Anti-Cancer Drugs 1998, 9, pp. 835–841

Introduction

Economic evaluation of cancer treatments: methodological and practical issues

Carin A Uyl-de Groot and C (Karien) R Touw
Institute for Medical Technology Assessment, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands. Tel: (+31) 10 408 8581; Fax: (+31) 10 452 2511.

Economic evaluation is a comparative analysis of alternatives in terms of both their costs and consequences. Therefore, the basic task of economic evaluation is to identify, measure, value and compare the costs and effects of the alternatives being considered. In this paper, the methodology of economic evaluation in general and in cancer in particular is reviewed and practical issues are illuminated. In the treatment of cancer patients not only survival and disease-free survival are important outcome parameters, but also quality of years alive. Hence, specific attention is given to the measurement and valuation of quality of life. Economic evaluation is intended to support health policy at different levels of decision making. In cancer treatment, health policy concerns both preventive, curative and palliative strategies, and decisions are often made at the micro and macro level. Economic evaluation can provide essential information on the costs and benefits of each option, and consequently on the optimal policy mix, and thus support decisions on the adoption and utilization of new treatments. Such information may assist policy makers in formulating regulatory policies and legislation, industry in developing products, health professionals in treating and serving patients, and consumers in making personal health decisions. [© **1998 Lippincott Williams & Wilkins.**]

Key words: Economic evaluation, methodology.

Introduction

Cancer is an important cause of illness and death, accounting for a high percentage of mortality in Western countries. In the Netherlands, about 30% of all deaths is due to cancer and the prevalence, an indicator of the present burden of illness to society, is clearly rising.[1] In the last decades cancer treatment has shown a rapid evolution. It is now a multi-disciplinary treatment strategy incorporating surgery, radiotherapy, chemotherapy and immunotherapy. The high incidence and prevalence of cancer make this disease a major economic issue. The direct medical costs are considerable, and are still rising due to the increased use of expensive drugs, radiotherapy equipment, the growing attention to various kinds of palliative interventions and survival success. In the Netherlands, the total direct medical costs of malignant cancer amounted to $2335 million in 1994, i.e. 4% of total health care costs. Approximately 80% of this expenditure was produced by in- and out-patient hospital care and approximately 12% by extramural care (including extramural administered pharmaceuticals).[2] It is expected that in 2020, as a result of ageing, these costs will have increased much more rapidly than total health care costs. Finally, the high prevalence of morbidity, mortality and the consequent loss in production also cause high indirect costs.

As health care budgets have grown, increasing emphasis is being placed on identifying and improving value for money. Therefore, efficacy can no longer be the only criterion that determines whether or not a technology should be used in caring for patients in general and cancer patients in specific. This is true at the level of public health policy as well as at the level of clinical practice. For example, the Dutch Health Insurance Executive Board has concluded that cost-effectiveness should be taken into account when approving insurance coverage for new treatment modalities. Practising oncologists, faced with pressures to control health care costs, are increasingly being asked to incorporate considerations of cost into their decisions regarding the care they provide to their patients. Note that although economic evaluation could provide important information to decision makers, it addresses only one dimension of health care programme decisions. Economic evaluation is most useful and appropriate when preceded by evaluation of the efficacy and effectiveness.[3]

This paper will briefly discuss basic methods of economic evaluations. Economic evaluation could be

Correspondence to CA Uyl-de Groot

defined as 'a comparative analysis of alternatives in terms of both costs and consequences'. The basic tasks of any economic evaluation are to identify, measure, value and compare costs and consequences of the alternatives to be considered. This will be discussed in the first sections. As cancer treatment may have important side effects and the disease itself strongly affects quality of life, not only life-years gained, but also the quality of the life-years gained are at issue. Because of this trade-off between the adverse effects of treatment against the adverse effects of the disease itself, quality of life measurement deserves special attention in economic evaluations of cancer treatment. The next section deals with timing of economic evaluation. This will be followed by a section discussing methodological and practical issues of economic evaluation in general, and in cancer treatment in particular. The use of results of economic evaluations are covered in the final section.

