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Economic evaluation of drugs

The cost–effectiveness of paclitaxel (Taxol®) + cisplatin is similar to that of teniposide + cisplatin in advanced non-small cell lung cancer: a multicountry analysis

Lieven Annemans, Giuseppe Giaccone[1] and Alain Vergnenègre[2]
HEDM Research & Consulting, Mechelen, Flemish Free University of Brussels, 1860 Meise, Belgium. [1]Academisch Ziekenhuis, VU Amsterdam, 1081 HV Amsterdam, The Netherlands. [2]Hôpital Universitaire de Cluzeau, 87042 Limoges, France.

A large randomized clinical trial in advanced, previously untreated, non-small cell lung cancer (NSCLC) patients revealed better response rates and better tolerance for paclitaxel+cisplatin (TAXCIS) compared to teniposide+cisplatin (TENCIS). Since economic evidence is receiving increasing attention in health care, we conducted an economic evaluation based on the trial results in The Netherlands, Belgium, France and Spain. The evaluation was based on (i) differences in drug costs, (ii) differences in chemotherapy administration and (iii) the economic consequences of significantly different clinical outcomes in the trial: anemia, thrombocytopenia, neutropenia, neuropathy and arthralgia/myalgia. Data regarding medical resource utilization were obtained from clinician interviews using a Delphi technique and validated by patient charts analysis. Differences in medical management occurred across countries, but TAXCIS was cost-additive in all countries, i.e. the extra cost of chemotherapy was only partially compensated by savings in medical resource use, resulting in a net cost per patient of US$2311. In the trial, TAXCIS therapy produced a 37% response rate compared to 26% for TENCIS. The cost per extra responder for TAXCIS is on average US$21011, which is comparable to the cost per responder obtained with TENCIS (US$27266). Thus, the cost–effectiveness of TAXCIS, expressed in cost per responder, is similar to the cost–effectiveness obtained with TENCIS. [© 1999 Lippincott Williams & Wilkins.]

Key words: Chemotherapy, cost, cost–effectiveness, non-small cell lung cancer, paclitaxel, teniposide.

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Correspondence to L Annemans, Brusselsesteenweg 91, 1860 Meise, Belgium.
Tel/Fax: (+32) 2 2709434;
E-mail: la.hedim@skynet.be

Introduction

Lung cancer is a major problem world-wide. It is now the leading cause of cancer-related mortality for men and women in North America,[1] and the number of lung cancer cases is still expected to increase.

Non-small cell lung cancer (NSCLC) accounts for 75% of all new lung cancer cases.[2] Significant life prolongation in NSCLC patients depends on surgical resection, but at the time of initial presentation, unfortunately, the vast majority of patients are inoperable, because of advanced disease or the presence of co-morbid medical conditions. For these reasons, patients with advanced NSCLC survive for a median of 6–8 months, with only a 10–20% 1 year survival rate.

The role of systemic chemotherapy in NSCLC patients still remains debatable for many clinicians. Nevertheless, studies have clearly demonstrated that effective systemic chemotherapy in selected patients can improve survival, quality of life and performance status. Newer third-generation chemotherapy appears to be more effective than second-generation cisplatin-based chemotherapy for patients with stage IIIB and IV disease in terms of response rates.[3] When combined with platinum compounds, response rates exceeding 50% have been achieved with the new generation drugs, with median survivals of longer than 1 year.

Paclitaxel promotes polymerization of tubulin dimers to form microtubules and stabilizes microtubules by preventing depolymerization. In advanced NSCLC, many trials have been undertaken with paclitaxel at different doses, in different combinations and with different infusion times, showing that combination therapy and higher doses achieve higher response

rates.[4-13] Lower infusion time is associated with less toxicity but does not seem to influence efficacy. The latter is important, since if the infusion times can be shortened, the regimen could be used on an outpatient basis.[14]

