ClinicoEconomics and Outcomes Research

Dovepress
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REVIEW

Pharmacoeconomic considerations in the treatment of breast cancer

This article was published in the following Dove Press journal:
ClinicoEconomics and Outcomes Research
14 June 2010
Number of times this article has been viewed

Athanasios Pallis[1]
Vasiliki Tsiantou[2]
Efi Simou[3]
Nikos Maniadakis[4]

[1]Department of Medical Oncology, University General Hospital of Heraklion, Crete; [2]Department of Health Economics, [3]Department of Epidemiology and Biostatistics; [4]Department of Health Services Organization and Management, National School of Public Health, Athens, Greece

Abstract: Breast cancer is the most common malignancy in women worldwide and causes great economic burden. The aim of this paper is to present the available clinical and pharmacoeconomic evidence associated with different therapies for breast cancer. As significant progress was made in recent years and there are many alternative treatments, which are indicated according to the stage and the type of the disease, the age and health status of patient, and vary from surgery to hormonal treatment and chemotherapy. A broad literature review was undertaken and the paper presents the evidence available regarding the effectiveness and cost-effectiveness of the alternative options. Despite the high cost of most therapies and perceptions that treatments in this area may not be cost-effective, due to a combination of high costs and short survival, based on the literature review treatment options for breast cancer are in general deemed to be cost-effective. Time horizon, stage of the disease, patient age, therapy onset, benefit duration and time to recurrence may influence the results. Pharmacoeconomic analyses of alternative therapy options will improve decision-making and will help to optimize the use of scarce health care resources allocated to the care of breast cancer patients.

Keywords: breast cancer, cost, pharmacoeconomics

Introduction

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue. It is the second most common nonskin cancer, with approximately 430,000 cases occurring each year in Europe.[1] It is also the second leading cause of cancer-related death in women in the Western world after lung cancer,[2] with about 132,000 deaths each year and a five-year overall survival of 79.5%.[3]

Current treatment options for breast cancer depend on disease characteristics (ie, stage, grade, Her-2 status, number of positive lymph nodes, hormone receptor status of the tumor) and on patient characteristics (such as age and menopausal status).

This paper aims at incorporating two distinct, yet important, features of oncology. Firstly, clinical concepts related to the treatment of breast cancer with hormone therapy and chemotherapy and, secondly, a pharmacoeconomic evaluation of the various approaches to the treatment of this common disease.

Epidemiology

Globally, breast cancer incidence rates are highest in North America and northern Europe, and lowest in Asia and Africa.[4] Incidence rates in Japan and urban China have been rising in recent years. These international differences are thought to be related to societal changes occurring during industrialization (eg, changes in fat intake, body

Correspondence: Nikos Maniadakis
Department of Health Services Organization and Management, National School of Public Health, 196 Alexandras Avenue, 11521 Athens, Greece
Tel +30 694 523 7716
Fax +30 210 722 7222
Email nmaniadakis@esdy.edu.gr

weight, age at menarche, and/or lactation, and reproductive patterns, such as fewer pregnancies and later age at first birth).

The lifetime probability of developing breast cancer is one in six overall (one in eight for invasive disease). Previous breast cancer, early menarche, late menopause, hormone replacement therapy, oral contraception, obesity, and alcohol consumption are associated with an increased risk of breast cancer. Although the majority of breast cancer cases occur in women who have no family history of the disease, family history and genetic predisposition also play an important role, because women who carry mutations of breast cancer susceptibility genes (BRCA1 or 2) are at a higher risk of developing breast cancer.[5]

The incidence of breast cancer increases rapidly with age during the reproductive years and then increases at a slower rate after about age 50, the average age at menopause. The cumulative incidence of breast cancer among women in Europe and North America is about 2.7% by age 55, about 5.0% by age 65, and about 7.7% by age 75.[6] Incidence rates are high in more developed countries, whereas rates in less developed countries are low but increasing.[7]

About 20% of all breast cancer cases occur in women younger than 50 years of age (premenopausal) and 60% of these cases are estrogen receptor-positive, compared with 80% being estrogen receptor-positive in women older than 50 years (postmenopausal).[8] Breast tissue contains receptors for the female hormones estrogen and progesterone. These receptors allow the breast tissue to grow or change in response to changing levels of those hormones.

Breast cancer is a disease with a great epidemiologic and economic burden. The total cost of breast cancer includes not only the medical cost (ie, cost of screening, prevention, pharmaceutical treatment, surgical intervention, and palliative care) but also the indirect cost of the disease in terms of lost productivity and premature deaths, given that a significant percentage of the prevalence of breast cancer affecting women younger than 50 years of age.

Economic burden

The majority of studies that report the financial burden of breast cancer take into account the payer's perspective, whereas the estimation of the societal cost of the disease is less commonly investigated. However, estimations of the total cost show that the direct cost is the smallest contributor to the total cost per patient, being dependent on the stage of the disease, the therapeutic intervention, and the patient's age. Evidence from multiple studies has shown that the cost increases with the stage of the disease and age. In addition, differences in the cost per patient may also arise from alternative therapeutic schemes.