Basic methods of economic evaluation

There are four techniques of economic evaluations, i.e. cost-minimization, cost-effectiveness, cost-utility and cost-benefit analysis. These techniques differ in the way the costs and consequences are dealt with. It is important to ensure that the appropriate method is being used in any particular context.

In a cost-minimization analysis, the alternatives will only be evaluated in terms of costs. The treatment options being compared are assumed to be identical in their effectiveness and risk of complications and side effects. A cost-effectiveness analysis enables us to compare between alternatives with both differing costs and differing effectiveness. Effectiveness is measured in natural units such as life-years saved. Cost-effectiveness is a relative concept, the ratio must always be calculated in terms of a comparison with a 'best alternative'. This analysis requires a single measure of effectiveness. However, when treatments have a range of outcomes a cost-effectiveness analysis will not suffice.

More recently, cost-utility analysis has emerged, which applies so-called utility values which aggregate different dimensions of benefits. The most common utility measure used is the 'quality-adjusted life-year' (QALY), which combines the outcomes survival and quality of life during the survival period.

Another method is the cost-benefit analysis. This analysis differs from a cost-effectiveness and cost-utility analysis in that it calculates the benefits in monetary terms as well as costs. A cost-benefit analysis could be useful in allocating limited budgets between competing services. The monetary value of health benefits can be estimated by measuring the patients' willingness-to-pay through questionnaire surveys.[4] However, this approach is unlikely to become routinely applied in health care.

Independent of the economic analysis chosen, the analysis must follow the same stages. Williams *et al.* distinguished the following basis stages (see Table 1):[5]

(a) *Problem definition.* This stage consists of a clear definition of the problem, statement of the study perspective and the economic technique for how the results will be analyzed.

(b) *Identification of options.* At least two options must be compared. In an economic evaluation the best alternative treatment should be included as control. In cancer, randomized clinical trials are often used to evaluate the clinical efficacy. By linking an economic evaluation to such a clinical trial, information of costs and effects will be available in a early phase of the development process of new technologies. When the clinical trial does not include the best alternative an economic evaluation is impossible.

(c) *Identification of relevant costs and outcomes.* All cost and outcomes relevant to the study perspective must be identified. Both costs and outcomes will be influenced by the study perspective, the economic method and the health care technology under analysis.

(d) *Measurement and valuation of costs and outcomes of each option.* This will be described in the section below.

(e) *Allowance for differential timing of costs and outcomes.* Simply adding total costs and outcomes over time is not adequate, because people have distinct preferences for delaying costs and bringing forward benefits. Due to the existence of a time preference both costs and outcomes should be discounted.

(f) *Sensitivity analysis: assessment of risk and uncertainty.* Data on costs and outcomes may be subject to uncertainty. The impact of key variables and assumptions should be demonstrated through the use of sensitivity analysis.

(g) *Presentation of results.* This should be done in a way which shows whether the original problem has been solved. The original problem, the method of analyses, uncertainties and results should be presented clearly. Furthermore, the possibility of generalization to other settings should be indicated.

Table 1. Basic stages of an economic analysis

(a)	Problem definiction
(b)	Identification of options
(c)	Identification of relevant costs and outcomes
(d)	Measurement and valuation of costs and outcomes
(e)	Allowance for differential timing of costs and outcomes
(f)	Assessment of risk and uncertainty
(g)	Presentation of results

The following two sections will discuss the identification, measurement and valuation of costs and outcomes.

Identification, measurement and valuation of costs

Identifying costs

In identifying the relevant costs, it is useful to make a distinction between direct and indirect costs. Direct costs are the resources involved in the patients' treatment and follow-up. These costs could be direct medical costs (such as hospital days, outpatient visits, medication, blood transfusions and medical procedures) and direct non-medical costs (such as costs of home care and patient's travel costs). Indirect costs are resources lost due to the treatment and illness (e.g. loss of production). Traditionally, indirect costs are valued as changes in the productivity of the patient in the labor market, i.e. the human capital approach. Recently, the friction cost method is applied more frequently as this method allows for taking into account the effect of unemployment.[6] The importance of non-medical costs and indirect costs varies between treatments and patient groups.

