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Cost-minimisation analysis comparing gemcitabine/cisplatin, paclitaxel/carboplatin and vinorelbine/cisplatin in the treatment of advanced non-small cell lung cancer in Italy

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Received 14 July 2004; received in revised form 15 November 2004; accepted 17 November 2004

KEYWORDS

Chemotherapy;
Gemcitabine;
Paclitaxel;
Vinorelbine;
Non-small cell lung cancer;
Cost-minimisation;
Pharmacoeconomics

Summary A retrospective cost-minimisation analysis was conducted comparing novel chemotherapies for the treatment of chemo-naïve patients with locally advanced, recurrent, and/or metastatic non-small cell lung cancer (NSCLC). Resource use information was obtained from a Phase III randomised trial investigating the efficacy and toxicity of gemcitabine/cisplatin (Gem/Cis), paclitaxel/carboplatin (Pac/Carbo) and vinorelbine/cisplatin (Vin/Cis) combination regimens in 612 patients with advanced NSCLC. Since there were no statistically significant differences between the three treatments in terms of progression-free or overall survival in this trial, a cost-minimisation analysis was considered to be the appropriate type of economic evaluation. The perspective was that of the national

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healthcare provider in Italy. Medical resource use was obtained from the clinical trial database, from which mean cost streams were calculated for each treatment group. The mean total treatment costs per patient were €8094, €11,203 and €9320 for the Gem/Cis, Pac/Carbo and Vin/Cis regimens, respectively. Based on resource consumption in a clinical trial, Gem/Cis had the lowest overall mean costs of the three chemotherapy regimens. Gem/Cis therefore has the potential to save costs in the treatment of advanced NSCLC in Italy.

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1. Introduction

Lung cancer remains the leading cause of cancer-related death in Europe and North America, accounting for nearly 30% of all cancer deaths [1]. Approximately 80% of all lung cancers are non-small cell lung cancer (NSCLC), and more than 70% of patients with NSCLC present with locally advanced or metastatic disease [2,3]. The prognosis for patients with NSCLC remains poor: approximately 80% of patients die within 1 year of diagnosis, and the 5-year survival rate is estimated at 14% in the USA and 8% in Europe [4].

Currently, cisplatin-based regimens are considered the standard treatment for advanced NSCLC, but the proportion of patients with advanced NSCLC receiving chemotherapy varies widely across countries [5]. Chemotherapy prolongs survival and palliates tumour-related symptoms [6,7], and has been shown to be cost-effective [1].

New chemotherapeutic agents such as gemcitabine, paclitaxel and vinorelbine have been extensively tested in chemo-naïve patients with NSCLC, and randomised clinical trials have demonstrated the activity of these new agents alone or in combination with platinum derivatives for the treatment of locally advanced and metastatic NSCLC [8–16]. However, comparative studies have failed to demonstrate the superiority of any one of these so-called third-generation agents over the others in terms of improved tumour response rate or survival, although they do have different toxicity profiles [3,8,9,17].

Given the similarity in the effectiveness of combination chemotherapy regimens, decisions regarding treatment for advanced NSCLC should take into account the toxicity profiles, convenience and costs. Healthcare utilisation data are beginning to be collected prospectively during clinical trials of chemotherapeutic regimens so that economic analyses can be performed.

Gemcitabine has already undergone extensive economic evaluation, and been shown to be cost-effective when used alone or in combination with cisplatin for treating advanced NSCLC

[5,18]. The aim of the present study was to compare the mean costs of three chemotherapy regimens – gemcitabine/cisplatin (Gem/Cis), paclitaxel/carboplatin (Pac/Carbo) and vinorelbine/cisplatin (Vin/Cis) – in the treatment of chemotherapy-naïve patients with locally advanced, recurrent and/or metastatic NSCLC in Italy, using resource utilisation data from a phase III randomised clinical trial [9].

2. Methods

2.1. Patients and treatments

Resource utilisation data for the economic analysis were collected prospectively during a phase III randomised trial conducted in 41 centres in Italy, which compared Gem/Cis, Pac/Carbo and Vin/Cis in 612 chemotherapy-naïve patients with locally advanced (stage IIIB) and/or metastatic (stage IV) NSCLC [9]. The median age of the patients was 63 years, approximately 78% were male, the majority (92%) had Eastern Cooperative Performance Group (ECOG) performance status 0–1, and 81% had stage IV disease.

