Evaluating the Supportive Care Costs of Severe Radiochemotherapy-Induced Mucositis and Pharyngitis

Results From a Northwestern University Costs of Cancer Program Pilot Study With Head and Neck and Nonsmall Cell Lung Cancer Patients Who Received Care at a County Hospital, a Veterans Administration Hospital, or a Comprehensive Cancer Care Center

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BACKGROUND. Few studies have examined the costs of supportive care for radiochemotherapy-induced mucosits/pharyngitis among patients with head and neck cancer (HNC) or lung cancers despite the documented negative clinical impact of these complications.

METHODS. The authors identified a retrospective cohort of patients with HNC or nonsmall lung cancer (NSCLC) who had received radiochemotherapy at 1 of 3 Chicago hospitals (a Veterans Administration hospital, a county hospital, or a tertiary care hospital). Charts were reviewed for the presence/absence of severe mucositis/pharyngitis and the medical resources that were used. Resource estimates were converted into cost units obtained from standard sources (hospital bills, Medicare physician fee schedule, Red Book). Estimates of resources used and direct medical costs were compared for patients who did and patients who did not develop severe mucositis/pharyngitis.

RESULTS. Severe mucositis/pharyngitis occurred in 70.1% of 99 patients with HNC and in 37.5% of 40 patients with NSCLC during radiochemotherapy. The total median medical costs per patient were $39,313 for patients with mucositis/pharyngitis and $20,798 for patients without mucositis/pharyngitis ($P = .007$). Extended inpatient hospitalization accounted for $12,600 of the increased medical costs (median 14 days [$19,600] with severe mucositis/pharyngitis vs 5 days [$7000] without; $P = .017$). For patients who had HNC with mucositis/pharyngitis, incremental inpatient hospitalization costs were $14,000, and total medical costs were $17,244. For patients who had NSCLC with mucositis/pharyngitis, these costs were $11,200 and $25,000, respectively.

CONCLUSIONS. In the current study, the medical costs among the patients with HNC and NSCLC who received radiochemotherapy were greater for those who developed severe mucositis/pharyngitis than for those who did not. ***Cancer*** **2008;113:1446–52.** © *2008 American Cancer Society.*

KEYWORDS: mucositis, pharyngitis, cost analysis, head and neck.

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Mucositis and pharyngitis are common treatment-limiting side effects noted among patients with head and neck cancer (HNC) and lung cancer.[1] Ninety percent of patients with HNC develop mucositis/pharyngitis after radiochemotherapy, and approximately two-thirds of those patients experience severe and debilitating toxicities.[1] Although the rates of mucositis/pharyngitis are lower among patients with nonsmall cell lung cancer (NSCLC) than patients with HNC who receive radiochemotherapy, it still may interfere with therapy, permit local or systemic infection, and reduce quality of life.[1] Although the negative effects of this toxicity on clinical and quality-of-life variables in HNC have been well documented, only 1 prior study has reported on the economic impact of treating radiochemotherapy-associated toxicity in patients with HNC.[2] To our knowledge, no studies have assessed the economic impact of treating this complication in patients with NSCLC. Herein, we report on the types of resources used and the incremental medical costs of treatment for radiochemotherapy-associated, severe mucositis/pharyngitis among a cohort of patients with HNC or NSCLC who received cancer treatment at a Veterans Administration (VA) hospital, a county hospital, or a tertiary care comprehensive cancer center.

MATERIALS AND METHODS

Medical records for patients with HNC or NSCLC who received care between 2003 and 2005 at 1 of 3 large referral hospitals in Chicago were reviewed for this study. One of the hospitals was an academic comprehensive cancer center (Robert H. Lurie Comprehensive Cancer Center at Northwestern University), 1 was a county hospital (John H. Stroger Jr. Hospital of Cook County), and 1 was a VA Medical Center (Jesse Brown VA Medical Center-Lakeside Division). Charts were included if patients were aged $\geq$18 years, had a pathologic diagnosis of stage I through IV HNC or stage I through IV NSCLC, and had completed radiochemotherapy regimens.

Information abstracted from medical charts included baseline clinical and demographic characteristics, comorbidities, medications, medical devices, laboratory tests, inpatient hospitalizations, and clinic visits. For operational purposes, mucositis/pharyngitis was defined as toxicity that resulted in documentation in physician chart notes. Grade of toxicity often was not reported. The abstraction period for each patient began on the date radiochemotherapy was initiated and ended 2 months after radiochemotherapy was completed. Two individuals abstracted the data independently, and a local panel of 3 lung cancer or HNC oncology specialists provided input on clinical considerations, such as mucositis/pharyngitis-related medications.

