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ORIGINAL ARTICLE

Healthcare resource utilization and associated cost analysis of the PROCLAIM study in patients with stage III non-small-cell lung cancer

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ABSTRACT

Objective: To analyze patient-reported swallowing difficulties, healthcare resource utilization and associated costs during the PROCLAIM study.

Methods: Patients with stage III non-squamous non-small cell lung cancer received pemetrexed-cisplatin (PemCis) combined with concurrent thoracic radiotherapy followed by consolidation pemetrexed, or concurrent chemoradiotherapy with etoposide-cisplatin (EtoCis) followed by standard consolidation chemotherapy. Patient-reported swallowing function was measured using diaries. Resource utilization (hospitalizations, transfusions, concomitant medications) was compared between treatment arms using Fisher's exact test and independent *t*-test. Medical resource use costs were analyzed using nonparametric Wilcoxon rank sum test.

Results: Patient-reported difficulty in swallowing function (diary score $\geq$4) was 33.8% in the PemCis arm and 29% in the EtoCis arm. Overall resource use, including hospitalizations, was similar between treatment arms; however, fewer patients in the PemCis arm received transfusions and selected concomitant medications. Concurrent phase analyses were consistent with the overall study. A significantly lower percentage of patients (31.1% vs. 40.8%) were hospitalized in the PemCis arm. Total costs were significantly higher in the PemCis arm. Other medical costs (excluding study treatment costs) during the concurrent phase were lower for patients in the PemCis arm, due to significantly lower hospitalization costs and lower use of concomitant medications. Subgroup analysis yielded similar results.

Conclusions: Patient-reported difficulty in swallowing post-baseline and resource utilization were consistent with previously reported safety outcomes. In the overall study, higher total costs for PemCis were driven by study drug cost. When adjusting for treatment duration, other monthly medical costs were favorable to PemCis. Patients on pemetrexed remained longer on therapy, suggesting better tolerability.

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PROCLAIM; pemetrexed; resource utilization; cost analysis; Stage III NSCLC

Introduction

Lung cancer is the leading cause of cancer-related mortality, causing >1.6 million deaths worldwide[1]. Around 80%–85% are cases of non-small-cell lung cancer (NSCLC) with one-third with locally advanced disease at diagnosis[2,3]. Standard of care for patients with inoperable stage III NSCLC with good performance status (PS) is concurrent platinum-based doublet chemoradiotherapy. The ideal concurrent chemotherapy regimen has not been determined. The prognosis after concurrent chemoradiotherapy is still poor; thus, there is a need for more effective and less toxic regimens. The role of consolidation therapy remains controversial[4]. The estimated lung cancer treatment costs in the first year post-diagnosis are around $60,000 and $8000 per year thereafter, with an increase of >$90,000 during the last year of survival[5].

Pemetrexed, a multitargeted antifolate, combined with cisplatin is a standard of care for advanced non-squamous NSCLC. Pemetrexed–cisplatin (PemCis) has a relatively well tolerated safety profile when administered at full systemic dose with definitive thoracic radiotherapy (TRT)[6–9]. In the

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PROCLAIM phase 3 study, PemCis combined with concurrent TRT followed by consolidation pemetrexed did not demonstrate superior survival when compared to the etoposide-cisplatin (EtoCis) with concurrent TRT followed by standard consolidation chemotherapy for stage III unresectable non-squamous NSCLC[10]. The study showed a significantly lower incidence of possibly treatment-related grade 3 to 4 adverse events (AEs), including neutropenia, in the PemCis arm during the overall treatment period. In the concurrent phase, the incidence of grade 3 to 4 neutropenia and febrile neutropenia was significantly lower in the PemCis arm. Significantly lower occurrence of any grade of thrombocytopenia was also observed in the PemCis arm[10]. A slightly higher percentage of patients in the PemCis arm compared to EtoCis arm had grade 2 to grade 4 dysphagia during the overall study. More patients completed the planned concurrent treatment in the PemCis arm and received consolidation treatment. Patients in the PemCis arm were planned to stay longer on treatment per study design (4 cycles of consolidation vs. 2 cycles in the control arm)[10].