Of the 612 patients enrolled, 607 were randomised to receive either Gem/Cis ($n=205$), Pac/Carbo ($n=201$) or Vin/Cis ($n=201$). The doses and treatment schedules are summarised in Table 1. Total drug dose was based on a mean body surface area of 1.8 m^2 per patient. Patients who reached stable disease received a maximum of six cycles of therapy, whereas patients who demonstrated an objective response (complete or partial) could receive up to eight cycles. Dose adjustments within a cycle were made on the basis of haematological and non-haematological toxicities as specified in the protocol [9].

The primary endpoint of the trial was overall response rate, and the study was sufficiently powered to detect a 15% difference in the overall response rate between the Gem/Cis or Pac/Carbo arms and the Vin/Cis arm. Time to disease progression and overall survival were secondary endpoints.

Table 1 Dosage and treatment schedules for the chemotherapy regimens

Gem/Cis (n=205)	21-day cycle Gemcitabine: 1250 mg/m ² , two doses per cycle (days 1 and 8) Cisplatin: 75 mg/m ² , one dose per cycle (day 2) Mean cycles per patient = 4.02
Pac/Carbo (n=201)	21-day cycle Paclitaxel: 225 mg/m ² , one dose per cycle (day 1) Carboplatin: 400 mg/m ² (AUC 6 mg/mL/min Calvert's formula), one dose per cycle (day 1) Mean cycles per patient = 4.23
Vin/Cis (n=201)	28-day cycle Vinorelbine: 25 mg/m ² , four doses per cycle (days 1, 8, 15 and 22) Cisplatin: 100 mg/m ² , one dose per cycle (day 1) Mean cycles per patient = 3.25

2.2. Treatment-related costs

The economic analysis was based on the intention-to-treat population in the clinical trial. Direct healthcare costs were identified for each regimen, using the following categories: (1) chemotherapy acquisition costs (third-generation agent and platinum agent); (2) chemotherapy administration costs; (3) hospitalisation costs associated with adverse events; (4) costs of other medical resources (e.g. radiotherapy, blood transfusions, non-protocolled laboratory blood tests, concomitant medications).

Chemotherapy acquisition costs were determined by multiplying the expected chemotherapy cost per cycle by the mean number of cycles administered. The protocol-specified chemotherapy dose was used for this calculation. Chemotherapy administration costs per patient were determined by multiplying the expected number of administration days by the unit cost per drug administration day (all chemotherapy administrations were assumed to be outpatient). The number of administration days was calculated by multiplying the number of administration days per cycle by the mean number of cycles per patient.

The costs of hospitalisations due to adverse events were determined according to the proportions of patients suffering an event in the clinical trial, and the proportion of those patients who were then hospitalised for treatment of that event. The hospitalisation cost per patient was calculated

as follows:

$$H_C = \sum P_{AE} \times P_H \times C$$

where H_C is the mean hospitalisation cost, P_{AE} the probability of suffering each adverse event, P_H the probability of being hospitalised for that event, and C the unit cost of a hospitalised episode; \sum represents the fact that costs are summed across all adverse events reported in the clinical trial.

Hospitalisation costs associated with adverse events were calculated for grade 3/4 febrile neutropenia, thrombocytopenia, anaemia, vomiting, neutropenia, renal failure, and grade 2/3 neuropathy. The probability of being hospitalised for one of these events was 100%, with the exception of grade 3/4 thrombocytopenia (9%). These probabilities were derived from consultation with clinical experts and study of the trial datasets.

Finally, the costs of other medical resources (radiotherapy, blood transfusions, non-protocolled laboratory blood tests, concomitant medications) were determined by multiplying the expected cost per patient by the proportion of patients requiring the intervention. Since data on radiotherapy use were not available from the trial, the percentage of patients requiring radiotherapy was assumed to be the same for each treatment group and was based on that reported by Comella et al. [10] for Gem/Cis (23.33%). All medications used concomitantly with chemotherapy in the clinical trial were grouped according to chemical/therapeutic class, and a representative drug and corresponding defined daily dose for each category was found. Calculations of days of therapy in each category were based on product information, prescriptive information provided in the trial protocol and data drawn from the trial records detailing the type and duration of concomitant medication therapy for each patient.

Protocol-driven laboratory tests were excluded from the analysis. The per-patient cost of other laboratory tests was calculated by multiplying the probability of requiring tests by the mean number of tests by the mean cost of a test. The mean cost of a laboratory test was the sum of the cost of blood sampling plus the mean cost of different types of laboratory tests administered in the trial (weighted by frequency). For costing blood transfusions, both packed red blood cell and platelet outpatient transfusions were counted.