A review of the published studies of the cost of illness arising from breast cancer in the US concluded that the lifetime cost per patient varied between US$20,000 and US$100.000, with chemotherapy being the greatest driver of the total direct cost.[9] A more recent study regarding the assessment of cost and resource utilization of breast cancer patients in US concluded that the mean monthly cost per patient was US$2,896, driven mainly by costs attributable to hospitalization, and followed by pharmacotherapy costs, and costs of surgical interventions.[10] In California the total economic cost of breast cancer (indirect cost was included) was US$1.43 billion in 2001.[11]

In Sweden, the findings of a study that attempted to estimate the cost of breast cancer confirmed, as expected, that an increased stage of disease translates into increased resource use and cost. Specifically, the annual total cost for patients with metastatic breast cancer was US$46,500. However, the researchers concluded that the indirect cost was lower for patients older than 65 years.[12] This finding can be partly explained by the fact that people younger than 65 years are still working, so that the cost of lost productivity due to sick leave, early retirement, and premature mortality is greater.[13]

The treatment of metastases is also a significant contributor to the total cost of breast cancer.[14,15] In the US it was estimated that the mean total cost of a metastatic breast cancer patient was almost nine times greater than for a noncancer patient.[16] Finally, the economic burden of surviving breast cancer[17] or breast cancer recurrence[18] is also of great importance, mostly as regards the overuse of medical resources for followup.

Efficacy of therapy

Surgical treatment

Surgery is the cornerstone of management of early breast cancer. Breast cancer surgery has significantly evolved during the last decades. The operation evolved from radical mastectomy to modified radical mastectomy and to "skin-sparing" mastectomy, introduced in 1991.[19] The introduction of radiotherapy (RT) and its success in eliminating subclinical foci of disease allowed the development of breast conservation therapy (BCT). With the emergence of BCT, women with invasive breast cancer may now preserve their breast without compromising the oncological outcome. Several prospective randomized clinical trials have demonstrated

Table 1 Preferred regimens for the adjuvant treatment of early breast cancer

TAC regimen[88]
Docetaxel 75 mg/m^2 day 1
Doxorubicin 50 mg/m^2 day 1
Cyclophosphamide 500 mg/m^2 day 1
Every 21 days for six cycles
AC regimen[89]
Doxorubicin 60 mg/m^2 day 1
Cyclophosphamide 600 mg/m^2 day 1
Every 21 days for four cycles
AC followed by paclitaxel regimen[90–92]
Doxorubicin 60 mg/m^2 day 1
Cyclophosphamide 600 mg/m^2 day 1
Every 21 days for four cycles followed by paclitaxel 175 mg/m^2 weekly for 12 weeks
Dose-dense AC followed by paclitaxel[93]
Doxorubicin 60 mg/m^2 day 1
Cyclophosphamide 600 mg/m^2 day 1
Every 14 days for four cycles followed by paclitaxel 175 mg/m^2 day 1 every 14 days for four cycles
AT regimen[94]
Doxorubicin 60 mg/m^2 day 1
Docetaxel 60 mg/m^2 day 1
Every 21 days, for four cycles
TC regimen[95]
Docetaxel 75 mg/m^2 day 1
Cyclophosphamide 600 mg/m^2 day 1
Every 21 days, for four cycles
EC regimen[96]
Epirubicin 100 mg/m^2 day 1
Cyclophosphamide 830 mg/m^2 day 1
Every 21 days, for eight cycles
FAC regimen[97,98]
5-Fluorouracil 500 mg/m^2 days 1 and 8
Doxorubicin 50 mg/m^2 day 1
Cyclophosphamide 500 mg/m^2 day 1
Every 21 days, for six cycles
FEC regimen[99]
5-Fluorouracil 500 mg/m^2 days 1 and 8
Epirubicin 60 mg/m^2 days 1 and 8
Cyclophosphamide 75 mg/m^2, po, days 1–14
Every 21 days for six cycles
FEC followed by docetaxel[100]
5-Fluorouracil 500 mg/m^2 day 1
Epirubicin 100 mg/m^2 day 1
Cyclophosphamide 500 mg/m^2 day 1
Every 21 days, for three cycles followed by docetaxel 100 mg/m^2 day 1 every 21 days for three cycles
FEC followed by paclitaxel[101]
5-Fluorouracil 600 mg/m^2 day 1
Epirubicin 90 mg/m^2 day 1
Cyclophosphamide 600 mg/m^2 day 1
Every 21 days, for three cycles followed by paclitaxel 100 mg/m^2 weekly for eight weeks
CMF regimen
Cyclophosphamide 100 mg/m^2, po, days 1–14
Methotrexate 40 mg/m^2 days 1 and 8
5-Fluorouracil 600 mg/m^2 days 1 and 8
Every 28 days, for six cycles

Abbreviations: TAC, docetaxel-doxorubicin-cyclophosphamide; AC, doxorubicin-cyclophosphamide; AT, doxorubicin-docetaxel; TC, docetaxel-cyclophosphamide; EC, epirubicin-cyclophosphamide; FAC, 5-fluorouracil-doxorubicin-cyclophosphamide; FEC, 5-fluorouracil-epirubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-5-fluorouracil; po, oral.

equivalent survival outcome between mastectomy and BCT.[20–24] The absolute contraindications for BCT include a history of prior therapeutic RT, which would result in an excessively high total radiation dose to the chest wall; multicentric disease (two or more primary tumors in separate quadrants of the breast); and diffuse, malignant-appearing microcalcifications on mammography. Pregnancy is an absolute contraindication to the use of breast irradiation: however, it may be possible to perform breast-conserving surgery in the third trimester, deferring breast irradiation until after delivery. Relative contraindications to BCT include connective tissue disease, which results in poor tolerance of RT, and a sizeable tumor in a smaller breast where the subsequent cosmetic outcome would be unacceptable.

