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Carboplatin plus pemetrexed offers superior cost-effectiveness compared to pemetrexed in patients with advanced non-small cell lung cancer and performance status 2

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ABSTRACT

Objective: Pemetrexed plus carboplatin offers survival advantage in first line treatment of advanced lung cancer patients with performance status of 2. We estimated the cost-effectiveness of this combined regimen compared to pemetrexed alone in a Brazilian population.
Methods: A cost-effectiveness analysis was conducted based on a randomized phase III trial in patients with advanced non-small cell lung cancer (NSCLC) and ECOG performance status of 2 (PS2), comparing doublet regimen pemetrexed plus carboplatin with pemetrexed alone. The perspective adopted was the public health care sector over a three-year period. Direct medical costs and survival time were calculated from patient-level data and utility values were extracted from the literature. Sensitivity analyses were performed to evaluate uncertainties in the results.
Results and conclusion: The combined regimen pemetrexed plus carboplatin yielded a gain of 0.16 life year (LY) and 0.12 quality-adjusted life year (QALY) compared to pemetrexed alone. The total cost was 17,674.31 USD for the combined regimen and 15,722.39 USD for pemetrexed alone. The incremental cost-effectiveness ratio (ICER) was $12,016.09 per LY gained and $15,732.05 per QALY gained. The factors with the greatest impact on the ICER are pemetrexed price and the time to progression utility value. The cost-effectiveness acceptability curve showed an upper 90% probability of pemetrexed plus carboplatin being cost-effective with a threshold between two and three GDP per capita. Our study suggests superiority of the combined pemetrexed plus carboplatin regimen in terms of efficacy as well as cost-effectiveness in advanced NSCLC patients with a poor performance status of 2.

1. Introduction

Advanced lung cancer patients have poor survival rates, especially those who present marginal or poor performance status (ECOG PS $\geq$ 2) at the time of diagnosis [1]. The performance status coefficient is a widely used method for assessing the functional status of cancer patients and it is a reliable prognosis factor in lung cancer.

While in epidemiologic surveys PS2 accounts for around 40% of lung cancer patients [2], these patients are underrepresented in clinical trials due to their higher toxicity risk or their inability to withstand aggressive treatment [3].

Current protocols recommend single-agent or platinum-combined chemotherapy as a first line of treatment for PS2 patients [4,5], based on a small number of trials that analyzed subgroups containing elderly and/or PS2 inclusion. As single-agents, vinorelbine, paclitaxel and gemcitabine offer 4.5, 1.2 and 0.6 months of survival, respectively, when compared with the best supportive care [3]. The CALGB 9730 trial indicated an overall survival gain when combining carboplatin to paclitaxel compared to paclitaxel alone (median 4.7 vs. 2.4 months overall survival; HR 0.60, 95% CI 0.40–0.91)[6]. Results for the first two dedicated PS2 trials have been recently published. The CAPPA-2 study was stopped early due to slow accrual, but showed an advantage of the doublet cisplatin and gemcitabine compared to gemcitabine alone in 57 patients (median 5.9 vs. 3 mo; HR 0.52, 95% CI 0.28-0.98) [7]. Our group recently conducted a large trial comparing pemetrexed

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and pemetrexed plus carboplatin. In that study, the platinum doublet regimen showed improved progression-free (median 5.8 vs. 2.8 mo; HR 0.46; 95% CI 0.35 to 0.63) and overall survival (median 9.3 vs. 5.3 mo; HR 0.62, 95% CI 0.46 to 0.83), despite being slightly more toxic than expected [8].

Some authors claim it is too early to decide which is the best practice for treating this PS2 subpopulation [9,10], but all agree lung cancer represents an economic burden to health care. In addition to safety and efficacy, decisions regarding treatment should also consider costs and quality of life, especially in advanced stage diseases. In this study, we conducted the first economic analysis in a head to head trial with pemetrexed in a PS2 population. We evaluated the cost-effectiveness of the combined carboplatin plus pemetrexed regimen compared to pemetrexed alone for advanced non-small cell lung cancer (NSCLC) patients with PS2 status, from the perspective of the Brazilian public health care system.

2. Methods

We estimated costs, life year (LY) and quality-adjusted life year (QALY) using patient level data and information from the literature. The setting was the Brazilian public health care system and the study timeline was set at three years.