Measurement of costs

Most often, cost data will be assembled retrospectively or prospectively using data from randomized clinical trials, literature survey and/or expert opinion. Data on a number of activities will be collected by means of clinical report forms, hospital information systems or an individual registration system (e.g. by performing patient file research). Clinical report forms are often incomplete for economic purposes. For example, only laboratory and medical procedures relevant for the clinical study are filled in, and not all performed tests and procedures. Furthermore, in many countries existing information systems are finance oriented and not patient oriented. This often implies that a separate registration system will be used.

In cancer treatment sometimes there is an enormous amount of cost data. Therefore, before starting the trial, we should identify which costs could be measured prospectively and which retrospectively. In general, relevant costs which would vary and can only be measured retrospectively are collected at the same time as the clinical study (e.g. nursing time in wound healing). A problem is that sometimes cost calculations should be performed when the clinical study has already been finished. This happens when the clinicians or pharmaceutical industry realize that cost may be of importance when they show the results.

Another issue is that it is not always known which costs are relevant. To simplify data collection one could choose not to take some activities into account and to use a proxy to take those activities into account. For example, patients with acute leukemia receive an enormous amount of medication during the remission induction and consolidation treatment (sometimes more than 40 different drugs per treatment per patient). As it is very time consuming to register all drugs, it may be an option to neglect the less expensive drugs, e.g. drugs cheaper than $10. However, patients with acute leukemia will receive drugs for a long period (4–6 weeks) and sometimes drugs will first be administered orally (less than $10) and thereafter when a drug therapy fails, it will be administered i.v., i.e. often more than $10. Furthermore, most economic researchers do not exactly know the cost of drugs.

Valuation of cost data

Unit prices should be determined for each of the activities identified, reflecting the real use of resources. The choice should be made whether the unit prices will be based on tariffs or on actual resource costs. In general, cost price studies will be performed for the most important cost items (e.g. days in hospital). For other less important cost items (e.g. medical procedures) tariffs are taken into account. The importance of cost items depends on the study perspective (social, hospital, etc.), kind of treatment and the way the activities will influence the average treatment costs.

Identification, measurement and valuation of outcomes

Clinical response is the most widely used measure of treatment efficacy. However, traditional techniques

that rely on the results of physical or laboratory examinations do not quantify the extent to which the disease or its treatment affects the patient. Nowadays, there is increasing evidence that measures describing the patients' experience of the results of medical care are useful and important supplements to traditional physiological or biological measures of the consequences of disease.[7] Assessment of the impact of the disease and its treatment on the physical, psychological and social functioning of the patient, also referred to as (health-related) quality of life or health status, has become more and more an important tool in the evaluation of health care outcome. Particularly in the management of chronic diseases, where the aim of treatment is not primarily prolonging life, improvement of quality of life is an important issue.[8] The same holds for the field of oncology, where cure is not always possible and survival benefits must outweigh the major side effects of treatment.[9]

Nowadays, among researchers there is no real consensus about the definition of quality of life. It is agreed upon that quality of life is a subjective measure and that patients themselves are the best judges of their own quality of life. In general, quality of life is described as a multidimensional concept, where different domains such as physical, psychological, social and role functioning are of importance.

Since quality of life is a multidimensional concept, differences in quality of life may manifest in different dimensions and these variations may be in different directions for the dimensions. Here the question arises how to judge whether one patient is better off than another if his quality of life is better on one dimension, but worse on another. Therefore aggregating the consequences of the effects of a disease or its treatment on the different dimensions of quality of life in summary measure or index of the profile scores is needed. Such summary measures are currently obtained through a procedure in which health state descriptions are valued by subjects who are presented with a number of health state descriptions and who are requested to rank these states according to the degree of (un)desirability and to indicate how good or how bad each of those states is for them.[3]

Quality of life instruments

Three main types of questionnaires for the assessment of quality of life can be distinguished: disease-specific and generic instruments (both descriptive), and valuation instruments. Incorporation of a disease-specific, generic and valuation measure is advisable in economic evaluation studies.