Resource use was collected from the clinical trial when available. When resource use data were not available from the trial, data were derived from product information or other published literature.

Unit costs of medical resources in Italy were derived from official published sources, including FEDERFARMA, May 2003 [19], the Italian Ministry of

Health (Ministero della Sanità) [20] and published literature [21–23]. All unit costs are expressed in 2003 Euros (€).

The mean total treatment cost per patient for each regimen was calculated as the cost of the stream of resources utilised across all patients randomised to treatment in that arm.

2.3. Cost-minimisation analysis

The cost-minimisation analysis was based on the clinical effectiveness results reported by Scagliotti et al. [9] and the cost estimates derived in this study using the methods described above.

One-way sensitivity analyses were performed to quantify the effects of various cost drivers in the analysis. All resource unit costs, except study medications, were varied in both directions by 10%, and the associated mean costs per patient were recorded. Similar sensitivity analyses were performed for hospitalisation rates: costs and cost-effectiveness were estimated in a scenario where the rates of hospitalisation were 9% (the base-case assumption for thrombocytopenic episodes) for all types of adverse events. Costs were also estimated in the scenario where 100% of thrombocytopenic episodes were hospitalised. Finally, the sensitivity analysis looked at a practical adjustment to the dosing regimen of Gem/Cis in which cisplatin is given together with gemcitabine on the first day of a cycle.

3. Results

3.1. Clinical outcomes

The efficacy and safety results of the clinical trial have been published in detail elsewhere [9], but

the relevant clinical outcomes are summarised in Table 2. Median survival times (range 9.5–10 months), overall response rates (range 30–32%) and median time to progression (range 4.6–5.5 months) were comparable in all three treatment groups. The lack of significant differences confirms the applicability of our cost-minimisation analysis.

3.2. Treatment-related costs

The medical resource utilisation and unit costs based on the clinical trial and other published data are listed in Table 3.

Patients treated with Gem/Cis had lower total treatment costs (€8094) than those treated with Pac/Carbo (€11,203) or Vin/Cis (€9320) (Fig. 1). Chemotherapy acquisition was a major cost factor across all regimens, ranging from €1461 for Vin/Cis to €6615 for Pac/Carbo. The cost of hospitalisation for adverse events was greatest in patients treated with Vin/Cis (€4537), as were the costs of other medical resources (€2493).

The cost difference between the Gem/Cis and Pac/Carbo regimens (€3109 per patient) was mainly due to the much higher acquisition cost of chemotherapy for the Pac/Carbo regimen, despite the lower costs for drug administration and other medical resources (Fig. 2a). The mean cost saving associated with Gem/Cis compared with Vin/Cis was €1226 per patient. The cost difference was primarily due to the lower costs of hospitalisations associated with Gem/Cis, despite the higher cost of chemotherapy acquisition (Fig. 2b).

3.3. Sensitivity analysis

The results of the various scenarios confirm the main findings of the cost-minimisation analysis

Table 2 Clinical outcomes for each treatment group [9]

	Gem/Cis (n = 205)	Pac/Carbo (n = 201)	Vin/Cis (n = 201)
Response rates (% of patients)			
Complete response	0	0.5	0.5
Partial response	30	31	30
Stable disease	40	37	31
Progressive disease	18	18	17
Not determinable	13	14	23
Overall response rate (% of patients (95% CI))	30 (24–37)	32 (25–38)	30 (24–36)
Survival			
Median (months (95% CI))	9.8 (8.6–11.2)	10.0 (9.0–12.5)	9.5 (8.3–11.0)
1-year (% surviving)	37	43	37
Median time to progression (months (95% CI))	5.3 (4.4–6.3)	5.5 (4.6–6.4)	4.6 (3.9–5.6)

CI: confidence interval.

