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Cost-minimization analysis of a phase III trial comparing concurrent versus sequential radiochemotherapy for locally advanced non-small-cell lung cancer (GFPC-GLOT 95–01)

A. Vergnenegre[1]*, C. Combescure[2], P. Fournel[3], S. Bayle[4], C. Gimenez[5], P. J. Souquet[6], H. Lena[7], M. Perol[8] & J. Y. Delhoume[9]
GFPC (Groupe Français de Pneumo-Cancérologie)

[1]*CHU Limoges;* [2]*Université Montpellier 1, CHU Montpellier;* [3]*CHU Saint-Etienne;* [4]*CHU Brest;* [5]*CHU de Marseille;* [6]*CHU de Lyon Sud;* [7]*CHU de Rennes;* [8]*CHU de Lyon Croix Rousse;* [9]*CH de Périgueux, France*

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Background: We conducted an economic analysis of a phase III clinical trial comparing sequential radiochemotherapy (RT-CT) with concurrent RT-CT in patients with locally advanced non-small-cell lung cancer.
Patients and methods: The trial was a randomized multicenter study comparing three cycles of chemotherapy (arm A) followed by radiotherapy against an RT-CT combination (two cycles of platinum etoposide) followed by two cycles of platinum-vinorelbine (arm B). The economic analysis adopted the payer's perspective and only included direct costs. Costs (€, 1996–2003) were recorded until the cut-off date. A cost minimization analysis and a sensitivity analysis were carried out.
Results: Data from 173 patients were used in the economic study. Protocol costs tended to be higher in arm B, while relapse costs were significantly higher in arm A. The total number of hospital days was higher in arm B. The average total cost per patient was €16 074 in arm A and €15 245 in arm B ($P = 0.15$). The cost minimization analysis favored arm B. This advantage persisted in the sensitivity analysis.
Conclusions: Concurrent RT-CT was not the more costly strategy in this phase III trial, despite lengthier hospitalization for toxicity. Other studies of similar design are needed to confirm these results in future randomized trials.
Key words: cost minimization analysis, lung cancer, stage III NSCLC, radiochemotherapy, clinical trial

introduction

Cost is an increasing concern when comparing possible patient management strategies [1, 2]. Lung cancer, with its high incidence and grim prognosis, is a particularly good candidate for economic analyses [3], as the results offer a further basis for clinical decision-making, alongside efficacy, toxicity and quality of life [4, 5].

Economic analyses of lung cancer management have become increasingly common during the last decade [6]. They are generally based either on the global or per-patient cost of the disease [7–11] or on comparative management strategies [12–14]. Most such studies are based on models and expert opinions, but economic analysis of clinical trials has become more frequent in recent years [15–17].

Concurrent radiochemotherapy is routinely used before surgical resection with downstaging and good long-term results [18]. Chemoradiation is also offered for patients ineligible for surgery. Studies of concurrent radiotherapy and chemotherapy for locally advanced inoperable lung cancer (LC) comprise three published randomized studies [19–21] and one other phase III trial presented at international conferences [22]. Between 1996 and 2000, the Groupe Français de Pneumo-Cancérologie (GFPC) conducted a phase III trial designed to compare concurrent and sequential RT-CT [21]. The economic analysis was included in the initial trial protocol, allowing certain data to be collected prospectively.

The working hypothesis was that concurrent RT-CT might have more frequent adverse effects necessitating hospitalization, or might generate higher direct costs related to its mode of administration. The objective of this study was to search for a difference in cost analysis between the two strategies, which had the same effectiveness.

Correspondence to: Prof. A. Vergnenegre, Service de Pathologie Respiratoire, Hôpital Universitaire du Cluzeau, 87042 Limoges cedex, France.
Tel: +33-5-55-05-66-29; Fax: +33-5-55-05-68-15; E-mail: avergne@unilim.fr

patients and methods

clinical trial

Only a brief summary of the clinical trial is presented here. More details are available in the clinical paper [21].

This randomized multicenter phase III study was started in October 1996, after validation by an ethics committee. Eligible patients were those aged between 18 and 70 years, with an Eastern Cooperative Oncology Group (ECOG) score ≤1, weight loss ≤10% and previously untreated unresectable NSCLC. The main end point was survival.