The primary objective was overall survival. Secondary objectives of the PROCLAIM study were progression-free survival (PFS); overall response rate (ORR); safety[10]; patient-reported swallowing function post-baseline; and healthcare resource utilization including hospitalizations, transfusions and concomitant medications used during the study. Here, we present swallowing diary outcomes, healthcare utilization and cost analysis data. Associated costs related to study treatment and resource utilization were estimated and compared for each treatment arm, for the respective concurrent or consolidation study phases.

Methods

Patients with stage IIIA/B unresectable NSCLC and Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1 were randomized (1:1) to receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 intravenously every 3 weeks (q3w) for three cycles plus concurrent TRT (60–66 Gy) followed by pemetrexed consolidation q3w for four cycles (arm A: PemCis), or standard therapy with etoposide 50 mg/m^2 and cisplatin 50 mg/m^2 intravenously, q4w for two cycles plus concurrent TRT (60 to 66 Gy) followed by two cycles of consolidation platinum-based doublet chemotherapy (Arm B: EtoCis). Patients in Arm A received premedication, including folic acid and vitamin B12, according to the pemetrexed label. This study protocol was approved by each institution's ethics review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before any study-related treatment or procedures commenced. The PROCLAIM study was registered with the National Institutes of Health clinical trial registry at www.clinicaltrials.gov as #NCT00686959. All analyses presented here were conducted in the randomized and treated population with the exception of the swallowing diary analysis which was done on the randomized population.

Patient swallowing function was measured with a diary using a 5 point categorical scale defined per protocol: (1) no problems; (2) mild soreness; (3) swallowing solids with some difficulty; (4) inability to swallow solids; and (5) inability to swallow liquids. Patients rated their swallowing condition over the previous 24 hour period. The swallowing diary was completed weekly on the last day of the week during TRT, immediately prior to the consolidation phase, on days 8 and 29 during consolidation therapy, and at months 6, 9 and 12 during the follow-up period. The compliance rate was calculated by dividing the number of completed swallowing function diaries by the number of possible diaries multiplied by 100.

Fisher's exact test was used to compare the proportion of patients with post-baseline swallowing diary score $\geq$4 between treatment arms. Frequency distribution and summary of the number of completed assessments by treatment arm were obtained.

Details of hospitalizations, blood transfusion and selected concomitant medication use were collected during the treatment period and within 30 days from study treatment discontinuation (overall study). Granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage CSF (GM-CSF) administration were permitted for patients with febrile neutropenia, grade 4 neutropenia or documented infections while neutropenic, based on investigator's judgment. Use of G-CSF was to be discontinued at least 24 hours prior to next chemotherapy cycle and was contraindicated during chest radiotherapy because of complications and mortality[11]. Concomitant use of erythropoietic agents was permitted. Between-treatment-arm analyses were done using Fisher's exact test and independent *t*-test.

Unit costs were applied to patient-level resource use (study drug, hospitalizations, radiotherapy, selected concomitant medications, laboratory tests and other procedures) to estimate total direct costs to a third party US payer. Costs were summarized for each treatment phase separately, and for the overall treatment period (sum of the costs of the concurrent and consolidation phases) until treatment discontinuation. Here, we will focus on concurrent and overall study costs since consolidation is not provided as a standalone treatment in clinical practice. Costs incurred in the recovery period (in between treatment phases) were not included in this analysis. Unit costs (in 2015 US dollars) were derived from publicly available sources. Costs associated with the study drugs cisplatin, pemetrexed, etoposide, carboplatin, paclitaxel and vinorelbine were applied based on the dose (mg) received. Administration costs were applied each time that a patient received treatment. For each pemetrexed administration, a flat cost was applied to account for required pretreatment concomitant medication. Acquisition costs were obtained from the Red Book[12]; administration costs were from the Resource-based Relative Value Scale[13]. "Other medical costs" included costs associated with hospitalizations, radiotherapy, supportive care, concomitant medications, laboratory/evaluation/radiology visits and blood products. Per-day hospital costs were estimated from the Healthcare Cost and Utilization Project[14] data, which

provides a nationally representative average cost and length of stay for any hospitalization type. Supportive care included administration for pulmonary function tests or oxygen (intermittent or continuous), insertion of a gastric feeding tube, administration of intravenous fluid, esophageal dilation and endoscopy. Categorized concomitant medications included analgesics, antiemetics, anti-infective agents, erythropoietic agents, and G-CSF or GM-CSF[10]. Dosage of concomitant medications was assumed based on each medication's prescribing information. Duration of use was defined as per label for controlled substances and using the start and end date of medication for all other treatments.

