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Treatment Patterns, Costs, and Survival among Medicare-Enrolled Elderly Patients Diagnosed with Advanced Stage Gastric Cancer: Analysis of a Linked Population-Based Cancer Registry and Administrative Claims Database

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Purpose: To assess real-world treatment patterns, health care utilization, costs, and survival among Medicare enrollees with locally advanced/unresectable or metastatic gastric cancer receiving standard first-line chemotherapy.
Materials and Methods: This was a retrospective analysis of the Surveillance, Epidemiology, and End Results-Medicare linked database (2000~2009). The inclusion criteria were as follows: (1) first diagnosed with locally advanced/unresectable or metastatic gastric cancer between July 1, 2000 and December 31, 2007 (first diagnosis defined the index date); (2) ≥65 years of age at index; (3) continuously enrolled in Medicare Part A and B from 6 months before index through the end of follow-up, defined by death or the database end date (December 31, 2009), whichever occurred first; and (4) received first-line treatment with fluoropyrimidine and/or a platinum chemotherapy agent.
Results: In total, 2,583 patients met the inclusion criteria. The mean age at index was 74.8±6.0 years. Over 90% of patients died during follow-up, with a median survival of 361 days for the overall post-index period and 167 days for the period after the completion of first-line chemotherapy. The mean total gastric cancer-related cost per patient over the entire post-index follow-up period was United States dollar (USD) 70,808±56,620. Following the completion of first-line chemotherapy, patients receiving further cancer-directed treatment had USD 25,216 additional disease-related costs versus patients receiving supportive care only (P<0.001).
Conclusions: The economic burden of advanced gastric cancer is substantial. Extrapolating based on published incidence estimates and staging distributions, the estimated total disease-related lifetime cost to Medicare for the roughly 22,200 patients expected to be diagnosed with this disease in 2014 approaches USD 300 millions.

Key Words: Gastric cancer; Treatment patterns; Costs; Survival; Claims data

Introduction

In the United States (US), it is estimated that a total of 22,220 cases of gastric cancer will be diagnosed in 2014, representing 1.3% of all new cancer cases, and 10,990 deaths will occur as a result.[1] Gastric cancer predominantly affects older individuals. In the US, the annual incidence of this malignancy in people younger than 65 years is 2.9 per 100,000 people, compared with 39.4 per 100,000 people among those aged 65 years or older.[2] Patients with early-

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stage gastric cancer are often asymptomatic or have non-specific symptoms. Consequently, in the US, only 25% of patients have localized disease at the time of diagnosis. Conversely, 30% have regional spread at the time of diagnosis, and 34% have distant metastases. The remaining 11% of patients are unstaged.[2]

In countries with a relatively low incidence of gastric cancer, such as the US, population-based screening is costly and unwarranted. However, people with high-risk conditions (e.g., older individuals with chronic gastric atrophy, pernicious anemia, gastric polyps, or familial cancer syndromes) may benefit from early detection efforts.[3] Although patients diagnosed with localized gastric cancer in the US have a reasonable possibility of being cured (estimated 5-year relative survival [5YS] of 63.2%), those diagnosed with regional spread have an estimated 5YS of only 28.4%, and those diagnosed with distant metastases have a 5YS of only 3.9%.[2]

Among patients diagnosed with advanced gastric cancer (locally advanced/unresectable or metastatic disease), chemotherapy is typically used to palliate symptoms and prolong survival. Current (2014) National Comprehensive Cancer Network (NCCN) guidelines recommend the use of a combination of platinum- and fluoropyrimidine-based cytotoxic agents as the first-line chemotherapy regimen for this population.[4] Research suggests that patients with metastatic gastric cancer receiving first-line chemotherapy have improved survival (8~12 months) compared with patients receiving best supportive care only (3~5 months).[5] For patients who fail first-line therapy, NCCN guidelines suggest single-agent chemotherapy as second-line therapy.[4]

As 62% of patients diagnosed with gastric cancer are 65 years old or older at diagnosis,[2] the current economic impact of gastric cancer on the Medicare system, which serves as the primary insurance provider for the elderly in the US, has not been widely evaluated. The objective of this study was to assess real-world treatment patterns, health care utilization and associated costs, and survival among Medicare-enrolled patients diagnosed with locally advanced/unresectable or metastatic gastric cancer who received NCCN-recommended first-line treatment with fluoropyrimidine- and/or platinum-based chemotherapy.

Materials and Methods

1. Study design and data source

The linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database was analyzed from 2000 through 2009 in this retrospective longitudinal cohort study. The SEER-Medicare database, its contents, and methods of collection are described in detail elsewhere.[6-11] At the time of this study, data for elderly SEER patients with an incident cancer diagnosis between 1991 and 2007 were available together with their linked Medicare claims through 2009 (for services covered under Medicare Parts A and B). However, data on outpatient prescription drug claims covered under Medicare Part D were only available for 2007 through 2009, as the Medicare Part D prescription drug plan did not take effect until 2006.

2. Patient selection

Patients were initially eligible for this study if they had a diagnosis of gastric cancer (International Classification of Diseases for Oncology, Third Edition [ICD-O-3] codes: C16.0 to C16.9), which includes cancer of the gastroesophageal junction (GEJ), during the period from July 1, 2000 through December 31, 2007. The patient sample was further restricted to those for whom gastric cancer was either the first diagnosed malignancy or for whom there was no evidence of another cancer type within 5 years prior to their gastric cancer diagnoses. The date of the first observed gastric cancer diagnosis defined the gastric cancer index date. Patients were also required to be 65 years of age or older at the gastric cancer index date, which excluded patients who were, at the gastric cancer index date, enrolled in Medicare because of disability and/or end-stage renal disease. Patients were further required to have continuous Medicare Part A and B enrollment from 6 months prior to the gastric cancer index date through the end of follow-up as defined by death or the end of the database (December 31, 2009), whichever occurred first. Patients with any health maintenance organization enrollment during this period were excluded from the study,[12,13] as were patients diagnosed with in situ gastric cancer.

In addition to the aforementioned criteria, the cohort was additionally restricted to patients with at least one claim for a chemotherapy agent following the gastric cancer index date. Patients with evidence of chemotherapy, depending upon disease stage and gastrectomy status at the gastric cancer index date, were required to meet the following additional criteria:

1) Diagnosed with metastatic (distant) disease and received a fluoropyrimidine (i.e., fluorouracil or capecitabine) and/or a platinum agent (i.e., cisplatin, carboplatin, or oxaliplatin) with or without other chemotherapy agents as the first-line chemotherapy; or

2) Diagnosed with early-stage (i.e., localized, regional, unknown) disease, underwent gastrectomy (International Classification of Diseases, 9th Revision, Clinical Modifications [ICD-9-

CM] procedure codes 43.5–43.99; CPT codes 43620, 43621, 43622, 43631, 43632, 43775, 43845), and subsequently received a fluoropyrimidine and/or a platinum agent at least 3 months after gastrectomy.

The latter treatment criterion assumed no adjuvant chemotherapy was received within 3 months after gastrectomy. Thus, the subsequent fluoropyrimidine and/or platinum chemotherapy regimen was considered first-line treatment following disease progression.

3. Study measures

1) Patient characteristics

Patient demographic and clinical characteristics assessed at the index date were age, sex, race, SEER region, urban/non-urban status of residence, census region, primary tumor location, stage at initial gastric cancer diagnosis, and site(s) of metastasis. The Charlson Comorbidity Index (excluding gastric cancer) was calculated to obtain a measure of the patients' overall comorbidity burden during the 6-month period preceding the gastric cancer index date.[14] The presence of ascites during the follow-up period was also recorded. Human epidermal growth factor receptor 2 (HER2) status was determined via proxy based on the use of either trastuzumab or lapatinib, as the use of these agents is typically limited to patients who are HER2-positive.