Recently, a multicountry phase III EORTC trial in 332 patients with advanced, previously untreated NSCLC compared paclitaxel (175 mg/m^2 on day 1)+cisplatin (80 mg/m^2) (TAXCIS) versus teniposide (100 mg/m^2 on days 1, 3 and 5)+cisplatin (80 mg/m^2 on day 1) (TENCIS).[15,16] Two databases resulted from the trial, with small differences, depending on the interpretation of some outcomes. In particular, 15 patients (six TENCIS and nine TAXCIS) were considered 'stable disease' in the 'BMS database' but 'partial response' in the 'EORTC database'. We based our analysis on the more conservative BMS database. A significantly better response rate with TAXCIS was shown [37% partial or complete remission versus 26% for TENCIS (according to the EORTC database, these figures are, respectively, 40 and 28%, which is more in benefit of TAXCIS)], as well as better Quality of Life (QoL) results in most dimensions.[15,16] However, no differences in median survival time (9.5 versus 9.9 months, respectively) or 1 year survival were found. Also, time to progression was similar in both groups (5.1 and 5.0 months, respectively).

Significant differences were found in hematological toxicity, in favor of TAXCIS. In contrast, however, TAXCIS was more frequently associated with neurotoxicity, although this was mild in the majority of cases.

The lower incidence of hematological toxicity and the more convenient schedule for TAXCIS (only 1 instead of 3 days) may possibly be associated with economic advantages. However, in the EORTC trial no data regarding resource utilization was collected.

Since health economic evidence is receiving increasing attention in the decision-making process for pharmaceutical interventions, we conducted an economic evaluation based on the clinical results from the trial. The economic consequences of better efficacy and tolerance may differ from one country to another, e.g. because of more or less intensive management of adverse events. Hence, one cannot as such translate economic results obtained in one country to other countries. Therefore, it was decided to conduct the analysis in four different countries. Thereby, the primary objective was not to compare the results between the countries, but to assess the impact of different patient management and different unit costs for health care resources on the cost-effectiveness of TAXCIS.

Materials and methods

The study was conducted from the health care payer perspective. In each of the considered countries, health care is paid by a health care insurance system. Costs included the chemotherapy cost, the cost of drug administration and the costs associated with those outcomes which were significantly different in the clinical trial (see later). We concentrated only on differences since economic evaluations are based on incremental analysis: 'what is the extra cost of treatment X versus treatment Y'. Costs were expressed as the intensity of medical resource consumption, multiplied by the direct cost per unit. These unit costs were ascertained from official listings, and provided by the Institute for Medical Technology Assessment in the Netherlands, and by the research organizations HEDM in Belgium and ARCOS in France and Spain.

In The Netherlands, a record review was organized of 62 patients from three centers, who had been included in the trial between January 1995 and March 1996. From the records, the medical practice related to chemotherapy administration and to the clinical outcomes of interest was collected. The records included 31 TAXCIS-treated and 31 TENCIS-treated patients, and were analyzed together with the corresponding hospital invoices of each patient.

Unfortunately, resource use outside the hospital is generally not reported in hospital records.[17] Also, in retrospective analysis the past management is measured, which might differ from the current management.

Therefore, clinical opinion about medical practice was obtained in parallel through a Delphi technique involving nine clinicians (four pulmonary specialists and five oncologists), selected at random. A questionnaire was sent to the respondents in three different rounds. Questions referred to the percentage of patients receiving different types of care (medication, tests, interventions and consultations) and intensity of care (dose, number of interventions or testsa and length of stay). A full copy of the questionnaire is available upon request.

After the first round the median, 10th and 90th percentile were communicated to the participants. Based on this, each respondent could revise his original opinion, which in general leads to convergence of opinion. In a third round, the clinicians provided a 'validity' score (from 1 to 4) indicating the level of agreement with the final group averages. We refer to Evans for a detailed review of this technique.[18]

The results of the two methods were very similar (see Results). Therefore, in the other countries, only

the Delphi technique was applied for collecting the data regarding medical practice.

Given the short median survival time expectancy of these patients and the equal median time to progression in both treatment arms, a time horizon of maximum 6 months was used.