Disease-specific instruments measure the consequences of a specific disease or disease category and/or its treatment. They are very sensitive to changes in health status of patients with that disease. Cancer-specific questionnaires are, for example, the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30), the Rotterdam Symptom Checklist (RSCL) and the Functional Assessment of Cancer Therapy (FACT) scale.[10-12] They contain detailed questions on, for example, the consequences of hair loss, weight loss, nausea and vomiting.

Generic questionnaires are developed to measure changes in all health dimensions affecting quality of life, irrespective of the underlying condition. These instruments allow for comparison of the relative impact of a disease or its treatment on quality of life across different populations, but are less responsive to changes in specific conditions. Examples of generic questionnaires are the Short Form-36 (SF-36), the Nottingham Health Profile (NHP) and the Karnofsky Performance Index.[13,14]

In utility measurement both health status and a preference value of that health status is measured. The EuroQoL instrument allows for such valuation of health status in terms of utilities, providing a single summary score of quality of life. The utility scores of the EuroQoL have been elicited by members from the general population who have been asked to rate a sample of the 243 health states that are theoretically possible.[15]

In economic evaluation research, carried out from a societal perspective, an overall index of health status allowing for comparisons of health status irrespective of disease or diagnosis is required. Utility measures of quality of life are therefore used to determine if patients are on the whole better off as the result of therapy. Combining the utility scores with data on survival allows for the calculation of QALYs gained. However, utility measures may fail to reveal the dimensions of quality of life on which the patients improved versus those on which they worsened. The simultaneous use of a health profile and/or specific instruments can complement the utility approach by providing this valuable information.[3]

Interview schedule and follow-up time

In order to obtain relevant information on the changes in quality of life of a patient during a disease and its treatment, it should be measured before, during and after treatment. The timing of the assessments should

correspond to natural changes that occur during the disease and its treatment. Timing of measurements should be the same in both treatment arms.[16]

An economic evaluation requires lifelong follow-up, which means that quality of life measurement should be expanded to capture long-term effects at follow-up. A modeling approach, e.g. using a simulation or a Markov model, will almost always be necessary to calculate the total number of QALYs gained.[17]

Timing of economic evaluations

The timing of economic evaluations depends on the development phase of the technology. In general the development process of new drugs will have the following phases. After laboratory research and studies in animals, the first use by humans (healthy volunteers) is initiated to test pharmacological features and toxicity (phase I). Thereafter, the drug will first be administered to patients to evaluate clinical efficacy (phase II). The following phase (III) is clinical research, i.e. in cancer mostly a randomized clinical trial. The aim is to register the new drug for a certain medical indication. Phase IV consists of the evaluation of the long-term safety of the new drug.

Economic evaluation could focus on existing technologies (i.e. ex post evaluation). Most often modeling approaches will be used to evaluate the cost-effectiveness. However, in cancer often new treatment modalities are subject to study (i.e. ex ante evaluation). When new treatment modalities will be evaluated most often an add-on or 'piggy-back' economic evaluation will be performed, meaning that the economic evaluation is linked to a phase III clinical trial.

There are several reasons for performing an add-on economic evaluation. First, data on costs and effectiveness will be available in an early development phase of a technology. Secondly, the extra costs of economic evaluations are relatively low, because there is an existing study design, patient recruitment and treatment. Thirdly, doctors and patients will have a high compliance, as they are already participating in the clinical trial. However, there are also some methodological and practical issues by linking economic evaluation to a clinical trial. Economic evaluations are focused on effectiveness and clinical trials attempt to demonstrate the efficacy of a technology. In Table 2 some methodological issues, which may arise, are summarized.