Table 3 Medical resource utilisation for each treatment group and unit costs

Medical resource	Gem/Cis	Pac/Carbo	Vin/Cis	Unit cost (€)
Drug administration (administration days per patient)				
Outpatient	12.1	4.2	13.0	63.72
Inpatient	0	0	0	389.67
Hospitalisations (% patients)				
Febrile neutropenia	0.5	1.0	3.0	2910.23
Thrombocytopenia	3.3	0.7	0.05	4790.65
Vomiting	6.6	0.5	12.6	2492.00
Neuropathy	4.0	29.8	7.0	3253.00
Anaemia	17.7	6.1	19.2	3393.64
Neutropenia	38.1	50.3	64.6	2910.23
Renal failure	0.5	0	5.0	27,481.17 ^a
Other medical resources				
Radiotherapy (% patients)	23.3	23.3	23.3	2845.00
Packed red blood cell transfusion (% patients)	10.7	4.5	13.4	103.25
Platelet transfusion (% patients)	2.4	0	0	21.24
Laboratory tests (% patients)	22.0	5.5	19.4	
Average no. of tests performed per patient	2.9	3.8	3.1	4.02
Concomitant medications (units per patient)				
Dexamethasone	38.6	14.0	48.5	0.07
Ranitidine	5.9	7.6	8.8	3.38
Ondansetron	44.2	31.1	43.8	14.75
Furosemide	2.0	4.2	2.1	0.06
Pheniramine maleate	12.4	27.0	6.2	0.31
Ciprofloxacin	5.1	3.7	4.7	2.93
Filgrastim	0.6	1.4	2.3	141.77
Erythropoietin	3.3	1.0	3.8	180.66
Tramadol	10.4	4.3	6.0	0.76
Ketorolac trometamol	12.9	6.5	7.5	1.04
Heparin	4.2	3.7	9.4	10.9
Betamethasone phosphate	22.9	22.2	5.1	0.09
Chemotherapy				
Platinum agent (vials required per patient)				
450 mg vials	0	4.23	0	195.82
50 mg vials	8.04	25.38	9.75	18.02 (Cis); 21.59 (Carbo)
25 mg vials	4.02	0	3.25	9.41
10 mg vials	4.02	0	3.25	6.44
Novel agent (vials required per patient)				
1000 mg vials	16.08	0	0	137.75
200 mg vials	16.08	0	0	28.58
100 mg vials	0	16.92	0	276.77
50 mg vials	0	0	13.0	94.92
30 mg vials	0	4.23	0	131.34

^a Dialysis cost per 9.73 months (mean survival time across treatment arms).

(Table 4). It is clear that the major cost driver in the treatment of NSCLC is chemotherapy acquisition costs and that other resource use in the trial generally did not have a significant impact on the conclusions. The largest effect on costs was produced by varying the hospitalisation rates for the adverse events: total treatment costs per patient varied from €6134 to €9688 (Gem/Cis), from

€8765 to €11,538 (Pac/Carbo), and from €5197 to €9341 (Vin/Cis). Changes to hospitalisation costs also affected costs for Vin/Cis, which ranged from €8866 to €9773 per patient, but had little effect on Pac/Carbo costs (€10,932 to €11,475 per patient) or Gem/Cis costs (€7862 to €8326 per patient). Similarly, changes in the costs of concomitant medications had a clear impact on Pac/Carbo

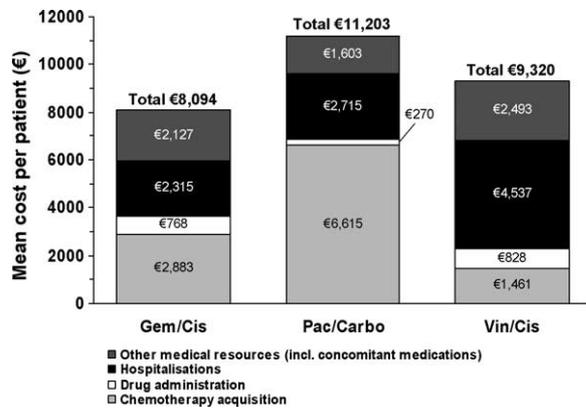


Fig. 1 Mean treatment-related costs per patient for each treatment group.