Clinical data

The clinical trial provided data on efficacy, QoL and safety. The following outcomes were significantly different between both strategies:

- Grade III/IV ($<1.0 \times 10^6$/l) neutropenia, *without* fever (temperature <38°C): in 86% of TENCIS and in 54% of TAXCIS patients.
- Grade IV ($<0.5 \times 10^6$/l) neutropenia, *with* fever (febrile neutropenia): in 36% of TENCIS and 5% of TAXCIS patients.
- Grade III (25-49 $\times 10^6$/l) or IV ($<25 \times 10^6$/l) thrombocytopenia: in 36% of TENCIS and in 2% of TAXCIS patients.
- Grade III (4-4.9 mmol Hb/l) or IV (<4 Hb/l) anemia: in 22% of TENCIS patients and in 10% of TAXCIS patients.
- Grade II (5.0-5.8 mmol Hb/l) anemia: in 50% of TENCIS patients and in 33% of TAXCIS patients.
- Peripheral neuropathy, grade II or III: in 6% of TENCIS patients and in 28% of TAXCIS patients.
- Arthralgia/myalgia, grade II or III: in 5% of TENCIS and in 19% of TAXCIS patients.

Results

Comparing Delphi results with patient charts in The Netherlands

Tables 1 and 2 show the outcomes resulting from chart review and clinical interviews in The Netherlands. With regard to chemotherapy administration, the clinicians tend to underestimate resource use, compared to the resource use from the records. Typically, the length of hospital stay was frequently underestimated by the clinicians. The expert panel also tends to underestimate or ignore the resource use associated with more severely ill patients, e.g. patients with combined hematological adverse events. However, in the case of non-febrile neutropenia and thrombocytopenia, the record analysis results in lower costs compared to estimates of the Delphi panel. This was likely due to the change in practice over recent years. For instance, the use of granulocyte colony stimulating factor (G-CSF) is likely to have increased compared to early 1995-1996.

Table 1. Costs (Dfl) of chemotherapy administration in The Netherlands, calculated from resource use data, collected from clinical opinion (Delphi) and patient charts

Cost item	Delphi	Charts
Administration cost one cycle TAXCIS	1006	1727
Administration cost one cycle TENCIS	1984	2908
Administration cost other cycles TAXCIS	1006	1397
Administration cost other cycles TENCIS	1984	3013

Table 2. Costs (Dfl) of adverse events in The Netherlands, calculated from resource use data, collected from clinical opinion (Delphi) and patient charts

Cost item	Delphi	Charts
Non-febrile neutropenia: cost of one episode	1676	132
Febrile neutropenia: cost of one episode	7738	6310
Thrombocytopenia: cost of one episode	492	421
Anaemia: cost of one episode	866	973
Peripheral neuropathy: cost of one episode	262	214
Arthralgia/myalgia: cost of one episode	57	133

When calculating total costs based on the Delphi results and the patient records, the differences become very small. Therefore, and because the Delphi method is a less time consuming and less costly method, we applied it in the other countries for data collection regarding resource utilization.

Cost analysis

The costs can be divided into different categories, i.e. those related to the chemotherapy drug and its administration, those associated with hematological adverse events, and those associated with non-hematological adverse effects.

For each cost category a table summarizes and compares the expected average costs for the four countries. In the interest of ease of comparison, all costs have been expressed in US$ (exchange rates: 1 US$ = 37.6875 BEF = 6.1176 FF = 2.05858 Hfl = 154.805 Pesetas). The details regarding resource utilization

(e.g. number of visits, number of tests length of hospital stay) and local costs are available in separate country-specific reports upon request.

Table 3 shows the average costs related to the therapy of TENCIS and TAXCIS. The chemotherapy administered was considered over four cycles, since the average duration in the EORTC trial was 4.1 for TENCIS and 4.6 for TAXCIS. Given the doses of paclitaxel (175 mg/m^2), teniposide (100 mg/m^2, 3 times) and cisplatin (80 mg/m^2), and given an average body surface of 1.8 m^2, the total dose in milligrams over the four cycles was calculated as being 2040 mg for teniposide, 1190 mg for paclitaxel and 544 mg for cisplatin, thereby taking into account average dose reductions for adverse events, as reported in the EORTC trial.

Table 3 shows that the acquisition cost for TAXCIS is much higher than the cost for TENCIS, while the administration cost for the former is lower in all countries. The administration cost is higher in France than in the other countries because of a higher hospitalization cost per day.

Table 4 shows the expected average costs with regard to the treatment of hematological side effects. The expected costs of treating a given adverse event are calculated by multiplying the probability of that adverse event, as reported in the EORTC trial, by the cost of managing it.

There are clear differences in practice and in costs between the four countries.