In addition to the aforementioned characteristics, overall survival (OS) was assessed as an additional background characteristic and was calculated from the index date to death or the end of the database (December 31, 2009), whichever occurred first. Patients who survived beyond the database end date were censored. OS was also calculated from the completion of first-line chemotherapy.

2) Cancer-related treatment patterns and costs

The number and percentage of patients receiving cancer-related treatments including radiotherapy, chemotherapy, biologic therapy, and palliative surgery were evaluated using the Medicare medical and pharmacy claims data. Among patients receiving chemotherapy, the distribution of first-, second-, and third-line chemotherapy regimens and the chemotherapy agents received within each regimen was assessed. Additionally, for each patient receiving a first-, second-, or third-line regimen, the number of treatment cycles that were completed within each line was estimated. The determination of the line of treatment and number of cycles for a given course of treatment was performed using methods presented in prior published studies, in which a change in chemotherapy agents generally indicated a new line of therapy.[5,15-17] For each line of therapy, the duration of treatment was calculated from the first chemotherapy administration date to the last chemotherapy drug administration date within each line of the chemotherapy regimen.

In addition to evaluating cancer-related treatments, supportive care received during the follow-up period was assessed, including growth factors, iron therapy, antibiotics, antivirals, antiemetics, antifungals, pain medication, and nutritional support. The utilization of injectable formulations of these treatments administered by health care providers was captured on the basis of procedure codes recorded in the Medicare claims under Medicare Part B. However, any self-administered forms of these medications dispensed via outpatient pharmacies were only captured for patients with Medicare Part D enrollment and linked pharmacy claims data in 2007 through 2009, as Medicare Part D prescription claims were unavailable prior to this period. The number and proportion of patients undergoing diagnostic tests, including positron emission tomography, endoscopy, computed tomography, magnetic resonance imaging, radiography, and blood tests, were assessed.

Both cancer-directed and supportive care treatments were defined on the basis of the evidence of relevant Health Care Common Procedure Coding System (HCPCS) procedure codes, ICD-9-CM procedure codes, generic and brand drug names, national drug codes, and certain ICD-9-CM diagnostic codes and administrative revenue codes (code list provided in Appendix 1).

Costs were calculated using the Medicare paid amount in the medical and pharmacy claims database for each gastric cancer-related treatment and supportive care claim observed following the index date. All cost data were adjusted at the claim level to 2012 US currency (United States dollar, USD) using the medical care component of the US Consumer Price Index.

3) Overall health care utilization and costs

Gastric cancer-related and all-cause health care utilization and costs were assessed as a whole and by major care settings, including inpatient, hospital outpatient, emergency department, physician office, skilled nursing facility, hospice, and other ancillary care. Place of service codes associated with each medical claim were used to determine care setting-specific utilization and costs. Gastric cancer-related health care utilization and associated costs were drawn from the following sources: (a) medical claims with a gastric cancer diagnosis (primary or secondary) code (ICD-9-CM: 151.x); (b) outpatient pharmacy claims (i.e., Medicare Part D claims for 2007~2009) for gastric cancer-related supportive care medications (e.g., nutritional supplements); and (c) medical claims for gastric

cancer-related therapies covered by Medicare Parts A and B (e.g., intravenous chemotherapy, radiotherapy). All cost data represented the actual amounts paid by Medicare to providers for each service encounter and treatment observed, and as previously described, the data were adjusted at the claim level to 2012 USD.

4. Statistical analyses

All analyses were conducted using SAS ver. 9 (SAS Institute, Cary, NC, USA). Patients were categorized on the basis of treatments received after the completion of first-line chemotherapy. Those receiving additional cancer-related treatments (i.e., chemotherapy, biologics, or radiotherapy) after completing first-line chemotherapy were categorized as 'additionally treated,' and all remaining patients were categorized as 'supportive care only.' The previously described study measures were assessed and reported as a whole and by these two patient groups.

We further analyzed OS, treatment patterns, and heath care utilization and costs over various follow-up periods as follows:

1) Overall follow-up period: the period between the index gastric cancer diagnosis date and death or the end of the database (December 31, 2009), whichever occurred first

2) Post-first-line chemotherapy period: the period between the day immediately following the first-line chemotherapy administration end date and death or the end of the database, whichever occurred first

3) First-line chemotherapy period: the period between the index date and the first-line chemotherapy regimen end date

4) Second-line chemotherapy period: the period between the day immediately following the first-line chemotherapy regimen end date and the last date of the second-line chemotherapy regimen among those who received second-line chemotherapy

The second-line chemotherapy period was not applicable to the supportive care only group, as they did not receive any additional cancer-directed treatment following the completion of their first-line chemotherapy.

Descriptive analyses were conducted, and mean values, standard deviations, median values, and interquartile ranges were reported for continuous variables. Numbers and percentages were used to describe categorical variables. Unadjusted differences between the two groups (i.e., additionally treated vs. supportive care only) were tested using Student's t-test for continuous measures and chi-squared tests for categorical measures. The Kaplan-Meier method was used to descriptively assess OS.

The conduct of this study was approved by the National Cancer Institute and the Institutional Review Board at RTI International (Committee on the Protection of Human Subjects, Federal-Wide

Table 1. Patient characteristics: overall and by treatment cohort

Characteristic	Overall (n=2,583)	Additionally treated* (n=1,415)	Supportive care only* (n=1,168)	P-value†
Age at index gastric cancer diagnosis				
Mean±SD	74.8±6.0	74.4±6.0	75.2±5.9	<0.001
Median	74	74	75	
Age group (yr)				
65~74	1,322±51	748±53	574±49	
75~84	1,100±43	586±41	514±44	
≥85	161±6	81±6	80±7	
Sex				0.002
Female	831±32	418±30	413±35	
Male	1,752±68	997±70	755±65	
Race				0.033
White	2,060±80	1,153±81	907±78	
Asian	142±5	83±6	59±5	
Black	206±8	98±7	108±9	
Hispanic	76±3	33±2	43±4	
Other	96±4	47±3	49±4	
Unknown	3±0	1±0	2±0	

Table 1. Continued

Characteristic	Overall (n=2,583)	Additionally treated* (n=1,415)	Supportive care only* (n=1,168)	P-value†
Location of residence				0.169
Big metro	1,551±60	822±58	729±62	
Less urban	159±6	89±6	70±6	
Metro	705±27	401±28	304±26	
Rural	26±1	17±1	9±1	
Urban	142±5	86±6	56±5	
SEER region				0.254
Midwest	365±14	207±15	158±14	
Northeast	724±28	395±28	329±28	
South	319±12	159±11	160±14	
West	1,175±45	654±46	521±45	
Primary tumor location‡				<0.001
Body of stomach	195±8	89±6	106±9	
Cardia, NOS	1,111±43	705±50	406±35	
Fundus of the stomach	92±4	48±3	44±4	
Gastric antrum	338±13	155±11	183±16	
Greater curvature of the stomach, NOS	73±3	39±3	34±3	
Lesser curvature of the stomach, NOS	177±7	97±7	80±7	
Overlapping lesion of the stomach	182±7	83±6	99±8	
Pylorus	49±2	27±2	22±2	
Stomach, NOS	366±14	172±12	194±17	
Stage at initial diagnosis				0.072
Localized	418±16	253±18	165±14	
Metastatic	1,386±54	742±52	644±55	
Regional	541±21	288±20	253±22	
Unstaged	238±9	132±9	106±9	
Site of metastasis				0.027
Distant lymph node(s)	84±6	60±7	24±4	
Distant metastasis except distant lymph node(s)	509±35	280±34	229±36	
Distant metastasis plus distant lymph node(s)	107±7	60±7	47±7	
None	629±43	341±41	288±45	
Unknown	136±9	84±10	52±8	
Charlson comorbidity index score§				
Mean±SD	2.4±2.4	2.3±2.3	2.5±2.5	0.043
Median	2.0	2.0	2.0	

Values are presented as mean±SD, median only, or number (%). P-values were calculated using Student's t-test for continuous variables and Fisher's exact test for dichotomous variables. SD = standard deviation; SEER = Surveillance, Epidemiology and End Results; NOS = not otherwise specified. *Patients receiving cancer-related treatments after the first-line chemotherapy completion date were categorized as 'additionally treated,' and the remainder were otherwise classified as 'supportive care only.' †Additionally treated vs. supportive care only. ‡Includes patients with a tumor site of the gastroesophageal junction. §Including lymphoma, leukemia, except malignant neoplasm of the skin; also excludes gastric cancer.

