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RESEARCH NOTES

USING APPROPRIATE COMPARISONS IN ECONOMIC EVALUATIONS

An Exercise in Belgium

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Abstract

This paper considers standard effective treatments for non-Hodgkin's lymphoma and early breast cancer in premenopausal women. The literature assesses the treatments' effectiveness, and expected charges for different treatments in the context of the Belgian Health Insurance System are compared. Ovariectomy in breast cancer (770 ECU) and conventional chemotherapy in non-Hodgkin (2,745 lymphoma ECU) prove equally effective and are less costly in comparison with chemotherapy (1,904 ECU) in breast cancer or chemotherapy and autologous bone marrow transplantation (19,262 ECU) in non-Hodgkin's lymphoma. Further unbiased insights in competitive treatments' costs and outcome could save money and enhance developments in cancer care.

Keywords: Costs, Effectiveness, Non-Hodgkin's Lymphoma, Breast Cancer

Between 1975–79 and 1987–91, the incidence of cancer increased to 18.6% in men and 12.4% in women (7). During this century, cancer has developed into one of the leading causes of death, accounting for 23.5% of total deaths. In young and middle-aged adults, cancer mortality rates have declined as a consequence of changes in living habits and environmental factors (5). Information campaigns, earlier detection, and better treatment options have led to better prognoses for those who are offered treatment.

During the last few years, medical technology has developed rapidly. A wide range of new, and sometimes spectacular therapies are currently available to help

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patients facing cancer. An obvious example is breast cancer. New developments in diagnostic methods, such as screening with mammography and echography, can be used for the detection of small tumors and may prevent mastectomies. Additional treatments such as surgical castration, chemotherapy, and hormonotherapy give patients better chances of survival. Non-Hodgkin's lymphoma patients (in their first remission phase) can undergo intensive chemotherapy with rescue by autologous bone marrow transplantation instead of conventional chemotherapy or a combination chemotherapy. All these developments are beneficial to patients but are also accompanied by substantial increases in health care consumption and associated costs.

Cancer treatment is expensive. In the United States, direct costs for treatment of all cancers were estimated for 1990 to be around US $35 billion, representing 6% of all health care expenses (3). While it is difficult to say whether overall expenses for cancer are either too high or too low in relation to the seriousness of the disease, specific new treatments often represent relatively high additional costs for modest additional benefits. Therefore, more attention has recently been paid to treatment quality control and cost-effectiveness of treatment.

Economic constraints are pertinent in today's health care environment both in the United States and in Europe, because they make it impossible to widely adopt all potentially effective treatment options at any time without seriously destabilizing national welfare systems. An explicit and formal way of assessing both the effectiveness and the cost of treatments simultaneously in order to improve efficiency is offered by the techniques of economic evaluation, especially cost-effectiveness studies or cost-minimization studies. If the aim of health care is to maximize the total health of a population within a given limited budget, then economic evaluations deliver crucial information to reach this goal. Standard effective treatments that may be less challenging and rewarding might be overlooked in clinical and economic research. New but often more expensive treatments, with relatively modest or no improved effectiveness in comparison, receive more attention. This may lead to inefficient allocation of health care budgets.

Consideration of economic aspects of treatment alternatives has entered the scientific literature concerning different types of cancer (21), such as breast cancer (9;23) and non-Hodgkin's lymphoma (24). Both are diseases that are increasing in incidence. In the United States, a rise of 24% for breast cancer and 73% for non-Hodgkin's lymphoma has been observed in the past 20 years (19). A similar trend is present in Europe with an even stronger positive trend for non-Hodgkin's lymphoma (4). For both cancer types, relatively expensive new treatments have recently become available and are considered in general to be "more effective" than standard treatments.

In this paper we present a small exercise carried out in the context of the Belgian health care insurance system, comparing the expected charges to be paid for different treatment strategies in the early stages of breast cancer and in non-Hodgkin's lymphoma. Of all European Union (EU) countries, Belgium ranks second in age-standardized cancer incidence and first in age-standardized cancer mortality in males, and third and fourth, respectively, in females (10).

According to the Belgian national cancer registry (17), the incidence of breast cancer in 1992 was 98.1 per 100,000 women, representing 4,934 new cases annually. The annual incidence for non-Hodgkin's lymphoma is 4.6 for men and 4 for women, representing about 500 cases.

MATERIALS AND METHODS

The exercise presented here consists of the description of standard treatment protocols, a review of the evidence on outcomes with the various treatments, the calculation of the associated costs (based on charges), and the comparison of costs and outcomes.