In The Netherlands and Belgium there is, for instance, more preventive use of G-CSF than in Spain or France. The costs of testing are, however, generally lower in these countries than in Spain or France, mainly because the tests have a lower unit cost. The unit cost for hospitalization and the hospitalization rate for adverse events are higher in France than in the other countries. This explains why total hospital costs are higher for this country.

Table 5 shows the expected average costs with regard to the treatment of non-hematological side-effects. Here, hospital costs are the cost drivers in all four countries. Again, because of the higher hospital unit cost, France has higher overall expected costs than the other countries.

Table 6 presents the total costs for both chemotherapies. The results show that the high drug cost of TAXCIS can only partially be recovered by savings in chemotherapy administration and the treatment of adverse events.

Despite differences in medical management, the results are very comparable across the four countries. On average, a TAXCIS-based treatment costs US$2625 more than a TENCIS-based treatment.

Cost–effectiveness (CE) analysis

CE analysis is a commonly used technique, where both the costs and consequences of treatments are exam-

Table 3. Drug and administration costs (US$) associated with chemotherapy based on clinical opinion (Delphi)

	The Netherlands		Belgium		Spain		France	
	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS
Total cost of chemotherapy drugs	*1383*	*8573*	*841*	*6267*	*750*	*5970*	*438*	*6349*
Administration cost—1st cycle	*964*	*489*	*583*	*265*	*642*	*182*	*1508*	*804*
% day-clinic—1st cycle	50	0	59	57	67	85	11	21
cost per day for day-clinic	182	182	133	133	136	136	222	222
% hospital—1st cycle	100	100	42	43	33	15	89	79
length of stay—1st cycle	3.13	1.75	3.17	2.00	4.13	1.88	2.26	1.86
cost per day for hospital stay	279	279	220	220	237	237	514	514
Administration cost—next cycles	*964*	*489*	*561*	*207*	*628*	*168*	*1470*	*749*
% day-clinic—next cycles	50	0	65	72	63	92	21	29
cost per day for day-clinic	182	182	133	133	136	136	222	222
% hospital—next cycles	100	100	35	28	38	8	79	71
length of stay—next cycles	3.13	1.75	3.33	1.80	3.63	2.25	2.42	1.88
cost per day for hospital stay	279	279	220	220	237	237	514	514
Total administration cost—all cycles	*3855*	*1955*	*2267*	*885*	*2526*	*687*	*5918*	*3050*

Table 4. Costs (US$) associated with hematological adverse events based on clinical opinion (Delphi)

	The Netherlands		Belgium		Spain		France	
	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS
Probability of non-febrile neutropenia:	0.86	0.54	0.86	0.54	0.86	0.54	0.86	0.54
hospital[a]	7	7	45	45	58	58	144	144
drugs	17	17	498	498	239	239	80	80
tests	15	15	18	18	54	54	31	31
prevention with G-CSF	776	776	1063	1063	299	299	35	35
cost of one episode	814	814	1624	1624	651	651	291	291
Expected cost (= cost × probability)	700	440	1397	877	560	352	250	157
Probability of febrile neutropenia:	0.27	0.03	0.27	0.03	0.27	0.03	0.27	0.03
hospital[a]	1287	1287	1327	1327	1153	1153	2680	2680
drugs	461	461	1352	1352	805	805	600	600
tests	167	167	275	275	302	302	388	388
prevention with G-CSF	1844	1844	1322	1322	446	446	946	946
cost of one episode	3759	3759	4276	4276	2706	2706	4613	4613
Expected cost (= cost × probability)	1353	188	1539	214	974	135	1661	231
Probability of thrombocytopenia:	0.36	0.02	0.36	0.02	0.36	0.02	0.36	0.02
hospital[a]	110	110	478	478	175	175	1016	1016
tests	33	33	62	62	83	83	51	51
transfusions	97	97	153	153	88	88	25	25
cost of one episode	239	239	693	693	346	346	1093	1093
Expected cost (= cost × probability)	86	5	250	14	124	7	393	22
Probability of severe anemia:[b]	0.46	0.2	0.24	0.1	0.24	0.1	0.24	0.1
hospital[a]	218	218	206	206	120	120	469	469
tests	24	24	12	12	59	59	31	31
transfusions	185	185	127	127	121	121	60	60
cost of one episode	426	426	345	345	300	300	561	561
Expected cost (= cost × probability)	307	183	173	114	150	99	281	185
Probability of moderate anemia:			0.22	0.1	0.22	0.1	0.22	0.1
hospital[a]			54	54	50	50	17	17
tests			6	6	28	28	14	14
transfusions			13	13	11	11	2	2
cost of one episode			73	73	89	89	33	33
Expected cost (= cost × probability)			16	7	20	9	7	3

[a]Including hospital stay, day clinic, ambulatory visits.
[b]For The Netherlands: moderate anemia was included in severe anemia.

