chemoprevention have yet to be established.

Economic expectations

Clinical expectations from therapy drive economic expectations, as is presented in Table 2. Economic arguments for or against the use of endocrine therapies will ultimately depend on the reference situation for comparative analysis. In the adjuvant setting, a comparator may be chemotherapy or chemoendocrine therapy or 'do nothing', depending on standard treatment for that specific prognostic group of patients (see Table 1 above). In advanced disease, comparison with tamoxifen is warranted if first-line endocrine therapy is the objective. For second- or third- line therapy, clinical and economic benefits of an agent should be compared to those of the agent they wish to substitute, e.g. aromatase inhibitors, progestins, chemotherapy or supportive care. Comparison with a 'do nothing' situation or placebo is not feasible in metastatic disease, as it would be unethical to deny patients with advanced disease some form or another of palliation for their symptoms.[8]

The use of tamoxifen or endocrine therapy as a preventive agent against breast cancer requires a movement away from the individual therapeutic framework to a broader public health perspective for evaluation. With chemoprevention, one is subjecting a potentially large population of disease-free women to therapy with the expectation of actual benefit (prevention of disease) in a limited number of patients. Although this argument applies to a certain extent to therapeutic approaches as well, it is particularly sensitive in the preventive setting as women exposed to drug may be subjected to some side-effects from endocrine therapy, even in the absence of disease.

The cost-effectiveness of chemoprevention is likely to depend on the characteristics of the target population (age, risk factors, previous medical history, etc.), their baseline risk of contracting breast cancer in the absence of chemoprevention, the epidemiology of the disease and the side effects expected from sustained long-term endocrine therapy.[9] Moreover, the marginal cost-effectiveness will be determined by the expected difference in baseline risk of disease in the prevented versus the unprevented population. By means of analogy, the marginal cost-effectiveness of a screening programme will be decreased if the underlying population has access to mammograms on a spontaneous basis or diagnostic mammography outside of the screening programme.[14] Similarly, if the population to which the impact of chemoprevention is being compared has aggressive screening or surveillance practices, this is likely to diminish the marginal impact expected from chemoprevention.[9]

Quality of life

The literature on quality of life in breast cancer patients is extensive; however, most studies have focused on choices between different chemotherapy regimens or between mastectomy and breast-conserving surgery.[15] Quality of life analysis is recommended in situations in which (i) there is a trade-off between the quantity (survival) and quality of life (toxicity, side-effects) associated with alternative therapies, and (ii) there is no survival benefit expected from therapy and clinical outcome measures such as response rates may not adequately represent patients' priorities for treatment decisions. A 1992 NCI report on quality of life identified the comparison of standard chemotherapy to higher intensity, shorter duration chemotherapy, and of standard chemotherapy versus tamoxifen as priority areas for prospective quality of life assessment in phase III breast cancer trials.[16]

Endocrine therapy presents a favorable toxicity profile with respect to chemotherapy. Indeed, quality of life studies have mostly been conducted with the intent to demonstrate that chemotherapy-induced toxicity was acceptable to patients when compared to less toxic endocrine approaches.[17,18] The evaluation of endocrine therapy itself is thus most often confined to the reference situation, with no assessment of the quality of life impact of agents with respect to placebo. In our review of the recent literature, no studies were found which specifically compared the quality of life impact of competing endocrine therapies nor of endocrine therapy with respect to placebo in new indications.

Two pioneer studies evaluated the impact of different schedules of chemotherapy with respect to chemoendocrine therapy or endocrine therapy in node-positive operable breast cancer. Despite their chemotherapy focus, these studies also revealed some interesting results related to endocrine treatment. Hürny *et al.*[17] looked at the results of the International Breast Cancer Study Group trial VII[19] and assessed quality of life for postmenopausal patients with node-positive breast cancer receiving either tamoxifen or chemoendocrine therapy. Patients receiving tamoxifen only had higher quality of life scores than patients receiving chemoendocrine therapy; however, these differences decreased over time, which suggests that patients' assessment of quality of life is influenced by their adaptation to their disease and treatment over time. Anticipation of chemotherapy also impacted upon patients' quality of life ratings. Goldhirsch *et al.*[20] conducted a Q-TWiST analysis of results from the Ludwig trial III, which compared chemoendocrine therapy for 1 year versus endocrine therapy for 1 year versus no adjuvant therapy in postmenopausal women with node-positive breast cancer after mastectomy (n=463).[21] The average Q-TWiST at 7 years was 6.7 months longer than for no adjuvant therapy (p=0.05) and 4.1 months longer than for endocrine therapy alone (p=0.20). Although this analysis supports the use of chemoendocrine therapy, the short duration of therapy (1 year), the arbitrary choice of utility measures and the simplistic assessment of treatment effecerapys limit the generalizability of results. Nonetheless, the study provided an interesting application of the Q-TWiST methodology to quality-adjusted survival analysis in breast cancer patients.