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Results

1. Patient characteristics

A total of 2,583 patients were identified for analysis after applying all inclusion and exclusion criteria (Table 1). Of these, approximately 55% (n=1,415) received additional cancer-directed therapy after the completion/discontinuation of first-line chemotherapy, and they were classified as 'additionally treated.' The remaining 45% of patients (n=1,168) were classified as 'supportive care only.' The mean patient age at the index date was 74.8±6.0 years. Additionally treated patients were approximately 10 months younger than patients in the supportive care only group (74.4±6.0 years vs. 75.2±5.9 years; P<0.001). Over two-thirds of patients were male, and approximately 80% were white, a trend that remained consistent across the additionally treated and supportive care only groups. Cardia not otherwise specified (NOS) was the most commonly observed (43%) tumor location site, which differed between the additionally treated and supportive care only groups (50% vs. 35%; P<0.001). Slightly more than half (54%) of all patients presented with metastatic (distant) stage disease at the initial gastric cancer diagnosis. Ninety-two percent of patients died during the follow-up period (Fig. 1A). The median survival was 361 days for the post-gastric cancer diagnosis period, compared with 167 days following the completion of first-line chemotherapy. Median survival was longer (272 days) in the additionally treated group than in the supportive care only group (72 days) after the completion of first-line chemotherapy (Fig. 1B). Additional survival estimates are presented in Appendix 2.

2. Cancer-directed treatment and supportive care utilization

Table 2 presents the details on overall cancer-directed treatment and supportive care utilization during the follow-up period. Among all patients, 48% had evidence of radiotherapy, and 2% had evidence of biologic therapy at any time during the overall follow-up period. Among the additionally treated group, 71% received second-line chemotherapy, 64% received radiotherapy, and 4% received biologic therapy. For both the additionally treated and supportive care only groups, fluorouracil (≥58%), cisplatin (≥24%), and carboplatin (≥20%) were the most commonly used first-line chemotherapy agents. Although less commonly utilized in second- and third-line treatment, fluorouracil remained the most common chemotherapy agent used (alone or in combination with other chemotherapies) in the post–first-line setting (37 and 30% of second- and third-line chemotherapy initiators, respectively). Following the gastric cancer index date, the majority of patients received supportive or palliative care medications, with antiemetics (86%) being the most common, followed by growth factors (66%), pain medications (50%), and antibiotics (28%). Additional data on supportive care utilization are provided in Appendix 3.

Among all patients, the distribution of first-, second-, and third-line chemotherapy agents and regimens received within each line of therapy are presented in Table 3. In the first-line setting, 55%, 24%, and 20% of patients received a two-drug combination (doublet therapy), three-drug combination (triplet therapy), and a single drug (monotherapy), respectively. Patients completed a mean of 5.5±6.4) cycles of first-line chemotherapy, with a mean total average therapy duration of 67±83 days. Patients receiving doublet therapy completed a greater mean number of chemotherapy cycles

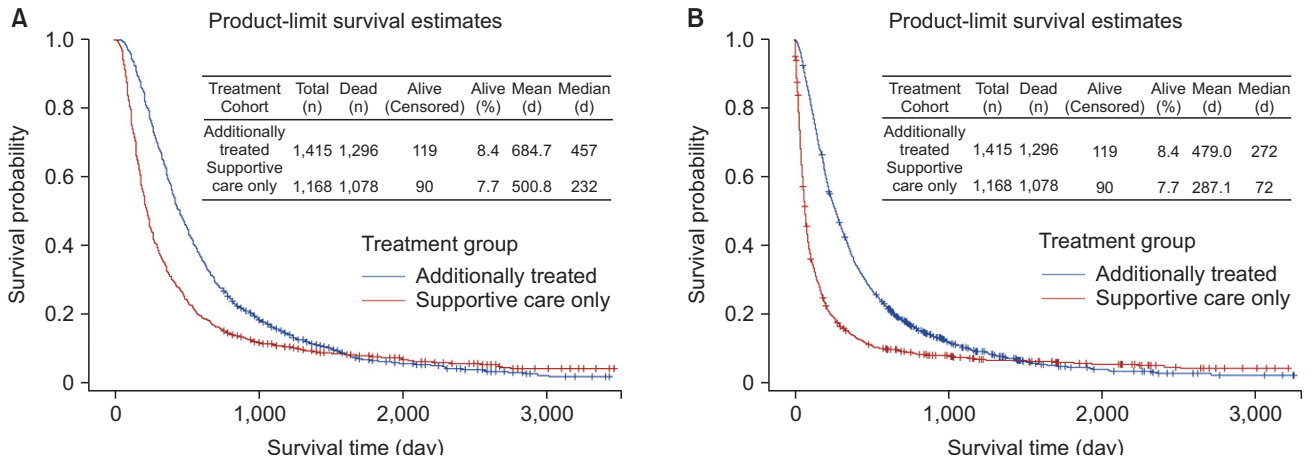

Fig. 1. Kaplan-Meier survival estimates. (A) Survival post gastric cancer diagnosis, by treatment Cohort. (B) Survival post completion of first-line chemotherapy, by treatment Cohort.

Table 2. Treatment patterns during the overall follow-up period*,†

Characteristic	Overall (n=2,583)	Additionally treated‡,§ (n=1,415)	Supportive care only‡,§ (n=1,168)	P-value‖
Post-index prevalence of broad treatment categories post-gastric cancer diagnosis				
Radiation therapy	1,252±48	908±64	344±29	<0.001
Biologic therapy¶	60±2	56±4.0	4±0	<0.001
Chemotherapy	2,583±100	1,415±100	1,168±100	NA
Prevalence of broad treatment categories during first-line chemotherapy				
Radiation therapy	1,108±43	764±54	344±29	<0.001
Biologic therapy	19±1	15±1	4±0	0.038
Chemotherapy	2,583±100	1,415±100	1,168±100	
Prevalence of broad treatment categories after first-line chemotherapy				
Radiation therapy	768±30	768±54	0±0	NA
Biologic therapy	49±2	49±3	0±0	NA
Chemotherapy	1,000±39	1,000±71	0±0	NA
Post-index prevalence of chemotherapy, by line of therapy				
Total receiving first-line chemotherapy	2,583	1,415	1,168	
Top 10 most common first-line chemotherapy agents**				
Fluorouracil	1,544±60	821±58	723±62	0.048
Leucovorin	852±33	399±28	453±39	<0.001
Cisplatin	672±26	396±28	276±24	0.013
Carboplatin	576±22	348±25	228±20	0.002
Paclitaxel	388±15	242±17	146±13	0.001
Docetaxel	297±11	176±12	121±10	0.107
Irinotecan	229±9	116±8	113±10	0.211
Etoposide	221±9	98±7	123±11	0.001
Capecitabine	206±8	104±7	102±9	0.215
Oxaliplatin	141±5	74±5	67±6	0.602
Total receiving second-line chemotherapy	1,000	1,000	0	
Top 10 most common second-line chemotherapy agents**				
Fluorouracil	366±37	366±37	0±0	NA
Leucovorin	234±23	234±23	0±0	NA
Docetaxel	210±21	210±21	0±0	NA
Cisplatin	195±20	195±20	0±0	NA
Paclitaxel	179±18	179±18	0±0	NA
Carboplatin	170±17	170±17	0±0	NA
Irinotecan	150±15	150±15	0±0	NA
Oxaliplatin	78±8	78±8	0±0	NA
Capecitabine	77±8	77±8	0±0	NA
Gemcitabine	60±6	60±6	0±0	NA
Total receiving third-line chemotherapy	456	456	0	
Top 10 most common third-line chemotherapy agents**				
Fluorouracil	137±30	137±30	0±0	NA
Docetaxel	105±23	105±23	0±0	NA
Irinotecan	92±20	92±20	0±0	NA
Cisplatin	82±18	82±18	0±0	NA
Leucovorin	73±16	73±16	0±0	NA
Carboplatin	63±14	63±14	0±0	NA
Paclitaxel	57±13	57±13	0±0	NA
Oxaliplatin	43±9	43±9	0±0	NA
Capecitabine	39±9	39±9	0±0	NA
Gemcitabine	33±7	33±7	0±0	NA