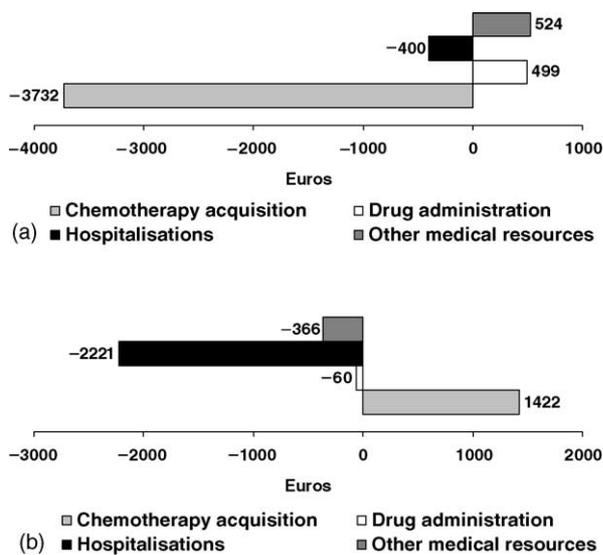


Fig. 2 Differences in cost (€) per patient between (a) Gem/Cis and Pac/Carbo and (b) Gem/Cis and Vin/Cis treatment groups, by medical resource.

results (€10,448 to €11,958 per patient) but little effect on the other treatment groups.

4. Discussion

Cost-minimisation analysis compares the costs of different treatment options under the assumption that the clinical outcome of the compared treatments or interventions is equivalent. It therefore focuses on comparing the cost of the treatment only, not the outcomes. Using this form of analysis, the treatment of choice is the option with the lowest overall cost. In the randomised trial in advanced NSCLC patients by Scagliotti et al. [9], there were no statistically significant differences between the three treatments (Gem/Cis, Pac/Carbo, Vin/Cis) in terms of progression-free or overall survival. Therefore, cost-minimisation was the appropriate form of economic evaluation. However, it should be noted that in the trial performed by Scagliotti et al. [9] there were some statistically significant differences between regimens with regard to quality-of-life endpoints. These differences raise the possibility of performing a cost-utility analysis using the study data. However, a cost-utility analysis was considered beyond the scope of the current analysis and was not performed as part of the present study.

The results of this retrospective economic analysis show that Gem/Cis was associated with lower total treatment costs than Pac/Carbo and Vin/Cis in the treatment of advanced NSCLC in Italy. Although the cost of chemotherapy was a major driver of the overall treatment costs for these platinum-based combination regimens, the costs of hospitalisations and other medical resources were also important

Table 4 Sensitivity analysis of mean total treatment costs for the three treatment groups

Sensitivity analysis	Mean total treatment costs (€) Gem/Cis	Mean and incremental total treatment costs (€)	
		Pac/Carbo (difference from Gem/Cis)	Vin/Cis (difference from Gem/Cis)
Base case	8094	11,203 (+3109)	9320 (+1226)
Hospitalisation rates (all 100%)	9688	11,538 (+1850)	9341 (-347)
Hospitalisation rates (all 9%)	6134	8765 (+2631)	5197 (-937)
Hospitalisation costs +10%	8326	11,475 (+3149)	9773 (+1447)
Hospitalisation costs -10%	7862	10,932 (+3070)	8866 (+1004)
Cisplatin administered on day 1 of cycle	7838	11,203 (+3365)	9320 (+1482)
Drug admin costs +10%	8171	11,230 (+3059)	9403 (+1232)
Drug admin costs -10%	8017	11,176 (+3159)	9237 (+1220)
Concomitant meds costs +10%	8527	11,958 (+3431)	9647 (+1120)
Concomitant meds costs -10%	7661	10,448 (+2787)	8992 (+1331)
Other resource costs +10%	8162	11,270 (+3108)	9388 (+1226)
Other resource costs -10%	8026	11,136 (+3110)	9252 (+1226)

factors. The chemotherapy acquisition costs were highest for Pac/Carbo and accounted for 59% of the total costs per patient. In comparison, chemotherapy acquisition accounted for 36% of the total costs of the Gem/Cis regimen and for only 16% of the total costs of the Vin/Cis regimen.

Our findings agree with previous economic evaluations in advanced NSCLC. In a recent retrospective cost-minimisation analysis of two randomised trials [8,10], Schiller et al. [24] found that Gem/Cis was associated with lower treatment-related costs than Vin/Cis, Pac/Cis or Pac/Carbo in five European countries (France, Germany, Italy, Spain, UK). Another retrospective analysis using published clinical trial data showed that Gem/Cis was associated with lower total treatment costs than Vin/Cis or Pac/Carbo [18]. In the latter analysis, the reduced costs with Gem/Cis were due to lower chemotherapy administration costs compared with Vin/Cis and lower chemotherapy drug costs compared with Pac/Carbo.