Axillary lymph node dissection (ALND) has traditionally been standard practice in the surgical management of early breast cancer. The benefits of ALND include its impact on disease control (ie, axillary recurrence and survival), while it also has significant prognostic value and plays an important role in treatment selection. Histological examination of removed lymph nodes at the time of ALND is thought to be the most accurate method for assessing the spread of disease to these nodes. In order to avoid the negative impact of ALND on quality of life, the sentinel lymph node (SLN) technique has been developed. This technique is increasingly being used as a method to determine whether full ALND is necessary. For patients who undergo SLN biopsy rather than initial ALND, completion ALND continues to be the standard treatment recommendation if the SLNs are positive.[25] The SLN technique should not be used in women with palpable axillary lymph nodes and in patients with inflammatory breast cancer.

Hormonal treatment

For patients with hormone receptor-positive tumors, hormonal treatment is one of the first choices for treatment.[6,26] Hormonal therapy acts by depriving the tumor cells of the proliferative stimulus provided by estrogen. This can be achieved by blocking the binding of estrogen to its receptor in the nucleus of responsive cells, as with tamoxifen. In premenopausal women, estrogens are directly produced in the ovaries until production declines during the menopause. After the menopause, estrogens are still produced (to a lesser extent) in nonovarian tissues, such as muscle and fat, by the enzyme aromatase, which converts androgens secreted by the adrenal cortex into estrogens. Aromatase inhibitors block the conversion of androgens to estrogens in the peripheral tissues in postmenopausal women, thereby reducing plasma levels of estrogens.[27]

Given the high incidence of estrogen receptor-positive breast cancer, it is clear that advances in endocrine treatment have the potential to result in significant decreases in breast mortality. Tamoxifen is one of the most studied agents in the treatment of estrogen receptor-positive breast cancer in both adjuvant and advanced disease settings. Tamoxifen provides protection against bone fractures in postmenopausal women and also lowers serum cholesterol levels. However, the long-term use of tamoxifen may be associated with vaginal bleeding, endometrial thickening, and increased risk of endometrial cancer and thromboembolic events.

Although tamoxifen has been the backbone of hormonal treatment for both pre- and postmenopausal women,[28,29] several randomized Phase III trials have evaluated the role of aromatase inhibitors in women with hormone receptor-positive breast cancers, either in the adjuvant[30–41] or in the advanced[42–46] disease setting. Although it is clear that aromatase inhibitors offer a significant benefit in terms of disease-free survival when compared with tamoxifen, it is not clear which approach is the most effective, ie, initial use of aromatase inhibitors, sequential use after 2–3 years of tamoxifen, or extended use after five years of tamoxifen. Although cross-study comparisons have severe limitations, trials evaluating the sequential approach report a hazard ratio ranging from 0.57 to 0.76, while the upfront approach results in a hazard ratio of 0.82–0.87. Thus, one could argue that the sequential approach is more effective. Although upfront trials do not report a survival benefit in favor of aromatase inhibitors, a pooled analysis of the ARNO 95, ABCSG 8, and ITA trials reported a survival benefit for the sequential approach.[47]

Chemotherapy

Chemotherapy is used in the treatment of both hormone receptor-positive and -negative patients in the adjuvant and advanced disease settings. Chemotherapy offers benefits in terms of symptom control, quality of life, and survival, and is considered the treatment of choice for many patients. However, it is also associated with significant toxicity. A number of different chemotherapy drugs, or classes of drug, are effective, including anthracyclines (doxorubicin, epirubicin), taxanes (docetaxel and paclitaxel), capecitabine, vinorelbine, gemcitabine, alkylating agents such as cyclophosphamide, and platinum-based drugs such as carboplatin.

Adjuvant chemotherapy

Adjuvant chemotherapy should be considered after definitive surgical treatment. The published results of the Early Breast Cancer Trialists' Collaborative Group overview analysis have clearly demonstrated that adjuvant polychemotherapy results in substantial reductions in the risk of recurrence and death from breast cancer in all age groups under the age of 70 years.[6] The decision whether or not to administer adjuvant chemotherapy should take into account the estimated absolute benefit, the patient's life expectancy, the presence or absence of prognostic factors, treatment tolerance, and patient preferences.

A number of prognostic factors have been associated with the risk of recurrence or death from breast cancer. The strongest prognostic factors are the patient's age, tumor size, tumor grade, number of lymph nodes involved, Her-2 status, peritumoral vascular invasion, and hormonal receptor status.[26,27] The absolute benefit of chemotherapy therefore varies according to both the patient's age and underlying prognostic factors.

According to the National Comprehensive Cancer Network (NCCN) guidelines,[48] patients with lymph node involvement or with tumors greater than 1 cm in diameter are appropriate candidates for adjuvant systemic therapy. On the other hand, the St Gallen International Expert Consensus takes into account all the above-mentioned prognostic factors in order to recommend adjuvant chemotherapy or not.[26] Furthermore, recent advances in DNA microarray technologies has allowed the development of classification systems of breast cancer by gene expression profile.[49] Five major subtypes of breast cancer have been identified by DNA gene expression profiling: estrogen receptor-positive/Her-2 negative (luminal A and luminal B subtypes); estrogen receptor-negative/Her-2 negative (basal subtype); Her-2 positive; and normal breast-like tumors.[49] In retrospective analyses, these profiles were found to be associated with the risk of relapse and death from breast cancer.

This approach could possibly be used for decision-making in adjuvant treatment of breast cancer patients, but it needs to be validated prospectively.