Table 2. Continued

Characteristic	Overall (n=2,583)	Additionally treated[‡,§] (n=1,415)	Supportive care only[‡,§] (n=1,168)	P-value[‖]
Post-index prevalence of supportive or palliative medications post-gastric cancer diagnosis				
Palliative surgery	41±2	33±2	8±1	<0.001
Growth factors	1,704±66	1,041±74	663±57	<0.001
Granulocyte-colony stimulating factors	838±32	565±40	273±23	<0.001
Erythropoietin-stimulating agents	1,541±60	946±67	595±51	<0.001
Iron therapy	164±6	93±7	71±6	0.627
Antibiotics	736±28	444±31	292±25	<0.001
Antivirals	34±1	22±2	12±1	0.299
Antiemetics	2,215±86	1,289±91	926±79	<0.001
Antifungals	62±2	41±3	21±2	0.072
Pain medications	1,286±50	782±55	504±43	<0.001
Bisphosphonate	139±5	105±7	34±3	<0.001
Nutritional support	570±22	342±24	228±20	0.005
Positron emission tomography	294±11	208±15	86±7	<0.001
Endoscopy	2,491±96	1,383±98	1,108±95	<0.001
Computed tomography scan	2,487±96	1,388±98	1,099±94	<0.001
Magnetic resonance imaging	237±9	142±10	95±8	0.100
Radiography	1,591±62	870±61	721±62	0.903
Blood test	2,503±97	1,394±99	1,109±95	<0.001

Values are presented as mean±standard deviation. Granulocyte-colony stimulating factors included filgrastim, pegfilgrastim, and sargramostim; erythropoietin-stimulating agents included erythropoietin and darbepoetin. The P-value is for overall differences among those who received a combination therapy. Patients who did not receive combination therapy were excluded from the calculation. NA = not applicable; *The date of the first observed diagnosis of locally advanced, unresectable, or metastatic gastric cancer diagnosis defined the gastric cancer index diagnosis date. [†]Locally advanced, unresectable, or metastatic gastric cancer-related treatments and supportive care assessed during the entire available follow-up period (i.e., gastric cancer index diagnosis date until death or the end of the database). [‡]Patients receiving cancer-related treatments after the first-line chemotherapy completion date were categorized as 'additionally treated,' and the remaining patients were otherwise categorized as 'supportive care only.' [§]Gastric cancer-related supportive care assessed from the first-line chemotherapy completion date to the date of death or the database end date. [‖] Additionally treated vs. supportive care only. [¶]Biologic therapy included trastuzumab, lapatinib, bevacizumab, cetuximab, and panitumumab. **The denominator is the number of patients who received this line of therapy.

(6.1±6.9) than those receiving triplet therapy (5.5±6.4 cycles) or monotherapy (3.9±3.8 cycles). Among patients initiating first-line chemotherapy with a platinum agent and/or fluoropyrimidine (n=2,583), 39% (n=1,000) initiated second-line chemotherapy. Among these patients, 36%, 40%, and 21% received monotherapy, doublet therapy, and triplet therapy, respectively. Single-agent docetaxel, fluorouracil with leucovorin, and single-agent paclitaxel were the three most commonly observed second-line chemotherapy regimens. Less than half (46%; n=456) of second-line initiators subsequently started third-line chemotherapy. Of these, 42% received monotherapy, and 39% received doublet therapy. Docetaxel monotherapy (10%) and irinotecan monotherapy (7%) were the most commonly used third-line regimens among these patients.

3. Gastric cancer-related utilization and costs

The average per-patient total gastric cancer-related treatment and supportive care cost was USD 26,904±30,071, of which 55% was related to gastric cancer-related treatment (USD 14,668±17,501) and 45% was dedicated to supportive care (USD 12,236± 18,251) (Table 4). Chemotherapy-related costs (including drug and administration costs) accounted for 68% (USD 10,036±15,055) of the total gastric cancer-related treatment costs. The total cost of supportive care was driven by the use of growth factors (49%; USD 6,043± 11,421]). The average total cost of treatment was 8-fold higher in the additionally treated group (USD 21,585±26,989) than in the supportive care only group (USD 2,695±14,437; P<0.001), with chemotherapy accounting for nearly 37% of the cost. For both

Table 3. Chemotherapy utilization patterns during the overall follow-up period*,†

Treatment	Number (%)	Therapy duration (d)		Number of cycles observed	
		Mean±SD	Median (range)	Mean±SD	Median (range)
First-line regimens					
All first-line regimens	2,583 (100.0)	67±83	42 (9~96)	5.5±6.4	4 (2~6)
Single drug	504 (19.5)	44±70	28 (1~45)	3.9±3.8	3 (1~5)
Combination of two drugs	1,425 (55.2)	70±79	44 (15~100)	6.1±6.9	4 (2~7)
Combination of three drugs	611 (23.7)	79±98	54 (17~114)	5.5±6.4	4 (2~7)
Combination of four drugs	41 (1.6)	76±72	57 (21~99)	4.3±4.3	3 (1~6)
Combination of five drugs	2 (0.1)	72±78	72 (17~127)	26.5±23.3	27 (10~43)
Most frequent regimens‡					
Fluorouracil/leucovorin	471 (18.2)	75±88	44 (9~116)	9.0±9.3	6 (3~12)
Carboplatin/paclitaxel	264 (10.2)	75±76	51 (23~107)	5.8±5.9	4 (2~6)
Fluorouracil	254 (9.8)	34±54	28 (3~38)	4.0±4.1	4 (2~6)
Etoposide/fluorouracil/leucovorin	175 (6.8)	59±60	44 (3~95)	7.6±7.1	6 (3~10)
Cisplatin/irinotecan	173 (6.7)	77±88	57 (8~106)	5.5±5.1	4 (2~8)
Capecitabine	143 (5.5)	61±96	26 (1~72)	3.3±3.4	2 (1~4)
Cisplatin/fluorouracil	139 (5.4)	44±45	31 (8~60)	2.6±2.1	2 (1~3)
Second-line regimens					
All second-line regimens	1,000 (100.0)	65±88	36 (8~93)	4.7±6.4	3 (1~6)
Single drug	358 (35.8)	57±95	31 (1~72)	4.9±7.7	3 (1~6)
Combination of two drugs	403 (40.3)	64±79	37 (8~97)	4.8±5.9	3 (1~6)
Combination of three drugs	205 (20.5)	79±87	53 (15~110)	4.6±4.7	3 (1~6)
Combination of four drugs	33 (3.3)	87±110	31 (8~158)	2.1±3.5	1 (1~2)
Combination of five drugs	1 (0.1)	122±0	122 (122~122)	1.0±0.0	1 (1~1)
Most frequent regimens‡					
Docetaxel	83 (8.3)	56±54	43 (15~85)	5.0±3.7	4 (2~6)
Fluorouracil/leucovorin	70 (7.0)	68±97	30 (8~96)	7.7±8.7	5 (2~10)
Paclitaxel	63 (6.3)	71±80	43 (15~99)	6.3±5.3	4 (2~10)
Carboplatin/paclitaxel	62 (6.2)	74±65	64 (29~113)	5.7±5.6	4 (2~7)
Cisplatin/irinotecan	50 (5.0)	89±99	64 (15~141)	6.3±5.8	5 (2~8)
Capecitabine	49 (4.9)	48±80	24 (1~41)	2.9±3.0	2 (1~3)
Third-line regimens					
All third-line regimens	456 (100.0)	55±80	36 (6~78)	4.5±7.8	3 (1~6)
Single drug	193 (42.3)	49±99	25 (1~64)	5.2±10.9	3 (1~6)
Combination of two drugs	178 (39.0)	55±60	36 (7~84)	4.1±4.1	3 (1~5)
Combination of three drugs	71 (15.6)	70±73	43 (8~109)	4.0±4.3	2 (1~4)
Combination of four drugs	12 (2.6)	65±39	71 (37~92)	2.9±3.8	1 (1~2.5)
Combination of five drugs	2 (0.4)	93±129	93 (1~184)	1.0±0.0	1 (1~1)
Most frequent regimens‡					
Docetaxel	46 (10.1)	53±57	44 (8~71)	5.5±4.2	4 (2~8)
Irinotecan	31 (6.8)	45±49	29 (8~65)	4.5±4.1	3 (2~5)
Cisplatin/irinotecan	24 (5.3)	73±71	51 (16~129)	5.5±4.4	4 (2~8.5)
Capecitabine	23 (5.0)	42±61	18 (1~66)	2.7±2.4	2 (1~4)
Carboplatin/paclitaxel	21 (4.6)	59±52	43 (22~89)	3.5±2.7	3 (2~4)
Paclitaxel	21 (4.6)	72±84	57 (27~71)	7.5±9.2	4 (3~7)