Individual level data were obtained from a randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in the first line management of patients with advanced NSCLC and exclusively PS2 [8]. Eligible patients had cytologic or histologic confirmation of stages IIIB and IV, were chemotherapy-naïve, and a PS2 score determined by two independent oncologists. The intervention consisted of pemetrexed 500 mg/m^2 alone or pemetrexed 500 mg/m^2 plus carboplatin (AUC 5), both administered intravenously every 3 weeks for up to four cycles or until disease progression, whichever came first [8].A total of 205 patients were enrolled between April 2008 and July 2011 and followed-up until death. The primary end point was overall survival but the trial also compared progression-free survival, response rate and toxicity. At the end of the first year in the trial, 72% of patients were already deceased [8].

This was a multicenter study, with more than 70% of patients from the Instituto Nacional de Cancer and the rest from PUC-RS, Instituto do Cancer Arnaldo Vieira Carvalho, Instituto do Cancer do Ceara, Hospital Amaral Carvalho, Hospital do Cepon, Hospital Lifecenter, Hospital da Caridade de Ijui and Monte Sinai Cancer Center. The study was approved by the institutional review board of each participating institution and all patients signed an informed consent form.

2.1. Health benefits

Benefits were measured in terms of LY and QALY gained. The survival time was extracted from the trial and depicted in three states: time to progression (TTP, defined as the interval from random assignment to the first evidence of progressive disease or death), progressive disease (PD), and death. The LY gained was the sum of survival time of the TTP and PD states.

The QALYs were then calculated by weighting LY with the corresponding state utility. As quality of life measurements were not estimated in the trial, utility weights were taken from Nafees et al. [11]. Those authors defined health states associated with the treatment of stable, responsive and progressive metastatic NSCLC.

2.2. Costs

All costs were estimated for each patient as a function of the resource consumption (obtained from the clinical trial records) and unitary costs. Only direct medical costs were considered. Estimations were calculated originally in local currency units and then converted to US dollars using the purchase power parity conversion factor. The costs were discounted at an annual rate of 5% [12], which allows us to bring down the costs for year 2 and 3 to the current value.

Chemotherapy costs were based on drug dosage per milligram and the number of cycles recorded. Drug prices were the average purchase prices reported by the public sector. The costs of adverse events were calculated when grade toxicity was higher than 3 or patients needed hospitalization. Each type of adverse event was charged according to the reimbursement procedure defined by the public health care system (SUS) as many times as it occurred. We obtained reimbursement information from the DATASUS database [13]. Costs related to patient monitoring were subdivided into radiological exams, laboratorial exams and medical appointments. The basic clinical routine included one chest CT scan every two months during the therapy and one every three months until progression. The laboratorial exams include complete blood count, creatinine, urea, bilirubin, hepatic transaminases and alkaline phosphatase. Exams were done before each chemotherapy cycle and every three months until disease progression. An average of one outpatient consultation was conducted per chemotherapy cycle, plus an additional consultation per month until the end of follow-up. The costs of progressive disease care were not included in the model. A lack of information regarding the therapeutic approach used after disease progression, coupled to a small difference in the survival rate of the two groups after progression, suggest that the disease takes the same course until death, regardless of treatment. Thus, we assume that patients in both groups receive the same treatment following disease progression. This would lead to similar costs between groups, which would not affect our analysis.

The unitary values for each parameter considered in the model are listed in Table 1.

2.3. Model analyses

A total of 165 patients were included in the analyses. The economic model included only adenocarcinoma patients. At the start of the trial, pemetrexed was indicated regardless of histology. However, during the course of inclusion, pemetrexed was indicated only for adenocarcinoma, which became an eligibility criterion during the trial (diagram in Fig. 1). Missing data were not observed in variables relevant to our analysis. Due to the skewed nature of the cost distribution, differences between mean costs were calculated using the bootstrapping method with ten thousand interactions.

For each strategy, we evaluated the incremental cost-effectiveness ratio (ICER), which is the ratio between the difference of costs ($\text{Cost}_B - \text{Cost}_A$) and the difference of effects ($\text{Effect}_B - \text{Effect}_A$), in which A and B represent the two strategies compared. In our analysis, the ICER represents the incremental cost per additional LY or QALY, and a lower ICER indicates a more cost-effective strategy.