Despite the high incidence of breast cancer and the extensive research in this field, no chemotherapy regimen can be considered as "standard" treatment for early breast cancer. Preferred adjuvant regimens according to NCCN guidelines are presented in the Table.[48] Allocation to about six months of anthracycline-based polychemotherapy (eg, with fluorouracil-doxorubicin-cyclophosphamide or fluorouracil-epirubicin-cyclophosphamide) reduces the annual breast cancer death rate by about 38% for women younger than 50 years when diagnosed and by about 20% for those aged 50–69 years when diagnosed, largely irrespective of the use of tamoxifen and of estrogen receptor status, nodal status, or other tumor characteristics. Such regimens are significantly ($P = 0.0001$ for recurrence, $P < 0.00001$ for breast cancer mortality) more effective than cyclophosphamide-methotrexate-5-flurouracil chemotherapy.[6] Similarly, the inclusion of taxanes in the adjuvant treatment of breast cancer resulted in a 17% reduction in the risk of relapse ($P < 0.00001$) and a 15% reduction in the risk of death ($P < 0.00001$) compared with taxane-free regimens.[50]

Advanced disease

Compared with the treatment options for early-stage breast cancer, few data exist regarding the optimal use of chemotherapy for metastatic breast cancer (MBC). A variety of chemotherapy agents, either as single-agent or combination regimens, are considered effective in the treatment of MBC: anthracyclines (doxorubicin, epirubicin, liposomal doxorubicin), taxanes (paclitaxel, docetaxel), antimetabolites (gemcitabine, capecitabine), and microtubule inhibitors (vinorelbine). A significant but still controversial issue in the treatment of MBC remains the choice between using a combination of cytotoxic chemotherapies or sequential single agents.[51] Combination regimens result in higher response rates and a longer time to tumor progression (TTP) compared with sequential single agents; however, they do not offer substantial survival benefit.[52,53] Furthermore, combination treatment is associated with significantly higher toxicity and adverse events.[54] On the basis of available data, sequential monotherapy is recommended as the preferred choice in advanced disease, in the absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control.[48,51]

A recently published study randomly allocated 715 women with MBC to first-line chemotherapy with paclitaxel with or without bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor.[55] This trial yielded a significant prolongation of TTP in favor of bevacizumab, but failed to show a statistically significant difference in terms of overall survival.

Trastuzumab in Her-2 positive disease

Her-2/neu is a member of the erb family and is a proto-oncogene located on chromosome 17q21. Approximately 18% to 20% of breast cancers have amplification and/or overexpression of this gene, which encodes the cell surface molecule HER2, a transmembrane glycoprotein receptor with tyrosine kinase activity.[56] Trastuzumab (Herceptin, Genentech, Roche) is a recombinant DNA-derived, chimeric, humanized monoclonal antibody that binds to the extracellular domain of Her-2.

Patients with Her-2 positive MBC should receive treatment with trastuzumab, either in combination with cytotoxic chemotherapeutic agents[57–60] or as single agent.[61] Patients with Her-2 positive MBC should continue anti-Her treatment after progression on first-line trastuzumab-containing regimens. Patients could continue trastuzumab following progression on trastuzumab-containing regimens, given that several trials have demonstrated a benefit.[62,63] A recent Phase III trial demonstrated that the combination of lapatinib with capecitabine in patients with MBC refractory to trastuzumab offers a significant prolongation of TTP compared with capecitabine alone.[64] Additionally, in heavily pretreated women with MBC refractory to trastuzumab, the combination of trastuzumab plus lapatinib resulted in a longer TTP compared with lapatinib monotherapy.[65]

Five randomized Phase III trials evaluated the role of trastuzumab in combination with chemotherapy as adjuvant treatment in early breast cancer.[66–69] All these trials demonstrated a statistically significant reduction in the risk of relapse and some of them also reported a survival benefit.[66,67] On the basis of these trials trastuzumab is recommended for Her-2 positive tumors $\geq$1 cm.[48] It is not clear whether trastuzumab should be administered for one year[66,67,69] or for a shorter period on the basis of the FinHer trial.[68]

Metastatic bone disease

Metastatic bone disease is one of the most common metastases in breast cancer. Breast cancer patients with bone metastatic disease should be treated with bisphosphonates.[70] Bisphosphonate treatment is associated with fewer skeletal-related events, pathological fractures, and less need for radiation treatment and surgery to treat bone pain.[71–73] Bisphosphonate treatment is given in addi-

tion to chemotherapy or hormonal therapy, but it should be underlined that bisphosphonate is a palliative measure and does not offer a survival benefit.

Adverse effects

Hot flushes are a common side effect of both tamoxifen and aromatase inhibitors, although they occur more frequently in patients receiving aromatase inhibitors.[29] Arthralgias are also more frequent in patients receiving aromatase inhibitors compared with tamoxifen and their incidence ranges from 18% to 36% in clinical trials.[29] However, the mechanism by which arthralgias are created is not clearly understood. Furthermore, studies designed to look at the effect of aromatase inhibitors on bone mineral density have shown a significant decrease in bone mineral density in the aromatase inhibitor groups compared with placebo groups and hence an increase in the incidence of fractures in comparison with tamoxifen.[74] With respect to cardiovascular disease, although tamoxifen is considered to be cardioprotective, it is not clear whether aromatase inhibitors are associated with a higher incidence of cardiovascular events. The BIG 1–98 study reported an increase in cardiovascular events compared with tamoxifen,[32] while the MA.17 study reported no difference.[75]

Adjuvant treatment with a combination of trastuzumab and chemotherapy has been associated with a significant increase in the risk of congestive heart failure and arrhythmias.[76,77] In the above-mentioned trials, the percentage of severe (Class III/IV) congestive heart failure, or cardiac-related death for patients receiving trastuzumab ranged from 0% (59) to 4.1%.[77] Additionally, concerns have been raised about the long-term cardiac risks in patients receiving trastuzumab, based on a longer followup.[78]

Brain metastases are increasingly being reported as the site of first relapse in women with breast cancer who are receiving trastuzumab for Her-2-overexpressing disease. A trend towards a higher number of central nervous system metastases as the first event in the trastuzumab-containing arms has been reported for the N9831/NSABP B-31[66] and HERA[67] trials. However, it seems unlikely that the use of trastuzumab in the adjuvant setting "increases" the risk of brain metastases.[79] It is more likely that the central nervous system represents a sanctuary site due to the inability of trastuzumab to cross the blood-brain barrier.

