available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Economic evaluation of cancer therapies: More and better studies will lead to better choices in cancer care

*Carin A. Uyl-de Groot**

Institute for Medical Technology Assessment, Erasmus MC, University Medical Centre, PO Box 1700, 3000 DR Rotterdam, The Netherlands
Department of Clinical Epidemiology & Biostatistics, VU Medical Centre, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 14 August 2006
Accepted 14 August 2006
Available online 27 September 2006

Keywords:
Economic evaluation
Cost
Cost-effectiveness
Cost-utility
Cancer
Chemotherapy
Methodology

ABSTRACT

Randomised phase III trials are the ideal setting for prospective collection of economic and health related quality of life (HRQL) data. Many studies combine prospective clinical data with economic assumptions or data collected in separate costing studies. To extrapolate the trial outcomes to lifelong consequences, modelling approaches are often used. Also, in situations where no randomised trial data are available, modelling approaches are often applied. In this paper some methodological and practical issues are described. The aim of the economic evaluations is to support decision-making. As many new promising anti cancer drugs are forthcoming, the questions of how decision-makers will use the results of the economic evaluations and how patients can optimally benefit from these new drugs arise.

1. Introduction

Cancer accounts for a major burden of mortality and morbidity in most industrialised countries. During the last few decades, fundamental and clinical research have provided a better understanding of cancer and as a result improved prognosis in terms of overall survival, disease-free survival and quality of life of patients can be perceived. For example, in the Netherlands, the 5-year survival rates in men improved from 30% in the seventies to 45% in 2001. In women this percentage improved from 45% in the seventies to 60% in 2001.[1] The development of refined diagnostics, new surgical techniques and new anti cancer drugs and performing many controlled clinical trials has lead to this progression. However, it is expected that in 2015 the number of patients with cancer in the Netherlands and in most European countries will increase by 40%, mainly as of result of ageing.[1]

In the nineties, most industrialised countries spend 3–6% of their gross domestic product (GDP) on cancer care.[2] It is expected that the costs on cancer care will increase further. Budgetary pressures, compounded by financial constraints and rising costs, especially of new cancer drugs, have shifted payers' and providers' attention to the evaluation of treatment effects using endpoints other than clinical efficacy. Policy-makers, regulatory authorities and clinicians increasingly require information on the cost and cost-effectiveness of treatment. Economic evaluation provides the opportunity to compare alternative treatments, keeping in mind both costs and effectiveness. The results of these evaluations become more and more important in the decision to include new alternatives in clinical practice. In light of significant activity reported with some of the novel biological drugs and their elevated cost, a major question is arising to their availability for unrestricted use.

* Tel.: +31 10 408 8571; fax: +31 10 408 9081.
E-mail address: c.uyl@erasmusmc.nl.
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.08.008

The purpose of economic evaluation is to aid decision-makers in choosing between competing diagnostics or therapies within the constraints of a fixed pool of resources. It allows for an objective comparison of alternatives in terms of costs and effects. The area of new, expensive cancer drugs is particularly suitable to economic evaluation as the extra costs per patient are usually high and expected benefits are still small for large groups of patients.

During the last decades, there has been growing literature on economic evaluation in health care. However, there is a great deal of variation in methodology and reporting of these studies. This manuscript describes some methodological and practical issues of economic evaluations in the cancer area. There are also some basic issues in economic evaluations that are applicable to all studies, like choice of analyses (e.g. cost-benefit, cost-effectiveness, cost-utility) and choice of discount rate for costs and outcomes. These issues are well described in the literature[3,4] and will not be addressed in this paper.

2. Economic evaluation

2.1. General

If costs have to be taken into account in clinical decision-making, the problem arises of how to incorporate this. Ideally, resource allocation decisions should encompass a comprehensive assessment of direct and indirect costs as well as reliable measurement of clinical benefit which take into account patients' preferences and needs.[3–5] In this respect, health-related quality of life (HRQL) is recognised as a major outcome for the evaluation of new therapies.

As a result, a more extensive framework is needed in health care with the same objectives: the determination of a unique preferential ordering of (health care) programmes.[3] This ordering of health care programmes should not be limited to a specific disease area.