Patients were stratified by stage (IIIA–N2/IIIB) before being randomly assigned to receive sequential (arm A) or concurrent therapy (arm B). In arm A, three cycles of chemotherapy were administered first, consisting of cisplatin 80 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1, 8, 15 and 21, every 4 weeks. Patients with an objective response or stable disease after chemotherapy began to receive radiotherapy 4 weeks after the third cisplatin–vinorelbine administration. Radiotherapy consisted of 66 Gy in 33 2-Gy fractions, 5 days a week over 6.5 weeks.

Chemotherapy and radiotherapy began simultaneously in arm B. The first and second cycle of cisplatin 20 mg/m^2 and etoposide 50 mg/m^2 was administered on day 1, 5, 29 and 34. On day 78, two cycles of consolidation chemotherapy began, consisting of cisplatin 80 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1, 8, 15 and 21, every 4 weeks.

The patients' characteristics were compared with the chi-square test (or Fisher's exact test or the Kruskal–Wallis test in case of a non-normal distribution). Survival data were compared with the log rank test and a Cox model [21].

economic analysis

This economic analysis adopted the payer's perspective.

Only direct costs [23] were taken into account. As specified in the initial clinical trial protocol, direct medical costs [24] included all care dispensed to the patients, based on unit costs (diagnostic work-up; chemotherapy in daycare centers or classical hospital wards; radiotherapy in classical hospital wards, daycare centers or on an ambulatory basis). All hospitalizations for adverse effects were included, while adverse effects not requiring hospitalization were not taken into account [25]. The former adverse effects mainly comprised grade III and IV toxicity, as previously described in the French global cost analysis [11]. Grade I and II toxicity can generate certain costs but, in the French health care system, these costs are low compared with hospital costs and can be taken into account in a sensitivity analysis.

At the end of the protocol the patients were divided into two categories. For the first one, the following data were recorded prospectively for patients who completed the treatment protocol and entered post-treatment follow-up: monitoring, relapses and their treatments, terminal care and death; or simple monitoring until the cut-off date. Relevant standardized forms were included in the patient's notebooks used for the clinical trial.

Regarding the second category, patients who were excluded or lost to follow-up, data were collected retrospectively by each investigator. If this was not possible patients were censored at the last contact.

Since 1997, France has used a national cost scale for all hospitalized patients, based on diagnosis related groups (DRGs) [26]. The scale applies both to patients admitted to classical hospital wards and to patients treated in daycare centers. The different items on this scale are divided into fixed costs (medical and non-medical wages, administrative expenses, etc.) and variable costs (cytostatic drugs, other medications, laboratory tests, etc.) [27]. We used fixed costs as representative of costs in French hospitals and introduced variable costs specific to this study. When analyzing adverse effects necessitating hospitalization, we used all the cost items on the national scale. When analyzing treatment costs, and especially chemotherapeutic agents, we used the price per milligram, as defined by the pharmaceutical industry.

The costs of ambulatory consultations and examinations are standardized in France [28]. Transport [29] was costed per kilometer, assuming that patients with complications and those receiving terminal care required an ambulance, and that all other patients required a taxi. We also used the terminal care costing system of the French national costs scale [26]. Home-based care was not evaluated in our study, but it was rarely available in France at the time. In addition, any such patients would probably have been equally distributed between the two arms of this randomized trial, and about 95% of patients were admitted to hospital for their terminal care.

Costs were calculated according to the period of the study (1996 to 2003) and were updated on the period with a rate of 5% per year (according to the date of death or censoring).

First, time periods were defined identically for costs and efficacy. Mean efficacy per patient was estimated in each arm in terms of life expectancy (area under the curve of the Kaplan–Meier survival estimate) [31]. If the patients survived during the time period, costs were applied to the interval. In the other cases (death or censoring) the mean cost per patient in each arm was estimated by weighting the probabilities of the Kaplan–Meier survival estimate at each time point with the mean costs recorded during the corresponding time period [32, 33]. The standard deviation and covariance between the mean cost and mean efficacy in each arm were also calculated. The Kaplan–Meier estimator ensures the asymptotic normality of the estimators [32]. This estimator takes into account not only losses to follow-up (censorship based on survival) but also missing economic data (censorship based on cost data). We verified that the patients included in the economic study were comparable with the entire clinical study population.