Economic analysis

In order to evaluate the cost-effectiveness of the various approaches to the treatment of breast cancer, we undertook a literature review of recently published studies evaluating the aforementioned therapies. The terms "breast cancer" and "cost" were used as key words in the various databases. The search was limited to articles published from 1999 to 2009 and included only English language studies. Studies which evaluated the cost-effectiveness of screening programs, diagnostic techniques, and effectiveness of alternative treatments were excluded from the review. Studies that had not undertaken an original economic evaluation and reported results from literature reviews only were also excluded. The remaining studies were classified into two categories, ie, those that reported the economic burden of the disease and those that evaluated the cost-effectiveness of the treatments. The pharmacoeconomic evaluations were classified based on the substance used for treatment.

Overall, the majority of the studies present unanimity regarding the methodology followed. Cost-effectiveness analysis and the development of a Markov model were the most popular methodologic approaches in the studies reviewed. Quality-adjusted life years (QALYs) and life years gained (LYG) were the preferred measures of benefit, while the majority of the studies were carried out under the third-party payer or health system perspective. All studies performed a sensitivity analysis in order to investigate the robustness of their results. The parameters that seem to be the most influential are the time horizon, stage of the disease, age of the patient, as well as time of therapy initiation, duration of benefits and time to recurrence.

Cost-effectiveness of drug therapy

Tamoxifen

Tamoxifen is used for both the prevention and the treatment of breast cancer. The use of tamoxifen therapy over a five-year period has been proved to be cost-effective regarding breast cancer risk reduction. The incremental cost per QALY gained was Aus$38,271.[80] A cost-utility analysis compared tamoxifen with tamoxifen plus chemotherapy as adjuvant therapy in postmenopausal women with early breast cancer in the UK. Tamoxifen plus chemotherapy was more effective but at the same time more expensive compared with tamoxifen alone. The incremental cost per QALY gained was £3,483, indicating that the combination of tamoxifen with chemotherapy was cost-effective.[81]

Aromatase inhibitors

The majority of the pharmacoeconomic evaluations identified in our review concerned aromatase inhibitors, both non-steroidal (anastrozole, letrozole) and steroidal (exemestane).

Assessment of sequential use of exemestane after two or three years of tamoxifen in postmenopausal women with early-stage breast cancer was the main objective in several economic evaluations. Even though the time horizon of the studies was different, as was the currency used, the conclusion was the same in all studies, and demonstrated that sequential treatment with exemestane was cost-effective. The incremental cost per QALY gained was estimated at US$20,100 in the USA,[82] Can$24,185 in Canada,[83] and €20,000 in Sweden.[84]

In the case of advanced breast cancer the use of exemestane instead of megestrol was cost-effective. In the US the incremental cost per LYG was US$10,600[85] while in Europe it was ranged from €3,700 in Germany to €9,091 in the Netherlands.[86] Similarly, letrozole represents a cost-effective alternative to megestrol in the UK National Health Service (NHS) setting, with an incremental cost per LYG of £3,588.[87]

Chemotherapy

Taxanes are a therapeutic class used in chemotherapy. Taxanes can be administered as single agents or in combination with other taxanes, antimetabolites, or anthracyclines.

A recent economic evaluation of the cost-effectiveness of taxanes in the adjuvant treatment of breast cancer reported a cost per QALY for taxane compared with nontaxane-containing chemotherapy of £12,000–£43,000, depending on the taxane under consideration and the specific trial used as the basis of the analysis.[88] A cost-utility analysis in Thailand assessed the cost effectiveness of doxorubicin-cyclophosphamide adjuvant therapy versus cyclophosphamide-paclitaxel in women with early-stage breast cancer. Although the estimated benefits for the patient were better in the case of the combination therapy, the incremental cost per QALY was THB738,111 (~US$22,250), thus prohibiting the implementation of this therapy in Thailand.[89]

In the UK in 2001, a Markov model was designed to assess the cost-utility ratios of three different taxanes in patients with advanced breast cancer.[90] Docetaxel was the most cost-effective treatment compared with paclitaxel and vinorelbine. The incremental cost for docetaxel per QALY gained was £1,995 over paclitaxel and £14,055 over vinorelbine. A similar study was carried out in Canada, where the study population was patients with metastatic breast cancer. The average cost per quality-adjusted progression-free survival ranged from Can$31,220 for vinorelbine to Can$110,072 for docetaxel.[91] A more recent study of the cost-effectiveness of docetaxel over paclitaxel for the treatment of MBC patients reported that docetaxel was a cost-effective therapy, with an incremental cost per LYG of Can$30,337.[92] Another study compared taxanes with standard second-line chemotherapy in patients with MBC. The cost-utility analysis showed that the cost per QALY ranged from US$13,922 for standard chemotherapy to US$49,739 for docetaxel. The authors reported that, although current chemotherapy was the cheapest approach, it offered the least number of LYG. Thus, the best alternative was vinorelbine-mytomycin C therapy.[93]