Adverse-event-related costs are those associated with management of AEs and may include concomitant medications, hospitalizations and blood products that were needed to treat the AE; thus, these costs could also appear in other categories.

Costs were compared using the nonparametric Wilcoxon rank sum test; sensitivity analyses were conducted. A subgroup analysis was performed excluding patients with unusually long hospitalizations (exceeding the 95% threshold of length of stay).

Results

In the PROCLAIM study, 283 patients were randomized and began treatment with PemCis (Arm A) and 272 patients began treatment with EtoCis (Arm B) comprising the safety population.

Randomized patients with at least one post-baseline swallowing diary score were included in the analysis of patient-reported swallowing function (284 patients in the PemCis arm; 269 in the EtoCis arm) with a mean number of assessments of 13.4 (standard deviation; SD = 5.4) in the PemCis arm and 11.4 (SD = 5.5) in the EtoCis arm. Compliance rates for completed swallowing diaries were similar in both treatment arms (mean [SD] of 80.8% [25.1] in the PemCis arm vs. 78.4% [32.7] in the EtoCis arm). Swallowing difficulty, as defined by reporting difficulty in swallowing liquids or solids (score $\geq$4) at any time post-baseline during the study, was 33.8 % of patients in the PemCis arm (95% CI: 26.7, 37.5) and 29.0 % in the EtoCis arm (95% CI: 21.3, 31.7) with a p value of .15 during the overall study[10].

Hospitalizations during the overall study were similar between the two treatment arms (Table 1). However, a lower percentage of patients (31.1% vs. 40.8%) were hospitalized in the PemCis arm compared to the EtoCis arm during the concurrent phase of the study, including patients hospitalized due to drug-related AEs. In the concurrent phase as well as during the overall study, patients in the PemCis arm had longer hospital stays compared to the EtoCis arm (concurrent: 11.1 vs. 9.7 average days; overall: 13.1 vs. 9.5 average days, Table 1).

The most common possible treatment-related AE leading to hospitalization in both treatment arms during the overall study, and in the concurrent phase, was esophagitis (PemCis: 7.8% and 7.4%, respectively; EtoCis: 7.7% in both treatment periods). In the overall study, febrile neutropenia was the second most frequent cause of hospitalization in both treatment arms (PemCis: 2.5%; EtoCis: 4.8%).

A lower percentage of patients received one or more transfusions in the PemCis arm compared to the EtoCis arm but the total number of transfusions was similar in both arms during the concurrent phase and the overall treatment period (Table 2).

A similar number of patients in each arm received any selected concomitant medications, including antiemetics, analgesics and systemic anti-infective drugs, during the concurrent phase and the overall treatment period (Table 3). A lower percentage of patients received concomitant erythropoietic agents in the PemCis arm compared with the EtoCis arm (concurrent phase:1.1% vs. 3.7%; overall study: 3.2% vs. 7.7%, a statistically significant difference) (Table 3). The percentage of patients administered G-CSF / GM-CSF during both concurrent phase and overall study was significantly lower in the PemCis arm compared to the EtoCis arm.

Total costs, and study treatment costs, were both significantly higher (p value <.0001) in the PemCis treatment arm for the concurrent phase, consolidation phase and overall treatment period (Table 4, Supplementary Table 1). However, other medical costs, including costs associated with selected concomitant medications, hospitalizations, supportive care and blood products, were lower in the PemCis treatment arm than in the EtoCis arm during the concurrent phase and were similar in the two arms while combining costs of concurrent and consolidation phases. The hospitalization costs in the PemCis arm were significantly lower in the concurrent phase; however, costs were comparable across arms during the overall study, mainly because patients who received PemCis remained longer in the study (median of 4.5 months

Table 1. Study hospitalizations.