For the economic analysis, we assigned a value to each medical resource, as described in detail previously.[3] In brief, unit costs for each resource were obtained from standard sources, such as hospital bills for inpatient stays, the Medicare physician fee schedule for outpatient services, and the Red Book for pharmaceuticals.[4] The Red Book is a nationally recognized reference that contains average wholesale prices, direct prices, and federal upper limit prices for prescription pharmaceuticals. Standard unit costs were multiplied by each individual utilization number of services to estimate per patient costs for individual resources. The individual costs for each patient were then added to generate a total per patient cost estimate.

Cost estimates for each individual resource and total per patient costs were compared for patients with severe mucositis/pharyngitis versus those without severe mucositis/pharyngitis using the Mann-Whitney 2-tailed test, as described in our prior cost studies.[5,6] Total per patient costs were normalized by log transformation and were analyzed using multivariate regression analysis to identify the factors associated with higher total costs.[2,7] The analysis was conducted from the provider's perspective in 2005 U.S. dollars. For simplicity, we report median values for cost and resource utilization, although, qualitatively, the findings were similar when evaluated according to the log-transformed cost estimates.

The study was approved by the Institutional Review Boards at the Northwestern University Robert H. Lurie Comprehensive Cancer Center and at Cook County Hospital and by the Research and Development Committee at the Jesse Brown VA Medical Center. Waivers of informed consent and Health Insurance Portability and Accountability Act of 1996 authorization were obtained. The research was conceived and conducted by the study investigators, who were solely responsible for analysis and interpretation of the data and preparation of this article. The sponsor reviewed and commented on the design of the study and the article but was not involved in interpretation of the findings or in the decision to publish.

RESULTS

In total, 139 patients with HNC (n = 99) or NSCLC (n = 40) were evaluated in this study (Table 1). Seventy-five percent of patients in the cohort were

TABLE 1
Patient Demographics

Characteristic	No. of Patients (%)								
	Patients With HNC			Patients With NSCLC			All Patients		
	With Mucositis/Pharyngitis, N=70	Without Mucositis/Pharyngitis, N=29	All Patients with HNC, N=99	With Mucositis/Pharyngitis, N=15	Without Mucositis/Pharyngitis, N=25	All Patients With NSCLC, N=40	With Mucositis/Pharyngitis, N=85	Without Mucositis/Pharyngitis, N=54	All Patients, N=139
Age, y									
Mean	56	55	56	61	63	62	57	58	57
Median	59	56	58	62	62	62	59	58	59
Range	27-78	35-72	27-78	42-72	45-85	42-85	27.78	35.85	27-85
Sex									
Men	56 (80)	25 (86.2)	81 (81.8)	8 (53.3)	19 (76)	27 (67.5)	64 (75.3)	44 (81.5)	108 (77.7)
Women	14 (20)	4 (13.8)	18 (18.2)	7 (46.7)	6 (24)	13 (32.5)	21 (24.7)	10 (18.5)	31 (22.3)
Stage									
I	0	0	0	1 (6.7)	2 (8)	3 (7.5)	1 (1.2)	2 (3.7)	3 (2.2)
II	4 (5.7)	0	4 (4)	0	1 (4)	1 (2.5)	4 (4.7)	1 (1.9)	5 (3.6)
III	12 (17.1)	4 (13.8)	16 (16.2)	10 (66.7)	10 (40)	20 (50)	22 (25.9)	14 (25.9)	36 (25.9)
IV	44 (62.9)	21 (72.4)	65 (65.7)	2 (13.3)	5 (20)	7 (17.5)	46 (54.1)	26 (48.1)	72 (51.8)
Not reported	10 (14.3)	4 (13.8)	14 (14.1)	2 (13.3)	7 (28)	9 (22.5)	12 (14.1)	11 (20.4)	23 (16.5)
Race/ethnicity									
Caucasian	32 (45.7)	7 (24.1)	39 (39.4)	7 (46.7)	8 (32)	15 (37.5)	39 (45.9)	15 (27.8)	54 (38.8)
Black/African American	17 (24.3)	17 (58.6)	34 (34.3)	2 (13.3)	6 (24)	8 (20)	19 (22.4)	23 (42.6)	42 (30.2)
Asian	5 (7.1)	2 (6.9)	7 (7.1)	0	1 (4)	1 (2.5)	5 (5.9)	3 (5.6)	8 (5.8)
Hispanic	4 (5.7)	0	4 (4)	0	0	0 (0)	4 (4.7)	0	4 (2.9)
Unknown	12 (17.1)	3 (10.3)	15 (15.2)	6 (40)	10 (40)	16 (40)	18 (21.2)	13 (24.1)	31 (22.3)
Treatment center									
VA hospital	3 (4.3)	5 (17.2)	8 (8.1)	1 (6.7)	10 (40)	11 (27.5)	4 (4.7)	15 (27.8)	19 (13.7)
Tertiary referral center	40 (57.1)	6 (20.7)	46 (46.5)	14 (93.3)	15 (60)	29 (72.5)	54 (63.5)	21 (38.9)	75 (54)
County hospital	27 (38.6)	18 (62.1)	45 (45.5)*	0	0	0	27 (31.8)	18 (33.3)	45 (32.4)