A common therapeutic scheme in chemotherapy is the combination of taxanes with antimetabolites, and especially the use of capecitabine combined with docetaxel as therapy for the treatment of MBC. In our review, three different studies evaluating this treatment scheme in comparison with single-agent taxane therapy were identified and they reported that the combination therapy was cost-effective in the treatment of MBC.[94–96] A Markov model was developed to estimate the cost-effectiveness of gemcitabine-paclitaxel in patients with MBC and reported an incremental cost-effectiveness ratio (ICER) of £38,699 per QALY gained, which is higher than the threshold defined by the NHS.[97]

Despite the high incidence of breast cancer and the great amount of data in the field of first-line therapy, limited economic evidence is available about the cost-effectiveness of the various treatment options presented. An economic evaluation for first-line sequential therapy was reported by the National Institute for Health and Clinical Excellence (NICE).[98] The scenario studied considered that all patients would have been treated with anthracyclines in the adjuvant setting. The analysis showed that the most cost-effective treatment sequence, based on a threshold of £30,000 per QALY, was docetaxel monotherapy followed by capecitabine monotherapy followed by vinorelbine monotherapy. The ICER for this sequence was estimated to be £23,332 per QALY. When applying a threshold of £20,000 per QALY, the most cost-effective sequence was docetaxel monotherapy followed by capecitabine monotherapy, followed by no further chemotherapy.

Trastuzumab

A recently published systematic review evaluated the cost-effectiveness of adjuvant trastuzumab treatment.[99] Cost-effectiveness ratios reported ranged from US$5,020/QALY to US$134,610/QALY. Most studies reported favorable cost-effectiveness values (ie, below US$50,000/QALY). About 84.6% were conducted using a Markov model based on data from clinical trials and 15.3% were analyzed by other economic or cost models; 84.6% reported

sensitivity analysis, 11 studies (84.6%) clearly described a justification for selecting the study design, and only 15.3% noted study limitations. A NICE guideline evaluated all the available data for trastuzumab adjuvant studies and estimated incremental costs per QALY gained with adjuvant trastuzumab treatment ranging from £16,000 to £33,000.[100] A cost-effectiveness analysis reported by Belgian health care authorities estimated the incremental cost-effectiveness ratio based on a lifetime simulation at €10,315 per QALY gained.[101]

The cost-effectiveness of trastuzumab in combination with standard treatment in HER-2 positive breast cancer patients was estimated in several studies identified in our review. The economic results and benefits differ based on the stage of the disease. However, both clinical and economic benefits were superior for the stage III patients.[102] The authors of a Belgian study found that nine weeks of trastuzumab was dominant over no trastuzumab treatment.[102] Similar results were reported by the authors of an Australian study, who found that nine weeks' trastuzumab was dominant over no trastuzumab, reporting an incremental cost of Aus$1,700 per QALY gained for nine-weeks of trastuzumab compared with standard treatment alone.[103]

Bisphosphonates

Our review identified seven economic evaluations of bisphosphonates as a treatment intervention in metastatic bone disease. The majority of these studies compared third-generation bisphosphonates (zoledronic acid, ibandronate) with second-generation (pamidronate) or first-generation (clodronate) bisphosphonates. An economic study conducted in the UK compared five types of bisphosphonates with no treatment from the NHS perspective. According to the findings of the study, the use of bisphosphonates in the management of patients with bone metastases was cost-saving to the NHS. In fact, zoledronic acid was the dominant strategy of all the five types compared in the study.[104]

Two different studies assessed the economic consequences of zoledronic acid versus pamidronate as the therapeutic strategy in patients with at least one bone metastasis. The perspective of both studies was the health system, but the results were different. The first study was carried out in the UK and concluded that pamidronate was the preferred strategy because it could lead to a reduction of 11% in health care costs.[105] The second was undertaken in Spain and the conclusion was that, although zoledronic acid was more expensive, its higher cost could be counterbalanced by the savings in infusion time and better outcomes.[106]

In the case of breast cancer patients who suffer from bone metastases and are concurrently undergoing oral hormonal therapy, oral ibandronate is the dominant treatment option compared with zoledronic acid and pamidronate.[107] On the other hand, there are studies that, although agreeing that bisphosphonates (especially third-generation bisphosphonates[108]) are effective in the secondary prevention of bone complications in breast cancer metastases, conclude either that this strategy is too expensive[109] or that the cost of providing it will be large given the prevalence of metastatic breast cancer.[110]

Overall, the costs of bisphosphonate therapy appear to be higher than the cost savings from the prevention of skeletal-related events. The costs per QALY have been estimated to be >US$100,000.[111]

Aromatase inhibitors versus tamoxifen

Adjuvant setting

Postmenopausal

In postmenopausal women, the standard of care for hormone receptor-positive tumors was five years of tamoxifen. This approach was associated with a 40% reduction in the risk of recurrence and 34% reduction in the risk of death.[6] Until recently, trials testing durations of tamoxifen longer than five years had not shown additional benefit, but the ATLAS (Adjuvant Tamoxifen, Longer Against Shorter) trial, showed a small but significant reduction in the risk of recurrence with 10 years compared with five years of tamoxifen therapy.[112]

However, during the last decade tamoxifen's role has been challenged by the aromatase inhibitors, namely letrozole, anastrozole (nonsteroidal) and exemestane (steroidal). In early breast cancer, and especially in postmenopausal women with hormone receptor-positive cancer, initial adjuvant therapy with letrozole was found to be cost-effective compared with tamoxifen, with an incremental cost per QALY of Can$23,662.[113] Letrozole can be used as first-line therapy for advanced breast cancer and it is a cost-effective option. This was suggested by two different studies evaluating the costs and benefits of this treatment scheme. The first was carried out in Japan and showed a cost of US$4,969 per LYG over tamoxifen,[114] while the second yielded a cost per LYG of £5,917.[115]