SD = standard deviation. *The date of the first observed diagnosis of locally advanced, unresectable, or metastatic gastric cancer defines the gastric cancer index diagnosis date. †Chemotherapy utilization patterns assessed during the follow-up period (i.e., gastric cancer index diagnosis date until death or the end of the database). ‡The denominator is the number of patients who received this line of therapy.

Table 4. Gastric cancer-related treatment and supportive care costs* (USD)

	Periods of gastric cancer-related treatment and supportive care costs assessment‡					
	Overall Cohort	Additionally treated†			Supportive care only†	
	Overall follow-up (n=2,583)	All post–first-line chemotherapy (n=1,415)	First-line chemotherapy (n=1,415)	Second-line chemotherapy (n=1,415)	All post–first-line chemotherapy (n=1,168)	First-line chemotherapy (n=1,168)
Overall gastric cancer-related treatment and supportive care costs						
Mean±SD	26,904±30,071	21,585±26,989	15,066±13,834	12,699±15,675	2695±14,437	12,401±15,019
Median	17,524	12,072	11,124	7,657	500	8,314
Overall gastric cancer-related treatment costs						
Mean±SD	14,668±17,501	11,376±16,436	9,293±9,360	6,924±10,279	29±307	7,369±10,435
Median	9,299	5,850	6,859	3,470	0	4,442
Radiation therapy						
Mean±SD	4,335±8,154	3,001±6,752	3,211±5,553	2,250±5,940	0±0	2,061±6,037
Median	0	162	0	0	0	0
Biologic therapy						
Mean±SD	297±3,108	431±3,827	91±1,288	228±2,770	0±0	25±487
Median	0	0	0	0	0	0
Chemotherapy, overall						
Mean±SD	10,036±15,055	7,944±14,260	5,992±8,179	4,446±8,381	29±307	5,283±8,838
Median	4,312	2,558	2,925	1,515	0	2,396
Chemotherapy, drugs						
Mean±SD	7,797±12,975	6,343±12,485	4,634±7,202	3,516±7,598	0±0	3,946±7,524
Median	2,804	1,541	1,638	686	0	1,253
Chemotherapy, administration§						
Mean±SD	2,239±3,332	1,601±2,813	1,358±1,862	929±1,697	29±307	1,337±2,510
Median	1,104	479	808	272	0	672
Overall supportive care costs						
Mean±SD	12,236±18,251	10,209±15,708	5,772±6,983	5,775±9,793	2,666±14,420	5,032±6,970
Median	6,540	4,701	3,496	2,593	487	2,727
Palliative surgery						
Mean±SD	765±9,884	745±5,426	51±1,347	592±4,847	695±13,307	31±1,072
Median	0	0	0	0	0	0
Growth factors						
Mean±SD	6,043±11,421	5,648±11,141	2,750±5,661	2,965±6,369	926±3,406	2,264±5,035
Median	1,631	1,435	37	528	0	0
Granulocyte-colony stimulating factors						
Mean±SD	2,372±7,176	2,159±7,156	1,280±3,949	1,141±4,196	208±703	872±3,305
Erythropoietin-stimulating agents						
Mean±SD	3,671±7,080	3,489±6,916	1,470±2,889	1,825±3,997	718±3,292	1,392±3,000
Median	778	648	0	0	0	0
Iron supplements						
Mean±SD	28±213	16±164	11±91	11±154	12±214	17±99
Median	0	0	0	0	0	0
Antibiotics						
Mean±SD	25±315	28±415	3±22	15±260	10±63	7±60
Median	0	0	0	0	0	0
Antivirals						
Mean±SD	3±54	3±67	0±1	3±67	1±19	1±17
Median	0	0	0	0	0	0

Table 4. Continued

	Periods of gastric cancer-related treatment and supportive care costs assessment‡					
	Overall Cohort	Additionally treated†			Supportive care only†	
	Overall follow-up (n=2,583)	All post–first-line chemotherapy (n=1,415)	First-line chemotherapy (n=1,415)	Second-line chemotherapy (n=1,415)	All post–first-line chemotherapy (n=1,168)	First-line chemotherapy (n=1,168)
Antiemetics						
Mean±SD	1,128±1,822	823±1,590	697±1,049	470±1,010	17±110	638±1,229
Median	472	218	328	101	0	217
Antifungals						
Mean±SD	2±76	1±7	0±1	0±6	0±7	3±113
Median	0	0	0	0	0	0
Pain medications						
Mean±SD	47±553	47±420	6±66	16±142	15±162	24±625
Median	0	0	0	0	0	0
Bisphosphonates						
Mean±SD	170±1,350	194±1,214	61±696	87±655	26±453	42±504
Median	0	0	0	0	0	0
Nutritional support						
Mean±SD	903±4,411	813±4,480	281±1,537	461±2,856	319±2,443	354±1,923
Median	0	0	0	0	0	0
PET						
Mean±SD	298±1,171	164±956	251±840	96±642	34±330	121±559
Median	0	0	0	0	0	0
Endoscopy						
Mean±SD	1,467±1,634	732±1,358	960±847	480±1,122	288±927	906±975
Median	975	166	704	0	0	656
CT scan						
Mean±SD	927±862	671±779	483±450	401±530	222±436	431±413
Median	693	471	360	273	62	320
MRI						
Mean±SD	62±307	33±248	48±225	17±126	14±124	24±133
Median	0	0	0	0	0	0
Radiography						
Mean±SD	61±94	35±67	29±63	19±47	22±50	35±65
Median	20	0	0	0	0	0
Blood test						
Mean±SD	307±316	255±291	143±137	142±174	65±146	133±149
Median	218	170	105	99	20	94

USD = United States dollar; SD = standard deviation; PET = positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging. *Gastric cancer-related treatment costs included radiation, chemotherapy and biologic therapy costs; gastric cancer-related supportive care costs included palliative surgery, growth factors, iron supplements, antibiotics, antivirals, antiemetics, antifungals, pain medications, bisphosphonates, nutritional support, PET, endoscopy, CT, MRI, radiography, and blood tests. †Patients receiving cancer-related treatments after the first-line chemotherapy completion date categorized as 'additionally treated,' otherwise considered as 'supportive care only.' ‡Gastric cancer-related treatment and supportive care costs were assessed during the following pre-defined periods of assessment: (1) Overall follow-up period: the period between the index gastric cancer diagnosis date and death or the end of the database (December 31, 2009), whichever occurred first; (2) Post–first-line chemotherapy period: the period between the day immediately following the first-line chemotherapy administration end date and death or the end of the database, whichever occurred first; (3) First-line chemotherapy period: the period between the gastric cancer index date and the first-line chemotherapy regimen end date; and (4) Second-line chemotherapy period: the period between the day immediately following the first-line chemotherapy regimen end date and the last date of the second-line chemotherapy regimen among patients who initiated second-line chemotherapy. §Patients with chemotherapy administration claims without a corresponding chemotherapy drug claim after the completion of first-line chemotherapy were included in the supportive care only group. However, the chemotherapy administration costs have been reported for these patients.