	Overall study		Concurrent phase	
	PemCis $N = 283$	EtoCis $N = 272$	PemCis $N = 283$	EtoCis $N = 272$
Patients with $\geq$1 hospitalization[a], ***n*** (%)	127 (44.9)	136 (50.0)	**88 (31.1)**	**111 (40.8)**
Due to AEs related to study drug	82 (29.0)	77 (28.3)	59 (20.8)	64 (23.5)
Due to AEs not related to study drug	64 (22.6)	81 (29.8)	**37 (13.1)**	**54 (19.9)**
Total number of hospitalizations	200	204	116	143
Duration per admission/hospitalization				
Average days (standard deviation)	**13.1 (17.4)**	**9.5 (9.2)**	11.1 (12.3)	9.7 (9.1)
Median (range) in days	8.0 (1.0–181.0)	7.0 (1.0–68.0)	7.0 (1.0–73.0)	7.0 (1.0–68.0)

Abbreviations. AEs, Adverse events; EtoCis, Etoposide, cisplatin and concurrent thoracic radiation therapy, followed by consolidation with cytotoxic chemotherapy of choice; PemCis, Pemetrexed, cisplatin and concurrent thoracic radiation therapy followed by consolidation pemetrexed.
[a]Patients could have been admitted for multiple AEs.
Statistically significant differences are shown in bold text and are based on p value <.05 determined by Fisher's exact test.

Table 2. Patients who received transfusions.

	Overall study		Concurrent phase	
	PemCis $N = 283$	EtoCis $N = 272$	PemCis $N = 283$	EtoCis $N = 272$
Patients who received ≥ 1 transfusion, *n* (%)	66 (23.3)	78 (28.7)	38 (13.4)	50 (18.4)
Transfusions, *n* (%)				
Fresh frozen plasma	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.4)
Packed red blood cells	64 (22.6)	74 (27.2)	35 (12.4)	47 (17.3)
Platelets	9 (3.2)	5 (1.8)	8 (2.8)	3 (1.1)
Whole blood	5 (1.8)	2 (0.7)	3 (1.1)	2 (0.7)
Total number of transfusions	163	151	81	76

Abbreviations. EtoCis, Etoposide, cisplatin and concurrent thoracic radiation therapy, followed by consolidation with cytotoxic chemotherapy of choice; PemCis, Pemetrexed, cisplatin and concurrent thoracic radiation therapy followed by consolidation pemetrexed.

Table 3. Patients who received selected concomitant medications during study treatment or within 30 days of discontinuation[12].

	Overall study		Concurrent phase	
	PemCis $N = 283$ *n* (%)	EtoCis $N = 272$ *n* (%)	PemCis $N = 283$ *n* (%)	EtoCis $N = 272$ *n* (%)
Patients who received any concomitant medication	274 (96.8)	259 (95.2)	270 (95.4)	253 (93.0)
Antiemetics	222 (78.5)	207 (76.1)	221 (78.1)	203 (74.6)
Serotonin (5HT3) antagonists	208 (73.5)	191 (70.2)	206 (72.8)	185 (68.0)
Other, including NK1 antagonists	152 (53.7)	136 (50.0)	149 (52.7)	133 (48.9)
Analgesics	215 (76.0)	213 (78.3)	204 (72.1)	197 (72.4)
Non-steroidal anti-inflammatory agents	83 (29.3)	87 (32.0)	71 (25.1)	71 (26.1)
Opioids	158 (55.8)	153 (56.3)	152 (53.7)	136 (50.0)
Anti - infectives (systemic)	192 (67.8)	174 (64.0)	155 (54.8)	144 (52.9)
Antibiotics	161 (56.9)	148 (54.4)	121 (42.8)	107 (39.3)
Antivirals	15 (5.3)	14 (5.2)	8 (2.8)	13 (4.8)
Antifungals	88 (31.1)	78 (28.7)	73 (25.8)	72 (26.5)
Erythropoietic agents	**9 (3.2)**	**21 (7.7)**	3 (1.1)	10 (3.7)
G - CSF / GM - CSF	**23 (8.1)**	**65 (23.9)**	**14 (5.0)**	**37 (13.6)**

Abbreviations. EtoCis, Etoposide, cisplatin and concurrent thoracic radiation therapy, followed by consolidation with cytotoxic chemotherapy of choice; G-CSF, Granulocyte colony-stimulating factor; GM-CSF, Granulocyte–macrophage colony-stimulating factor; PemCis, Pemetrexed, cisplatin and concurrent thoracic radiation therapy followed by consolidation pemetrexed.
Statistically significant differences are shown in bold text and are based on p value $<.05$ determined by Fisher's exact test.