Secondly, the cost of each component was evaluated then aggregated according to the different parts of the study, as follows: concurrent or sequential radiochemotherapy (named costs per protocol), costs of early relapse (at final evaluation of the protocol) or follow-up, costs of relapses and costs of terminal care.

Complications were recorded alongside the study and are included in the protocol costs (as cost consequences of the treatment) or in the relapse costs. Terminal care was defined as the period just before death. It corresponded to palliative care and was not considered as a complication.

Given the similar efficacy of the two arms in terms of overall survival, the economic analysis was based on difference between the average costs of the two strategies with their confidence intervals. Due to the model calculation, the standard deviation of the costs was very small and we compared only aggregated costs by using Wald's bilateral test. One-way sensitivity analysis was used to define the threshold at which the costs of the two arms would be equal, by varying costs from −30 to +30%. Two selected variables were defined as the two major cost components (arm B protocol costs and arm A relapse costs). Two-way sensitivity analysis was used to define the preferred arm area with these two variables.

All statistical analyses were done using S-Plus software (Splus 6 for Windows, Insightful Corporation, Seattle, USA).

results

the sample

Between October 1996 and May 2000, 201 patients were eligible for the trial. The cut-off date was 1 July 2003. The median follow-up was 4.8 years.

Only 173 patients were used in this analysis. Twenty-eight patients were censored because of missing economic data. We compared the 173 patients included in the economic analysis with the 28 censored patients. The only difference was in the stage distribution (more stage IIIAN2 in the censored group).

However, there was no difference between two arm distribution (the randomization took the stage into account).

results of clinical trial

Table 1 lists hematologic and non-hematologic adverse events occurring in the two arms. Neutropenia and grade III neuropathy were more frequent in arm A than in arm B. However, the largest difference concerned esophagitis, which was more frequent in arm B. The number and duration of hospitalizations during the protocol phase were both higher in arm B than in arm A (Table 2). In terms of effectiveness, the survival analysis showed no global difference [21] between the two arms (log-rank test 0.24). Actuarial survival data showed 3 and 4-year survival rates of 18.6% and 14.2% in arm A and 24.8% and 20.7% in arm B, respectively [21]. There was a trend towards longer survival in arm B [21].

results of the economic analysis

Tables 3 and 4 give details of cost components and overall cost calculation, according to a discount rate of 5% and 0%. Despite more toxicities and more frequent hospitalization days, the mean total cost per patient was not different between the two arms: €16 074 ± 229 for arm A and €15 245 ± 345 for arm B ($P = 0.15$). Some cost items differed significantly between the two groups but these differences compensated for one another. Cost minimization calculation did not show any difference between the two arms (zero is included in the 95% confidence interval): €829 per patient (+296, –1 957) in favour of arm B.

Figures 2 and 3 depict one-way sensitivity analysis as arm B and arm A cost components were varied from −30% to +30%. In the two figures, the differences of the costs favoured arm B. Finally, two-way sensitivity analysis was carried out with two variables: arm B protocol costs and arm A relapse costs. As shown in Figure 4, arm B was the preferred arm (in terms of area) with these two variables and the defined variations.

discussion

This is the first comparative economic analysis of concurrent and sequential radiochemotherapy for locally advanced inoperable lung cancer. The concurrent treatment was not more costly than sequential treatment. Concurrent RT-CT is not currently a standard in the treatment of locally advanced NSCLC [34] but the clinical results of the published or

Table 1. Toxicity (WHO grade) by treatment arm

Toxicity	Sequential treatment ($n = 99$)	Concurrent treatment ($n = 94$)	P[a]
Grade 3–4 neutropenia	86 (87%)	76 (81%)	0.26
Grade 4 neutropenia	71 (71%)	47 (50%)	0.002
Grade 3–4 anemia	27 (27%)	19 (20%)	0.25
Grade 3–4 thrombocytopenia	15 (15%)	16 (17%)	0.72
Grade 3–4 infection	12 (12%)	14 (15%)	0.57
Renal grade 1–2	15 (15%)	8 (8.5%)	0.15
Peripheral neuropathy			
Grade 1	16 (16%)	12 (13%)	0.5
Grade 2	6 (6%)	4 (4%)	0.57
Grade 3	4 (4%)	0	0.049
Esophagitis grade 3–4	6 (6%)	29 (31%)	<0.0001
Mucositis grade >2	2 (2%)	6 (6.5%)	0.13
Nausea-vomiting grade 3–4	19 (19%)	21 (22%)	0.59
Pneumonitis grade 3–4	11 (11%)	5 (5%)	0.17

[a]Chi-square test or Fisher's exact test.

