Cost-effectiveness of hypothetical new cancer drugs in patients with advanced small-cell lung cancer: results of a markov chain model

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Background: In the last decade, a number of new treatment modalities have been developed for patients with small cell lung cancer (SCLC). The clinical effects are encouraging, but little is known about the costs and cost-effectiveness of new drugs.

Methods: A Markov chain model has been developed to project patient outcomes and costs for patients with advanced SCLC. All patients in the control group were treated with etoposide–cisplatin chemotherapy. Patients in the study group received a hypothetical new drug. The model consisted of four states: response, stable disease, progressive disease, and death. Estimates of transition probabilities were calculated using published data on survival and recurrence-free survival. For the cost analysis and utility calculation, published data and expert opinion were used as sources. The duration of the follow-up was maximal 2 years.

Results: The total treatment costs in the etoposide–cisplatin group amounted to €16 038 and in the alternative treatment groups between €16 644 and €18 171. The number of life years and quality adjusted life years (QALYs) gained were very small, around 16 days. The cost-effectiveness ratio varied between €22 208 and €81 443 and the cost–utility ratio varied accordingly. Results of the sensitivity analysis showed that the results were robust in favor of etoposide–cisplatin treatment.

Conclusion: SCLC is an illness with a poor prognosis which needed substantial healthcare resources to optimise patient survival and overall quality of life. New treatment modalities with better outcome and favourable cost-effective profiles can hopefully be developed.

Keywords: small cell lung cancer, costs, cost-effectiveness, modeling

Introduction

Lung cancer is the leading cause of cancer death in many countries. It is one of the most lethal malignancies and its incidence is increasing worldwide (ASCO 1997; Greenlee et al 2000; Banerjee et al 2002). Small-cell lung cancer (SCLC) accounts for approximately 20%–25% of newly diagnosed cases (Carney 1996; Oliver et al 2001). Often the symptoms of lung cancer are not obvious until the disease is at an advanced stage and most patients have locally advanced or metastatic disease at the time of diagnosis (Demetri et al 1996). Over the last few years, a number of new chemotherapeutic agents have been developed for the treatment of SCLC. These so called third generation agents have shown increased survival and improved response rate compared to older regimens. Furthermore, these new agent may play an important role in palliating symptoms and maintaining quality of life.

The costs associated with the treatment of patients with SCLC can be significant. However, the only European cost study did not include treatment of SCLC, but diagnostic methods and hematopoietic growth factors (Oliver et al 2001). Thus, while the improved clinical effects are encouraging, little is known about the cost and cost-effectiveness of new drugs. In this article, we examine the cost-effectiveness of

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etoposide plus cisplatin and compare it with an alternative hypothetical new drug. The question is how effective should this new drug be and at what cost to be considered cost-effective.

Design and methods
Patients

The studies reviewed consisted of patients with extensive SCLC confirmed by histology. Extensive disease is defined as a disease beyond one hemi-thorax, including medianastinal lymph nodes and/or supraclavicular lymph nodes. Other eligibility consisted of, among others, no previous chemotherapy or radiation therapy, no history or prior malignant disease, a World Health Organization (WHO) performance status ≤2, uncontrolled severe heart disease, and several blood values (among others; neutrophils, platelets, creatinine) (For details, see: Carney 1996; ASCO 1997; Pujol et al 2001; Banerjee et al 2002).

Markov chain analysis

A Markov chain model has been developed, which projects patient outcomes and costs of treatment for patients with advanced SCLC. The model has four states, namely 'Response' (R), 'Stable disease' (SD), 'Progressive disease' (PD), and 'Death' (D). Tumor response was defined according to the WHO recommendations (WHO 1979). A complete response was defined as the complete disappearance of all lesions with a negative histology or repeat fiberoptic bronchoscopy biopsies. A partial response was defined as equal to or greater than a 50% reduction in the product of the two longest perpendicular diameters of the indication lesions. Response, ie, both partial and complete responses, must have lasted a minimum of 4 weeks to be confirmed. 'SD' was defined as a less than 50% reduction or a less than 25% increase in this product. 'PD' was defined as equal to or greater than a 25% increase in this product or the appearance of new lesions (Pujol et al 2001). Patients may move from their one state to another, provided that transition is permitted (see Figure 1).