Table 4. Medical resource utilization cost.

	Overall study		Concurrent phase	
Category	PemCis $N = 283$	EtoCis $N = 272$	PemCis $N = 283$	EtoCis $N = 272$
Follow up, months, mean ± SD	**4.47 ± 1.46**	**3.50 ± 1.11**	2.37 ± 0.46	2.31 ± 0.51
Total cost, $, mean ± SD	**51,313.90 ± 33,166.11**	**22,425.24 ± 26,087.53**	**28,856.03 ± 25,745.12**	**17,526.22 ± 23,307.13**
Study treatment cost, $, mean ± SD	**31,203.67 ± 11,217.62**	**2957.81 ± 900.48**	**15,719.30 ± 3447.07**	**1872.54 ± 289.21**
Other costs[a], $, mean ± SD	20,110.22 ± 32,883.10	19,467.43 ± 26,141.99	13,136.73 ± 25,725.51	15,653.68 ± 23,325.07
Monthly other costs[b], $, mean ± SD	**5939.39 ± 11,482.57**	**6743.95 ± 10,590.52**	**6091.81 ± 12,048.32**	**7320.59 ± 11,488.58**
Adverse-event-related cost[c], $, mean ± SD	17,618.29 ± 32,804.57	16,901.28 ± 25,765.38	**11,273.62 ± 25,585.69**	**13,866.95 ± 23,146.59**
Hospitalization cost, $, mean ± SD	16,071.19 ± 31,775.90	14,395.61 ± 24,578.96	**10,443.80 ± 24,931.24**	**12,502.26 ± 22,297.54**
Radiotherapy cost, $, mean ± SD	485.86 ± 108.03	480.54 ± 94.25	485.86 ± 108.03	480.54 ± 94.25
Supportive care cost[d], $, mean ± SD	45.27 ± 238.88	45.87 ± 212.73	0.00 ± 0.00	0.00 ± 0.0
Concomitant medication usage cost, $	3158.12 ± 3615.92	4238.32 ± 5242.10	2032.67 ± 2064.07	2498.43 ± 2997.28
Laboratory/evaluation/radiology visit cost, $, mean ± SD	**192.48 ± 129.55**	**161.20 ± 126.16**	**94.47 ± 32.41**	**89.77 ± 43.27**
Blood products cost, $, mean ± SD	157.31 ± 373.15	145.89 ± 325.66	79.93 ± 258.38	82.69 ± 216.71

Study treatment cost includes hospital visits and other procedural costs associated with study drug administration. Overall study results include costs incurred during the concurrent phase and the consolidation phase. Costs incurred during the recovery phase or follow-up are not included in this analysis.
Abbreviations. EtoCis, Etoposide, cisplatin and concurrent thoracic radiation therapy, followed by consolidation with cytotoxic chemotherapy of choice; PemCis, Pemetrexed, cisplatin and concurrent thoracic radiation therapy followed by consolidation pemetrexed; SD, Standard deviation.
[a]Include hospitalizations, radiotherapy, supportive care, concomitant medications, laboratory/evaluation/radiology visits and blood products.
[b]Calculated by the total other costs divided by the difference in start and end dates for a period per 30.5 days.
[c]Include concomitant medications, hospitalizations and blood products associated with an adverse event and these costs may also appear in other categories.
[d]Supportive care comprised administration for pulmonary function tests, administration of oxygen (intermittent or continuous), insertion of a gastric feeding tube, administration of intravenous fluid, esophageal dilation and endoscopy.
Statistically significant differences are shown in bold text and are based on p value $<.05$ determined by Wilcoxon rank sum test.

of which 2.6 months correspond to consolidation treatment) than patients who received EtoCis (3.5 months; 1.6 months of consolidation). After adjusting other medical costs by treatment duration, the PemCis arm had significantly lower costs per month than the EtoCis arm during the overall study ($p = .0075$). Selected concomitant medication usage costs were lower in the PemCis arm in the overall study and the concurrent phase, a difference that was not statistically significant.

