Analysis of Health Care Resource Use Costs in the PROCLAIM Trial

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BACKGROUND

- Standard of care for inoperable stage III non–small cell lung cancer (NSCLC) is concurrent chemoradiotherapy.[1,2] The ideal concurrent chemotherapy regimen has not been determined. The role of consolidation chemotherapy remains controversial.[2]
- Pemetrexed (Pem) is a multitargeted antifolate with selective activity in nonsquamous NSCLC.[3,4]
- Pem-platinum combinations can be administered at full systemic doses with concurrent thoracic radiotherapy (TRT).[5]
- PROCLAIM, a phase 3 study comparing concurrent Pem-cisplatin (Cis) and TRT followed by consolidation Pem versus etoposide-Cis (EtoCis) and TRT followed by a consolidation platinum doublet of choice, did not meet its primary endpoint of superior survival.[6]
- The PROCLAIM Pem arm had significantly lower incidence of drug-related Grade 3-4 adverse events (AEs) (all events combined), including neutropenia, during the overall treatment period. Grade 3-4 neutropenia and febrile neutropenia were also significantly lower in the Pem arm during the concurrent phase.[6]
- While overall resource use was similar between treatment arms, the number of patients receiving transfusions, erythropoeitic agents, and colony-stimulating factors was lower in the Pem arm, consistent with the lower incidence of Grade 3-4 anemia and neutropenia during overall treatment. During the concurrent phase, resource utilization is consistent with the overall treatment, with significantly lower hospitalizations in the Pem arm.[7]
- In this study, we present medical resource use (MRU) costs in PROCLAIM.

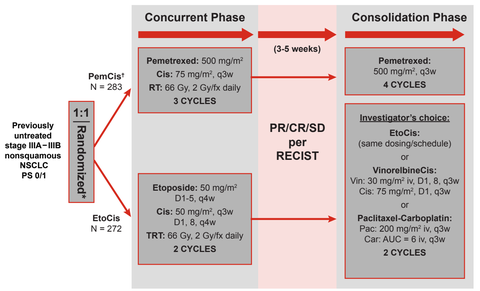
OBJECTIVE

- To estimate and compare the direct medical costs for each arm and phase of the PROCLAIM trial. The analysis was conducted from a health care payer's perspective.

COMPARATORS

- Costs were analyzed for each arm and phase of the PROCLAIM trial. The study treatment arms, PemCis and EtoCis, are presented in Figure 1.

Figure 1. PROCLAIM Trial Study Design and Treatment Arms



AUC = area under the curve; Car = carboplatin; CR = complete response; D = day; fx = fraction; Gy = grays; Gy/fx = grays per fraction; iv = intravenous; Pac = paclitaxel; PR = partial response; PS = performance status; q3w = every 3 weeks; q4w = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; SD = stable disease; Vin = vinorelbine.

Note: Outcomes previously reported for PROCLAIM: overall survival; progression-free survival; overall response rate; 1-, 2-, and 3-year survival; first sites of disease failure in terms of relapse; and safety (overall study, concurrent phase, and consolidation phase).

* Stratified for Eastern Cooperative Oncology Group performance status (0 vs. 1); positron emission tomography scan staging (yes vs. no); gender; and disease stage (IIIA vs. IIIB).

† Folic acid, vitamin B_{12}, and dexamethasone administered in PemCis.

METHODS

Study Population

- The primary analysis population consisted of all patients who had been randomized and treated based on the treatment to which they were randomized. Characteristics of the overall study population have been presented elsewhere.[6,7]
- Subgroup analysis was conducted on a sample of patients excluding those with "outlier" hospitalizations (i.e., hospitalizations exceeding the 95% threshold of length of stay). Characteristics of the excluded are in Table 2.

Costs

- MRU costs considered in the analysis included the following: study drugs, concomitant medication, hospitalization costs, radiation therapy, laboratory tests, and other MRU (e.g., blood products, supportive care, and pulmonary function tests).
- Study drug costs (acquisition and administration) were estimated based on number of administrations and total milligrams used.
- Concomitant medications included drugs from classes identified as categories of interest as specified in the PROCLAIM clinical study report: analgesics (nonsteroidal anti-inflammatory agents, opioids); antiemetics and antinauseants (serotonin [5HT3] antagonists, others including NK1 antagonists); anti-infective agents (antibiotics, antivirals, antifungals); erythropoietic agents; and granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor.
- 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.
- All drug acquisition costs were obtained from the Red Book[8] and administration costs from the Resource-Based Relative Value Scale (RBRVS).[9]
- Hospitalization costs were estimated based on length of stay (as reported in the PROCLAIM trial) multiplied by a cost per day of $2,636.89[10] and inflated to 2015 values using the medical consumer price index.[11]
- Radiation therapy, laboratory test, and other MRU costs were estimated based on number of units used (as reported from the PROCLAIM trial) multiplied by the unit cost.[10] Costs of blood products were obtained from the published literature.[12]
- 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. Costs incurred in the recovery period (in between treatment phases) were not included in this analysis.