In the metastatic breast cancer setting, one is most often comparing endocrine therapies amongst themselves. Quality of life is of crucial importance in advanced disease, as treatment cannot promise any survival benefit. Every effort should thus be made to palliate symptoms and minimize discomfort and toxicity for the patient. As was mentioned above, toxicity profiles are the key differentiating factor between endocrine therapies. The question is, do these differences translate into significant quality of life discrepancies for the patient? For patients with metastatic disease, the transient toxicities of endocrine therapy may pale in comparison to the debilitating effects of disease progression. Existing cancer-specific health-related quality of life instruments, i.e. the Rotterdam Symptom Checklist,[22] the EORTC QLC-C30[23] and the Functional Assessment in Cancer Therapy (FACT) scale,[24] have been shown to be sensitive to the presence of disease symptoms and major treatment effects. Whether these instruments are able to capture more subtle differences between generally non-toxic endocrine agents within the context of a clinical trial remains to be verified.

There may be room here for alternative tools for decision analysis, such as patient preference assessments for different therapies.[25] Given the increased level of sophistication of patient populations, it is likely that patient and provider preferences will have an increasingly explicit role in guiding treatment decisions in the future. Similary, growing budgetary constraints in oncology practice are likely to decrease providers' elasticity to variations in price and efficacy between competing therapies. The cost-utility model for metastatic breast cancer developed by Hillner and Smith[26,27] and later adapted by Hutton *et al.*[28] for the comparison of chemotherapy regimens is an elegant example of how patient preferences for alternative treatments can be incorporated into economic analysis. These economic data may help validate or complement established treatment guidelines and ultimately guide clinical decision making.[27,29]

Economic evaluations of endocrine therapy

Adjuvant setting

The work of Smith and Hillner, based on the results of the 1992 Early Breast Cancer Trial Group meta-analysis, set the ground for further economic analyses in breast cancer.[26,27] This meta-analysis included all randomized controlled trials conducted worldwide on any systemic adjuvant therapy started before 1985, which represented 133 trials of 75 000 women.[30] The cost-effectiveness model produced from these data suggested that tamoxifen, either alone or in combination with chemotherapy, was only cost-effective in ER+ women presenting breast cancer.

Published cost-utility studies of tamoxifen as adjuvant therapy for breast cancer show cost-per-QALY ratios ranging from $4300 to $214 000, depending on the patient group considered.[8] These cost-utility ratios are reproduced below and confirm current clinical guidelines recommending tamoxifen use in ER+, N+ women (Table 3). The differences between cost-utility ratios can partly be explained by (i) different age groups leading to different natural life expectancy, (ii) different relapse rates in untreated N− versus N+ patients, and (iii) differences in the reduction in the hazard ratio caused by tamoxifen therapy between the four groups.[8] One interesting discrepancy between the results of these economic analyses and clinical guidelines is that cost-utility ratios are actually more

favorable in the N+ premenopausal patient group than in postmenopausal N+ women, probably on account of the former's longer life expectancy.

Although insightful, these cost-utility ratios must be regarded with caution as the models were based on estimates of benefit which have considerable variation around the mean. Moreover, the full impact of tamoxifen therapy over several years, in terms of its positive and negative systemic effects, was not taken into account. Results need to be replicated with more recent, longitudinal clinical data.

Advanced disease

At St Guy's hospital in London, a study of the cost of treating breast cancer from time of first relapse to death was conduced through retrospective chart review.[31] The costs of endocrine therapy, chemotherapy, radiotherapy, radiological and laboratory investigations were evaluated retrospectively for 50 women who had died of breast cancer. The mean cost of treatment per patient was £7620 (range: £317–27 860) for an average duration of advanced disease of 27 months. The largest cost component (56% of costs) was hospital stays. Chemotherapy drug costs accounted for 8% of costs, palliative radiotherapy, 7%, and endocrine therapy, 2%. Similar cost analyses were conducted in Australia[32] and the Netherlands,[33] with similar results. To our knowledge, no comparative economic evaluations of endocrine therapies in metastatic disease have been published to date.