A subgroup analysis excluded patients with a hospital stay longer than 95% of all hospitalization durations, in order to estimate the hospitalization costs of an average patient through removal of outliers. The length-of-hospital-stay threshold was 24.5 days, excluding 17 (3.1%) patients from

the study population: 8 from the PemCis arm and 9 from the EtoCis arm, with a mean duration per hospitalization of 34.53 ± 9.47 days (range: 25–63 days). The commonest reasons for long hospitalizations were gastrointestinal disorders secondary to radiation therapy including esophagitis and dysphagia. The need to provide parenteral nutrition was reported by investigators as the cause for hospitalization prolongation in some of those cases. Of the 8 patients in the PemCis arm, 7 were hospitalized during the concurrent phase and 4 of them were also hospitalized during the consolidation phase, either due to hospitalizations spanning both phases or due to new hospitalizations. All 9 patients in the EtoCis arm were hospitalized during the concurrent phase and 2 of them were also hospitalized during the consolidation phase. Thus, detailed subgroup analyses are presented for concurrent phase and overall treatment.

The results of the subgroup cost analysis were consistent with the overall randomized and treated population with total and study treatment costs significantly higher (p value $<.0001$) in the PemCis arm in the concurrent phase and the overall study (Table 5). Other cost factors included in Table 4 did not vary much in the subgroup analysis.

After excluding patients with long hospital stays in the subgroup analysis (2.8% patients in the PemCis arm and 3.3% patients in the EtoCis arm), the cost of hospitalizations and AE-related costs in the overall study reduced by approximately $3700 in the PemCis arm and approximately $2700 in the EtoCis arm. Similar results were observed in the concurrent phase. For the overall study, patients in the PemCis arm had significantly ($p = .0066$) lower other medical costs per month ($4825) than those in the EtoCis arm ($5820).

Discussion

In the PROCLAIM study, patient-reported difficulty in swallowing presented here is consistent with previously published investigator-reported safety outcomes[10]. While overall resource use, including hospitalizations, was similar between treatment groups, the number of patients receiving transfusions, erythropoietic agents and G-CSF/GM-CSF was lower in the PemCis arm, consistent with the previously reported lower incidence of grade 3 and 4 anemia and neutropenia during overall treatment[10]. During the concurrent phase there were significantly fewer hospitalizations in the PemCis arm; otherwise, resource utilization is consistent with the overall treatment[15]. Healthcare resource utilization, together with previously presented safety and disease control results, suggest good tolerability and overall treatment benefit (including significantly higher disease control rate in the PemCis arm) for patients receiving pemetrexed[10].

The assessment of patient-reported outcomes such as symptoms of disease or complications of therapy has become an integral part of clinical trials of advanced lung cancer. Reports from the meta-analyses of combined modality therapy have shown that the major impact of this therapy has been an increase in esophagitis[16]. Thus, the PROCLAIM study focused on assessing swallowing function as a means to assess the negative impact of combined modality therapy.

Patient-reported difficulty in swallowing (score ≥ 4 in the swallowing diary) at any time during the study was 34% in the PemCis arm and 29% in the EtoCis arm, which is broadly similar to the investigator-reported incidence of grade 2–4 dysphagia during the overall treatment phase: 27% in the PemCis arm and 23% in the EtoCis arm. Swallowing difficulty for patients may affect body weight. Here, incidence of possibly treatment-related weight loss during the overall treatment phase was 16.3% in the PemCis arm and 16.5% in the EtoCis arm with the majority (15.2% and 16.2%, respectively) of these events being grade 1–2.