All patients were initially assumed to be in the state 'SD'. Estimates of overall survival and survival to progressive disease were derived from Kaplan-Meier curves for these endpoints presented in the literature. Additional assumptions needed to be made for the probabilities of these events from within the states 'R', 'SD', and 'PD', based on the opinions of clinical experts. We assumed that the probability of death in the 'PD' state was 8 times that of 'SD' patients. We

assumed the probability of transition to progressive was 4 times more likely if the patient was in 'SD' than in 'R'. The magnitude of the probability of 'R' was calculated so as to give approximately the same number of responders as was found in the literature. The probability of remaining in the state 'R' was calculated so that the median time spent in that state was equal to that found in the literature. Treatment was assumed to be given only to patients in 'SD' or response and was given for a maximum of 6 cycles. 'R' was assumed to occur only in the first 3 cycles.

All patients received at least two treatment cycles. Thereafter they may move to any other state. Patients who move to 'R' and who leave that state are assumed to have entered the state 'PD' or to have died. Patients in 'PD' either remain in that state or die. 'D' is an absorbing state. Transition probabilities are assumed to depend on the disease state, but not on other factors such as age and sex. Each state had an associated cost (which is also time dependent), which is used in the cost and cost-effectiveness calculations. As a result, patients randomly progressed through a series of states until death or the time of maximum follow-up. During this progress, the patient accrued costs due to treatment. Transitions are assumed to occur at the end of each cycle, which was assumed to be of 4 weeks in length. The patients are followed for a maximum of 2 years.

Patients received chemotherapy only while they remained in the states R or SD. Chemotherapy, consisting of etoposide and cisplatin, was given for a maximum of 6 cycles. During each 28-day treatment cycle, etoposide was administered on days 1, 2, and 3 at a dose of $100\,mg/m^2$ followed by a one-week rest period. Cisplatin was administered on day 2 of each course at a dose of $100\,mg/m^2$. Based on expert opinion, a transition to response was only possible in the first three cycles. 'PD' patients will get
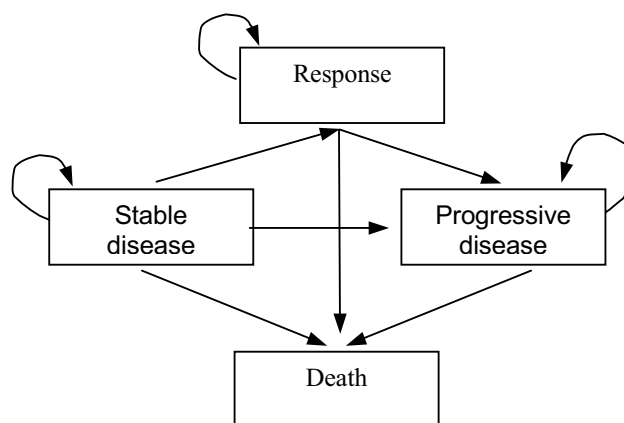

Figure 1 Structure of the Markov model.

best supportive care. Patients, who die, got terminal care. The effects of second-line treatment were not taken into account.

Estimates of the transition probabilities were calculated using published data on survival and recurrence-free survival (Carney 1996; ASCO 1997; Pujol et al 2001; Banerjee et al 2002). All estimates were reviewed by two experts.

Modeling the effect of a new drug

In this analysis, we considered a number of scenarios. We assumed that the hypothetical new drug was both clinically more effective than current treatments and more expensive than etoposide–cisplatin. More specifically, we assumed that the new treatment increased the probability of achieving a response, with a subsequent decrease in moving to 'SD' or 'PD'. On the cost side, we took into account a small rise and a fairly significant rise in the cost of chemotherapy.

Costs

The societal perspective was taken. The study focused on direct medical costs. Considering the severity of the disease and the typically advanced age of patients at diagnosis, the indirect costs, ie, costs due to lost productivity, would be slight and therefore not be included.