Similar results were reported from pharmacoeconomic studies investigating the cost-effectiveness of the use of anastrozole over tamoxifen in different countries. Even

though the currency used was different, the conclusion was that anastrozole is a cost-effective choice as adjuvant therapy for early breast cancer.[116–120] The use of letrozole in the extended adjuvant treatment was also proved to be cost-effective, yielding an ICER of Can$34,058 per QALY in Canada[121] and US$28,728 per QALY in the US.[122]

Three different approaches have been tested against the "gold standard" of five years of tamoxifen, ie, upfront aromatase inhibitors, two to three years of tamoxifen followed by aromatase inhibitors for a total of five years, and extended treatment with sequential aromatase inhibitors after five years of tamoxifen.

Two large Phase III trials with more than 17,000 patients evaluated anastrozole[30,31] and letrozole[32] for five years versus five years of tamoxifen, and both studies demonstrated an improvement in disease-free survival in favor of aromatase inhibitors (hazards ratio [HR] for anastrozole: 0.87, 95% CI 0.78–0.97; $P = 0.01$; HR for letrozole: 0.82, 95% CI 0.71–0.95; $P = 0.007$). However, both studies failed to yield any difference in overall survival. Interestingly, the letrozole trial (BIG 1-98 trial) also evaluated the sequential approach (2–3 years of tamoxifen followed by letrozole for a total of five years or three years letrozole upfront followed by tamoxifen for a total of five years), but data from these arms are not yet available.

A randomized Phase III trial randomized 4,724 patients to exemestane after 2–3 years of tamoxifen or to continue tamoxifen for a total of five years[34] and demonstrated a significant prolongation of progression-free survival in favor of exemestane (HR: 0.76, 95% CI 0.66–0.88; $P = 0.0001$).[33,34] Similarly, a combined analysis of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 and the Arimidex-Nolvadex (ARNO 95) trial revealed a significant 40% reduction in the risk of relapse when anastrozole was administered after two years of tamoxifen, compared with five years of tamoxifen (HR: 0.60, 95% CI 0.44–0.81; $P = 0.0009$).[35] Finally, a smaller Italian study demonstrated a statistically significant benefit in terms of progression-free survival in favor of the switching strategy.[36,37]

The National Cancer Institute of Canada (NCIC) MA 17 trial randomized 5,187 patients to letrozole for five years or to placebo, after completion of five years of tamoxifen.[39,75] The study was terminated early, when a planned interim analysis demonstrated a significant improvement in disease-free survival in favor of letrozole, which was confirmed after a longer followup (HR: 0.58, 95% CI 0.45–0.76; $P < 0.0001$)[75] Likewise, a study from the National Surgical Adjuvant Breast and Bowel Project B-33 study asked a similar question using exemestane and revealed a trend towards higher four-year progression-free survival in favor of exemestane (HR: 0.68, $P = 0.07$).[40] Finally, an ABCSG trial tested extended treatment with three years of anastrozole in approximately 900 patients and revealed a borderline statistically significant improvement in disease-free survival in favor of extended treatment (HR: 0.64, 95% CI 0.41–0.99; $P = 0.048$).[38]

A detailed economic analysis evaluated these three different therapeutic approaches in terms of QALYs gained versus tamoxifen (or placebo in the case of extended therapy after five years of tamoxifen).[123] The analysis used a state transition model (Markov) approach to simulate the disease outcomes of patients up to a time horizon of 35 years post-surgery. The cost-effectiveness results when anastrozole or letrozole were used upfront versus tamoxifen were estimated to be £32,000 and £21,600 per QALY, respectively. In the case of the sequential strategy, data are available only for anastrozole and exemestane. (As mentioned above, the BIG 1-98 trial, which is evaluating the sequential approach for letrozole, has not yet published results for the sequential arm.) The cost-effectiveness results for the sequential approach were estimated to be £23,200 and £19,200 per QALY for anastrozole and exemestane, respectively. Finally, in the extended adjuvant setting, data were available only for letrozole and the cost per QALY was calculated to be £9,800.

In these estimations it was assumed that the benefit of aromatase inhibitors observed during the study period was gradually lost during the following 10 years (meaning that it was assumed that after the study period the recurrence rate would be significantly higher for aromatase inhibitors compared with tamoxifen and that at year 15 the number of patients without disease recurrence would be similar in the aromatase inhibitor and tamoxifen arms). When an alternative scenario with "benefits maintained" was tested, the cost-effectiveness was reduced by almost 50% to approximately £10,000–12,000, £5,000 and £3,000 for the upfront, sequential, and extended approaches, respectively.[123]

Premenopausal

Concerning premenopausal women, the optimal management of endocrine-responsive early breast cancer remains controversial. Tamoxifen is the gold standard for hormone receptor-positive early breast cancer.[28] Oophorectomy with either ablation or suppression using a luteinising hormone-releasing hormone (LHRH) analog results in a reduction of approximately 30% in breast cancer recurrence and mortality.[6] The combination of ovarian suppression with the use of LHRH analogs and tamoxifen is a widely used approach; however, it is not clear whether this combination

offers a benefit compared with tamoxifen alone.[6,124] Although aromatase inhibitors have shown benefits superior to those of tamoxifen in postmenopausal women,[19] their benefits in premenopausal women are unknown. In premenopausal women, the use of aromatase inhibitors leads to an increase in gonadotropin secretion, because of the reduced feedback of estrogens to the hypothalamus and pituitary, and a subsequent stimulation of ovarian activity.[27] The combination of aromatase inhibitors with a GnRH analog can achieve complete estrogen blockade by suppression of ovarian function and of peripheral estrogen synthesis.[27]