This study is not an exhaustive analysis of all treatments for breast cancer or non-Hodgkin's lymphoma. Only representative treatment schemes are considered.

For early breast cancer, we will briefly review the evidence on the effectiveness of adjuvant treatment in premenopausal patients with T_o-3, N_o-2, M_o breast cancer. Given that surgical or radiotherapeutic ovariectomy and CMF cyclophosphamide, methotrexate, and fluorouracil chemotherapy have been found to be equally effective, we will compare the expected costs associated with each treatment alternative, estimated on the basis of official Belgian charges and fees.

We will discuss our findings in light of recent economic evaluations of adjuvant therapy in early breast cancer, none of which has included ovariectomy as a comparator.

Our second exercise concerns the effectiveness and costs associated with three different treatment options for patients with intermediate and high-grade non-Hodgkin's lymphoma in first remission: combination of methotrexate and CVB (cyclophosphamide 1,500 mg/m^2, carmustine 300 mg/m^2, and etoposide 250 mg/m^2) chemotherapy with autologous bone marrow transplantation, compared with induction (mixantrone 12 mg/m^2, cyclophosphamide 1,200 mg/m^2, vindesine 2 mg/m^2, bleomycin 10 mg, prednisone 60 mg/m^2, inthrathecal methotrexate 15 mg) chemotherapy followed by consolidation with the LNH84 (aspariginase iu/m^2, methotrexate 3 g/m^2, ifosfamide 1,500 mg/m^2, etoposide 250 mg/m^2, and cytarabine 100 mg/m^2) regimen and to the current standard treatment with the CHOP (cyclophosphamide 750 mg/m^2, hydroxydaunorubicin 50 g/m^2, vincristine 1.4 mg/m^2, prednisone 100 mg/m^2) regimen.

With respect to the cost estimations, costs related to the main treatment that precedes the adjuvant treatments (e.g., surgical mastectomy and/or postoperative radiotherapy for premenopausal breast cancer) are not considered. The costs for treating side effects, familial impact, transportation, other unplanned events, and long-term follow-up costs are also not included.

The cost estimations of the treatment consists of costs for hospitalization, remuneration for the oncologists, and drug prescriptions. The cost of hospitalization is obtained by multiplication of the average charge per hospital day with the number of hospital days. On January 1, 1994, one hospital day was charged at approximately 175 ECU. For outpatients, a lump sum of 87 ECU is used instead. Note that university hospitals are allowed to charge a higher per diem price. Differences with average per diem hospital charges have to be understood in terms of the prevailing Belgian budget techniques, responsible for the hospitals' resource allocation. In short, university hospitals must meet higher staffing and education requirements, e.g., a larger number of nurses. Their budgets also incorporate a substantial part of the working capital and they have investments in costly equipment, such as magnetic resonance imaging in radiotherapy. Finally, according to equally measured activity performance criteria (data on nursing activities, treatment profiles, and hospital stay), university hospitals may require higher funding.

Fees for the oncologists, costs of laboratory tests, blood tests, and other medical care were obtained by the multiplication of the frequencies of administration described in the treatment scheme with the official prices defined by the Belgian National Institute of Health Insurance.

Chemotherapy doses were calculated for a typical patient with a weight of 70 kg and a height of 1.75 cm. Recommended doses as prescribed in the package inserts were applied, and the prices used were for the most economical package sizes available.

We compared the charges to be paid by the Belgian Health Insurance for the three treatment strategies for early breast cancer and for non-Hodgkin's lymphoma as described above.

RESULTS: EFFECTIVENESS AND COSTS OF ADJUVANT TREATMENT IN EARLY BREAST CANCER

The effectiveness of adjuvant treatment in early breast cancer was convincingly shown by the meta-analysis carried out by the Early Breast Cancer Trialist's Collaborative Group and published in 1992 (8). The reductions in recurrence-free survival were 8.4% with polychemotherapy alone, 6.6% with tamoxifen at 10 years, and 10.5% with ovariectomy at 15 years (among women under age 50 only). All those gains were highly significant ($p < .001$). The reductions are even higher for node positive patients, with 8.7% for polychemotherapy, 8.8% for tamoxifen, and 10.5% for ovariectomy.

The overall reductions in the annual rate of death were 16% with polychemotherapy alone, 17% with tamoxifen, and 25% with ovarian ablation. The estimated absolute reduction in 10-year mortality per 100 women treated under age 50 was 10 ± 3 for polychemotherapy alone and 11 ± 4 for ovarian ablation alone, suggesting the equivalence of both treatments in this age group.