For the cost analysis, the micro-costing approach proposed by Gold et al (1996) has been used. Estimates of the associated costs are based on resource use and on Dutch unit prices or Dutch tariffs (Oostenbrink et al 2000). Unit prices are based on previous studies performed at our institute and specific cost studies are performed for the most relevant items of resource use. Tariffs derived from the 'Farmacotherapeutisch Kompas' are used for medication and prices for general tests such a laboratory testing, x-rays, CT-scans etc. are derived from the 'Diagnostisch Kompas' (van Leusden 2000; van der Kuy 2002). For our analyses 2002 prices and tariffs are used. Costs are expressed in Euros ($€1 ≈ US\$1.03$). Table 1 shows an overview of the most important unit prices.

Using data from the literature, we estimated the cost of one treatment cycle, including treatment of toxicity, to be €1391.20 ($€1 ≈ \$US1.03$). Table 2 gives a breakdown of the costs. We estimated the cost of follow-up of patients in response or in stable disease to be €101.62, the cost of follow-up of patients in 'PD' state to be €684.37, and the

Table 1 Most important cost items

Cost items	Unit prices (€ as of 2002)
Hospital day	297.36
Day care	135.00
Outpatient visit	61.32
Etoposide–cisplatin	303.94
Ondansetron 8 mg intravenous	28.54
Ondansetron 8 mg oral	9.04
Hematology tests	8.46
Biochemistry tests	14.10
X thorax	43.92
CT thorax	211.911
CT abdomen	83.91
CT brain	160.31
MRI brain	211.91
Bone scan	140.62
ECG	9.70
Erythrocytes transfusion	183.95
Platelets transfusion	44.15
Terminal care	7450.00

Abbreviations: CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; X, Rontgen.

cost of a subsequent cycle in which death occurred, ie, the terminal costs, to be €7450 (Smeenk et al 1998).

Utilities

In calculating life years and quality adjusted life years (QALYs), we used utilities derived from an overview study in patients with lung cancer and expert opinion (Oliver et al 2001). The utility scores assigned to each state were 0.85 ('R'), 0.7 ('SD'), 0.55 ('PD'), and 0 ('D').

For each cycle in the model, the following quantities were calculated: cumulative cost, patients' survival per state, the incremental cost-effectiveness (CE) ratio and cost-effectiveness adjusted for quality of life (ie, cost-utility [CU]).

Table 2 Cost breakdown for etoposide–cisplatin treatment and costs of follow-up per state (cost of one cycle)

	Unit cost (€)	P[1]	Cost (€)
Treatment			
Chemotherapy	303.94	1.00	303.94
Anemia	654.82	0.25	163.71
Febrile neutropenia	3959.51	0.23	910.69
Thrombocytopenia	25.38	0.15	3.80
Nausea/vomiting	69.73	0.13	9.06
Total treatment costs per cycle			*1391.20*
Follow-up per state			
• Response			101.62
• Stable disease			101.62
• Progressive disease			684.37
• Terminal			7450.00

Note: [1]P = percentage of patients suffering symptoms of toxicity.

Table 3 Transition probabilities

	From/To	Response	Stable disease	Progressive disease	Death
Cycle 1–3	Response	0.800	0	0.198	0.002
Cycle 4–6		0.800	0	0.195	0.005
Next cycles		0.800	0	0.196	0.004
Cycle 1–3	Stable	0.260	0.522	0.210	0.008
Cycle 4–6	Disease	0	0.805	0.181	0.014
Next cycles		0	0.669	0.314	0.017
Cycle 1–3	Progressive	0	0	0.919	0.081
Cycle 4–6	disease	0	0	0.919	0.081
Next cycles		0	0	0.841	0.159

Results

After reviewing the literature and based on expert opinion, it was concluded that a three-steps model would be appropriate (Carney 1996; ASCO 1997; Pujol et al 2001; Banerjee et al 2002). We divided the cycles into 3 categories: cycles 1–3 (treatment allowing the possibility of a response), cycles 4–6 (treatment but no possibility of a response), and subsequent cycles. The transition probabilities for each category are given in Table 3.

For the alternative arms, we assumed that the probability of a response after the first treatment cycle was 0.30 or 0.35, with a corresponding decrease in the probability of progressive disease (0.17 and 0.12 respectively).

Percentage survival at 6 months, 1 and 2 years were 76.3%, 33.4%, and 4.4% respectively in the etoposide–cisplatin arm (see Table 4). Survival was higher under the alternative scenarios. More patients remained in the response state in the alternative arms than in the etoposide–cisplatin arm.