The framework starts from quantification of all costs and benefits. However, the measurement of benefits should be modified. Instead of monetary units, such as the willingness to pay, non-monetary units may be used. In standard cost-effectiveness analysis (CEA), the benefits are expressed in terms of 'natural unit', e.g. the number of survivors after a certain period or an improvement in quality of life. When different dimensions of benefits are aggregated, e.g. so called utilities are combined with life years, it is called a cost-utility analysis (CUA). These analyses are particularly relevant in the case of cancer, because disease states and treatments with different arrays of effects for the patients' HRQL are often seen. Benefit measurement in economic evaluation in trying to cover all relevant outcome aspects specifically aims at summary values which can bear the claim that they represent overall societal preference values.[3,4] The results of economic evaluations would be expressed in terms of a ratio, e.g. incremental costs per quality adjusted life year (QALY). These ratios allow comparison across all diseases. So far, however, the methods used for assessing and quantifying treatment outcomes in terms of utilities and costs differ widely between studies. Therefore, comparison across studies and diseases should be treated with caution.

2.2. Issues specific to cancer

In the literature, economic evaluation of cancer therapies span a wide range of methods and approaches, depending, among others, on the objectives of the study and the scope of the analysis. Some of the main issues are described below.

2.2.1. Choice of perspective

Economic evaluation can be done to measure the impact of a new technology on the hospital budget, the health care system in general, third-party payers, the patient and his family or society. In general the preferred choice of perspective in economic evaluation in general is that of society. Most (pharmaco)economic guidelines stated that this is the preferred perspective. The societal perspective means that all costs and benefits for all parties in society should be accounted for. First, this implies that patient costs (both out of pocket expenses and time-investments) and care by close relatives should be included. Second, the production loss due to cancer is also a cost to society, and the associated indirect costs should be included in the analysis. In cancer these costs are usually substantial as many patients do not work during the treatment period. Third, accepting society's perspective also has an impact on the unit prices you want to use. This implies that the real use of resources should be measured and valued rather than the charges paid by patients or third-party payers.

In cancer, many economic studies used a hospital's perspective, although it is stated that a societal perspective was taken into account. However, in the meanwhile, indirect costs and direct non-medical costs were neglected or presumed to be equal between the two alternatives. Taking into account the financial burden of new expensive cancer drugs on the hospital budget, it could be justified to focus on direct medical (hospital) costs. However, be aware that this may have consequences for the comparability with other interventions.

2.2.2. Choice of approach

Approaches often applied in cancer research are the CEA alongside randomised clinical trials and modelling. Clinical trials are performed in artificial research environments and do not provide all the economic information necessary for decision-making.

Thus, by using the alongside clinical trial approach, potential issues arise from the reconciliation of the study requirements for clinical and economic evaluations. These issues disclose the different perspectives of clinical studies versus economic evaluations. In the clinical study, effectiveness should be demonstrated in a well-defined patient group on the basis of a sensitive (clinical) outcome indicator. The economic study has the aim to support a policy decision on an intervention or programme by assessing its general cost-effectiveness in routine medical practice, comparing the best alternatives available.

2.2.3. Choice of alternatives

The choice of alternatives within a clinical trial determines the suitability of the trial for an alongside economic evaluation. If the trial does not include the usual or the best alternative treatment as a control, an economic evaluation is

impossible.[5] Placebo comparisons are rarely relevant for economic evaluations. These comparisons are frequently essential in determining efficacy, but are only suitable in economic evaluation if the no-treatment option reflects the best alternative action.

2.2.4. *Choice of end points, sample size and power, follow-up*

These issues pertain both to the principal question of which outcome measure is the most important, and to the practical question of which end point results in a feasible sample size, given a reasonable time frame and the usual values for precision and power.[6] The choice of primary endpoint in a clinical study may not correspond with the desired endpoint for an economic evaluation. Generally, primary outcomes in economic evaluations are cumulative life years gained, QALYs gained, and differential costs.