2.4. Sensitivity analysis

A full univariate sensitivity analysis was carried out to explore the impact of uncertainty in each parameter of the estimated ICER. Drug costs varied from the reference drug price to the generic drug price (50% cheaper). The unitary costs of procedures established by the SUS varied between ±20%, allowing for market price fluctuations or reimbursement adjustments.

The utility values for each health state varied according to the impact of grade III–IV adverse events (including nausea/vomiting, diarrhea, fatigue, neutropenia and febrile neutropenia) to represent implicit adverse events regarding toxicities or natural illness

Table 1
Summary of parameters and the range used in the sensitivity analysis.

Parameters	Range			Reference
	Baseline	Low	High	
Discount rate	0.05	0	0.1	[12]
Unitary costs (US$)				
Hospitalization costs (every 4 days)	241.74	193.39	290.08	[13]
Pemetrexed cost (per mg)	5.76	2.88	5.76	[17]
Carboplatin cost (per mg)	0.23	0.12	0.28	[17]
Computed tomography, thorax	89.74	71.79	107.69	[13]
Laboratorial exams	10.43	8.34	12.51	[13]
Medical appointment	6.58	5.26	7.89	[13]
Adverse event management (grade 3 to 5)	Each toxicity has a cost	−20%	+20%	[13]
Effective parameters				
Time to progression state utility	0.65	0.31	0.67	[11]
Progression state utility	0.47	0.43	0.47	[11]

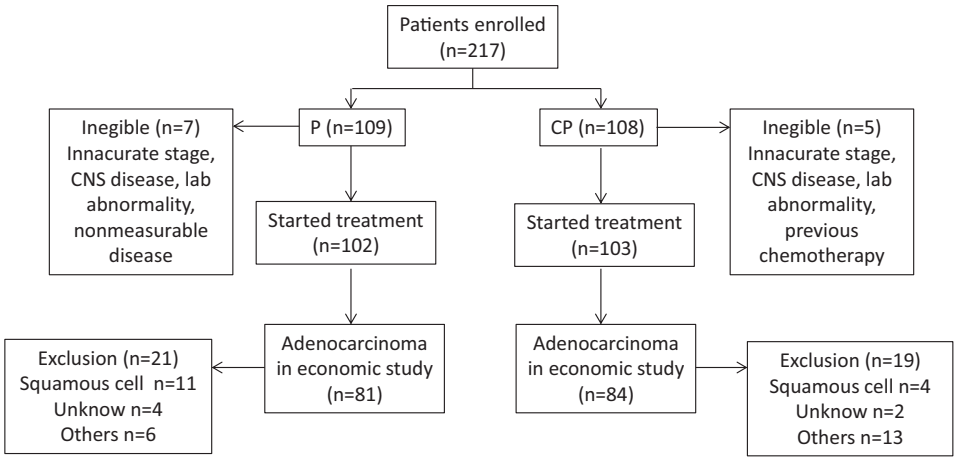

Fig. 1. CONSORT diagram showing patient registration, treatment and assignments, and exclusions to input on economic model. CP: carboplatin + pemetrexed; P: pemetrexed.

decline. Based on Nafees et al. [11], the minimal point of the TTP state was estimated by declining the base utility value with disutility values from adverse events. The maximum value came from adding an additional utility gain to the base value for responsiveness to chemotherapy. The range of PD utility was estimated based on the standard error [11].

We also performed a scenario analysis comparing the cost of a 500 mg vial of pemetrexed in the United Kingdom (£800) [14], USA (3,000 USD) [15] and Canada (2,145 CAN) [16] with the Brazilian price (R$ 4,376) [17].

We also explored sampling uncertainty, given that single samples are a very common concern in clinical trials. The bootstrapping technique was used to resample likely samples 10,000 times in order to redefine the ICER point estimate and its confidence interval. Also, a cost-effectiveness acceptability curve (CEAC) was constructed based on ceiling ratios to better establish the value of therapy according to willingness-to-pay.

3. Results

The summary model results for the base-case analysis are shown in Table 2. The combined therapy group received more chemotherapy cycles, resulting in the highest cost treatment. Even though the cost of carboplatin is not excessively high, it can result in additional costs due to its toxicity (78 against 51 adverse events, grades 3–5). The treatment of adverse events was charged differently, depending on the type of management implemented, but the combined regimen showed a higher mean cost overall. When

Table 2
Summary of costs and the incremental cost-effectiveness ratio between pemetrexed and carboplatin plus pemetrexed in advanced lung cancer patients with PS2.