Table 2. Methodological issues by add-on economic evaluation

(a)	Study design
(b)	Sample size
(c)	Duration of follow-up
(d)	Determination of outcome
(e)	Determination of costs
(f)	Interpretation and extrapolation of results

Study design

A randomized controlled comparison is preferred both in an economic evaluation and in a clinical trial. However, in some cases the formation of a control group may be difficult for ethical or organizational reasons. For example, the administration of taxoid treatment in patients with advanced breast cancer or ovarian cancer. This drug will be administered to patients who do not react to standard chemotherapy. Thus, there is no other option than palliative (supportive) treatment. In this case, a randomized controlled study will not be ethical. In such a situation, one could choose for a modeling approach.

Sample size

In a clinical study, the sample size calculation is based on a minimum number of patients, *a priori* data on expected differences between two alternatives and several statistical assumptions. The calculation for an economic study is more difficult as mostly there is no *a priori* data on costs and effects. Furthermore, often the treatment costs could have great variation and an askew distribution (e.g. lengthy hospital stays). In general, the same patient numbers as in clinical studies will be taken into account. When the primary endpoints in the clinical study will be survival, then the outcome for the economic evaluation will be life-years. In this case no problems are expected concerning the number of patients included in the economic evaluation.

Duration of the follow-up period

From an economic point of view a lifelong follow-up will be needed. In a clinical study, the study duration will depend on the impact of a new technology; ranging from a few days to a few years. Therefore, often a modeling approach (e.g. Markov model) will be used to calculate lifelong consequences.

Determination of outcome

To evaluate a specific therapy in clinical studies, the end points most commonly used are survival rates, disease- and/or symptom-free survival, response rates and response duration. When quality of life is taken into account, there is more emphasis on side effects of treatment and physical and psychological aspects of life. For this purpose, the use of a disease-specific quality of life questionnaire will suffice. From the economic perspective, the objective of studying quality of life is to determine the contribution of changes in quality of life to a summary measure for the outcome on an intervention. Economic evaluation requires the use of a generic and a valuation instrument at a disease non-specific level. However, the inclusion of a cancer-specific instrument may be advisable, particularly for reasons of explanation if changes in dimensions are small or conflicting. The precise combination of instruments depends on the required psychometric and specific patient features and feasibility aspects.[18]

Determination of costs

Case registry forms, as normally used in cancer trials, provide insufficient information as tabulation of major cost items is usually incomplete. Contrary to these forms, hospital administration data are usually complete, but they do not contain all cost items. For example, medication is most often not registered by means of a hospital information system. As a result, the collection of cost data will often consist of a mixture of case registry forms, patient questionnaires, hospital data and occasionally on-site observations. Additionally, hospital administrative data provide information on fixed costs (overheads), and patient questionnaires are useful for obtaining information on direct patient's costs, indirect costs and costs related to out-patient care.[17]

Another issue is the identification of activities which are performed due to the trial, but which will not be performed in daily practice. In general, monitoring patients in clinical trials is more intensive than monitoring patients in daily practice. To detect any problems or side effects of treatment, more consultations, laboratory and medical procedures will be performed. An economic study aims at evaluation of the real cost of treatment, because otherwise it would have consequences for the extrapolation to other settings. So these additional costs should be identified and excluded from the analysis.

Interpretation and extrapolation of the results

From an economic perspective, the generalizability of clinical trial results (extern validity) may be rather limited due to a variety of reasons. Clinical trials attempt to demonstrate validly the effectiveness of a technology and, consequently, the design (patient selection, treatment allocation, treatment guidelines) is rigorous. The internal validity of the trial results is important. Moreover, trial patients are more compliant, clinical investigators are more competent and the hospital setting offers more facilities than its counterparts in general practice. The better a clinical trial satisfies design criteria, the more easily the study results will be accepted for their reproducibility and scientific soundness.[17] Through sensitivity analyses, the impact of certain variables on the outcome could be demonstrated.