An increased probability of response leads to a somewhat improved survival. The gain in life years at 2 years amounted to approximately 0.02 in favor of alternative treatment A and 0.044 in favor of alternative B (see Table 5). However, as these gains are spent in disease stages with a higher quality of life the gain in QALYs is a little higher.

Table 4 Percentage of patients surviving and in response

		Etoposide–cisplatin	Alternative A	Alternative B
Response after 1st cycle		26.0	30.0	35.0
Follow-up				
6 months	Survival	76.3	77.9	79.9
	Response	16.1	18.5	21.6
1 year	Survival	33.4	34.8	36.6
	Response	4.2	4.9	5.7
2 years	Survival	4.4	4.6	5.0
	Response	0.2	0.3	0.3

These results indicated that, under the assumptions of our model, treatment led to an increased survival of only a few weeks.

In Table 5, the treatment costs are also presented. We assumed that the new treatment raises the cost of chemotherapy from €1391.20 to either €1500 per cycle (a modest increase) or to €2000 (a substantial increase). The total costs in the new treatment groups were higher due to the cost of chemotherapy itself being higher, more patients received the full course of chemotherapy and (a few) more patients required follow-up treatment. Most of this difference occurred during the actual treatment cycles. Afterwards, these differences did not change substantially.

The incremental cost-effectiveness ratios ($\Delta C/\Delta E$) and cost-utility ratios ($\Delta C/\Delta U$) are given in Table 6. The ratios ranged from €22 116 to €81 443. These figures should be treated cautiously as the magnitude of the denominator was small, making the estimate unstable.

Sensitivity analysis

A sensitivity analysis was performed to assess the effect of changes in treatment protocol, response rate, the costs of the hypothetical drug and using a discount rate.

The most important factor in our model is the treatment protocol. We compared the results of our model by comparing the results with a model in which only 4 treatment cycles were given. This 4-treatment schedule is slightly cheaper than that used in our model with savings of €144 after 6 months. However, it is also less effective with only 68.2% of patients surviving to that time. By two years, the difference in effectiveness largely disappears (4.0% survival vs 4.4%) while the difference in costs increases to €1055.

Increasing the response rate only resulted in a small gain in life years and QALYs. Furthermore, a higher response rates implied higher treatment costs. Higher treatment costs resulted in proportional higher CE and CU ratios.

Table 5 Total cumulative life years and quality-adjusted life years (QALYs) per patient

	Response after first cycle	Follow-up			
		Outcome	6 months	1 year	2 years
Etoposide–cisplatin	0.26	Life years	0.4793	0.7055	0.8360
		QALYs	0.3202	0.4564	0.5319
Alternative A	0.30	Life years	0.4844	0.7183	0.8556
		QALYs	0.3297	0.4718	0.5516
Alternative B	0.35	Life years	0.4907	0.7343	0.8801
		QALYs	0.3415	0.4910	0.5762
		Cost of treatment cycle	6 months	1 year	2 years
Etoposide–cisplatin	0.26	1391	7511	13151	16038
Alternative A	0.30	1500	7946	13633	16644
	0.30	2000	8105	13851	17017
Alternative B	0.35	1500	8939	14623	17633
	0.35	2000	9259	15006	18171

Discounting with a rate of 4% results in CE rates varying from €31097 to €50075 and CU rates varying from €30778 to €36211. Treatment with etoposide–cisplatin still remained dominant.

Discussion

There is a rapid growth in health economic literature. Within oncology, studies in lung cancer are relatively under-represented, despite the fact that lung cancer is the leading cause of death (Dranitsaris et al 1998; Goodwin and Shepherd 1998). Furthermore, lung cancer is accountable as a major source of morbidity, mortality, and healthcare costs. It is estimated that lung cancer is responsible for 20% of all cancer care costs and concerns exists that this spending is associated with limited benefits (Dranitsaris et al 1998).