The usual primary end points in cancer trials are remission rates, fixed time (e.g. 1 year or 5 year) survival rates, and progression-free or disease-free survival rates. From a clinical viewpoint, the choice of the analytical follow-up time (for example, 1 year or 5 years) may be difficult if the intervention has lifelong influence on survival (e.g. breast cancer) or if the impact of alternatives on survival differs over time. Statistical methodology exists to deal with incomplete empirical follow-up (censoring of observations), enabling comparisons of survival rates.[7]

In economic evaluation, lifelong follow-up is preferred. Except for rare cases with either complete recovery or death within the empirical follow-up time, lifelong consequences cannot be observed. What happens after censoring should be explicitly estimated, which requires advanced statistical analyses. Usually mathematical modelling is applied, based on comprehensive data of patients at the time of censoring.

It has been shown in other patient groups that patients with incomplete follow-up could be largely responsible for difference in costs between treatments.[7] In this study, guidance on how to deal with the data of patients with incomplete follow-up are described. In summary, three steps should be taken, namely investigation of the distribution of costs, investigation of the amount and pattern of dropout and selection of methods to deal with incomplete data.

Another issue is that large systematic studies on patients with recurrent or terminal disease are rare. Consequently, valid lifelong estimates may be difficult to obtain.

Related to the end point definition and the empirical follow-up is the determination of the sample size. From a conceptual point of view, economic evaluation requires a separate sample size determination, based on distributions of costs and benefits in any of the alternatives distinguished. In practice, reference values for costs, life years and utility data are often missing. This may restrict sample size considerations to the clinical part of the trial. As a consequence it is possible that the economic comparisons are underpowered.

2.3. *Determination of outcome*

In economic evaluation, the determination of survival gain is rather straightforward, except for the modelling of incomplete observations. The measurement of HRQL changes is more complex.

In cancer, measurement instruments are divided into two main categories: the generic instruments and cancer specific questionnaires. Generic instruments are developed to monitor changes in all health dimensions and allow comparison of outcomes across different disease categories. In this respect the Short-Form 36 questionnaire is often used.[8] Cancer-specific instruments measure health problems specific for cancer. These instruments are more sensitive for specific problems concerning cancer. Cancer-specific instruments often used in clinical trials are the EORTC Core Quality of Life Questionnaire C-30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy (FACT) scale.[9,10] Sometimes, some specific cancer modules are added to these instruments in order to get more information on a specific cancer, like lung cancer, breast cancer or prostate cancer modules.

So far, clinical and economic evaluations coincide. However, economic evaluation also tries to arrive at a summary score of the patient benefits, taking into account both survival and quality of life.

To arrive at such a summary score, the following procedure applies. First, so-called utility values (a figure between 0 and 1 to indicate the preference value of a certain health state) have to be attached to outcomes. There are three dominant methods of acquiring utility values: direct rating, standard gamble (more convenient in surgical interventions) and time trade-off (more convenient in medical interventions). Utility values may be elicited from the general public (preferable within the societal perspective) and the patients themselves. If utility values for each characteristic health state have been acquired, the construction of QALYs becomes feasible, allowing the improvement in outcome to be expressed in terms of QALYs gained and, consequently, the construction of a cost-utility ratio.[3]

One of the problems often encountered was that no valuation instrument was included in the quality of lime measurement. New studies have been performed and are being performed in order to develop a set of utility weights capable of being used to convert a generic instrument or a cancer specific instrument in a single index capable of being used in the economic analysis of clinical trial data. These utility weights derived through these studies met some methodological problems. The easiest and best methodological way of getting a utility data set is simply to include a valuation instrument within the quality of life measurement.

2.4. *Determination of costs*

To determine the costs, the first step is to bring up the resources in suitable natural units, with an emphasis on the counting of variable cost items.[3,4] *A priori* estimation of the relative importance of these cost items should guide the data collection.[5] Case registry forms, as normally used in cancer trials, provide insufficient data, as tabulation of major cost items is usually incomplete. Contrary to these forms, hospital administration data are usually complete, but they usually do not contain all cost items, which can be related to patients. As a result, enumeration of hospital cost volumina is performed using a mixture of appended case registry forms, patient questionnaires, hospital data, and occasionally, on-site observations. Additionally, hospital administrative data provide

information on fixed costs and patient questionnaires are useful for obtaining information on direct patient's costs, indirect costs and costs related to outpatient care. Before starting a cost study it is very important to answer questions about which costs are relevant and how these costs could be collected in the most efficient way. For example, when quality of life has been taken into account, it may be possible to add some questions on indirect costs or costs related to outpatient care to the quality of life questionnaire.