Table 5. Gastric cancer-related* health care utilization and costs: overall and by treatment cohort and line of therapy

	Periods of gastric cancer-related utilization and costs assessment‡						
	Overall Cohort	Additionally treated†			Supportive care only†		
	Overall follow-up (n=2,583)	All post–first-line chemo-therapy (n=1,415)	First-line chemo-therapy (n=1,415)	Second-line chemo-therapy (n=1,415)	All post–first-line chemo-therapy (n=1,168)	First-line chemo-therapy (n=1,168)	P-value, additionally treated vs. supportive care only post–first-line chemotherapy)
Gastric cancer-related inpatient services							
Had ≥1 hospital admission, n (%)	2,098 (81.2)	835 (59.0)	817 (57.7)	480 (33.9)	622 (53.3)	792 (67.8)	0.004
Number of unique admissions							<0.001
Mean±SD	2±2	1±2	1±1	1±1	1±1	1±1	
Median	2	1	1	0	1	1	
Total days in hospital (among patients with at least 1 hospital admission)							0.973
Mean±SD	8±7	7±6	9±8	7±6	8±7	9±7	
Median	7	6	7	6	6	7	
Total inpatient costs (2012 USD)							<0.001
Mean±SD	34,401±38,214	15,444±23,539	17,829±23,894	6,911±13,741	12,011±25,427	23,756±31,623	
Median	25,967	8,094	9,089	0	5,725	13,929	
Gastric cancer-related ED visits							
Had ≥1 ED visit, n (%)	981 (38.0)	432 (30.5)	227 (16.0)	238 (16.8)	273 (23.4)	244 (20.9)	<0.001
Number of ED visits							<0.001
Mean±SD	1±1	0±1	0±1	0±1	0±1	0±1	
Median	0	0	0	0	0	0	
Total ED costs (2012 USD)							
Mean±SD	57±121	41±95	20±86	19±60	28±72	23±63	
Median	0	0	0	0	0	0	
Gastric cancer-related office or specialist visits							
Had ≥1 office or specialist visit, n (%)	2,580 (99.9)	1,403 (99.2)	1,415 (100.0)	1,395 (98.6)	983 (84.2)	1,160 (99.3)	<0.001
Number of office visits							<0.001
Mean±SD	40±34	29±30	20±15	17±17	8±16	19±18	
Median	29	20	16	12	3	14	
Total office or specialist visit costs (2012 USD)							
Mean±SD	20,705±28,687	1,625±27,355	11,689±13,768	8,734±12,650	1,794±4,276	10,145±14,629	<0.001
Median	10,386	5,830	6,683	3,795	557	5,404	

Table 5. Continued

	Periods of gastric cancer-related utilization and costs assessment‡						
	Overall Cohort	Additionally treated†			Supportive care only†		
	Overall follow-up (n=2,583)	All post–first-line chemo-therapy (n=1,415)	First-line chemo-therapy (n=1,415)	Second-line chemo-therapy (n=1,415)	All post–first-line chemo-therapy (n=1,168)	First-line chemo-therapy (n=1,168)	P-value, additionally treated vs. supportive care only post–first-line chemotherapy)
Gastric cancer-related hospital outpatient visits							
Had ≥1 hospital outpatient visit, n (%)	2,502 (96.9)	1,283 (90.7)	1,339 (94.6)	1,167 (82.5)	669 (57.3)	1,082 (93)	<0.001
Number of hospital outpatient visits							<0.001
Mean±SD	14±18	11±17	7±7	6±13	3±8	7±7	
Median	9	6	5	3	1	4	
Total hospital outpatient costs (2012 USD)							
Mean±SD	8,962±17,641	6,681±18,251	5,527±8,589	4,362±15,488	785±2,934	4,244±7,406	<0.001
Median	3,910	1,863	2,738	984	30	1,878	
Gastric cancer-related hospice visits							
Had ≥1 hospice service, n (%)	848 (32.8)	441 (31.2)	3 (0.2)	101 (7.1)	407 (34.8)	5 (0.4)	0.048
Number of hospice visits							0.051
Mean±SD	1±2	1±2	0±0	0±1	1±2	0±0	
Median	0	0	0	0	0	0	
Total hospice costs (2012 USD)							0.027
Mean±SD	2,173±6,456	2,097±6,720	32±766	646±4,229	2,198±5,765	29±655	
Median	0	0	0	0	0	0	
Gastric cancer-related SNF care							
Had ≥1 SNF admission, n (%)	307 (11.9)	107 (7.6)	50 (3.5)	52 (3.7)	97 (8.3)	78 (6.7)	0.510
Number of SNF admissions							0.518
Mean±SD	0	0	0	0	0	0	
Median	0	0	0	0	0	0	
Total SNF care costs (2012 USD)							
Mean±SD	1,107±4,137	752±3,553	276±2,004	327±2,197	629±2,809	573±2,941	0.456
Median	0	0	0	0	0	0	

Table 5. Continued

	Periods of gastric cancer-related utilization and costs assessment‡						
	Overall Cohort	Additionally treated†			Supportive care only†		
	Overall follow-up (n=2,583)	All post–first-line chemo-therapy (n=1,415)	First-line chemo-therapy (n=1,415)	Second-line chemo-therapy (n=1,415)	All post–first-line chemo-therapy (n=1,168)	First-line chemo-therapy (n=1,168)	P-value, additionally treated vs. supportive care only post–first-line chemo-therapy)
Gastric cancer-related outpatient pharmacy							
Had ≥1 outpatient pharmacy encounter, n (%)	439 (17.0)	244 (17.2)	135 (9.5)	188 (13.3)	143 (12.2)	125 (10.7)	<0.001
Number of outpatient pharmacy encounters							<0.001
Mean±SD	2±6	2±5	0±2	1±3	1±3	1±3	
Median	0	0	0	0	0	0	
Total outpatient pharmacy encounter costs (2012 USD)							
Mean±SD	157±1,287	128±774	55±682	66±485	30±247	97±1,361	<0.001
Median	0	0	0	0	0	0	
Gastric cancer-related ancillary care							
Had ≥1 ancillary care visit, n (%)	1,604 (62.1)	716 (50.6)	634 (44.8)	524 (37.0)	347 (29.7)	557 (47.7)	<0.001
Number of ancillary care visits							<0.001
Mean±SD	4±7	3±6	2±4	2±4	1±5	2±3	
Median	1	1	0	0	0	0	
Total ancillary care costs (2012 USD)							
Mean±SD	3,247±7,051	2,278±6,166	1,383±3,411	1,267±4,115	984±4,066	1,761±3,822	<0.001
Median	538	0	0	0	0	0	
Gastric cancer-related total health care utilization							
Had ≥1 medical encounter, n (%)	2,583 (100.0)	1,414 (99.9)	1,415 (100.0)	1,414 (100.0)	1,107 (94.8)	1,168 (100.0)	<0.001
Number of encounters							<0.001
Mean±SD	63±48	47±43	30±21	26±28	15±24	30±24	
Median	50	36	25	19	8	24	
Total costs (2012 USD)							
Mean±SD	70,808±56,620	43,674±45,715	36810±31,207	22,332±26,262	18,458±28,055	40,628±39,330	<0.001
Median	58,909	30,179	28,085	14,819	11,236	30,486	