Table 5: Costs (US$) associated with non-hematological adverse events, based on clinical opinion (Delphi)

	The Netherlands		Belgium		Spain		France	
	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS
Probability of peripheral neuropathy:	0.07	0.29	0.07	0.29	0.07	0.29	0.07	0.29
hospital[a]	119	119	182	182	236	236	1190	1190
tests	8	8	47	47	115	115	27	27
cost of one episode	127	127	230	230	351	351	1217	1217
Expected cost (= cost × probability)	8	36	14	64	21	98	73	341
Probability of Arthralgia—Myalgia	0.04	0.17	0.04	0.17	0.04	0.17	0.04	0.17
hospital[a]	16	16	63	63	52	52	246	246
drugs	5	5	5	5	9	9	6	6
tests	7	7	7	7	19	19	21	21
cost of one episode	28	28	75	75	81	81	274	274
Expected cost (= cost × probability)	1	5	4	14	4	15	14	52

[a]Including hospital stay, day clinic, ambulatory visits.

ined. In our analysis, the *difference* in total cost of both treatments (=the incremental cost) was divided by the difference in effectiveness (=the incremental effectiveness), to result in an incremental CE ratio.[19] Ideally, effectiveness should be expressed in terms of life years gained[20–25] or a combination of quality and QoL, such as quality-adjusted life years (QALY). However, since survival was the same in both groups and QALY data was not available, we withheld the percent *of responding patients* as the primary effectiveness parameter (26% in the TENCIS group versus 37% in the TAXCIS group). This parameter is relevant to clinicians and is frequently used as a measure of effectiveness in cancer research.

The calculated average and incremental CE ratios for the different countries are presented in Table 7. In The Netherlands and Spain, the average CE ratio of TAXCIS is higher compared to TENCIS, resulting in a higher incremental ratio. In contrast, TAXCIS was found to show a better CE ratio than TENCIS in France and Belgium, i.e. the incremental CE ratios are lower than the average CE ratios of TENCIS. The most remarkable difference is to be found in France. Care should be taken when interpreting these *average* CE ratios, especially since we did not focus on all NLCSC-related costs. Suppose that our analysis covers only 75% of the *total* cost of managing these patients during their chemotherapy regimen. The remaining 25% is assumed to be equal to both treatment alternatives. When adding this 'missing' 25% to the cost of both branches, the average CE ratios change. For instance, in Spain, 25% of the total 'missing' cost per patient would be US$1581. If this cost is added to both branches, the average CE ratios now become US$25803/responder and US$24195/responder for TENCIS and TAXCIS, respectively. In other words, the ratio for TAXCIS becomes lower than the ratio for TENCIS. The incremental ratio obviously does not change.

In general, if the average CE ratio for the more effective treatment TAXCIS is better when compared to TENCIS, without taking into account the 'missing' costs, this ratio will always be better no matter how high the level of missing costs. This is the case for France and Belgium. If the average CE ratio is worse for TAXCIS, without taking into account the 'missing costs' (see Spain and The Netherlands), the difference becomes smaller when the missing costs are taken into account. However, since the level of missing costs is unknown, it cannot be concluded that TAXCIS is less cost-effective in these countries. At most it can be concluded that both strategies are equally cost-effective.