The next step is to attach prices to these natural units. Frequently, prices differ substantially from the charges for a particular service. In general, for the most important cost items, such as inpatient days, outpatient visits or radiotherapy, separate cost price studies are performed. The average unit costs of these items are mainly derived from the hospital's accounting system and include costs of nursing personnel, medical materials, hotel costs, as well as mark ups for the costs of housing, general equipment and overheads. Costs of personnel should be based on actual scale salaries and include mark ups for social security and retirement premiums. In most studies the unit costs of diagnostic tests and other procedures are based on charges, and costs of medications are based on actual purchase prices with a mark up for the costs of the pharmacist department.

In the last step, volumina and prices are multiplied. In addition to the empirical costs determination, economic evaluation includes estimates of future costs (disease-related and disease-unrelated) if follow-up of patients is incomplete. Particularly if the tail of the survival distribution is long - the usual case in cancer - these long-term estimates are of vital importance: average costs (as used in cost-effectiveness ratios) may largely exceed median costs.

2.5. *Assessment of risk and uncertainty*

It is often necessary to make assumptions in estimating costs and effects. This should be tested by using sensitivity analysis, in which key variables are changed.

2.6. *Presentation of results*

The presentation of results must include a full description of which effects are measured, and specifically state what the trial objectives are. When there is uncertainty, ranges should be presented. Furthermore, the results should be placed in such a way that is possible to generalise the results to other settings. Over the last few years, the results of economic studies have been presented more and more by probabilistic modelling and cost-effectiveness planes.[3,11]

3. Discussion

There are many new therapies presently used in advanced stages of the disease where the gain in survival is not always long and the costs are increasingly high leading to questions concerning how good a new medicine should be in order to justify its cost.[12] Especially, the costs of new monoclonal antibodies like bevacizumab and cetuximab are of major concern for patients, doctors and policy makers. In the United States, the Centres for Medicare and Medicaid base their decisions about reimbursement on the criteria 'reasonable and necessary'. In the publication by Schrag it was stated that the federal government in the US should be able to negotiate with pharmaceutical companies in order to try to stop the escalating drug prices.[13] Otherwise, it becomes possible that health plans in the United States will not cover these drugs or that the premiums will be raised enormously. The solution to see what a patient can pay to determine which treatment he will receive is unethical and not acceptable.

New cancer drugs should have at least a significant improvement on survival and/or progression-free survival, and/or be substantially better tolerated when efficacy is the same.[14] Cost-effectiveness analyses can provide essential information on the costs and benefits of new drugs and consequently on the optimal policy mix, thereby supporting decisions on the adoption and utilisation of new drugs. As more economic evaluations have been performed, it becomes possible to make comparisons between health-care interventions in terms of their relative cost-effectiveness, in cost per life year gained, or cost per QALY gained. Therefore, critical assessment of the quality of these studies is important.

Cost-effectiveness ratios varied exceptionally. In cancer treatment, there are many studies presenting cost-effectiveness or cost-utility ratios. For example, the cost per QALY of administering paclitaxel or docetaxel in patients with metastatic breast cancer amounted to € 23611 and € 38796, respectively. The cost-utility ratio (in terms of cost per QALY gained) of these treatments compared to mitomycin/vinblastine amounted to € 77647 and € 199917.[14] Considering the height of the ratios, the little impact on survival and the knowledge that these treatments are applied in a severely ill patient group, it is clear that the rationale of administering new treatment modalities are not simply based on economic reasons.

A Dutch study investigated the relationship between disease severity and willingness to pay; the maximum acceptable cost per QALY for patients with non-Hodgkin's lymphoma would be € 45378.[15] NICE applies an acceptable cost per QALY gained between € 25600 and € 43800.[16] This range of acceptable cost-effectiveness seems to be independent of type of disease. However, in the case of cancer, also somewhat higher ICERs were sometimes accepted.