Table 2. Number of hospitalizations and length of stay (LOS) in the two arms during the protocol phase (from inclusion to the end of the radio and chemotherapy sequence)

	Arm A	Arm B	P value
Number of patients hospitalized	41	50	0.23 (chi-square test)
Average LOS per patient	9.34 days	14.7 days	0.0063 (Kruskal–Wallis test)

Only hospitalizations for toxicity (Table 1) are taken into account in this table. Drug administration is excluded.

Table 3. Average costs per patient according itemization and global cost of selected group (in €, 1996–2003, with a discount rate of 5% until death or censor)

	Arm A	Arm B
Protocol costs		
Chemotherapy	4003 (SD 54)	4263 (SD 66)
Radiotherapy	522 (SD 9)	323 (SD 5)
Antibiotics	87 (SD 1)	213 (SD 2)
Blood transfusions	140 (SD 2)	167 (SD 1)
Neutrophil growth factors	203 (SD 3)	231 (SD 5)
Survey procedures	1299 (SD 28)	1398 (SD 41)
Transportation	452 (SD 12)	386 (SD 18)
Total	6706 (SD 96)	6981 (SD 118)
Early relapse and follow-up costs		
Chemotherapy	1019 (SD 27)	1483 (SD 91)
Survey	327 (SD 10)	475 (SD 25)
Transportation	163 (SD 5)	266 (SD 20)
Total	1509 (SD 41)	2224 (SD 135)
Relapse after follow-up		
Chemotherapy	4377 (SD 66)	3663 (SD 71)
Radiotherapy	1369 (SD 13)	607 (SD 15)
Survey procedures	334 (SD 6)	404 (SD 6)
Transportation	418 (SD 4)	336 (SD 11)
Total	6498 (SD 87)	5010 (SD 98)
Terminal care		
Terminal care	1239 (SD 13)	896 (SD 10)
Transportation	120 (SD)	134 (SD 2)
Total	1360 (SD 14)	1030 (SD 12)
Overall costs	16074 (SD 229)	15245 (SD 345)

Hospitalizations for toxicity are included in the chemotherapeutic or radiotherapeutic costs for each line of treatment.
SD, standard deviation.

Table 4. Average costs per patient according itemization and global cost of selected group (in €, 1996–2003, with a discount rate of 0% until death or censor)

	Arm A	Arm B
Protocol costs		
Chemotherapy	4152 (SD 59)	4445 (SD 77)
Radiotherapy	543 (SD 9)	336 (SD 6)
Antibiotics	89 (SD 1)	217 (SD 2)
Blood transfusions	146 (SD 3)	171 (SD 2)
Neutrophil growth factors	108 (SD 1)	95 (SD 1)
Survey procedures	1725 (SD 32)	1793 (SD 49)
Transportation	212 (SD 4)	244 (SD 6)
Total	6975 (SD 109)	7301 (SD 143)
Early relapse and follow-up costs		
Chemotherapy	1090 (SD 32)	1652 (SD 114)
Survey	349 (SD 13)	524 (SD 31)
Transportation	175 (SD 6)	300 (SD 25)
Total	1614 (SD 51)	2476 (SD 170)
Relapse after follow-up		
Chemotherapy	4574 (SD 72)	3855 (SD 80)
Radiotherapy	1402 (SD 14)	645 (SD 19)
Survey procedures	352 (SD 7)	418 (SD 6)
Transportation	430 (SD 5)	360 (SD 13)
Total	6758 (SD 98)	5278 (SD 118)
Terminal care		
Terminal care	1276 (SD 13)	918 (SD 11)
Transportation	124 (SD 1)	139 (SD 2)
Total	1400 (SD 14)	1057 (SD 12)
Overall costs	16747 (SD 272)	16112 (SD 443)

Hospitalizations for toxicity are included in the chemotherapeutic or radiotherapeutic costs for each line of treatment.
SD, standard deviation.