HNC indicates head and neck cancer; NSCLC, nonsmall cell lung cancer; VA, Veterans Administration.

* Medical records only from patients with HNC were reviewed at the county hospital.

men, and the median age was 59 years (range, 27-85 years). Care was provided at the county medical center for 33%, and at the VA Medical Center for 14%. Most of the cohort (77.6%) had stage III or stage IV malignancies. Severe radiochemotherapy-associated mucositis/pharyngitis developed in 70% of the patients with HNC and in 38% of the patients with NSCLC, which represented all of patients who had mucositis/pharyngitis documented in physician notes.

The standard radiochemotherapy regimen for patients with HNC was single-agent cisplatin at a dose of 100 mg/m^2 administered 3 times during the course of radiation at 21-day intervals.[8] The standard radiochemotherapy regimen for patients with NSCLC was combined cisplatin and etoposide with concurrent radiation completed to a dose of 61 grays.[9]

Compared with patients who did not develop severe mucositis/pharyngitis, the patients with HNC or NSCLC who developed severe radiochemotherapy-associated oral mucositis/pharyngitis required more medical resources and incurred higher costs during the treatment phase (Table 2). The total median cost per patient was $39,313 for those with mucositis/pharyngitis and $20,798 for those without, resulting in a median incremental cost of $18,515 per patient (Table 2) ($P = .007$). A higher median cost for inpatient hospitalization was evident both for patients with HNC and for patients with NSCLC, although the difference was significant only for patients with HNC (Table 2).

The primary driver of the total cost appeared to be inpatient hospitalization, primarily to support alimentation, which was 2.8 times higher in the patients who developed severe oral mucositis/pharyngitis (median, $19,000 vs $7000; $P = .017$) (Table 2). A higher median cost was noted both for patients with HNC and for patients with NSCLC, but the difference was significant only for patients with HNC (Table 2). The greater inpatient hospitalization cost may be attributed to a longer duration of inpatient hospitalization for patients who developed severe oral mucositis/pharyngitis: The median duration of inpatient hospitalization was 14 days (range, 2.5-29 days) for patients who developed severe oral mucositis/pharyngitis and 5 days (range, 0-16.5 days) for patients who did not. The longer duration of hospitalization was noted both for patients with HNC (median, 15 days with severe mucositis vs 5 days without) and for patients with NSCLC (median, 13 days with severe mucositis vs 5 days without).

Supportive care pharmaceuticals accounted for a small amount of the total medical expenditures but were significantly more expensive in patients with versus patients without severe mucositis/pharyngitis (median, $195 vs $84, respectively; $P = .008$) (Table 2). The cost of procedures, including esophagogastroduodenostomy or G-tube placement/reinsertion, also was significantly greater among patients with mucositis/pharyngitis (Table 2). There was a trend toward a higher number of outpatient visits to the cancer clinic after hospital discharge ($P = .08$) for patients who developed severe mucositis/pharyngitis. The median number of clinic visits was 25 (range, 17-35 visits) versus 18 (range, 1-33 visits) for patients with and without severe mucositis/pharyngitis, respectively.

Multivariate regression models indicated that patient sociodemographic characteristics, tumor site (HNC vs NSCLC), and presence versus absence of severe mucositis/pharyngitis were significant predictors of cost. After adjusting for patient sociodemographic characteristics, type of cancer, and site of care, the development of mucositis/pharyngitis remained a significant predictor of total medical costs (Table 2).