It can be seen that under the assumptions of our model, the future treatment costs of SCLC will increase. As baseline treatment we considered etoposide–cisplatin therapy. Two-year costs amounted to approximately €16038. Considering an alternative treatment being more effective but also more costly, the costs increase to approximately €18171, an increase of around 12%. The number of life years gained was very small, only 0.0441 years, around 16 days. The number of QALYs gained was slightly higher (0.0443), indicating that the patient will spend more time in a higher quality of life state. However, even if there is a substantial rise in the rate of response, the patient can expect only a relatively small degree of benefit. In this study, we have concentrated on objective response as a measure of efficacy. Many physicians feel that this is not a particularly appropriate measure of this aspect, preferring to choose survival (Dranitsaris et al 1998). Since new treatment modalities extends survival by a relatively small amount compared with the existing treatment, symptom relief and quality of life should also be considered as appropriate measures of outcome in an economic model. Another remark is that we did not include the use of second line chemotherapy with a possible impact on survival. Further research should include these possible treatments. However, the impact on the incremental cost-effectiveness ratio (ICERs) are expected to be small, as both treatment strategies will incorporate these second line therapies.

The actual costs of the agents involved in chemotherapy constitute only a relatively small portion of the total cost of care of a patient. One important cost driver is hospital

Table 6 Incremental cost-effectiveness (CE) and cost-utility (CU) ratios for new treatment alternatives after two years (€)

	Response	Cost	Incremental CE ratio	Incremental CU ratio
Alternative A	0.30	1500	30949	30822
		2000	22208	22116
Alternative B	0.35	1500	81443	81108
		2000	48930	48191

admission. In future, some modalities may be administered on an outpatient basis, leading to a significant decrease in costs.

Some physicians may feel that the increased costs associated with new treatments especially associated with chemotherapy for advanced SCLC outweigh the limited survival benefits. However, patients also experience subjective improvement in symptoms such as pain, coughing, dyspnea, and hemoptysis. Physicians may consider that such treatments have an important role to play in palliative care far beyond considerations of cost.

Models have a number of strengths and weaknesses. Among the latter is that the accuracy of the model is dependent on the accuracy of the assumptions made within the model. Economic models attempt to reflect reality (current clinical practice) but are by definition merely a reflection. Further, it is often difficult to gain all necessary data from one source: in this study, we derived data on the disease progress from a literature review while the cost data is based on Dutch sources. On the other hand, such models are easily adaptable, can easily incorporate multiple end points, can be extended to reflect actual clinical practice (as opposed to randomized clinical trials). While in no way being a replacement for a randomized clinical trial, they can be used to aid decision making in the face of clinical and technological development.

New 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. Cost-effectiveness analyses intend to *support* decision-making. They can provide essential information on the costs and benefits of drugs and consequently on the optimal policy mix, thereby supporting decisions on the adoption and utilization of new drugs. As more economic evaluations have been performed, it becomes possible to make comparisons between healthcare interventions in terms of their relative CE, in cost per life year gained, or cost per QALY gained. CE ratios varied exceptionally. Considering the height of the ratios of applying new drugs and often little impact on survival, it is clear that the rationale of administering new treatment modalities are not simply based on economic reasons.

According to a recently conducted Dutch study investigating the relationship between disease severity and willingness to pay, the maximum acceptable cost per QALY for patients with non-Hodgkin's lymphoma would be €45 378 (Poley et al 2003; Uyl-de Groot and Giaccone 2005). It seems that NICE applies an acceptable cost per QALY gained between €25 600 and €43 800 (Devlin and Parkin 2004).

The height of the acceptability of a CE ratio should also depend on other factors such as available alternatives and severity of the disease. In general, this implies that in cancer, higher ratios should be accepted. In our opinion the threshold of the ICER should be around the Dutch findings for non-Hodgkin's lymphoma and the NICE thresholds. For patients with small cell lung cancer, the thresholds should probably be around €45 000 and €50 000 per QALY gained on the base of disease severity. Other factors such as incidence and prevalence of disease also will 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 will be. We strongly recommend to the authorities to be more willing to reimburse new cancer drugs, to the pharmaceutical companies to be more prudent with their price setting and to hospital management to allow doctors to use these new drugs.

Conclusion

SCLC is an illness with a poor prognosis using substantial healthcare resources to optimise patient survival and overall quality of life. New treatment modalities with better outcome and favourable cost-effective profiles can hopefully be developed.

Disclosure

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