	P (*n* = 81)	CP (*n* = 84)
Outcomes		
Number of cycles, mean	3.2	3.5
Number of adverse events, grade 3 to 5	51	78
Time to progression stage, survival mean (months)	4.1	7.3
Progression disease stage, survival mean (months)	4.4	3.3
Lifetime costs, mean (US$, 2012)		
Chemotherapy treatment	15,080.78	16,960.00
Adverse event - treatment	105.28	122.28
Adverse event - hospitalization	211.89	149.65
Radiological exams	213.83	314.10
Laboratorial exams	51.62	59.59
Medical appointments	60.19	73.23
Total cost, mean	15,722.37	17,674.29
Incremental cost	1,951.92	
Effectiveness		
LY gained, mean	0.71	0.88
Incremental LY	0.16	
QALY gained, mean	0.40	0.52
Incremental QALY	0.12	
Incremental ratio (Cost/Effect)		
ICER (US $/LY)	12,016.08	
ICER (US $/QALY)	15,732.04	

P: Pemetrexed strategy; CP: Carboplatin plus Pemetrexed strategy; LY: Life Year; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio.

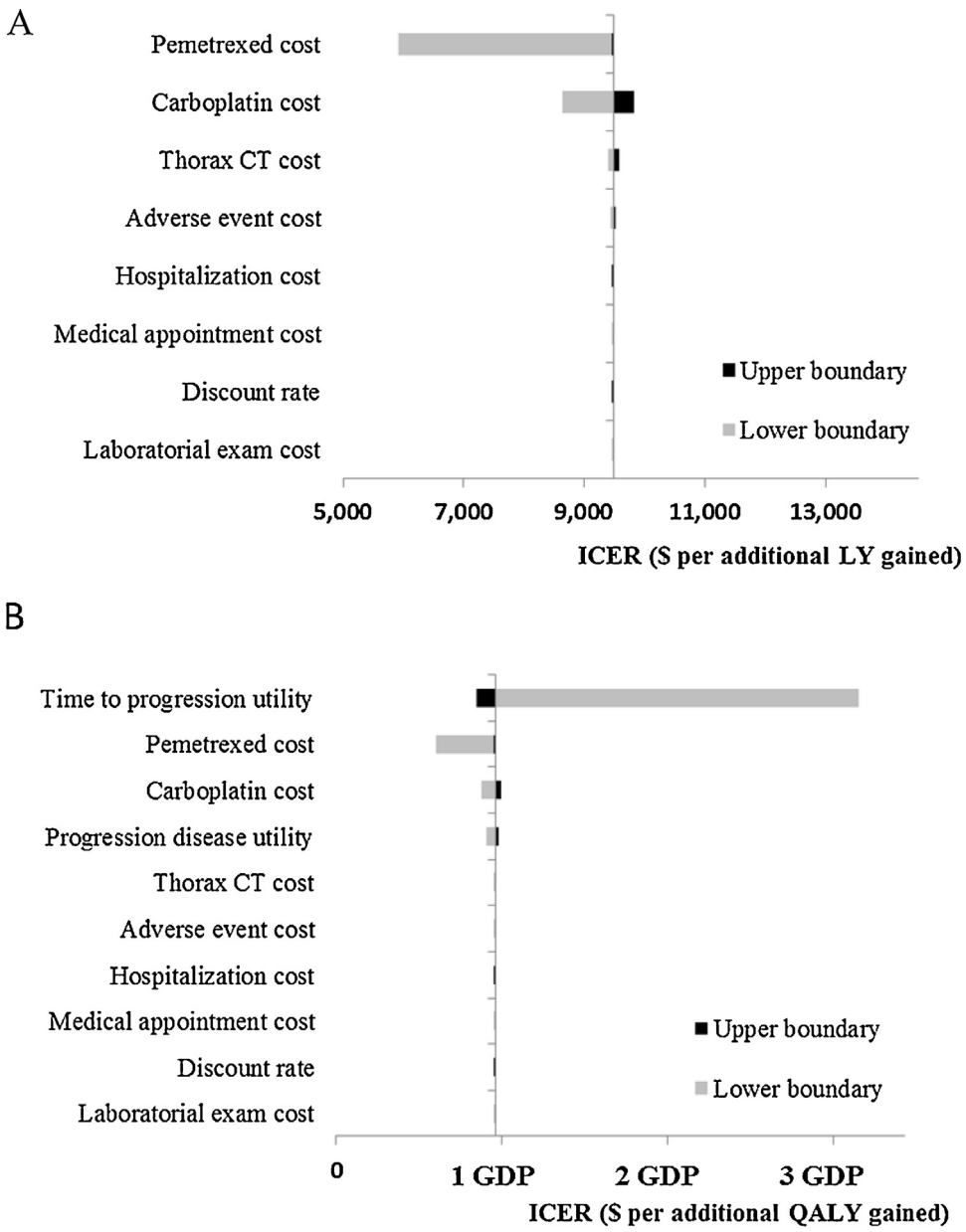

Fig. 2. Tornado Diagram showing the effects of each variable on estimated ICER and the upper (black bars) and lower (gray bars) boundaries. A. Influential on ICER cost per LY gained; B. Influential on ICER cost per QALY gained. CT: Computed tomography; GDP: Gross Domestic Product per capita; LY: Life Year; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio. One GDP per capita is 14,551 USD.