DISCUSSION

From this medical chart review study, we obtained detailed resource utilization information from a cohort of patients with HNC and NSCLC during a time when 70% and 38%, respectively, developed radiochemotherapy-associated mucositis/pharyngitis. For the patients who developed severe oral mucositis/pharyngitis, the median incremental cost of the toxicity was $17,244 for patients with HNC and $25,060 for patients with NSCLC. Most of this increase in cost was associated with inpatient hospitalization required for supportive care, primarily for alimentation.

Our estimates of the costs of severe radiochemotherapy-associated mucositis/pharyngitis can be compared with those reported in a recent study from the University of Texas M. D. Anderson Cancer Center.[2] In that study, the incremental cost associated with severe mucositis/pharyngitis was up to $6000, whereas our cost of toxicity estimate was almost 3-fold higher. This difference may be explained by the longer duration of hospitalization in our study. The incremental duration of hospitalization among cancer patients who developed treatment-related mucositis/pharyngitis in our study was 14 days versus only 1 day in the prior study. Elting et al noted that patients at the University of Texas M. D. Anderson Cancer Center received care at a time when the hospital was operating at maximum capacity and there

TABLE 2
Median Direct Costs for the Treatment of Patients With Head and Neck or Nonsmall Cell Lung Cancer According to the Presence/Absence of Severe Mucositis/Pharyngitis

	Median Cost (Range), $								
	Patients With HNC, n=99			Patients With NSCLC, n=40			All Patients, n=139		
Sources of Direct Medical Cost	Without Mucositis/ Pharyngitis, N=29	With Mucositis/ Pharyngitis, N=70	Incremental Cost for Patients With Mucositis/ Pharyngitis, n=99	Without Mucositis/ Pharyngitis, n=25	With Mucositis/ Pharyngitis, n=15	Incremental Cost for Patients With Mucositis/ Pharyngitis, n=40	Without Mucositis/ Pharyngitis, n=54	With Mucositis/ Pharyngitis, n=85	Incremental Cost for Patients With Mucositis/ Pharyngitis, n=139
Inpatient hospitalization	7000 (0-28,000)	21,000 (3850-42,000)	14,000*	7000 (2800-19,600)	18,200 (0-37,800)	11,200	7000 (0-23,100)	19,600 (3500-40,600)	12,600*
Tests and procedures	924 (651-2833)	3150 (887-10,139)	2226*	3756 (790-7022)	4536 (2623-11,022)	780	1094 (685-5111)	3419 (1136-10,195)	2325*
Imaging procedures	3510 (2457-6746)	5602 (3592-13,616)	2092*	10,102 (4807-16,031)	14,248 (8438-23,974)	4146	5900 (2678-10,225)	7 019 (3954-14,817)	1119
Clinic visits	960 (660-1530)	1470 (885-1920)	510	1320 (720-2880)	2280 (1200-3540)	960	1080 (660-1980)	1500 (1020-2100)	420
Mucositis/pharyngitis-related medication†	105 (14-299)	196 (77-432)	90	11 (0-134)	14 (0-205)	3	84 (2-195)	195 (53-306)	110*
Laboratory diagnostic tests	463 (221-715)	553 (314-887)	90	517 (262-971)	725 (451-1028)	208	494 (239-864)	595 (342-908)	101
Total	18,512 (7312-39,030)	35,756 (17,952-70,210)	17,244*	21,187 (14,787-62,108)	46,246 (28,565-68,700)	25,060	20,798 (9898-48,596)	39,313 (18,961-69,298)‡	18,515*

HNC indicates head and neck cancer; NSCLC, nonsmall cell lung cancer.

* Statistically significant ($P<.05$) in a Mann-Whitney test comparing patients with vs without toxicity.

† Mucositis/pharyngitis-related medications in the cost analysis included morphine, fentanyl patch, lidocaine, ensure supplement, oxycodone, fluconazole, nystatin, acetominophen, codeine, and hydromorphone.

‡ Statistically significant ($P<.05$) in multivariate analysis of variance with dependent variable defined as ln(cost). Models included patient sociodemographic characteristics, tumor site, and presence versus absence of severe oral mucositis/pharyngitis. The presence of oral mucositis/pharyngitis was a predictor of high total cost; being a woman was a significant predictor of high imaging procedure and outpatient visit cost; African-American race/ethnicity was a predictor of high laboratory test cost; NSCLC was a significant predictor of medication, imaging procedure, tests and procedures, and outpatient visit cost.

