Eur J Cancer, Vol. 29A, Suppl. 7, pp. S19–S22, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00
Pergamon Press Ltd

Outcome Measurement in Economic Evaluations of Growth Factors

Bengt Jönsson and Göran Karlsson

There are several ways of measuring outcome in an economic evaluation of filgrastim therapy. These measures imply different types of economic evaluation. In all cases, the filgrastim therapy is compared with no filgrastim therapy. Since different therapeutic strategies are connected with uncertain consequences, decision trees are helpful analytical tools. The potential implications of different types of economic evaluations are illustrated with a simple decision tree.

Eur J Cancer, Vol. 29A, Suppl. 7, S19–S22, 1993.

INTRODUCTION

IN ECONOMIC evaluations of medical interventions, costs are related to outcome. Ideally, the outcome measure should be related to the clinical endpoint of the therapy. Granulocyte colony-stimulating factors (filgrastim) have several clinical applications with different clinical endpoints. The choice of outcome measure is, hence, far from obvious. Different measures imply different types of economic evaluation. The aim of this study is to discuss methodological considerations in the choice of outcome measure for economic evaluations of growth stimulating factors.

COST MINIMISATION ANALYSIS— IDENTICAL OUTCOMES

Cancer treatment is characterised by several treatment activities. A major effect of filgrastim therapy is that the risk of infection, as manifested by febrile neutropenic events (FNE), is reduced. This means that the resources used for treating a FNE are reduced. The cost implications of filgrastim therapy are, therefore, not obvious. In a cost minimisation study, the total treatment costs with and without filgrastim therapy are analysed. The outcome in this type of study is whether or not filgrastim therapy saves costs.

A cost minimisation analysis is based on the assumption that the clinical outcomes of the treatment are identical for the alternatives. Assume that survival and quality of life are identical and that we are only interested in the costs. The two strategies can be described by way of a simple decision tree.

In Fig. 1, the consequences of the two arms are either a FNE or no FNE (No FNE). For every terminal node the cost is defined. The cost for the filgrastim therapy is indicated with Cost CSF, and the cost for the treatment of FNE is indicated with Cost FNE. The expected costs for the filgrastim therapy plus treatment for FNE with and without filgrastim therapy can be calculated and compared.

The total cost of FNE is determined by the costs of hospitalisation, antibiotics, therapeutics and diagnostics (Table 1). The cost of the filgrastim therapy can be estimated to 6620 Swedish Kroner (SEK) (7 days per cycle, 1 ml vial containing 300 μg).

Two randomised, placebo-controlled trials, one in the U.S.A. and the other in Europe, have demonstrated significant reductions in the relative risk of FNE following chemotherapy in patients receiving filgrastim therapy [1, 2]. The relative risk of FNE over all cycles was 2.1 times higher in placebo patients than in those receiving filgrastim therapy in the U.S.A. study, and 2.8 times higher in the European study.

Calculations from these figures result in Table 2. Using the probabilities from the European study, the net cost of filgrastim therapy is 2210 SEK, and according to the U.S.A. figures, 220 SEK. If the outcomes are found to be identical with and without filgrastim therapy, the cheapest treatment should be chosen, i.e. without filgrastim according to our calculations. However, if the avoidance of an FNE has a value of its own, a cost minimisation

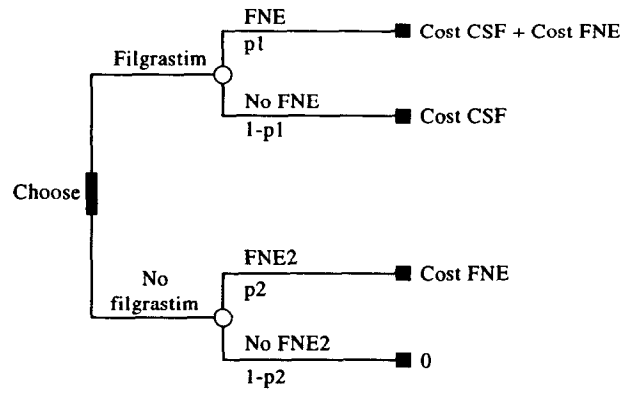

Fig. 1. Decision tree for a cost minimisation analysis of filgrastim therapy.