Sensitivity analysis

The above results do not take into account the possible *uncertainty* surrounding the data in our evaluation. In clinical research it is common to conduct statistical inference testing in order to test the stated research hypotheses. In this study, the null-hypothesis would be that there is no difference in CE ratios between the strategies. In health economic

Table 6. Total costs (US$) for TENCIS and TAXCIS

	The Netherlands		Belgium		Spain		France	
	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS	TENCIS	TAXCIS
Chemo (drug+administration)	5239	10528	3108	7151	3275	6656	6356	9399
Hematological side effects	2446	816	3375	1226	1828	602	2591	598
Non-hematological side effects	9	41	18	79	25	114	87	393
Total cost	*7694*	*11385*	*6500*	*8455*	*5128*	*7372*	*9034*	*10390*

Table 7. Total costs (US$), effectiveness (expressed in % responders) and cost–effectiveness [average and incremental (**Incr**)]

	The Netherlands			Belgium			Spain			France		
	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**
Cost	7694	11385	**3691**	6500	8455	**1955**	5128	7372	**2243**	9034	10390	**1356**
Effect	26%	37%	**11%**	26%	37%	**11%**	26%	37%	**11%**	26%	37%	**11%**
CE ratio	29592	30769	**33550**	25000	22852	**17775**	19724	19923	**20394**	34747	28080	**12323**

evaluation, statistical inference testing is, however, only possible when individual stochastic data on effects *and* costs are available. A frequently recommended method is then the bootstrapping technique.[26] In most economic evaluations, also in ours, the clinical data are stochastic but the cost data are deterministic. Therefore, it is recommended to conduct an extensive sensitivity analysis on those variables that are subject to uncertainty.[27] This involves here the clinical expert opinion, for which we calculated the p10 and p90 values of all statements. The most important medical practice variables are (i) the probability of hospitalization for hematological side-effects and (ii) the probability of G-CSF use in prevention of subsequent neutropenia.

Figure 1 presents the average and incremental CE ratios from Table 7; however, now with an indication of the 'minimal' and 'maximal' values that are obtained by applying simultaneously the lower and upper limits (p10 and p90) of the medical practice intensity regarding the above variables.

Apparently, the variation in medical practice influences the CE ratios but does not influence the conclusions. Only in France could the difference be regarded as 'significantly' different in favor of TAXCIS. 'Significantly' different should be interpreted here as 'different for the whole possible range of medical practice intensity'.

In most economic evaluations, sensitivity analysis is also undertaken on the key cost variables. Although there are no existing recommendations regarding the sensitivity margin, in many studies the key variables are changed over a range from −30 to +30% of the base value and the impact of this change on the conclusions is assessed.

We applied this technique to the cost of hospitalization (the charge per day) and the acquisition cost of Taxol®, as shown in Table 8.

The cost of TAXCIS is a very sensitive variable in the analysis for all four countries. An increase of this cost by 30% would obviously induce higher CE ratios for TAXCIS, i.e. make TAXCIS less cost-effective than TENCIS. A reduction by 30% would make TAXCIS more cost-effective in all countries and even cost saving in France (hence the negative incremental CE ratio). The impact of the hospitalization charge is also