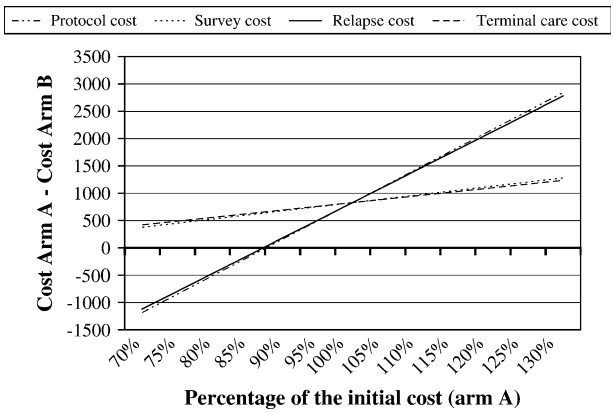

Figure 1. One-way sensitivity analysis based on arm A cost variations (−30% to +30%). The majority of the points favored arm B.

unpublished studies are in favor of this association in terms of effectiveness [19–22]. Our study provides another way to assess the management of this kind of patient.

The results of this economic study have some positive consequences: they have the merit of being based on a randomized trial in which costs were recorded prospectively in

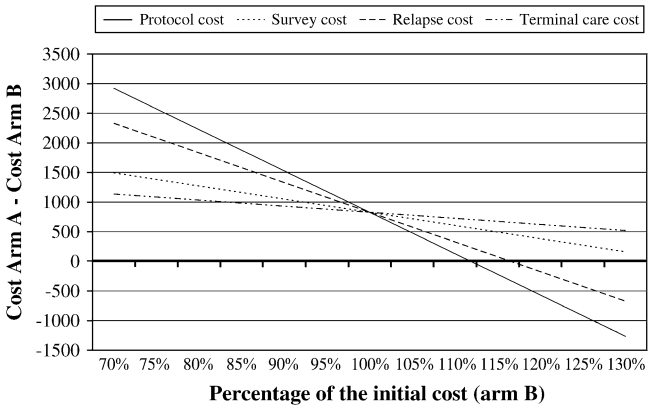

Figure 2. One-way sensitivity analysis based on arm B cost variations (−30% to +30%). The majority of the points favored arm B.

the majority of cases. In terms of medical decision-making [4], four criteria can be taken into account, namely safety, efficacy, quality of life and cost. In terms of efficacy, two trials favor RT-CT versus sequential therapy [19, 20], while the other two studies only show a trend [21, 22]. Toxicity is more frequent with concurrent treatment [21, 22] and it is important to know if this toxicity has economic consequences, after taking their clinical consequences into account. Our study provides a further decision criterion, based on cost considerations. Despite more adverse events, RT-CT is not more costly in a cost-minimization approach. These results should be integrated in the medical decision-making process and favor the association arm.

Our study has a number of limitations. First, unit hospital costs are particularly high in France. However, the number of hospitalizations was higher in the concurrent radiochemotherapy arm (mainly owing to esophagitis). Secondly, a number of patients were censored in the economic analysis, but they were equally distributed between the two arms. However, as for all censored data, it was not possible to estimate the impact these files might have had if they had been included. Sensitivity analysis can compensate for such missing data. Thirdly, only direct costs were taken into account, including those for adverse events necessitating hospitalization, as in previous economic analyses [23]. This means that grade I and II adverse events are not taken into account, but their costs are relatively low. Indirect costs are rarely recorded in economic studies of lung cancer [35]. In a randomized study, patients are attributed by chance to the different arms and profession is not a prognostic factor. For the French payer, all the patients are off work and receive daily financial compensation. Randomization may distribute the costs equally in each arm. Finally, we compared the costs of the two strategies, without attempting to determine the global costs.