Table 1. Costs involved in a febrile neutropenic event (FNE) in Sweden

	SEK	Per cent
Hospitalisation	16 200	73
Antibiotics (i.v.)	1600	7
Therapeutics	2754	13
Diagnostics	1516	7
Total	22 070	100

Source: Roche, Sweden. SEK, Swedish Kronor.

Correspondence to B. Jönsson at the Centre for Health Economics, Stockholm School of Economics, Box 6501, S-113 83 Stockholm, Sweden.
G. Karlsson is at the Center for Medical Technology Assessment, Linköping University, S-151 83 Linköping, Sweden.

Table 2. Calculation of the net cost of filgrastim

	European study	U.S.A. study
Difference in probability of FNE	0.2	0.29
Savings per cycle	4410 SEK	6400 SEK
Cost of filgrastim	6620 SEK	6620 SEK
Net cost of filgrastim	2210 SEK	220 SEK
Cost per FNE avoided	11 050 SEK	760 SEK

analysis is not enough. A cost-effectiveness analysis is more appropriate.

COST-EFFECTIVENESS ANALYSIS— COST PER FNE AVOIDED

The simple decision tree in Fig. 1 can, with a slight modification, be used for a cost-effectiveness analysis. An outcome measure — the effectiveness — is added to every terminal state. The simplest outcome measure is the avoidance of one FNE. The relevant evaluation measure is, hence, the marginal cost-effectiveness ratio.

Using the probabilities and costs figures in Table 2, the marginal cost per FNE avoided amounts to 11 050 SEK (2210/0.2) according to the European study, and to 760 SEK (220/0.29) according to the U.S.A. data.

When outcome is defined as the avoidance of one FNE, we do not specify in what respect(s) it has a value. The decision-maker has to value the effect. In many cases it will be an advantage to formulate the outcome measure in that manner.

However, such an outcome measure brings about a number of problems. For example, chemotherapy is mostly given in several cycles. If a treatment is made up by six cytotoxic cycles, there is a risk of FNE in every cycle. Is, then, the value of avoiding one FNE the same if the incidence of FNEs during the treatment process is reduced from, say, 3 to 2 or from 1 to 0? Probably not. Furthermore, cost per FNE avoided makes it difficult to compare this type of therapy with other therapies in cancer treatments, and other treatments within health care. In such a case, it is better to use an outcome measure which is compatible with the clinical endpoint of the treatment.

If the purpose of the therapy is cure and/or increased survival, it is better to express the outcome in terms of cure or survival. Complete remission (CR) is a measure of cure, which can be used. Another commonly used outcome measure in economic evaluations, where survival is an important outcome, is life-years gained. This takes us to the third alternative.

COST-EFFECTIVENESS ANALYSIS— COST PER LIFE-YEAR GAINED

There are two sources of increased survival rates due to the filgrastim therapy. Firstly, infections might lead to death. Regardless of the cure rate of the chemotherapeutic treatment, the survival rates and, hence, life-years gained will increase if infections are prevented due to the filgrastim therapy. Secondly, expectations of infections are often met by dose reductions in the cytotoxic treatment. For diagnoses where the cure rate depends on the intensity of chemotherapy, it will cause a decrease in the cure rate.

These factors can implicitly be included in a decision tree like that of Fig. 1 by adding the expected remaining life-years (or complete remissions) in the terminal nodes. However, as the cytotoxic treatment may be changed as a result of the occurrence of infection, the cost for this treatment might be influenced.

To make both sources of increased survival explicit, it could be an advantage to build a more detailed decision tree, which takes into account whether or not there has been dose reduction, neutropenia, infection and hospitalisation. The outcome measure is life-years gained. In this model, the cost per life-year gained can be calculated for filgrastim therapy compared to no filgrastim therapy. It is obvious that this model requires much more information than the previous one, but it also gives more interesting and relevant results.

However, life-years gained is only appropriate as outcome on measure in cases where survival is the only, or at least the most important, consequence. But avoidance of neutropenia and infections can also increase the quality of life during the treatment process. This effect is accounted for in the fourth outcome measure.