The number of patients hospitalized was similar in the two treatment arms during the overall study; however, significantly fewer ($p = .021$) patients treated with PemCis were hospitalized during the concurrent phase. Esophagitis was the commonest treatment-related AE leading to hospitalization in both treatment arms during the overall study and in the concurrent phase, a finding consistent with previous trials[15]. The percentage of patients hospitalized due to febrile neutropenia was higher in the EtoCis arm, a finding consistent with previously reported incidence of serious AEs of febrile neutropenia in the PemCis arm being half of that in the EtoCis arm (4.2% vs. 8.5%)[10]. The difference in days of hospitalization (average) between the PemCis and EtoCis arms was 3.6 days for the overall study and 1.4 days for the concurrent phase; and the median duration at hospital for the concurrent phase was same for both arms.

The smaller percentage of patients in the PemCis arm vs. the EtoCis arm receiving transfusions and using concomitant

Table 5. Medical resource utilization cost and subgroup analysis.

	Overall study		Concurrent phase	
Category	PemCis $N = 275$	EtoCis $N = 263$	PemCis $N = 275$	EtoCis $N = 263$
Total cost, $, mean ± SD	**47,752.60 ± 25,419.88**	**19,642.79 ± 21,229.86**	**25,935.56 ± 16,064.261**	**14,815.40 ± 18,152.75**
Other costs[a], $, mean ± SD	16,336.31 ± 23,774.92	16,673.59 ± 21,260.91	10,225.45 ± 16,192.99	12,941.10 ± 18,167.58
Monthly other costs[b], $, mean ± SD	**4825.34 ± 8908.33**	**5819.87 ± 9122.31**	5015.67 ± 9406.42	6167.69 ± 9568.91
Adverse-event-related cost[c], $, mean ± SD	13,833.26 ± 23,621.13	14,107.24 ± 20,795.86	**8363.58 ± 16,074.86**	**11,142.64 ± 17,869.42**
Hospitalization cost, $, mean ± SD	12,355.69 ± 22,570.67	11,653.05 ± 19,503.28	**7602.72 ± 15,638.22**	**9854.54 ± 17,120.80**

Overall study results include costs incurred during concurrent phase and consolidation phase. Costs incurred during the recovery phase or follow-up were not included in this analysis.

Abbreviations. EtoCis, Etoposide, cisplatin and concurrent thoracic radiation therapy, followed by consolidation with cytotoxic chemotherapy of choice; PemCis, Pemetrexed, cisplatin and concurrent thoracic radiation therapy followed by consolidation pemetrexed; SD, Standard deviation.

[a]Include hospitalizations, radiotherapy, supportive care, concomitant medications, laboratory/evaluation/radiology visits and blood products.

[b]Calculated by the total other costs divided by the difference in start and end dates for a period per 30.5 days.

[c]Include concomitant medications, hospitalizations and blood products associated with an adverse event and these costs may also appear in other categories.

Statistically significant differences are shown in bold text and are based on p value $<.05$ determined by Wilcoxon rank sum test.

erythropoietic agents is consistent with the lower incidence of possible treatment-related grade 3–4 anemia during both the overall treatment (8% vs. 13%, respectively) and the concurrent phase (5% vs. 8%, respectively) previously reported. Significantly fewer patients in the PemCis arm than in the EtoCis arm used concomitant G-CSF/GM-CSFs, which is consistent with the statistically lower incidence of grade 3–4 neutropenia (24% vs. 44%) and the lower incidence of grade 3–4 febrile neutropenia (5% vs. 9%) in the PemCis arm compared to the EtoCis arm reported by the same authors[10].

Findings in the concurrent phase were consistent with those of the overall study, with a trend in differential use of erythropoietic agents and CSFs being significantly lower in the PemCis arm.

With the favorable safety results of the PemCis arm and the recent inclusion of PemPlatinum regimens in combination with concurrent TRT in National Comprehensive Cancer Network (NCCN) treatment guidelines[16,17], the impact of treatment on costs for the healthcare system, including the patient, is important. Financial toxicity is a relevant concern for patients and clinicians when deciding the best treatment option. Assessing the cost of an entire treatment regimen, rather than a single drug, is necessary to provide an accurate and full perspective on the economic impact of a treatment strategy. Thus, we estimated costs based on the PROCLAIM data to provide information around the full financial burden associated with the treatments investigated. Additionally, to our knowledge this cost analysis is the first reported for a phase 3 chemoradiation trial in NSCLC.