Chemoprevention

One would expect the balance of costs to expected benefits to be quite different for chemopreventive therapy as compared to adjuvant or palliative therapy. Even if the results from large-scale clinical trials such as the Breast Cancer Prevention Trial Study (BCPT), involving 16 000 women, are positive, difficult issues remain to be addressed before proposing a generalization of chemoprevention. Namely, the selection criteria for the target population and the cost-effectiveness of wide-scale prevention are important hurdles to consider.[9] Chlebowski *et al.* did a 'back-of-the envelope' analysis of the cost-effectiveness expected from treating 8000 women with stage II breast cancer as adjuvant therapy versus giving 8000 women of high risk tamoxifen for 5 years (risk as defined in the BCPT trial). Only the cost of tamoxifen at 20 mg per day was calculated ($1000 per year in non-generic form). In the adjuvant setting, for 8000 women treated, 1000 relapses would be avoided and approximately 921 lives saved, which would roughly amount to $645 000 per cancer avoided and three times that amount per life-year saved. In the prevention setting, the expected reduction in breast cancer incidence is 40% and 62 cancers could be expected to be prevented, of which 66% would have survived anyway, hence only 21 life years are saved. The cost-effectiveness ratio is significant. Although these calculations are theoretical and do not account for all factors involved, they do highlight that the balance of costs and benefits in chemoprevention may not present favorably in economic terms. For the sake of comparison, breast cancer screening by mammography is associated with cost-effectiveness ratios ranging from $3500 to $242 000 in women aged over 50 years.[14] Meta-analyses have explained discrepancies in results by choice in a target population, incidence rates, screening modalities, quality of mammography and diagnostic services, and treatment patterns in the screened and unscreend populations.[34] There is no reason to expect similar cost-effectiveness results from these two distinct preventive settings. However, one can expect as much controversy on the economic value of large-scale chemoprevention as there has been about that of mass screening programmes.

Conclusion

Endocrine therapy is one of the fastest growing and most dynamic fields of research in oncological drug development. The low toxicity, good response and relatively low cost of agents makes endocrine therapy an attractive treatment option for breast cancer patients at different stages of their disease therapies. As budgets continue to shrink and treatment guidelines become challenged by new therapeutic and preventive approaches, decision analysis in breast cancer management is likely to become more explicit. Economic analysis can be a useful tool to guide clinical decisions in the management of this complex and chronic disease. Ultimately, the choice of therapy depends on the level of expected efficacy (in terms of antitumor effects) and on the determination of prognostic factors which can predict the success of therapies.[35] Economic analysis may play a crucial role in driving these choices, whether they be between competing therapies, target patient populations, timepoints for intervention or duration of therapy. One can only hope that economic analysis and the incorporation of patient preferences in therapy choices be used so as to offer the breast cancer patient the best therapeutic solution to her situation, expectations and needs.