QUALITY OF LIFE DURING THE TREATMENT PROCESS

The quality of life during the treatment process can be measured with psychometric instruments. There is a number of instruments whose aim is to measure the quality of life; see Cella and Tulsky [3] for a discussion of methodological aspects and for a review of quality of life measures used for cancer patients. These instruments can be classified into four categories:

Generic instruments

These are used for measuring general illness, e.g. the Nottingham Health Profile (NHP) and the Sickness Impact Profile (SIP). The primary advantage of these instruments is that they allow for the comparison of results across studies. The disadvantage is that they may not be sensitive enough to detect the specific aspects of quality of life that are important for cancer patients.

Disease-specific instruments

These are designed for cancer patients in general.

Diagnosis (tumour)-specific instruments

These are intended to be used for a certain kind of cancer patient only, for example, patients with breast cancer.

Study-specific instruments

These are designed especially for the study in order to pick up certain expected consequences.

For filgrastim treatment, an instrument aimed for general cancer appears to be most appropriate. General quality of life instruments are not sufficient to register problems specific for cancer patients, and instruments designed for specific cancer diagnoses, e.g. lung or breast cancer, will accentuate certain problems but will miss others. There are also problems with generalisation and instrument standardisation. One cancer-specific instrument is the EORTC Core Quality of Life Questionnaire, which has been tested on many cancer patients in several countries with promising results [4].

A problem with quality of life measurements is how they should be related to costs, as psychometric instruments mostly describe several aspects of quality of life separately, such as physical and social ability. In Table 3 we show the content of the EORTC Core Quality of Life Questionnaire. In order to be useful in a cost-effectiveness or cost–utility analysis, a single index is needed.

Table 3. Content of the EORTC Core Quality of Life Questionnaire

Physical functioning
Role functioning
Disease symptoms
Fatigue and malaise
Nausea/vomiting
Other gastrointestinal symptoms
Pain
Dyspnoea
Sleep disturbance
Cognitive disturbance
Emotional functioning
Social functioning
Financial impact
Global health status/quality of life

Source: [4].

The willingness to pay to achieve a better quality of life during the treatment process is one such single number. However, the economic evaluation then becomes a cost–benefit analysis. The contingent valuation method, based on hypothetical questions, might be a useful technique within health care for deriving the willingness to pay [5]. The most important conclusions from that method are that the "good", i.e. the improved quality of life during the treatment process, is unambiguously defined, and that the respondent finds the questions plausible and meaningful. This seems to be possible concerning adverse side-effects during the treatment period.

QUALITY-ADJUSTED LIFE-YEARS (QALY), HEALTHY YEARS EQUIVALENTS (HYE) OR UTILITY VALUES AS OUTCOME MEASURES

Ideally, we would like to have an effectiveness measure that takes into account the length as well as the quality of life. The traditional measure advocated by health economists has been QALYs [6]. Figure 2 illustrates the principle but also the problem with QALYs.

In the construction of QALYs, each life-year is quality adjusted with a utility value, where 1 indicates full health. The basic idea is that the utility value should reflect the health-related quality of life. The number of QALYs is the shaded area in Fig. 2. One life-year in a health state with utility value 0.6 gives the same number of QALYs — that is 0.6 — as 0.6 life-years with full health.

The QALY model does not specify how these utility values are derived. The standard gamble and the time trade-off techniques have the best theoretical foundations [6].

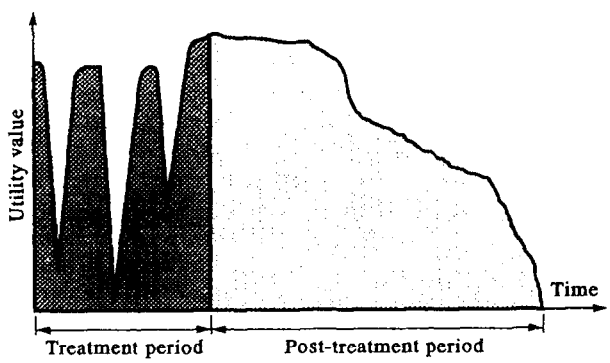

Fig. 2. Quality of life over time in cancer treatment.