TABLE 3
Estimated Costs of Cancer Treatment-related Toxicities Reported by the Northwestern University Costs of Cancer Program*

Treatment-related Toxicity (Reference)	Oncology Treatment	Cancer Diagnosis	No. of Patients	Medical Costs, $
Mucositis/pharyngitis (current study)	Radiochemotherapy	Nonsmall cell lung cancer	40	25,060
Neutropenia treated as an inpatient (Albain 2002[9])	Chemotherapy	Lymphoma	11	17,869
Mucositis/pharyngitis (current study)	Radiochemotherapy	Head and neck cancer	99	17,244
Neutropenia treated as an inpatient (Albain 2002[9])	Chemotherapy	Breast cancer	5	10,534
Neutropenia treated as an inpatient (Albain 2002[9])	Chemotherapy	Lung cancer/multiple myeloma	12	10,311
Neutropenia (Calhoun 2001[3])	Cis-platinum	Ovarian cancer	26	7546
Febrile neutropenia (Calhoun 2003[10])	Liposomal daunorubicin	AIDS-related Kaposi sarcoma	166	7138
Febrile neutropenia (Calhoun 2003[10])	Liposomal doxorubicin	AIDS-related Kaposi sarcoma	121	6717
Neutropenia treated as an outpatient (Albain 2002[9])	Chemotherapy	Breast cancer	17	5704
Anemia (Salma 2007[11])	Topotecan	Ovarian cancer	120	5181
Neutropenia (Salma 2007[11])	Topotecan	Ovarian cancer	120	3756
Thrombocytopenia (Calhoun 2001[3])	Cis-platinum	Ovarian cancer	15	3268
Febrile neutropenia treated in an emergency room (Courtney 2007[12])	Chemotherapy	Various	48	1455
Neutropenia treated as an outpatient (Albain 2002[9])	Chemotherapy	Lung cancer/multiple myeloma	14	1329
Neutropenia treated as an outpatient (Albain 2002[9])	Chemotherapy	Lymphoma	12	1201
Neuropathy (Calhoun 2001[3])	Cis-platinum	Ovarian cancer	42	688
Palmar-plantar erythrodysia (Salma 2007[11])	Liposomal doxorubicin	Ovarian cancer	115	104
Stomatitis/esophagitis (Salma 2007[11])	Liposomal doxorubicin	Ovarian cancer	120	101
Nausea and vomiting (Salma 2007[11])	Topotecan	Ovarian cancer	120	83
Diarrhea (Salma 2007[11])	Topotecan	Ovarian cancer	120	58

AIDS indicates acquired immunodeficiency syndrome.
* Calhoun EA, Bennett CL. Evaluating the total costs of cancer. The Northwestern University Costs of Cancer Program. Oncology (Williston Park). Jan 2003;17(1):109-114; discussion 119-121.[10]

were strong disincentives for providing supportive care in the inpatient setting.

The results of the current study can be contrasted with those reported previously by our group for other cancer-treatment–related toxicities (Table 3).[10] In particular, our costs of radiochemotherapy-associated mucositis/pharyngitis were similar to those reported for inpatient care for chemotherapy-associated neutropenia and were markedly greater than those reported for a wide range of other chemotherapy-associated toxicities, almost all of which were $\leq$$10,000 (Table 3). It also is evident from Table 3 that the most expensive toxicities were those that were treated in an inpatient setting.

This study had several limitations. First, neither this study nor most of the prior cost of toxicity studies prospectively evaluated the severity of mucositis/pharyngitis. Second, we did not include assessments of indirect costs, such as time lost from work for patients and caregivers. Our prior studies indicated that these costs range from $3800 to $4280 per episode of chemotherapy-associated neurotoxicity, neutropenia, or thrombocytopenia.[3] In addition, although the patterns of care were similar between the VA Medical Center and the county hospital, we did not compare differences among the 3 accrual sites because of sample size limitations. It may be valuable for future studies to determine cost differences among institutions and to collect cost data on larger sample sizes than that of this pilot study. Finally, because toxicity gradations were not available consistently in medical records, our study may have been biased toward patients with severe mucositis/pharyngitis reported in physician notes. Future studies should include patients with a broader range of radiochemotherapy-induced mucositis/pharyngitis severity.

In conclusion, the results of this study demonstrate that the incremental costs of radiochemotherapy-associated oral mucositis/pharyngitis are substantial and are greater than those previously reported for a wide range of chemotherapy-associated toxicities. Although recent studies have demonstrated the clinical benefit of intensive therapy,[11] interventions are needed that decrease the frequency and severity of this toxicity among patients with HNC or NSCLC who receive radiochemotherapy regimens.

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