Use of results of economic evaluations

Economic evaluation is intended to support health policy at different levels of decision making. In cancer treatment, health policy concerns preventive, curative and palliative strategies, and decisions are often made at the micro and macro level. Economic evaluation can provide essential information on the costs and benefits of each option and consequently on the optimal policy mix, and thus support decisions on the adoption and utilization of new treatment strategies. Such information may assist policy makers in formulating regulatory policies and legislation, industry in developing products, health professionals in treating and serving patients, and consumers in making personal health decisions. Examples of situations in which economic evaluation can play a valuable role are:

- *Research and development decisions*. The results of economic evaluation may be used for 'go/no go' decisions at critical points in the development process of new treatment modalities. Information can be used both by university hospitals and pharmaceutical firms.
- *Pricing decisions*. Economic evaluation can help to establish an appropriate price for a treatment modality. This information can be used both by government regulators and pharmaceutical firms.
- *Reimbursement decisions*. Government, hospitals, insurers and other payers can use the results of economic evaluation in their reimbursement policies. For instance, the results of economic

evaluation could influence decision making on whether or not to include new technologies in the package of (social) health insurance.

- *Clinical guidelines*. Hospital budgets are limited and doctors face financial restrictions. The results of economic evaluation may support the choice of treatment strategy and the selection of patients at the micro level, as well as negotiating budget transfers with hospital management. While developing clinical guidelines for providers not only the efficacy and effectiveness of treatment alternatives need to be considered, but also their cost-effectiveness.

However, decisions should not be based on the results of economic evaluation alone. Economic evaluations are used to inform decision making, not to replace it. Using results of economic evaluations requires that these are reliable and unambiguous, and that the evaluation is carried out in a rigorous manner. The methods used and the way in which costs and consequences are measured and valued must be made clear, in order to help policy makers to determine whether the study's results are relevant to their policy context.

References

1. Coebergh JWW. Incidence and prognosis of cancer in the Netherlands: studies based on cancer registries. *Dissertation*. Erasmus University Rotterdam, Rotterdam 1991.
2. Polder JJ, Meerding WJ, Koopmanschap MA, *et al. Cost of illness in the Netherlands*. Erasmus University, Rotterdam: Department of Public Health/Institute for Medical Technology Assessment 1997 (in Dutch).
3. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press 1997.
4. Johanssen M, Jönsson B. Economic evaluation in health care: is there a rate for cost-benefit analysis. *Health Policy* 1991; **17**: 1-23.
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. Koopmanschap MA, Rutten FFH. The impact of indirect costs on outcomes of health care programs. *Health Economics* 1994; **3**: 385-93.
7. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life; a conceptual model of patient outcomes. *J Am Med Ass* 1995; **273**: 59-65.
8. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210-6.
9. Cella DF, Tulsky DS. Quality of life in cancer: definition, purpose and method of measurement. *Cancer Invest* 1993; **11**: 327-36.
10. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365-76.
11. Haes JCJM de, Knippenberg FCE van, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990; **62**: 1034-8.
12. 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.
13. Ware JE. *SF-36 health survey. Manual and interpretation guide*. Boston, MA: The Health Institute, New England Medical Center 1993.
14. Hunt SM, McEwen J, McKenna SP. *Measuring health status*. London: Croom Helm 1986: 241-5.
15. EuroQoL Study Group. EuroQoL, a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 147-61.
16. Kiebert GM. Quality of life as an outcome in EORTC clinical trials. *Eur J Cancer* 1997; **33** (S4): S31-4.
17. Bonsel GJ, Rutten FFH, Uyl-de Groot CA. Economic evaluation alongside cancer trials: methodological and practical aspects. *Eur J Cancer* 1993; **29A**: S10-4.
18. Uyl-de Groot CA, Rutten FFH, Bonsel GJ. Measurement and valuation of quality of life in economic appraisal of cancer treatment. *Eur J Cancer* 1994; **30A**: 111-7.