patients required hospitalization due to adverse events, costs were recorded as the sum of procedures and inpatient care. The mean number of inpatient days recorded was eight days for the pemetrexed group and seven days for the combined treatment group. Follow-up costs (e.g., clinical and imaging exams) differed between arms because survival time was longer for patients in the combined therapy group. The estimated ICER for pemetrexed plus carboplatin compared with pemetrexed was US$ 12,016.09 per LY gained and US$ 15,732.05 per QALY gained.

3.1. Sensitivity analysis results

Drug costs had the greatest impact on the estimated ICER, especially pemetrexed costs (Fig. 2). In the scenario analysis, where the cost of pemetrexed varied between the reference countries (USA, Canada and UK), the ICER was linearly correlated with the cost, as show in Fig. 3.

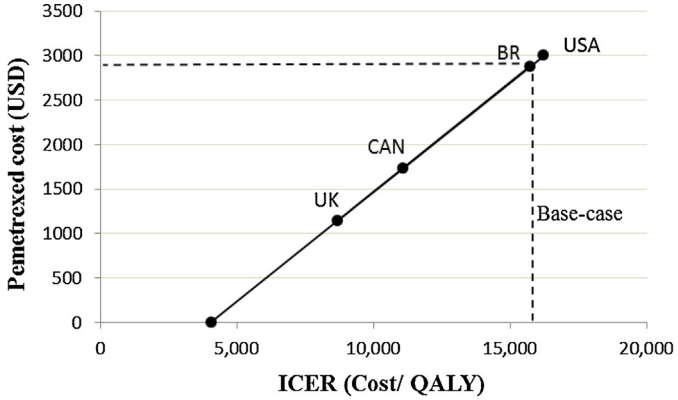

Fig. 3. One-way sensitive analysis of pemetrexed cost (500 mg vial). Base-case stated an ICER of $15,732.04 per quality-adjusted life year gained and pemetrexed cost equal to 2880 USD.