A recently published Phase III trial evaluated the role of LHRH combined with either tamoxifen or anastrozole as adjuvant treatment in 1803 premenopausal women.[41] Patients were also randomized to receive zoledronic acid or not. The primary endpoint of the trial was disease-free survival. There was no significant difference in disease-free survival between the anastrozole and tamoxifen groups (HR: 1.10, 95% CI 0.78–1.53; $P = 0.59$). In contrast, the addition of zoledronic acid to endocrine therapy, as compared with endocrine therapy without zoledronic acid, resulted in an absolute reduction of 3.2 percentage points and a relative reduction of 36% in the risk of disease progression (HR: 0.64, 95% CI 0.46–0.91; $P = 0.01$). The small amount of data available about the role of aromatase inhibitors in the adjuvant treatment of premenopausal women and the small followup period preclude the drawing of any solid conclusions. Additionally, no pharmacoeconomic data exist concerning this approach. However, given the fact that the above-mentioned study yielded no difference between the two arms in terms of disease-free survival or toxicity, and given that anastrozole is more expensive than tamoxifen, a cost-minimization analysis would likely yield tamoxifen as the treatment of choice.

Advanced disease setting

Postmenopausal

Tamoxifen has until recently been considered the drug of choice for first-line endocrine therapy in postmenopausal women, due to its efficacy and low toxicity. However, a number of Phase III studies have demonstrated that aromatase inhibitors are superior to tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer.[42–46] Although a meta-analysis of published randomized trials demonstrated a progression-free survival benefit (HR: 0.78, 95% CI 0.70–0.86), there was no overall survival benefit.[125] In the second-line setting, anastrozole, letrozole, and exemestane have all been shown to offer efficacy and tolerability advantages over megestrol acetate, the previous standard second-line endocrine therapy, in tamoxifen-resistant patients with hormone-dependent advanced breast cancer.[126–129] On the basis of these trials, aromatase inhibitors are recommended for postmenopausal women with estrogen receptor-positive breast cancer who have not previously received endocrine treatment or who have been previously treated with tamoxifen. For postmenopausal women who are antiestrogen naïve or who have relapsed more than one year after previous treatment, aromatase inhibitors appear to have superior outcomes compared with tamoxifen, although the differences are modest.

Results of the economic analysis indicate that letrozole is a cost-effective alternative first-line therapy compared with tamoxifen for postmenopausal women with advanced breast cancer, achieving additional life-years with a modest increase in costs, having a mean incremental cost per LYG of £2,342.[130] The incremental costs in the comparison between letrozole or anastrozole and tamoxifen were below £5,075 per LYG and £9,200 per QALY.[131] Similarly, results obtained for letrozole, anastrozole, or exemestane when used as second-line treatment versus megestrol revealed a maximum incremental cost-effectiveness ratio of £9,667 per LYG.

Premenopausal

The role of aromatase inhibitors in combination with an LHRH analog as first-line treatment has been evaluated in the context of Phase II trials.[132,133] However, there is only limited experience and a small amount of data to draw on, and further research is needed before this treatment can generally be recommended.

Trastuzumab versus chemotherapy

In Italy, standard chemotherapy was compared with 12-month adjuvant trastuzumab therapy. The incremental cost-utility ratio was €14,861 per QALY gained. Based on these results the conclusion was that in the long term trastuzumab is a cost-effective alternative.[134] In Norway the study was carried out with a societal perspective. In a 10-year time horizon, the cost per QALY ranged from €10,185 to €37,862 according to the overall improvement in survival. The authors suggested that trastuzumab may be cost-effective, provided that a minimum of 8% improvement in overall survival is accomplished.[135]

Conclusions

Significant progress has been made in the treatment of breast cancer during the last decade. Recent data support

the use of aromatase inhibitors in the treatment of estrogen receptor-positive breast cancer, either in the adjuvant or in the advanced disease setting, at least for postmenopausal women, while for premenopausal patients data exist only for the adjuvant setting. Newer and more effective chemotherapy regimens have been tested in the early disease setting. Trastuzumab is a standard of care in the treatment of Her-2 positive disease, in either the adjuvant or advanced disease setting. Recently, bevacizumab has been proven to offer a benefit in combination with chemotherapy. Furthermore, pharmacoeconomic analysis yielded that. Despite their cost, these drugs are in general cost-effective, in various settings and countries, with incremental cost-effectiveness ratios in line with those of many other reimbursed therapies.

However, a number of significant questions still remain unanswered. Which approach is the most effective in the adjuvant setting in postmenopausal women: up-front aromatase inhibitors, sequential, or extended after five years of tamoxifen? Could aromatase inhibitors in combination with LHRH analogs represent a "standard" option in premenopausal women in either the adjuvant or the advanced disease setting? Which is the "optimal" approach in the adjuvant treatment of early breast cancer? Is sequential chemotherapy a better approach than combination treatment in advanced disease? It is clear that prospective trials are needed to answer these questions. Many clinical trials are currently evaluating these research questions. It is hoped that one or more of these approaches will prove successful and lead to substantial progress in the treatment of this common and fatal disease. Pharmacoeconomic analyses of all alternative therapy options will improve decision-making and will help decision-makers to optimize the use of scarce health care resources allocated to the treatment of cancer and the care of patients.

Disclosures

The authors report no conflict of interest in this work.

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