The equivalence of ovariectomy and chemotherapy was confirmed by the results of the only head-to-head clinical trial reported to date (1), in which 332 premenopausal women with node-negative breast cancer, recruited over 10 years, were randomized to either ovariectomy or CMF chemotherapy after mastectomy or conservation therapy. After a maximum follow-up of 12 years, no significant differences in relapse rates or in event-free or overall survival were found. Total survival at 8 years was 60% overall, irrespective of treatment, with a hazard ratio of 1.12 (95% CI, 0.76–1.63) for CMF compared with ovariectomy.

From the perspective of Belgian health insurance, surgical ovariectomy is half as expensive as chemotherapy given on an outpatient basis and three times cheaper than chemotherapy given on an inpatient basis (770 ECU versus 1,904 ECU or 2,870 ECU, respectively). Radiotherapeutic sterilization is slightly more expensive than surgical ovariectomy (1,010 ECU).

Table 1 outlines the outcome and estimated resource utilization for each of the compared treatments.

RESULTS: EFFECTIVENESS AND COSTS OF TREATMENT FOR PATIENTS WITH INTERMEDIATE AND HIGH-GRADE NON-HODGKIN'S LYMPHOMA

The available evidence from randomized trials on treatment of patients with intermediate and high-grade non-Hodgkin's lymphoma in first remission does not suggest

Table 1. Different Additional Treatment Strategies in Premenopausal Breast Cancer (To-3, No-2, Mo): Outcome and Costs from the Viewpoint of Belgian Health Insurance

		Outcome		
Identification of the treatment	Description of the treatment	Recurrence-free survival 10 years	Overall survival 10 years	Total costs
Surgical ovariectomy	A surgical procedure, blood tests, 2 hospital days, estrogen and progesterone receptor	60%, control arm = 48%	65%, control arm = 57%	770 ECU
Radiocastration	Radiotherapy: simulation and 10 fields irradiated on an outpatient basis, blood tests, lab tests: estrogen and progesterone receptor	60%, control arm = 48%	65%, control arm = 57%	1,010 ECU
CMF chemotherapy, six cycles ambulatory	Six cycles of CMF chemotherapy on an outpatient basis, 12 one-day hospitalizations, 12 blood tests, lab tests: estrogen and progesterone receptor	44%, control arm = 35%	51%, control arm = 45%	1,904 ECU

better survival with intensive consolidation with high-dose CBV therapy followed by autologous bone marrow transplantation, as compared to intensive consolidation with the LNH84 regimen. Bone marrow transplantation has instead been shown to have a higher level of toxicity (12).

The first choice of chemotherapeutic regimen for the treatment of high-grade lymphomas remains the combination regimen CHOP, which has a five-year survival rate equal to that of more aggressive chemotherapeutic regimens (11).

Resource utilization and costs for these treatment options for non-Hodgkin's lymphoma in first remission are as follows: chemotherapy followed by autologous bone marrow transplantation is two to three times more expensive than chemotherapy followed by LNH84 and seven to eight times more expensive than CHOP (2,060–2,745 ECU versus 7,232 ECU versus 19,262 ECU).

Justification for the considerable increase in expected costs incurred by using more expensive treatments requires better evidence of superior treatment outcomes with these treatments. The baseline comparator, both for clinical and economic evaluations, should be the cheaper effective treatment, which is CHOP.

A different view of the outcome and estimated resource utilization for each of the compared treatments is shown in Table 2.

DISCUSSION: IMPLICATIONS FOR COST-EFFECTIVENESS–BASED PRIORITY SETTING

Smith and Hillner (22) and Hillner et al. (14), in an update of their first attempt to estimate the cost-effectiveness of adjuvant therapy in early breast cancer, take into account the findings of the EBCTCG meta-analysis and show that adjuvant chemotherapy in patients with premenopausal estrogen receptor–positive breast cancer is an efficient intervention. The incremental cost per quality-adjusted life-year (QALY) gained was less than 12,600 ECU for tamoxifen compared with no adjuvant therapy and for combined tamoxifen plus chemotherapy treatment compared with chemotherapy alone (except for node-negative women where the cost per QALY gained with combination therapy was approximately 29,400 ECU). The cost-effectiveness of adjuvant therapy in estrogen receptor–negative (ER−) premenopausal women was generally found to be much less favorable, around 168,000 per QALY gained in node-negative women and around 42,500 ECU per life year gained for node-positive women.