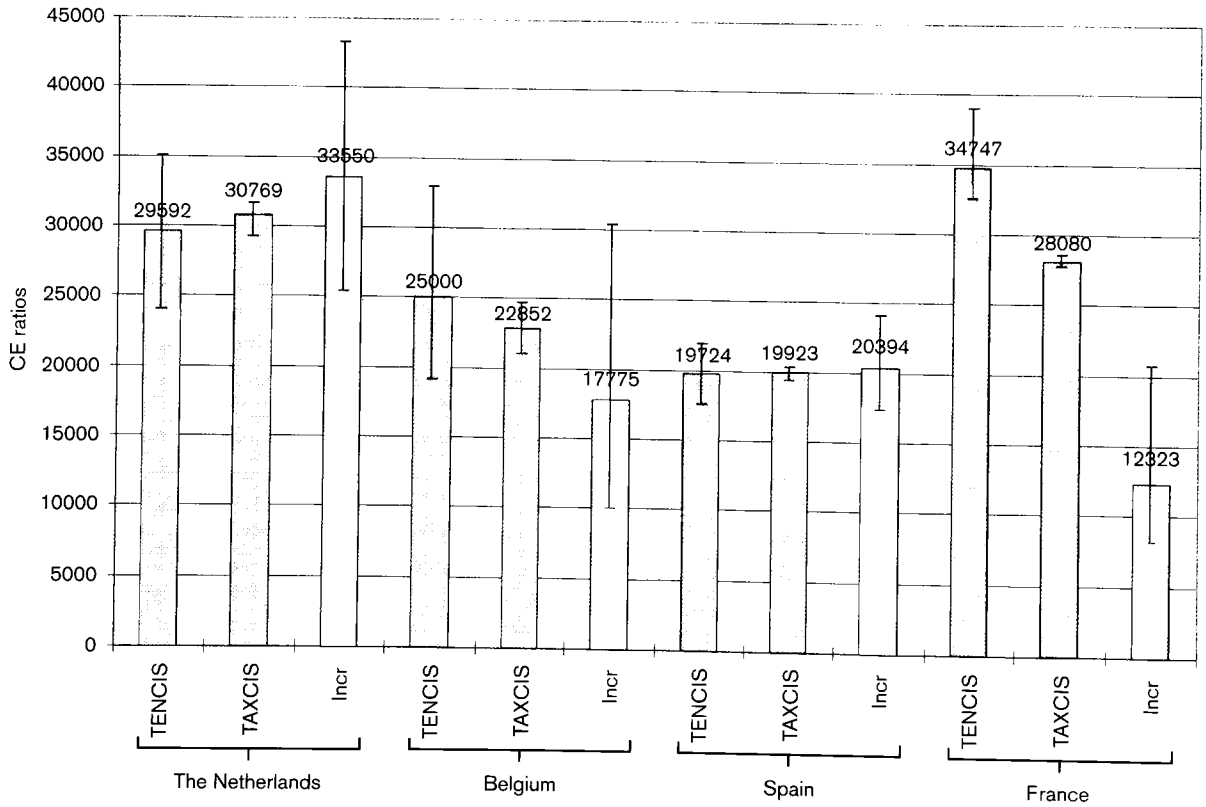

Figure 1. Cost–effectiveness expressed as cost (US$) per responder. The right column for each country represents the incremental (Incr) cost–effectiveness. The ranges indicate the minimum and maximum values of the cost–effectiveness results, calculated from minimal and maximal G-CSF use and hospitalization.

Table 8. Sensitivity analysis on cost of TAXCIS and hospital costs: the figures present average and incremental (**Incr**) CE ratios expressed as cost (US$) per responder (compare figures with bottom line of Table 7)

	The Netherlands			Belgium			Spain			France		
	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**
TAXCIS −30%	38758	30259	**10170**	32588	23103	**683**	25803	19354	**4113**	45502	30490	**−4992**
TAXCIS +30%	38758	44161	**56931**	32588	33265	**34866**	25803	29035	**36676**	45502	40786	**29639**
Hospital −30%	33533	35462	**40023**	29029	27275	**23128**	22178	23465	**26508**	36624	32542	**22894**
Hospital +30%	43984	38958	**27078**	36147	29093	**12421**	29428	24925	**14281**	54380	38734	**1753**

Table 9. Comparison of CE ratios calculated from two different clinical databases (EORTC and BMS): the figures present average and incremental (**Incr**) ratios expressed as cost (US$) per responder

	The Netherlands			Belgium			Spain			France		
	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**
Based on EORTC	25791	28051	**33323**	21351	20769	**19409**	17106	18142	**20559**	30264	25445	**14202**
Based on BMS	29592	30769	**33550**	25000	22852	**17775**	19724	19923	**20394**	34747	28080	**12323**

fairly straightforward. The higher the hospitalization charge, the more beneficial for the TAXCIS strategy, since more costs are avoided. As a result, the CE of TAXCIS becomes better when compared to TENCIS in all countries if hospital charges increase by 30% and vice versa.

Finally, we tested the impact of the database choice, since the data from the EORTC database and the BMS database differ slightly. Therefore, we calculated the CE ratios based on the EORTC data as well (see Table 9). The choice of database does not influence the conclusions, although the respective CE ratios derived from the different database do differ quite considerably.

Discussion

Our economic evaluation in NSCLC suggests that the high acquisition cost of TAXCIS was partly outweighed by lower hospitalization costs for its administration (only 1 day) and by a lower incidence of severe hematological adverse events. The resulting cost-effectiveness of TAXCIS, as expressed by cost per responder is comparable to TENCIS. Only in France is the cost-effectiveness of TAXCIS better.

The methods applied in our study are not free from criticism. First of all, the costs applied in the analysis are not real costs, but charges, which are to be paid by the system. The fact of using charges is, however, justified by the perspective of the study, i.e. the health care system. Indeed, when taking that perspective, the purpose of the study is to maximize the use of the health care budget, in other words to optimize the cost-effectiveness of the interventions covered by the system.