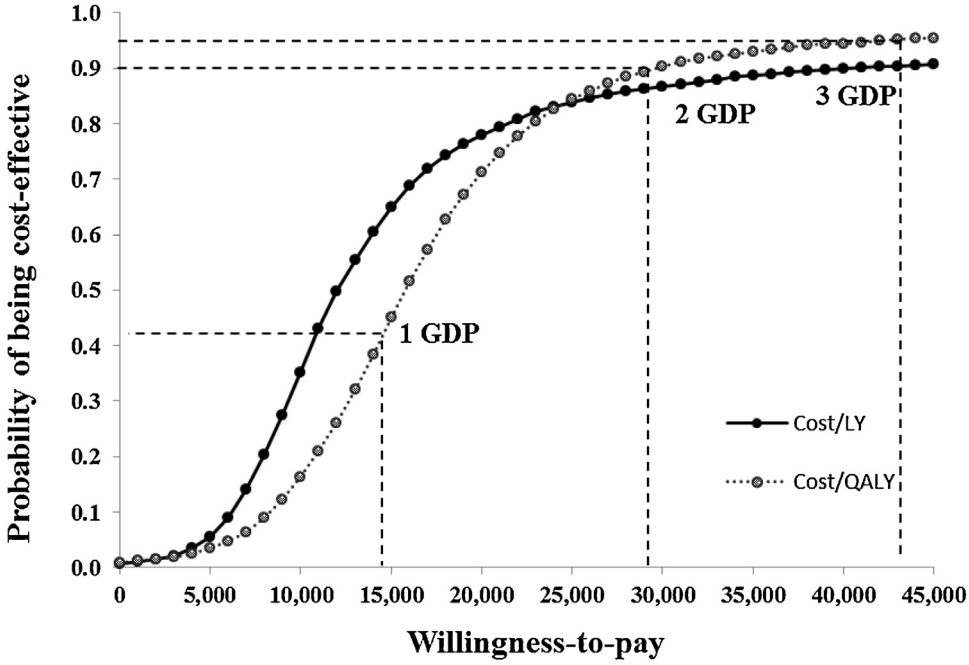

Fig. 4. The cost-effectiveness acceptability curves showing the chance of obtaining net benefits with the combined strategy compared to the single-agent strategy, at different willingness-to-pay thresholds in advanced lung cancer patients with PS2. GDP: Gross Domestic Product per capita; LY: Life Year; QALY: Quality-Adjusted Life Year. One GDP per capita is 14,551 USD.

However, when we analyzed the ICER for QALY, the TTP state utility was clearly the dominant variable in the model. This variable directly affects the effectiveness results, since TTP survival is the main effective difference between the arms. Fig. 2 presents a Tornado Diagram illustrating how each variable affected the ICER value. In a scenario where the TTP utility value would have been half the base-case value, the ICER would have doubled.

The bootstrapping method provided a comprehensive assessment of sampling uncertainty. The new mean ICER point estimate was US$11,034.86/LY ($CI_{95\%}$ 3,185.99–59,442) and US$16,571.61/QALY ($CI_{95\%}$ 2,320.77–45,824.87) after 10,000 interactions using the Monte Carlo simulation.

The CEAC shows the probability of cost-effectiveness of carboplatin plus pemetrexed over pemetrexed alone at various willingness-to-pay (WTP) thresholds (Fig. 4). Since the Brazilian government has not defined a value that determines whether a treatment is cost-effective (e.g., cost per QALY gained), we used the values established by the WHO, which is between one and three times the country's gross domestic product per capita (GDPpc). Using the value of the 2012 Brazilian GDPpc of US$ 14,551 (one GDPpc), the doublet regimen exhibited a 42% probability of being cost-effective. But when the WTP threshold reaches two or three times the GDPpc value, the doublet regimen had a probability of 90%–95% of being cost-effective.

4. Discussion

In the present study, we compared the cost-effectiveness of pemetrexed and carboplatin plus pemetrexed as the first line treatment for NSCLC patients with PS2. To the best of our knowledge, this is the first cost-effectiveness analysis in a dedicated NSCLC PS2 trial. Our data indicate that relative to pemetrexed alone, pemetrexed plus carboplatin is more likely to be cost-effective, considering a threshold of 3 GDPpc in the Brazilian context studied.

New drugs continuously become available to clinics, but only modest changes in the prognosis of advanced lung cancer patients have been achieved. Particularly in patients with poor performance status, oncologists disagree on whether to treat patients with chemotherapy or supportive care. Recent guidelines have highlighted the benefits of treating the PS2 population, but not patients with PS3 status or higher [4,18]. Clinical trials that analyzed the PS2 subpopulation separately indicated the benefits of using single drugs or a combined cisplatin plus paclitaxel regimen. In contrast with our PS2 dedicated study, all these trials were designed to include advanced disease, and PS2 patients were tested only in subgroup analyses.

One advantage of our study is the prospective cost data, which was collected at least until progression. The model was based on our previous multicenter trial conducted in Brazil and the US, in which more than 90% of patients were Brazilian [8]. Therefore, this model was run from the Brazilian public health care payer's perspective and included direct costs for drug acquisition, management of adverse events, hospitalization and patient monitoring. Although the trial originally included other histology types, our economic model included only adenocarcinoma patients, as described in Section 2.