References

1. Howell A, Downey S, Anderson E. New endocrine therapies for breast cancer. *Eur J Cancer* 1996; **32A**: 576-88.
2. Cancer Research Campaign. *Incidence—UK Fact Sheet II* 1992.
3. Rubens RD. Key issues in the treatment of advanced breast cancer. Expectations and outcomes. *Pharmacoeconomics* 1996; **9** (suppl 2): 1-7.
4. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma. Suggestions for a new method of treatment with illustrative cases. *Lancet* 1896; **ii**: 104-7.
5. Goldhirsch A, Wood WC, Ssenn HJ, *et al.* Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. *J Natl Cancer Inst* 1995; **87**: 1441-5.
6. NIH Consensus Conference. Treatment of early-stage breast cancer. *J Am Med Ass* 1991; **265**: 391-5.
7. Bajetta E, Zilembo N, Di Leo Q, *et al.* Hormone therapy in advanced breast carcinoma: present and future needs. *Cancer Treat Rev* 1994; **20**: 241-58.
8. Corry JF, Lonning PE. Systemic therapy for breast cancer: efficacy and cost-utility. *Pharmacoeconomics* 1994; **5**: 198-212.
9. Chlebowski RT, Butler J, Nelson A, Lillington L. Breast cancer chemoprevention. Tamoxifen: current issues and future prospective. *Cancer* 1993; **72** (3 suppl): 1032-7.
10. Kennedy MJ. Systemic adjuvant theapy for breast cancer. *Curr Opin Oncol* 1994; **6**: 570-7.
11. Mäenpää JU, Sirkka-Liisa A-F. Toremifene in postmenopausal breast cancer. Efficacy, safety and cost. *Drugs Aging* 1997; **11**: 261-70.
12. Brodie AMH, Njar VCO. Aromatase inhibitors and breast cancer. *Semin Oncol* 1996; **23** (4, Suppl 9): 10-20.
13. Perrone F, de Placido S, Gallo C, Carlomagno C, Lauria R, Bianco AR. Adjuvant chemoendocrine therapy for early breast cancer: is it worthwhile? (review). *Int J Oncol* 1995; **7**: 1129-37.
14. Wait S. The cost-effectiveness of breast cancer screening in France: from research to policy. In: Calvo F, Crepin M, Magdelenat H, eds. *Breast cancer advances in biology and therapeutics (21st Meeting of the International Association for Breast Cancer Research).* Paris: John Libbey Eurotext 1996.
15. Quality of life in breast cancer adjuvant therapy: validation and pilot testing of a combination of questionnaires. *The Breast* 1997; **6**: 97-107.
16. Nayfield SG, Ganz PA, Moinpour CM, Cella DF, Hailey BJ. Report from a National Cancer Institute (USA) workshop on quality of life assessment in cancer clinical trials. *Quality of Life Res* 1992; **1**: 203-10.
17. Hürny C, Bernhard J, Coates AS, *et al.* Impact of adjuvant therapy on quality of life in women with node-positive operable breast cancer. *Lancet* 1996; **347**: 1279-84.
18. Gelber RD, Goldhirsch A, Cavalli F. Quality-of-life-adjusted evaluation of adjuvant therapies for operable breast cancer. *Ann Int Med* 1991; **114**: 621-8.
19. The International Breast Cancer Study Group. Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. *J Clin Oncol* 1996.
20. Goldhirsch A, Gelber RD, Simes RJ, Glasziou P, Coates A. Cost and benefits of adjuvant therapy in breast cancer: a quality-adjusted survival analysis. *J Clin Oncol* 1989; **7**: 36-44.
21. Ludwig Breast Cancer Study Group. Randomized trial of chemoendocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastasis. *Lancet* 1984; **i**: 1256-60.
22. De Haes JCJM, Van Knippenberg FCE, Neijt JP: Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990; **62**: 1034-8.
23. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365-76.
24. Cella DF, Tulsky DS, Gray G, *et al.* The Functional Assessment of Cancer Therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993; **11**: 570-9.
25. Hill JE, Sutherland HJ, Meslin EM. Is there a role for preference assessments in research on quality of life in oncology? *Quality of Life Res* 1992; **1**: 31-40.
26. Smith TJ, Hillner BE. The efficacy and cost-effectiveness of adjuvant therapy of early breast cancer in premenopausal women. *J Clin Oncol* 1993; **11**: 771-6.
27. Hillner BE, Smith TJ, Desch CE. Assessing the cost effectiveness of adjuvant therapies in early breast cancer using a decision analysis model. *Br Cancer Res Treat* 1993; **25**: 97-105.
28. Hutton J, Brown R, Borowitz M, Abrams K, Rothman M, Shakespeare A. A new decision model for cost-utility comparisons of chemotherapy in recurrent metastatic breast cancer. *Pharmacoeconomics* 1996; **9** (suppl 2): 8-22.
29. Epstein RJ. Does the breast cancer dollar make sense? *Eur J Cancer* 1992; **28**: 486-91.
30. 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.
31. Richards MA, Braysher S, Gregory WM, Rubens RD. Advanced breast cancer: use of resources and cost implications. *Br J Cancer* 1993; **67**: 856-60.
32. Hurley SF, Huggins RM, Snyder RD, *et al.* The cost of breast cancer recurrences. *Br J Cancer* 1992; **65**: 445-9.
33. de Koning HJ, van Ineveld BM, de Haes JC, *et al.* Advanced breast cancer and its prevention by screening. *Br J Cancer* 1992; **65**: 950-5.
34. Brown ML, Fintor L. Cost-effectiveness of breast cancer screening: preliminary results of a systematic review of the literature. *Br Cancer Res Treat* 1993; **25**: 113-9.
35. Dess EC, Davidson NE. Management of early stage breast cancer: interventions and their effectiveness. *Dis Manage Health Outcomes* 1997; **2**: 270-80.