SD = standard deviation; ED = emergency department; USD = United States dollar; SNF = skilled nursing facility. *Gastric cancer-related health care utilization and costs during the follow-up period included medical encounters with gastric cancer diagnosis codes and outpatient pharmacy claims or medical claims for gastric cancer drugs or supportive care treatments. †Patients receiving cancer-related treatments after the first-line chemotherapy completion date were categorized as 'additionally treated,' and the remaining patients were otherwise classified as 'supportive care only.' ‡Gastric cancer-related health care utilization and costs were assessed during the following pre-defined periods of assessment: (1) Overall follow-up period: the period between the index gastric cancer diagnosis date and death or the end of the database (December 31, 2009), whichever occurred first; (2) Post–first-line chemotherapy period: the period between the day immediately following the first-line chemotherapy administration end date and death or the end of the database, whichever occurred first; (3) First-line chemotherapy period: the period between the gastric cancer index date and the first-line chemotherapy regimen end date; and (4) Second-line chemotherapy period: the period between the day immediately following the first-line chemotherapy regimen end date and the last date of the second-line chemotherapy regimen among patients who initiated second-line chemotherapy.

groups, gastric cancer-related treatment costs accounted for approximately 60% of the total costs incurred during the first-line chemotherapy period. This percentage also held across second- and third-line therapy among patients in the additionally treated group. The mean total costs per patient per line for the additionally treated group were USD 15,066±13,834 (first), USD 12,699±15,675 (second), and USD 7,199±14,593 (third).

Overall gastric cancer-related medical resource utilization and costs (inclusive of medical services, cancer-related drugs and administration, and supportive care treatments) incurred during the follow-up period are presented in Table 5. Inpatient medical encounters accounted for 49% (USD 34,401±38,214) of the total gastric cancer-related costs (USD 70,808±56,620). Following the completion of first-line chemotherapy, patients in the additionally treated group had an average 32 more gastric cancer-related medical encounters and incurred an additional USD 25,216 in disease-related costs compared with the supportive care only group ($P<0.001$). The greater utilization and costs observed in the additionally treated group compared with the supportive care only group was primarily attributable to additional cost incurred in the physician office setting (USD 14,458 greater costs; $P<0.001$). The mean cost per patient in the additionally treated group steadily declined between first- and second-line therapy (USD 36,810±31,207 and USD 22,332±26,262, respectively). All-cause utilization and costs are presented in Appendix 4.

Discussion

The objective of this study was to document treatment patterns, overall survival, and health care utilization and costs during and after the completion of platinum- and/or fluoropyrimidine-based first-line chemotherapy among Medicare-enrolled patients diagnosed with metastatic and/or unresectable gastric cancer in the SEER registry. Following the completion of first-line chemotherapy, approximately 55% of patients had evidence of further cancer-directed treatment, a finding consistent with data reported by Pasini et al.[18] The remaining 45% were administered supportive care only. Consequently, patients in the additionally treated group had more than 6-fold greater treatment-related and supportive care costs than patients in the supportive care only group following the completion of first-line chemotherapy. However, after the completion of first-line chemotherapy, the median survival time among patients in the additionally treated group was approximately 7 months longer than that the supportive care only group, which allowed more time for costs to be incurred for the former group.

The receipt of first-line chemotherapy with a platinum agent and/or fluoropyrimidine was a prerequisite for all patients included in this study. Fluorouracil alone or in combination with other agents was the most commonly used first-line chemotherapy regimen. The recorded first-line agents and combination regimens are consistent with previously published studies and the NCCN recommendations in place during the study period.[19-22] However, because of the restrictions on study eligibility other possible first-line regimens that did not contain either a platinum and/or fluoropyrimidine agent were not evaluated. This may account for a percentage of regimens excluded from the present study.

In this study, nearly 40% of patients received second-line chemotherapy, a finding consistent with a prior publication.[18] Among patients receiving second-line chemotherapy, docetaxel, paclitaxel, and 5-fluorouracil (alone and in combination with other agents) were the most commonly used second-line chemotherapy regimens. However, even the most frequently occurring second-line regimen, single-agent docetaxel, was used in only 8% of patients, indicating the extent to which second-line treatment selections varied in this study. Limited data supporting the use of second-line chemotherapy regimens exist, with no randomized trials published before 2011, leading to greater variability in utilized second-line chemotherapy agents as reflected in this study. These findings are also consistent with other published data available from this period.[23-29]

In addition to chemotherapy, nearly 50% of patients also had evidence of radiotherapy. However, post-gastric cancer diagnosis radiotherapy use patterns differed between cohorts, with more than two-thirds of patients in the additionally treated group receiving radiotherapy compared to only one-third of patients in the supportive care only group. Overall, differences in disease prognosis between patients in the additionally treated and supportive care groups may have influenced the use of radiotherapy.

For both study cohorts, more than 90% of patients died during the follow-up period, with a median OS of approximately 12 months. This finding is consistent with prior studies assessing OS among patients with metastatic gastric cancer who received first-line chemotherapy.[2,29] As expected, OS varied by stage at initial diagnosis, the receipt of cancer-directed treatment, and the type of cancer-directed treatment received after first-line chemotherapy. Patients diagnosed with early-stage disease (i.e., localized and regional) had longer median OS than those diagnosed with metastatic disease, a finding consistent with previous reports. The median OS

following first-line chemotherapy was 5.5 months, which differed by treatment status. Among patients receiving cancer-directed treatment, the median OS was 6.6 months longer than patients receiving only supportive care. These findings support several earlier studies reporting the benefits of second-line chemotherapy compared to no active treatment.[25,28,30] However, this finding could be explained by poorer performance status or the prognosis of patients receiving supportive care only after the completion of first-line therapy, limiting their eligibility for additional chemotherapy treatment. Such differences, if they existed, were not controlled for when making these comparisons.

In addition to information on treatment patterns and survival, this study provides details on the direct economic burden associated with gastric cancer-related treatments and supportive care, as well as the distribution of utilization and costs across different care settings (e.g., inpatient, physician office, hospital outpatient). In this study, the per-patient average lifetime all-cause costs exceeded USD 100,000 (Appendix 4), of which approximately 70% (mean, USD 70,808±56,620) comprised gastric cancer-related costs. Inpatient care accounted for more than half of the total all-cause and gastric cancer-related costs. In 2014, 22,220 new cases of gastric cancer were estimated to be diagnosed in the US, of which 62% were expected to occur among elderly patients (≥65 years), and among elderly patients, 34% (approximately 4700) will be diagnosed with metastatic gastric cancer.[2] Combining these incidence figures with our estimate of per-patient average lifetime gastric cancer-related costs (i.e., approximately USD 70,000), the estimated total disease-related costs to Medicare could exceed USD 300 million for the lifetimes of these patients. In general, gastric cancer exerts a considerable economic burden on the Medicare system, and these cost estimates could increase as the population in the US continues to age.

Few studies have assessed costs and utilization patterns among patients with gastric cancer. The available data are dated and/or limited in terms of evaluating all aspects of direct costs.[31-35] Thus, we believe the current study provides more comprehensive and complete direct utilization and cost data. These data more accurately reflect the cost of treating this population, and thus, they may help better inform future cost-effectiveness analyses for newer treatments.