In cost-effectiveness league tables constructed by the same authors (21), adjuvant therapy by tamoxifen or chemotherapy or combination treatment ranks favorably compared wih commonly accepted interventions such as medical therapy for moderate hypertension and maintenance renal dialysis, as well as a range of cancer treatments.

A review of the cost utility of systemic treatment in breast cancer (6) concludes that adjuvant tamoxifen and adjuvant chemotherapy in ER+ premenopausal patients give reasonable cost per QALY estimation and can be considered as efficient therapies.

A Danish study (2) comparing patients randomized in postoperative radiotherapy alone, radiotherapy plus cyclophosphamide monotherapy, and radiotherapy with CMF, measured temporary treatment-induced amenorrhea. The study showed that in both chemotherapy arms, more patients under 45 years of age than over 45 years developed amenorrhea (74% vs. 67% in C-arm; 68% vs. 60% in CMF arm). In the control arm, amenorrhea was substantially lower (4% vs. 17%). According

Table 2. Different Treatment Strategies in Non-Hodgkin's Lymphoma: Treatment Costs from the Viewpoint of Belgian Health Insurance

Identification of the treatment	Description of the treatment	Outcome		Cost
		3-year survival (11)	3-year overall survival (10)	
Induction ACVB/ NCVB + autologous bone marrow transplantation + consolidation CVB	4 cycles of ACVB/NCVB for induction ABMT outpatient, one-day hospitalization for induction, 28 days of hospitalization, blood tests, methotrexate, growth factors, transplantation, CVB for consolidation	69% (95 confidence interval, 62% to 76% with $p = .60$)		19,262 ECU
Induction ACVB/ NCVB + consolidation LNH84	4 cycles of ACVB/NCVB for induction, LNH84 for consolidation on an outpatient basis, one-day hospitalizations	71% (95 confidence interval, 64% to 78%, with $p = .60$)	53%, with $p = .68$	7,232 ECU
Conventional chemotherapy: CHOP	6 or 8 cycles of CHOP, one-day hospitalizations, 7 blood tests		55%, with $p = .68$	2,060 ECU or 2,745 ECU

to the authors, a substantial part of the effect of adjuvant chemotherapy is mediated by chemical castration.

A crucial element in cost-effectiveness analysis is the comparator to which costs and effects of a new treatment are compared. In the published economic evaluations of adjuvant treatment for early breast cancer, the comparisons were tamoxifen versus no adjuvant therapy, chemotherapy versus tamoxifen, and combination therapy versus chemotherapy alone. Ovariectomy either by surgery or radiotherapy was not included in any comparison. Nevertheless, the available evidence from the meta-analysis by the EBCTCG and the Scottish group suggest that ovariectomy is equally effective as drug therapy.

The potential for better survival by combining ovariectomy and chemotherapy was suggested by the EBCTCG meta-analysis (8). A recent study by Rivkin et al. (20) comparing chemotherapy and chemotherapy plus ovariectomy showed no improvement for the combination, however. The authors concluded that ovariectomy did not add any benefit to chemotherapy alone. The role of ovariectomy alone was not considered.

It has been stated after publication of the overview of adjuvant treatment in early breast cancer that ovariectomy deserves a re-examination as an adjuvant therapy for premenopausal women and that it should be seriously considered as an alternative to adjuvant chemotherapy in those women (12;14;18). Such a re-examination should not be limited to effectiveness but should also look at possible long-term adverse effects (such as decrease of bone density and vascular disease), effects on quality of life, and, given the large expense involved, to costs.

Our cost exercise shows that the former therapy might also be considerably cheaper than drug therapy. Therefore, the cost-effectiveness of ovariectomy compared with no adjuvant therapy is likely to be most favorable. The cost-effectiveness ratio of drug therapy alone compared with ovariectomy would probably be much less favorable (equally effective but more costly).

Of course, our exercise has many limitations. Data on resource utilization were not based on "real" cases, costs of side effects or long-term consequences were not considered, and our cost estimations may not reflect true opportunity costs because they represent only the Belgian situation. Our cost estimations may therefore be sensitive to differences in treatment patterns and relative costs. Nevertheless, despite how preliminary our estimations may be, they do clearly suggest that the research agenda for clinical research and economic evaluations in early breast cancer should be broadened toward important treatment alternatives that are currently overlooked. Doing so might impact dramatically the relative cost-effectiveness of various treatment options.