The drug treatments were not strictly identical in the two arms, given the variety of treatments authorized in France for concurrent administration with radiotherapy. This is a major criticism of our clinical trial but could not be avoided. The study was conducted in real clinical conditions [36] and we valued the protocol drugs because it was economic assessment of a clinical trial [37]. This underlines the value of more global

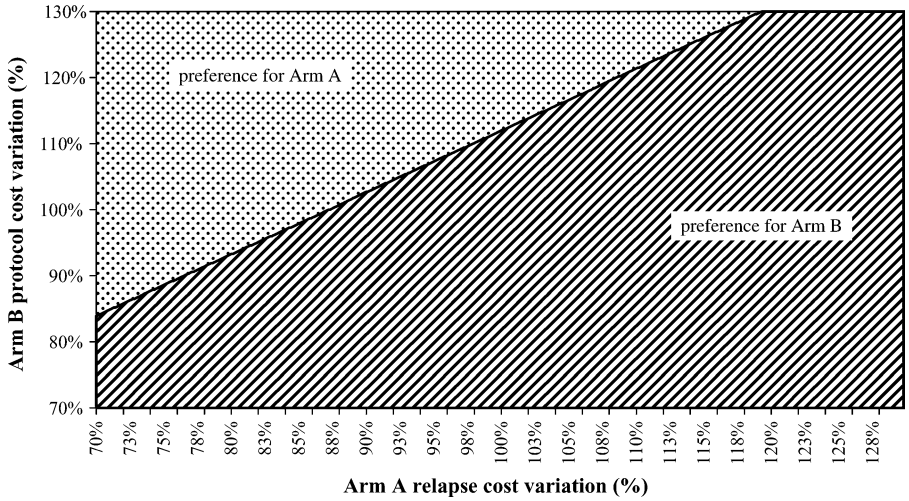

Figure 3. Two-way sensitivity analysis based on arm A relapse costs and arm B protocol costs. The graph depicts the two areas: the dotted area in which preference is for arm A and the striated area in which preference is for arm B. Arm B preference area is wider than arm A area.

models such as the one we have published elsewhere [11], as they enable the evolution of treatment practices to be taken into account. Sensitivity analyses of initial costs can only offer tentative information on the use of other drugs. For new cytostatic treatments, further studies are therefore required.

It is difficult to compare our results with those of other studies, owing to differences in the method of calculation and the specific radiochemotherapy combinations used. Our methodology is now widely used for cost-calculation: recording of the volume prospectively or retrospectively followed by cost valorization specific of a country [38]. In most studies only adverse events necessitating hospitalization are recorded [38, 39]. We recorded second-line treatments and follow-up, contrary to a recently published study which compared four treatment regimens [38]. This method seems to be more precise than economic evaluation of the first-line regimen. Evans et al. [40] considered that a global economic approach was more useful for clinicians.

Our mean costs were slightly lower than in the French global cost study [11], but they fall within the confidence interval of this latter study. Chouaïd et al. [11] used a model-based approach, while we analyzed a clinical trial dataset, possibly explaining the observed differences. In addition, in the sample Chouaïd used to create the model, radiochemotherapy was weakly represented because it was not a standard of care in France, outside of clinical trials [11].

Our data are even more difficult to compare with results from other countries. Only Evans et al. [13] have published model-based comparisons of radiochemotherapy in inoperable stage III NSCLC. The mean cost of treatment was 16 086 Canadian dollars (1995 values) for radiotherapy alone; $39 049 for post-operative radiotherapy after neoadjuvant chemotherapy and $22 303 for neoadjuvant chemotherapy plus radiotherapy (a figure close to that found here). The authors concluded that radiochemotherapy increased the incremental costs but that these strategies remained cost-effective for the Canadian health system. We compared sequential radiochemotherapy with concurrent radiochemotherapy, while the Canadian study focused on the addition of chemotherapy to the usual treatment strategy.

conclusions

This cost-minimization analysis of the GLOT GFPC 95–01 clinical trial favors concurrent RT-CT versus sequential treatment. Indeed, the costs associated with concurrent RT-CT were lower, despite more adverse events and hospital days. Two recent editorials underline the difficulties of assessing progress in lung cancer treatment and the need for a stepwise approach [41, 42]. This study, therefore, offers clinicians another viewpoint when making treatment choices. The clinical data, which appear to favour concomitant treatment, probably warrant a meta-analysis that will provide a new estimate of efficacy and might then permit cost–effectiveness studies, which have greater scientific value.

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