Analysis Methods

- Total costs for each patient were calculated as follows: $C_i = \sum_{j=1}^{n} P_j X_{ij}$,

  where C_i is the total cost for each subject i; X_{ij} denotes the quantity of each type of MRU (j) collected in the trial and used by subject i; P_j denotes the unit cost for each type of resource; and n represents the number of medical resources used by subject i over the course of the trial.
- Due to the skewed distribution of cost data, the MRU cost distributions were compared between treatment arms using the nonparametric Wilcoxon rank sum test to address skewness of the data.

Sensitivity Analysis

- Sensitivity analyses were conducted with the use of a bootstrapping resampling algorithm with 10,000 replications and presented as summary statistics (e.g., mean, median, and 95% confidence interval).

RESULTS

Base-Case Results

- Base-case results can be seen in Table 1.
- Per study design, average 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 1 mean additional month of treatment overall.
- Patients in the PemCis arm had significantly higher total costs and study treatment costs in both the concurrent phase and the overall treatment period ($P < 0.0001$).
- In the concurrent phase, treatment costs were partially offset by a reduction in adverse event–related costs.
- After adjusting other medical costs by treatment duration, total monthly other medical costs were significantly lower ($P < 0.05$) in the PemCis arm compared with the EtoCis arm in both the overall study and the concurrent phase.

Table 1. Medical Resource Utilization Cost

	Overall Study[a]		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,[a] $	**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, $	**31,203.67 ± 11,217.62**	**2,957.81 ± 900.48**	**15,719.30 ± 3,447.07**	**1,872.54 ± 289.21**
Other medical cost,[b] $	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 medical cost, $	**5,939.39 ± 11,482.57**	**6,743.95 ± 10,590.52**	**6,091.81 ± 12,048.32**	**7,320.59 ± 11,488.58**
Adverse event–related cost,[c] $	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, $	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, $	485.86 ± 108.03	480.54 ± 94.25	485.86 ± 108.03	480.54 ± 94.25
Supportive care cost,[d] $	45.27 ± 238.88	45.87 ± 212.73	0.00 ± 0.00	0.00 ± 0.0
Concomitant medication use cost, $	3,158.12 ± 3,615.92	4,238.32 ± 5,242.10	2,032.67 ± 2,064.07	2,498.43 ± 2,997.28
Laboratory/evaluation/ radiology visit cost, $	**192.48 ± 129.55**	**161.20 ± 126.16**	**94.47 ± 32.41**	**89.77 ± 43.27**
Blood products cost, $	157.31 ± 373.15	145.89 ± 325.66	79.93 ± 258.38	82.69 ± 216.71

EtoCis = included etoposide, cisplatin, and concurrent thoracic radiation therapy, followed by consolidation with cytotoxic chemotherapy of choice; PemCis = included pemetrexed, cisplatin, and concurrent thoracic radiation therapy followed by consolidation pemetrexed; SD = standard deviation.

Note: All costs are presented as mean values ± SD. Bolded results indicate a significant P value (< 0.05) determined by Wilcoxon rank sum test.

[a] Overall study results include those costs incurred during either the concurrent phase or the consolidation phase. Costs incurred during the recovery phase or follow-up were not considered in this study.

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

[c] Included concomitant medications, hospitalizations, and blood products associated with an adverse event specifically; a subset of other medical costs.

[d] Supportive care was composed of administration of pulmonary function tests, administration of oxygen (intermittent or continuous), insertion of a gastric feeding tube, administration of intravenous fluid, esophageal dilation, and endoscopy.

Subgroup Results

- We performed a subgroup analysis excluding 17 patients (3.1% of the total study population) with a hospitalization stay longer than 24.5 days (95% of all hospitalization stays) to estimate the hospitalization cost of an average PROCLAIM patient.
- The mean duration of hospitalization for the 17 excluded patients (8 in the PemCis arm and 9 in the EtoCis arm) was 34.53 days (SD 9.47; range 25-63 days). Timing and reasons for long hospitalizations of the excluded patients can be seen in Table 2. A majority (n = 12) of the excluded patients were from European study sites (6 in Belgium, 2 in Germany, 2 in Spain, 2 in the United Kingdom).