In the costing analysis of the PROCLAIM study, the significantly higher total costs for the PemCis arm compared to the EtoCis arm were driven by study drug cost. Other medical costs (excluding study treatment costs) during the concurrent phase were lower for the PemCis arm due to significantly lower hospitalization costs and lower use of selected concomitant medications. When adjusting for treatment duration in the overall study monthly other medical costs were also favorable for the PemCis arm.

Per study design, treatment duration during the concurrent phase was similar in the two arms but was longer in the PemCis arm during the consolidation phase, resulting in approximately one mean additional month of treatment overall. In the concurrent phase, treatment costs were partially offset by a significant reduction in adverse-event-related costs ($p = .008$), including hospitalizations and selected concomitant medication usage in the PemCis arm. However, in the overall study adverse-event-related costs were similar in both arms, since lower concomitant medication usage in the PemCis arm could not compensate for the higher hospitalization costs in the consolidation phase. However, the monthly cost associated with other medical costs (excluding study treatment cost) was significantly lower in the PemCis arm. The results of the subgroup analysis excluding patients with longer period of hospitalization (>24 days) showed that 2.8% of PemCis patients and 3% of EtoCis patients accounted for 23% and 19% of total hospitalization costs, respectively, in the overall study and 27% and 21% of total hospitalization costs during the concurrent phase, respectively. High-grade esophagitis and dysphagia were a significant cause of prolongation of admissions and resource use in PROCLAIM.

This cost analysis has several limitations including insufficient power to detect significant differences in resource usage. It was conducted for the overall randomized and treated population and differences in clinical care patterns across countries may have had an impact on the overall results. Hospitalization costs were estimated based on a single cost per hospital day estimate multiplied by total hospital days and duration of use and dosage of concomitant medications were imputed using a prespecified costing algorithm. Finally, the clinical trial data may not be reproduced exactly in a real-world scenario. However, given this was a randomized study, these limitations are not expected to have biased the overall results.

Conclusions

In the PROCLAIM study, resource utilization and patient-reported difficulty in swallowing are consistent with previously presented favorable safety outcomes for pemetrexed and cisplatin combination. Higher total costs for the PemCis arm compared to the EtoCis arm were mainly associated with higher study treatment cost and longer overall treatment duration. During the chemoradiation phase, with similar duration between treatment arms, other medical costs (excluding study treatment costs) were lower for the PemCis arm. Patients on pemetrexed remained longer on planned therapy, suggesting better tolerability and possible treatment benefit.

Transparency

Declaration of funding

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Author contributions

All the authors contributed to the preparation of this manuscript and approved the final version for submission. All authors take responsibility for the accuracy and completeness of data and data analyses. R.G. was involved in the conception of study design, data collection, analysis and interpretation. S.S. was involved in the data collection and interpretation. N.D. was involved in the conception of study design, data collection and interpretation. M.P. and K.S. were involved in the data collection analysis and interpretation. Y.L.W. was involved in conception of study design, data collection, analysis and interpretation. B.P., M.W. and A.H. (study statistician) were involved in data analysis and interpretation. R.Z. was involved in the study design, analysis and interpretation. N.C. was involved in the concept and design of the study. B.S.A. was involved in the interpretation of data. K.W. was involved in the conception of the study design and interpretation of data. E.E.V. was involved in study conception and interpretation of data. The sponsor provided the study drugs, planned and performed the statistical analyses, and provided editorial and writing assistance.

Declaration of financial/other relationships

R.G. has disclosed that he is a consultant for INC Research and AbbVie, is on the advisory board for AbbVie and Inivata, and has received honoraria from AbbVie and Genentech. S.S. has disclosed that he has received research support from Varian Medical Systems and is on the advisory board for Eli Lilly and AstraZeneca. M.W. and R.Z. have disclosed that they are employees of RTI Health Solutions, a contract research organization that received funding from Eli Lilly to conduct the economic analysis in this study. N.C., A.H., B.S.A. and K.W. have disclosed that they are employees and shareholders of Eli Lilly and Company. E.E.V. has disclosed that he has a consultant or advisory role for AbbVie, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, Eli Lilly, Genentech, Leidos, Merck, Regeneron, Serono, Takeda and VentiRx. No potential conflict of interest was reported by the other authors. *CMRO* peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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