For the same reason, the labor time involved in the management of the patients was not calculated, since this element is only of interest to the hospital management and is only to be calculated if a hospital perspective is applied.

Use of the Delphi approach to collect data regarding medical practice is not yet well known among European clinical professionals. Nevertheless, it has been applied frequently in the US and has demonstrated reliability in different settings.[18] The best way to obtain reliable results is to organize three rounds and to avoid the experts meeting each other in a roundtable situation, since interviewer and peer bias might occur. The fact that we found very similar results from our Delphi panel and the patient chart review supports our use of the Delphi method, which is moreover relatively cheap to conduct. The disadvantage of not having individual cost data undoubt-

Table 10. CE ratios calculated based on physical functioning scores: the figures present average and incremental (**Incr**) CE ratios expressed as cost (US$) per point on the physical functioning scale

	The Netherlands			Belgium			Spain			France		
	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**	TENCIS	TAXCIS	**Incr**
Cost per physical functioning score point	164	152	**132**	138	113	**70**	109	98	**80**	192	139	**48**

edly has an impact on the quality of the uncertainty analysis. Sensitivity analysis is a recommended method to test the variance of the conclusions as a function of given deterministic variables, but is unable to draw statistical conclusions. Our sensitivity analyses enables us to conclude that TAXCIS is as cost-effective as TENCIS, with the exception of France, where it is likely to be more cost-effective. Only if there is a 30% reduction in acquisition cost of TAXCIS, does it become more cost-effective in the other countries as well.

When comparing our results with the published literature, it seems that the calculated costs match well with those reported before. For instance in Evans *et al.*[22] the average cost of a chemo-radiotherapy treated stage IIIb patient is equal to Can$8912 in Canada, which is of the same order of magnitude as our results (however, in our study no radiotherapy was involved). CE ratios for chemotherapy in advanced NSCLC have been calculated in different studies; however, all expressing effectiveness in Life Years Gained (LYG).[20–25] These studies show that chemotherapy is a cost-effective strategy with ratios ranging from US$2000 to US$18 000 per LYG. The fact that we had to restrict our cost-effectiveness analysis to the number of responders is a weakness of our study, but given the lack of difference in survival, it was the best alternative. We explored an alternative parameter, i.e. the QoL score for the patients in the EORTC trial, which was collected in some selected centers (n=86 in the TENCIS group and n=83 in the TAXCIS group). This was done at intervals of 6 weeks, starting at baseline, and using the EORTC quality of life core questionnaire (QLQ-C30) and the 'lung module' (LC-13) as evaluation techniques. Baseline values were not comparable for all QoL parameters and QoL differences at the different 6 week intervals provided mixed, variable or inconsistent results, albeit in favor of paclitaxel for most dimensions. The QoL dimension of 'physical functioning', including several relevant items related to the physical performance of the patients, showed equal values at baseline (80/100) for both study groups and showed consistent results over the entire assessment period of 24 weeks. At the end of the period, average physical functioning was reduced to 47/100 in the teniposide group and 75/100 in the paclitaxel group.

A CE analysis based on this end score would result in better CE ratios for TAXCIS in all countries (see Table 10). These results are promising but efforts should be made in future research to improve the validity of QoL data. Unfortunately, however, in rapidly progressive tumors, such as advanced NSCLC, drop-outs remain a major problem for quality of life studies.

A cost-utility analysis, leading to a cost/QALY ratio was not possible, since no utility measurements were done in the clinical trial.

Conclusion

Several economic publications in advanced NSCLC have shown that chemotherapy as such is a cost-effective strategy, ranging from US$2000 to US$18 000 per LYG, depending on the setting and the type of drug. Paclitaxel plus cisplatin does not offer additional survival in NSCLC patients, but improves significantly patient response and some dimensions of QoL. Expressed in cost per responder, paclitaxel plus cisplatin is equally cost-effective as teniposide plus cisplatin. Since response is regarded as an important clinical endpoint, our analysis suggests that paclitaxel plus cisplatin can be considered as a cost-effective intervention. However, we recommend to assess utility measures in responding and non-responding patients, which would make it possible to express the economic value of new therapies in cost/QALY.

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