Several limitations should be considered when interpreting the findings of this study. The identification of patients with gastric cancer and determination of gastric cancer-directed treatments and supportive care utilization were conducted using relevant codes (e.g., ICD-O-3, ICD-9-CM, and HCPCS). Thus, any coding errors may have led to misclassification of these patients or gastric cancer-directed treatments. We used ICD-O-3 codes (C16.0-C16.9) to identify patients with gastric cancer including patients with GEJ cancer. However, per ICD-O-3 recommendations, patients with GEJ cancer may also be coded using ICD-0-3 code C16.0 (i.e., cardia NOS). Consequently, for the 1,111 patients with a C16.0 diagnosis code, we were unable to distinguish how many specifically had GEJ cancer. Through the Medicare claims data, it was not possible to determine which factors (e.g., disease severity, extent of progression, response to first-line chemotherapy regimen, lack of suitable second-line therapy, or cure) affect the decision to not prescribe a second-line therapy. The lack of oral prescription drug data (i.e., Medicare Part D data are available only for the period of 2007~2009) for the entire study period likely underestimates the use of gastric cancer-related prescription medications. We applied several inclusion and exclusion criteria and further limited the population to patients with evidence of both Medicare and SEER-linked data. Thus, the findings may not be generalizable to all Medicare enrollees with gastric cancer. Finally, this study was descriptive in nature, and statistical tests performed were not adjusted to account for differences in selected covariates between the populations.

Despite the noted limitations, this publication serves as the first documented comprehensive study describing real-world treatment patterns, survival, and health care utilization and costs before and after the completion of platinum- and/or fluoropyrimidine-based first-line chemotherapy among Medicare-enrolled patients with metastatic and/or unresectable gastric cancer. Our findings indicate that this patient population exerts a substantial economic burden on the Medicare system, with primary cost drivers being inpatient, hospital outpatient, and physician office visits. Survival following the completion of first-line chemotherapy remains poor in this population; however, improved survival was observed among patients receiving second-line treatment compared with patients receiving supportive care only. In conclusion, newer treatment options that would help improve survival and lower the overall economic burden are required.

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References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
2. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2010 [Internet]. National Cancer Institute. Bethesda (MD): National Cancer Institute; [cited 2013 Apr]. Available from: http://seer.cancer.gov/archive/csr/1975_2010/
3. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014;23:700-713.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Gastric Cancer. Version 1. 2014 [Internet]. Fort Washington (PA): NCCN; [cited 2014 Jul 23]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
5. Ajani JA. Evolving chemotherapy for advanced gastric cancer. Oncologist 2005;10 Suppl 3:49-58.
6. National Cancer Institute. The Surveillance, Epidemiology, and End Results: Population Characteristics. 2013 [Internet]. Bethesda (MD): National Cancer Institute; [cited 2013 Dec 31]. Available from: http://seer.cancer.gov/registries/characteristics.html.
7. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40(8 Suppl):IV-3-18.
8. Warren JL, Harlan LC, Fahey A, Virnig BA, Freeman JL, Klabunde CN, et al. Utility of the SEER-Medicare data to identify chemotherapy use. Med Care 2002;40(8 Suppl):IV-55-61.
9. Brown ML, Riley GF, Schussler N, Etzioni R. Estimating health care costs related to cancer treatment from SEER-Medicare data. Med Care 2002;40(8 Suppl):IV-104-117.
10. Cooper GS, Virnig B, Klabunde CN, Schussler N, Freeman J, Warren JL. Use of SEER-Medicare data for measuring cancer surgery. Med Care 2002;40(8 Suppl):IV-43-48.
11. Virnig BA, Warren JL, Cooper GS, Klabunde CN, Schussler N, Freeman J. Studying radiation therapy using SEER-Medicare-linked data. Med Care 2002;40(8 Suppl):IV-49-54.
12. Sundararajan V, Hershman D, Grann VR, Jacobson JS, Neugut AI. Variations in the use of chemotherapy for elderly patients with advanced ovarian cancer: a population-based study. J Clin Oncol 2002;20:173-178.
13. Hershman D, Hall MJ, Wang X, Jacobson JS, McBride R, Grann VR, et al. Timing of adjuvant chemotherapy initiation after surgery for stage III colon cancer. Cancer 2006;107:2581-2588.
14. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol 2008;61:1234-1240.
15. Lang K, Marciniak MD, Faries D, Stokes M, Buesching D, Earle C, et al. Costs of first-line doublet chemotherapy and lifetime medical care in advanced non-small-cell lung cancer in the United States. Value Health 2009;12:481-488.
16. Ramsey SD, Howlader N, Etzioni RD, Donato B. Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: evidence from surveillance, epidemiology and end results-Medicare. J Clin Oncol 2004;22:4971-4978.
17. Ramsey SD, Martins RG, Blough DK, Tock LS, Lubeck D, Reyes CM. Second-line and third-line chemotherapy for lung cancer: use and cost. Am J Manag Care 2008;14:297-306.
18. Pasini F, Fraccon AP, DE Manzoni G. The role of chemotherapy in metastatic gastric cancer. Anticancer Res 2011;31:3543-3554.
19. Javle M, Hsueh CT. Updates in gastrointestinal oncology: insights from the 2008 44th annual meeting of the American Society of Clinical Oncology. J Hematol Oncol 2009;2:9.
20. Kilickap S, Yalcin S, Ates O, Tekuzman G. The first line systemic chemotherapy in metastatic gastric carcinoma: A comparison of docetaxel, cisplatin and fluorouracil (DCF) versus cisplatin and fluorouracil (CF); versus epirubicin, cisplatin and fluorouracil (ECF) regimens in clinical setting. Hepatogastroenterology 2011;58:208-212.
21. Van Cutsem E. The treatment of advanced gastric cancer: new findings on the activity of the taxanes. Oncologist 2004;9 Suppl 2:9-15.

22. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al; V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.
23. Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9:14-18.
24. Jo JC, Lee JL, Ryu MH, Sym SJ, Lee SS, Chang HM, et al. Docetaxel monotherapy as a second-line treatment after failure of fluoropyrimidine and platinum in advanced gastric cancer: experience of 154 patients with prognostic factor analysis. Jpn J Clin Oncol 2007;37:936-941.
25. Kim HS, Kim HJ, Kim SY, Kim TY, Lee KW, Baek SK, et al. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis. Ann Oncol 2013;24:2850-2854.
26. Lee JL, Ryu MH, Chang HM, Kim TW, Yook JH, Oh ST, et al. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. Cancer Chemother Pharmacol 2008;61:631-637.
27. Park SH, Kang WK, Lee HR, Park J, Lee KE, Lee SH, et al. Docetaxel plus cisplatin as second-line therapy in metastatic or recurrent advanced gastric cancer progressing on 5-fluorouracil-based regimen. Am J Clin Oncol 2004;27:477-480.
28. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer: a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306-2314.
29. Rosati G, Ferrara D, Manzione L. New perspectives in the treatment of advanced or metastatic gastric cancer. World J Gastroenterol 2009;15:2689-2692.
30. Kang JH, Lee SI, Lim do H, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012;30:1513-1518.
31. Bachmann M, Peters T, Harvey I. Costs and concentration of cancer care: evidence for pancreatic, oesophageal and gastric cancers in National Health Service hospitals. J Health Serv Res Policy 2003;8:75-82.
32. Elixhauser A, Halpern MT. Economic evaluations of gastric and pancreatic cancer. Hepatogastroenterology 1999;46:1206-1213.
33. Yabroff KR, Davis WW, Lamont EB, Fahey A, Topor M, Brown ML, et al. Patient time costs associated with cancer care. J Natl Cancer Inst 2007;99:14-23.
34. Sherman KL, Merkow RP, Shah AM, Wang CE, Bilimoria KY, Bentrem DJ. Assessment of advanced gastric cancer management in the United States. Ann Surg Oncol 2013;20:2124-2131.
35. Kalinka-Warzocha E, Plazas JG, Mineur L, Salek T, Hendlisz A, DeCosta L, et al. Chemotherapy treatment patterns and neutropenia management in gastric cancer. Gastric Cancer 2015;18:360-367.