In high grade non-Hodgkin's lymphoma, a comparison of costs and effects with autologous bone marrow transplantation (ABMT) versus CHOP has been carried out by the Institute for Medical Technology Assessment in the Netherlands (HOVON-3) (16). Detailed cost data were collected for 64 patients, all slow responders (partial remission after three cycles of CHOP) without bone marrow suppression, randomized between five cycles of CHOP (on an outpatient basis) and one cycle of CHOP followed by ABMT. Total average costs, including follow-up costs, were estimated as 41,340 ECU with ABMT compared with 12,780 ECU with CHOP. The costs associated with the initial treatment were 28,320 ECU per patient in the ABMT arm compared with 2,560 ECU per patient in the CHOP arm, hence an 11-fold difference. Survival at 2 years after randomization tended to be better with CHOP (81% alive) than with ABMT (65% alive), although the

difference was not statistically significant, leading to an infinite cost-effectiveness ratio for the transplantation regimen compared with the CHOP regimen. The authors concluded that CHOP was more cost-effective than ABMT.

New treatments for non-Hodgkin's lymphoma are being assessed, peripheral blood stem cell transplantation being one of them. In the light of the arguments mentioned above, clinical and economic evaluations should use the CHOP regimen as baseline comparator. Uyl-de Groot et al. (24) report that the costs of peripheral blood progenitor cell (PBPC) transplantations were 30% lower than the costs associated with ABMT in a study with 63 patients. They state that their results suggest that, for patients with malignant lymphomas or solid tumors who receive high-dose chemotherapy, PBPC transplantation is more cost-effective than ABMT. They also state that an economic analysis may be combined with future prospective trials to confirm the dominance of PBPC over ABMT in the patient groups considered here. Again, such an economic analysis could lead to favorable cost-effectiveness ratios for PBPC entering cost-effectiveness "league tables," thanks to the choice of a favorable comparator and overlooking the most appropriate comparator, which is the CHOP regimen.

In practice, a comparison of cost-effectiveness ratios is not without risk. Differences in applied methodologies to estimate costs and effects, and the choice of comparators can heavily influence the outcome of a cost-effectiveness exercise, pushing the respective treatments up or down a given cost-effectiveness "league table." Relevant comparators may also be forgotten or overlooked in cost-effectiveness analysis for a variety of reasons. One of the reasons is that the economic evaluation may be based upon clinical trials that did not include this particular comparator. Clinical trials usually compare treatments of the same modality, such as two chemotherapy regimens, while a third alternative, such as radiotherapy or surgery, is often not included for feasibility or other reasons (e.g., no interest from a potential sponsor or difficulties reaching agreements among the concerned medical specialties).

From a clinical point of view, a trial comparing two new experimental treatments might provide valuable information. From a policy point of view, however, the cost-effectiveness ratios derived from such a trial might be misleading and cause allocation inefficiencies if not accompanied by information on those alternatives not considered.

CONCLUSION

In this paper we analyzed resource utilization and associated costs for different treatment strategies with similar outcomes for two types of cancer. In the prevailing Belgian health care reimbursement system, this exercise shows clear differences: surgical ovariectomy in breast cancer (770 ECU) and conventional chemotherapy CHOP (2,745 ECU) in non-Hodgkin's lymphoma prove to have substantial savings in comparison to treatments with chemotherapy (1,904 ECU–2,870 ECU) and chemotherapy followed by autologous bone marrow transplantations (19,262 ECU), respectively.

In cancers where highly innovative experimental treatments are available, one might be easily induced to overlook standard effective treatments, which may be less challenging and rewarding to investigators, clinicians, economists, and private sponsors. Health care insurers and governmental bodies, whose interests are served

by having the most cost-effective treatments paid first, can reduce the temptation by taking the responsibility for funding the appropriate research.

The return on investment for society from funding lies not only in the establishment of state-of-the-art treatment but also in potentially substantial savings in constrained health care budgets resulting from better and unbiased insight on the costs and effects of competitive treatments, as illustrated by our costing exercise. Evidence on equivalent quality therapies, including economical aspects of these treatments, should be further discussed in scientific meetings. Scientifically assessed data should also reach patients through information sessions, while financial incentives ought to be given in favor of less costly equivalent-quality therapies.

For the most appropriate clinical research and economic evaluation to be carried out properly, independence should be granted through special funding. Savings due to the utilization of the results of such studies could be used to fund other studies and enhance further development and efficiency in cancer care.

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