Chemotherapy administration costs were not considered because reimbursement for chemotherapy in Brazil includes professional hours, overhead and any supplies inherent to protocols based on fixed values. The two interventions have not yet been incorporated into reimbursement values, but if that should happen, the charges would be adjusted to the drug regimen costs.

The model revealed an additional health benefit of 0.16 LY gained and 0.12 in QALY gained at an incremental cost of US$ 1,951.92 for the combined treatment. This marginal increment of health benefits is extremely relevant for this population, especially considering the improvement in TTP stage, which is the principal difference between the arms and provides a real clinical value to patients.

According to the World Health Organization, interventions are considered cost-effective if the cost per QALY gained is between 1 and 3 GPDpc [19]. Therefore, the combined treatment has high chances of being cost-effective. At a willingness-to-pay of 1 GDPpc (US$ 14,551), the probability of combined regimen being

cost-effective was 42%, but for 2 GDPpcs, the probability increased to 90%. The ICER point estimate was US$15,732.05 per QALY gained, a value close to 1 GDPpc. The Monte Carlo simulation showed the ICER interval to be below 3 GDPpcs (with 95% nonparametric confidence intervals), which is a robust result and confirms that the treatment is cost-effective.

The one-way sensitivity analyses highlighted the two most influential parameters that impact the ICER: time to progression utility and pemetrexed cost. When the quality of life decreased at the minimal point estimated in patients with the TTP state, the ICER was not cost-effective. However, the utility range considered a decrease in quality of life with the worst-case scenario (i.e., all adverse events happening together: disutilities of neutropenia, fatigue, nausea/vomiting, diarrhea and febrile neutropenia). In reality, the worst utility value has a low probability of occurring, but these results highlight that quality of life has a huge impact on health and that its improvement should be the target of new proposals. The main cost driver in our analysis was the cost of pemetrexed. Our study considered the reference price set by Eli Lilly before the Brazilian patent break from mid 2012. However, in our sensitivity analysis, we considered the new price implemented at the end of 2012, when pemetrexed cost was reduced in half and the ICER dropped 38%. The scenario analysis compared the Brazilian price of pemetrexed (base-case) with the price in the USA, Canada and the UK. Results suggest that our findings may be applicable to other health care systems. Of note, Canada and the UK have a lower pemetrexed price than Brazil, even without patent breaks. We speculate that the expiration of the patent in the US, Canada and UK would strengthen the case for the cost-effectiveness of pemetrexed plus carboplatin.

The model calculated chemotherapy costs per milligram consumed. However, in an analysis considering drug wastage, where costs are based on vial costs, chemotherapy costs increased by approximately 20% (where mean cost per mg was US$ 15,080.80 and US$ 16,960.02, becoming US$ 18,769.75 and US$ 20,088.72 for pemetrexed and the combined regimen, respectively). In fact, drug wastage is a reality in the pharmacy routine that depends on many factors, such as chemotherapy schedule and number of patients per day. If we considered drug wastage in our analysis, some routine assumptions could have been made, but these would only be assumptions. So, we kept the exact mg dosage in our drug calculation.

Our data have some limitations. First, we express our results in two primary health outcomes, LY and QALY gain. Since the trial did not measure utility value, we obtained utility values from Naffees et al. [11]. Brazil still does not have records of societal utility values or lung cancer states. Although our population behavior and health care characteristics are different from those of the UK, their study had appropriate utility values for the lung cancer stages used in our model. Also, it is important to generate QALY data from our population in order to compare these measurements across therapies and geographic areas. Also, reliance on a single trial to determine clinical effectiveness may be seen as a limitation of the economic model, but this was the first economic analysis conducted with a PS2 dedicated trial, which we believe represents an important contribution to the literature. Finally, performance status is a strong prognostic factor but comparable data were not available, even for different PS populations.

To the best of our knowledge, this is the first study to evaluate the cost-effectiveness of first-line chemotherapy in advanced lung cancer patients with PS2. Our results suggest that the combination of pemetrexed plus carboplatin is superior to pemetrexed alone. These data contribute to previously published efficacy results that have already been considered in treatment guidelines. Lower drug costs would facilitate the adoption of this strategy by different health systems, particularly in developing countries.

Conflict of interest

None declared.

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