In our analysis, all chemotherapy was administered on an outpatient basis; the chemotherapy administration costs were comparable between the Gem/Cis and Vin/Cis regimens and lower for the Pac/Carbo regimen. The main cost difference between the two cisplatin-based regimens was due to the lower costs for hospitalisation associated with adverse events in the Gem/Cis group. Previous studies have also indicated that the higher drug acquisition costs of gemcitabine regimens can be offset by a decrease in hospitalisation costs [25].

In our analysis, Pac/Carbo was more expensive in terms of total resource costs than either Gem/Cis or Vin/Cis. This is consistent with a recent economic analysis of the large Southwest Oncology Group (SWOG) trial, which reported that Pac/Carbo was significantly more expensive than Vin/Cis in patients with advanced NSCLC [26]. The major cost difference was due to the high acquisition costs of chemotherapy drugs in the Pac/Carbo regimen, which were not offset by lower costs elsewhere (such as for hospitalisations due to adverse events). Schiller et al. [24] also found that the main cost difference between Gem/Cis and Pac/Carbo was due to the higher acquisition costs of chemotherapy associated with Pac/Carbo in all five European countries studied. Indeed, Ramsey et al. [26] warned that widespread use of Pac/Carbo rather than Vin/Cis would substantially increase national expenditures for the treatment of advanced lung cancer.

Although the chemotherapy acquisition costs were much lower for the Vin/Cis regimen than the Gem/Cis and Pac/Carbo regimens, the costs for outpatient administration of the chemotherapy were

highest for this treatment group. This agrees with both economic analyses based on the clinical trial by Comella et al. [10], which found that Gem/Cis was associated with a lower total cost relative to Vin/Cis due to the higher administration costs of the latter regimen [18,24]. The analysis by Lees et al. [18] made assumptions that the use of resources such as hospitalisation, transfusion and concomitant medication would be identical in the two treatment groups. These assumptions may not be valid, however, since our analysis based on the clinical trial published by Scagliotti et al. [9] found that Vin/Cis treatment incurred higher costs associated with hospitalisation and other medical resources than either Gem/Cis or Pac/Carbo. In addition, Schiller et al. [24] found that hospitalisations provided the largest cost saving between the Gem/Cis and Vin/Cis regimens in France, Germany and Italy. Moreover, although not a consistent finding [27], some previous studies have found that Vin/Cis regimens are associated with higher toxicity and worse tolerability than Gem/Cis [10] or Pac/Carbo [17]. It must be noted that the chemotherapeutic regimens used in different clinical studies often vary in terms of dosages or mean cycle length. Both factors can have a large impact on overall treatment costs, making it difficult to compare cost results across studies.

The present study has some inevitable limitations. First, the resource utilisation data on which the analysis is based were to a certain extent protocol-driven. Although this is a recommended method for pharmacoeconomic assessment [28,29], the resource use may not accurately reflect real clinical practice. The analysis excluded protocol-driven costs where possible and focused on the main cost components. However, as patients in clinical trials are likely to be closely monitored and observed, the resource use is probably overestimated in this analysis. Second, direct non-medical costs (such as those associated with domestic help and home nursing and costs incurred by patients travelling to the clinic/hospital) and the indirect costs of lost productivity were not considered in the analysis since the study perspective was that of the national healthcare provider and it was therefore considered inappropriate to include these costs.

In contrast to many previous economic evaluations, the present analysis used outcome and resource utilisation data collected prospectively from the same source, thereby limiting selection bias. However, not all the resources documented in the clinical trial database were costed. As every drug for each patient was specifically documented, we would have had to look up the cost for hundreds

of individual drugs, many of which are similar in price. For the sake of simplicity, only the most frequently used concomitant medication or very expensive medication was costed and included in the analysis. Second-line chemotherapy and radiotherapy were not costed in the present analysis, although they were documented by Scagliotti et al. [9]. The requirements for second-line chemotherapy or radiotherapy appeared to be fairly well balanced between treatment groups [9], but no statistical analysis was performed on these data. It is possible, therefore, that the costs relating to second-line chemotherapy or radiotherapy may have influenced the results of the present analysis had they been included.

5. Conclusion

This retrospective cost-minimisation analysis has shown that Gem/Cis is associated with lower mean total costs than Pac/Carbo or Vin/Cis when used as first-line treatment for NSCLC. For decision makers with a limited budget, the Gem/Cis regimen therefore represents an efficient use of resources for patients with advanced NSCLC in Italy.

Acknowledgements

This study was supported by Eli Lilly and Company. The authors would like to thank Deirdre Elmhirst for her help in preparing the manuscript.

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