Table 2. Characteristics of Patients Excluded in Subgroup Analysis

Characteristic	PemCis N (%)	EtoCis N (%)
Total patients excluded	**8**	**9**
Study phase in which hospitalization occurred		
Concurrent	7 (87.5%)	9 (100.0%)
Consolidation	5 (62.5%)	2 (22.2%)
Reason for hospitalization		
Dysphagia	1 (12.5%)	1 (11.1%)
Esophagitis	3 (37.5%)	3 (33.3%)
Febrile neutropenia	0 (0.0%)	1 (11.1%)
Neutropenia	0 (0.0%)	1 (11.1%)
Leukopenia	0 (0.0%)	1 (11.1%)
Dyspnea	1 (12.5%)	0 (0.0%)
Hyponatremia	0 (0.0%)	1 (11.1%)
Decreased appetite	1 (12.5%)	0 (0.0%)
Weight decreased	1 (12.5%)	0 (0.0%)
White blood cell count decreased	0 (0.0%)	1 (11.1%)
Peripheral ischemia	1 (12.5%)	0 (0.0%)
Phlebitis	1 (12.5%)	0 (0.0%)
Superior vena cava syndrome	0 (0.0%)	1 (11.1%)
Lower respiratory tract infection	0 (0.0%)	1 (11.1%)
Infectious colitis	1 (12.5%)	0 (0.0%)
Pneumonia	1 (12.5%)	1 (11.1%)
Radiation esophagitis	1 (12.5%)	0 (0.0%)
Radiation pneumonitis	1 (12.5%)	0 (0.0%)
Unspecified	0 (0.0%)	1 (11.1%)

Note: Patients may have more than one AE leading to hospitalization. Seven of the 8 patients in the PemCis arm were hospitalized during the concurrent phase; 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; 2 of them were also hospitalized during the consolidation phase.

- Gastrointestinal disorders related to radiation, including esophagitis and dysphagia, were the most common reasons for prolongation of hospitalizations in both arms, as patients may have required nutritional support.

Table 3. Medical Resource Utilization Cost, Subgroup Analysis

	Overall Study[a]		Concurrent Phase	
Category	**PemCis N = 275**	**EtoCis N = 263**	**PemCis N = 275**	**EtoCis N = 263**
Total cost, $	**47,752.60 ± 25,419.88**	**19,642.79 ± 21,229.86**	**25,935.56 ± 16,064.26**	**14,815.40 ± 18,152.75**
Other medical cost,[b] $	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 medical cost, $	**4,825.34 ± 8,908.33**	**5,819.87 ± 9,122.31**	5,015.67 ± 9,406.42	6,167.69 ± 9,568.91
Adverse event–related cost,[c] $	13,833.26 ± 23,621.13	14,107.24 ± 20,795.86	**8,363.58 ± 16,074.86**	**11,142.64 ± 17,869.42**
Hospitalization cost, $	12,355.69 ± 22,570.67	11,653.05 ± 19,503.28	**7,602.72 ± 15,638.22**	**9,854.54 ± 17,120.80**

EtoCis = included etoposide, cisplatin, and concurrent thoracic radiation therapy, followed by consolidation with cytotoxic chemotherapy of choice; PemCis = included pemetrexed, cisplatin, and concurrent thoracic radiation therapy followed by consolidation pemetrexed.

Note: All costs are presented as mean values ± SD. Bolded results indicate a significant P value (< 0.05) determined by Wilcoxon rank sum test.

[a] Overall study results include those costs incurred during either the concurrent phase or the consolidation phase. Costs incurred during the recovery phase or follow-up were not considered in this study.

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

[c] Included concomitant medications, hospitalizations, and blood products associated with an adverse event specifically; a subset of other medical costs.

- Cost results in the subgroup analysis excluding those 17 patients were consistent with the overall randomized and treated population (Table 3). Hospitalization costs were reduced by > $2,600 (19%-27% reduction in costs) for both arms in the subgroup analysis compared with the base-case analysis.
- For the combined concurrent and consolidation phases, patients in the PemCis arm had significantly lower ($P < 0.05$) other medical costs per month ($4,825) than those on EtoCis ($5,820).

LIMITATIONS

- PROCLAIM was a multinational study and was not powered to detect significant differences in country-specific subgroups of study patients. As such, the cost analysis was conducted for the overall randomized and treated population. Differences in care patterns across countries may have had an impact on the overall results.
- Due to limited information on hospitalizations from the trial, costs were estimated based on a single cost per hospital day estimate multiplied by total hospital days.
- Because limited information was collected on concomitant medication use in the trial, duration of use and dosage were imputed using a prespecified costing algorithm.
- These limitations were not assumed to have biased the results, as the assumptions to address the limitations were applied consistently across both arms.

DISCUSSION AND CONCLUSIONS

- In the overall PROCLAIM study, higher total costs for PemCis compared to EtoCis were driven by study drug cost.
- Other medical costs (excluding study treatment costs) during the concurrent phase were lower for PemCis due to significantly lower hospitalization costs and lower use of concomitant medications.
- When adjusting for treatment duration (in both the overall study and the concurrent phase), other monthly medical costs were favorable for PemCis. This difference is predominately driven by reduced hospitalization costs and concomitant medication usage in the Pem patients.
- A very small proportion of the overall study patients (~3%) incurred approximately 19% to 27% of the hospitalization costs due to extended lengths of stay (most of them occurring in the concurrent phase). These hospitalizations were generally related to complications common to chemoradiotherapy treatments.
- As planned, patients on Pem remained on therapy longer, suggesting better tolerability and overall treatment benefit.

References:

See handout for references.

Disclosure:

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