Be aware that other factors such as incidence and prevalence of disease will also have an impact on the decision whether or not to reimburse new drugs. The higher the number of patients who need the new drug, the higher the budget impact for the hospital will be.

Another issue is that for economic purposes the results of clinical trials should also be tested in the real world. Such real world studies, also called 'outcomes research' can be used to evaluate the real effects of the new drug.[17] At the present time, there are a number of new drugs which have been introduced in the health care system and are being reimbursed, for which no cost-effectiveness after the introduction have been performed. For the very expensive drugs or perhaps for all new drugs, re-evaluating these drugs not only in terms of (late) toxicity, but also in terms of other outcome parameters such as survival, progression free survival, quality of life and costs, should be recommended. In the Netherlands and some other European countries drugs could first be temporarily

reimbursed and after the results of the re-evaluation are available, be reimbursed for longer periods, if the results remain good. For economic purposes results gained in the real world are essential in order to get high extern validity of study results.

In conclusion, in light of the many new promising, but expensive, anti cancer drugs, well performed economic analyses are very important. These evaluations, together with other data such as clinical data, can hopefully lead to reasoned application of these new drugs. This could lead to better care for patients with cancer.

Conflict of interest statement

None declared.

REFERENCES

1. "Steeringcommittee Cancer" van Koningin Wilhemina Fonds Kankerbestrijding. *Cancer in the Netherlands: trends, prognoses and implications for demand*. Drukkerij van den Boogaard Oisterwijk b.v.; 2004 [In Dutch].
2. Jönsson V, Clausen SR, Hansen MM. Pharmacoeconomic aspects in the treatment of curable and incurable cancer. *Pharmacoecon* 1995;**8**:275–81.
3. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford, UK: Oxford University Press; 2005.
4. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-effectiveness in health and medicine*. first ed. New York: Oxford University Press; 1996.
5. Williams C, Coyle D, Gray A, et al. European School of Oncology Advisory Report to the Commission of the European Communities for the "Europe Against Cancer Programme": Cost-effectiveness in cancer care. *Eur J Cancer* 1995;**31A**:1410–24.
6. Bonsel GJ, Rutten FFH, Uyl-de Groot CA. Economic evaluation alongside cancer trials; methodological and practical aspects. *Eur J Cancer* 1993;**29A**:S10–4.
7. Oostenbrink JB, Al MJ. The analysis of incomplete cost data due to dropout. *Health Econ* 2005;**14**:763–76.
8. Ware JE. *SF-36 health survey. Manual & interpretation guide*. Boston, MA: The Health Institute, New England Medical Center; 1993.
9. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality of life instrument for use in international clinical trials in oncology. *J Nat Cancer Inst* 1993;**85**:365–76.
10. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**:570–9.
11. Hout van BA, Al MJ, Gordon GS, Rutten FFH. Costs, effects and c/e ratio's alongside a clinical trial. *Health Econ* 1994;**3**:309–19.
12. Schrag D. The price tag on progress – chemotherapy for colorectal cancer. *N Engl J Med* 2004;**351**:317–9.
13. Uyl-de Groot CA, Giaccone G. Can we afford an unrestricted use of new biological agents in GI oncology. *Curr Opin Oncol* 2005;**17**:392–6.
14. Uyl-de Groot, Vermorken JB, Hanna MG, et al. Immunotherapy with autologous tumor cell-BCG vaccine in patients with colon cancer: a prospective study of medical and economic benefits. *Vaccine* 2005;**23**:2379–87.
15. Poley MJ, Stolk EA, Brouwer WB, van Busschbach JJ. "Necessity" determined on the basis of disease severity when prioritizing health care interventions. *Ned Tijdschr Geneeskd* 2003;**146**:2312–5 [in Dutch].
16. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 2004;**13**:437–52.
17. Ramsey S, Willke R, Briggs A, et al. *Alongside clinical trials: the ISPOR RCT-CEA task force*. ISPOR Workpaper, March 2005 [www.ispor.org/workpaper].