As seen from Fig. 2, the quality of life (utility value) and the length of life are estimated separately, and thereafter amalgamated into a single measure in the construction of QALYs. This could be an advantage in the empirical construction of an outcome measure, but if QALYs should accurately reflect the true preferences of the patient the quality of life and the duration have to be mutually utility independant [7]. By this means, the evaluation of these health states is independent of the duration of these health states. To be more precise, utility independence should be related to risky choices. Mutual utility independence exists if choices between uncertain outcomes concerning health states are not affected by the duration and if choices between uncertain remaining length of life are not affected by health states. This is a necessary condition for QALYs to express the true preferences. This assumption is more important for cancer treatments as compared with many other treatments since the quality of life often varies considerably over time, depending on side-effects of the cytotoxic therapy. The variation is reinforced by the fact that the cytotoxic treatment is given in cycles. The quality of life after the primary treatment can also vary greatly, depending on, for example, the occurrence of relapse.

Whether or not the assumption about utility independence holds is not clear. There is evidence that this is the case, but there are also results that contradict this evidence [8].

That QALYs might not reflect the true preferences of the patient has been pointed out in the literature, and healthy years equivalents (HYEs) have been suggested as an alternative to QALYs [9]. The HYEs for a defined period of time with less than full health is defined as the (hypothetical) number of life-years at full health which the patient values as equal to the longer period with less than full health. By using time trade-off, HYEs can be derived directly. Algorithms based on the expected utility theory is an alternative [10].

Hence, the integration of quality of life into a single outcome measure brings about problems if quality of life varies over a period of time. One way out of this problem is to describe and value the whole course from treatment to death. This is possible in the construction of HYEs, but this raises another problem: how should a whole course be described and valued? The proper answer to that question is still open.

These measures can be used as outcomes measures, measuring the length as well as the quality of life after the treatment. But they can also be used as measures for the quality of life during the treatment process as complements to or substitutes for psychometric instruments or willingness to pay as discussed above.

The choice of outcome measure

The outcome measures presented here focus on different aspects of the treatment. In cases where the intent is cure, complete remissions and life-years gained are appropriate, but for palliative treatments it is the quality of life during the treatment process which is important. It is, hence, important to specify in what context the outcome measure is going to be used.

The incorporation of quality of life in outcome measures for economic evaluations is connected with problems which might be greater for cancer treatments than for many other therapies. There are techniques available all of which have advantages and weaknesses. There is a need for further methodological analysis of the appropriate way of integrating quality of life in outcome measures for economic evaluation.

1. Crawford J, Ozer H, Stoller R, *et al.* Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991, **314**, 164–170.
2. Green JA, Trillet VN, Manegold C. r-metHuG-CSF (G-CSF) with CDE chemotherapy in small cell lung cancer (SCLC), interim results from a randomised placebo controlled trial. *Proc Am Soc Clin Oncol* 1991, **10**, 243.
3. Cella DF, Tulsky DS. Measuring quality of life today: methodological aspects. *Oncology* 1990, **4**, 29–69.
4. Aaronson NK, *et al.* The EORTC Core Quality of Life Questionnaire: interim results of an international field study. In Osoba D, ed. *Effect of Cancer on Quality of Life*. Boca Raton, Florida, CRC Press, 1991, 185–203.
5. Johannesson M, Jönsson B. Economic evaluation in health care: is there a role for cost-benefit analysis? *Health Policy* 1991, **17**, 1–23.
6. Torrance GW. Measurement of health state utilities for economic appraisal. A review. *J Health Econ* 1986, **5**, 1–30.
7. Keeny RL, Raiffa H. *Decisions with Multiple Objectives: Preferences and Value Tradeoffs*. New York, John Wiley & Sons, 1976, 227.
8. Karlsson G. *Hälsoekonomisk analys av denatla implantat*. Linköping Studies in Arts and Science 69. Linköping University, Linköping, 1991, 83–100.
9. Mehrez A, Gafni A. Quality-adjusted life years, utility theory and healthy years equivalents. *Med Decision Making* 1989, **9**, 142–149.
10. Mehrez A, Gafni A. The healthy-years equivalents: how to measure them using the standard gamble approach. *Med Decision Making* 1991, **11**, 140–146.