Resources and Costs Associated with the Treatment of Advanced and Metastatic Gastric Cancer in the Mexican Public Sector: A Patient Chart Review

Miguel Quintana¹ · José A. Toriz¹ · Diego Novick² · Kyla Jones³ · Brenda S. Botello⁴ · Juan Alejandro Silva¹

Published online: 31 July 2017

© The Author(s) 2017. This article is an open access publication

Abstract

Background Little evidence is available on the management and cost of treating patients with advanced or metastatic gastric cancer (GC). This study evaluates patient characteristics, treatment patterns, and resource utilization for these patients in Mexico.

Methods Data were collected from three centers of investigation (tertiary level). Patients were ≥ 18 years of age, diagnosed between 1 January 2009 and 1 January 2015, had advanced or metastatic GC, received first-line fluoropyrimidine/platinum, and had ≥ 3 months follow-up after discontinuing first-line treatment. Data were summarized using descriptive statistics.

Results The study sample totaled 180. Patients' mean age was 57.2 years (± 12.4) and 57.0% were male; 151 (83.9%) patients received second-line chemotherapy. A total of 16 and 19 regimens were identified in first- and second-line therapy. Of the sample, 51 (28.3%) received third-line therapy, and $<10\%$ received more than three lines of active chemotherapy. Supportive care received in first- and second-line chemotherapy, included pain interventions (12.2 and 7.9%), nutritional support (3.3 and 1.3%), radiotherapy (6.1 and 16.6%), and transfusions (13.3 and 10.6%), respectively. Using Mexican Institute of Social Security

(IMSS) tariffs, the average total cost per patient-month in first- and second-line therapy was US\$1230 [95% confidence interval (CI) 1034–1425] and US\$1192 (95% CI 913–1471), respectively. Administration and acquisition of chemotherapy comprised the majority of costs.

Conclusions This study shows considerable variation in first- and second-line chemotherapy regimens of patients with advanced or metastatic GC. Understanding GC treatment patterns in Mexico will help address unmet needs.

Key Points for Decision Makers

A considerable variety of chemotherapy regimens in first- and second-line therapy of patients with advanced or metastatic GC was observed; however, conformity was seen in the most frequently selected regimens.

Administration and acquisition of chemotherapy comprised the majority of costs; the frequent use of regimens including capecitabine may reflect a conscious move of doctors towards cost-saving measures.

✉ Diego Novick
novick_diego@lilly.com

¹ Department of Medical Oncology, Hospital de Oncología, Centro Médico Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico

² Eli Lilly and Company, Surrey, UK

³ Tecnología e Información para la Salud, Mexico City, Mexico

⁴ Eli Lilly and Company, Mexico City, Mexico

1 Introduction

Over the last 50 years, the reduction in incidence and mortality due to gastric cancer (GC) worldwide has been significant [1]. However, despite this, GC remains highly ranked in both incidence and mortality due to cancer; in 2012 the World Health Organization (WHO) ranked it as the fifth most common malignancy and the third most

common cause of cancer death worldwide [2]. In particular, GC has a high burden of disease in developing countries, where approximately 60% of all cases are detected [3], and where stomach cancer is ranked among the most frequent type of cancer in terms of incidence and mortality [4].

The high mortality rate associated with GC is in part due to its lack of distinct symptoms, which allow GC to go unnoticed until advanced stages, where treatment options are limited [5]. While surgery is considered standard treatment for early-stage GC, the chemotherapy recommended for advanced stages remains relatively nonstandardized in terms of regimen selection. International guidelines recommend a two-drug combination of fluoropyrimidine and platinum in first-line treatment, without recommending specific regimens or specific product endorsements [6–8]. In second-line chemotherapy, ramucirumab, paclitaxel, docetaxel and irinotecan are labeled as the preferred treatment options by the National Comprehensive Cancer Network (NCCN; 2014), however only ramucirumab has formal approval in the indication. Nonetheless, in terms of real-world experience, little evidence is reported on GC management practices that identify the most frequently implemented strategies from the wide range of options available.

This lack of data is surprising as, according to the few published studies available, the economic burden of GCs is relatively high and data regarding treatment patterns could potentially identify areas of cost saving. Presented as an abstract of a retrospective study, in 2011 Knopf et al. collected monthly resource utilization data on patients with GC versus a nondiagnosed control, for the period 2007–2009. The mean monthly costs for patients with GC was US\$10,653, versus US\$571 for the control group [9]. Knopf et al. posited that while GC has a low prevalence in the US, the cost per patient has an overproportionate impact in the cost of care when compared with other cancers. In a study by the US National Cancer Institute, the cost of GC was estimated to be US\$1.82 billion in 2010 [10]. In a third study in the US by Yabroff et al., it was observed that the cost of GC, in terms of initial care, was approximately US\$5348, while for the last year of patient care the cost rose to US\$7435 [11].

Mexico is currently considered a medium-risk area of GC, as defined by incidence rate; in 2012, the WHO estimated a rate of 7.9 per 100,000 inhabitants [2]. Nevertheless, national resources rank GC as the second cause of death associated with cancer, and the first cause of mortality in the country due to digestive tract neoplasms [12]. However, similar to international literature, there is little published evidence on patient management, resource utilization and economic burden, and none on the economic impact of the disease [13].

This study was developed to better understand the current treatment patterns of patients diagnosed with GC in Mexico in order to support public policy regarding GC treatment programs. The primary objectives of the study were to (1) describe the demographic and clinical characteristics of the target patient population in Mexico, and (2) identify and describe treatment patterns used in standard practice. Secondary objectives were to estimate direct costs associated with the treatment of these patients. This study focuses on second-line therapy.

2 Methods

A retrospective, observational study was designed to collect data regarding patient characteristics and institutional resource use from medical records in the Mexican public system. The target population was patients diagnosed with metastatic/unresectable GC (including gastroesophageal junction) between 1 January 2009 and 1 January 2015, and treated in tertiary-level centers of investigation. We defined the index date as the date recorded for diagnosis of advanced or metastatic GC.

A sample size of 200 was set as a target. Ethics approval was obtained, and data capture respected international patient privacy regulations.

Inclusion criteria were:

- Patients completed first-line chemotherapy that included a platinum analog and a fluoropyrimidine, with or without another medication, and continued with either second-line treatment or palliative therapy;
- Patients were >18 years of age at the time of diagnosis;
- Medical records were required to have a follow-up of ≥ 3 months following the last administration of first-line treatment, except those recording a documented death:
- This criterion was applied due to a pilot analysis of data collected within the first 3 days which showed that the number of patients with either (1) less than 3 months of follow-up, or (2) documented death within 3 months, exceeded one-third of the collected sample.

The prespecified criterion regarding minimum follow-up was included in order to allow for analysis on types of agents used in second-line treatment in a situation where a large percentage of patients was being lost to follow-up. This loss of follow-up was experienced in a similar study conducted by the sponsor in Brazil, where a high percentage of patients left third-level facilities once receiving best supportive care (BSC) [14]. As such, the sponsor recommended the inclusion of this criterion in order to

prioritize the capture of resource utilization of patients who remain in tertiary-level hospitals over the calculation of the percentage of patients who are treated in second-line with an active chemotherapy and the resource utilization of BSC.

Exclusion criteria consisted of patients who had participated, or were currently participating, in any controlled clinical study, and patients with a second malignant disease diagnosed before or after the diagnosis of metastatic/unresectable GC.

2.1 Data Collection

Data were captured using a paper Data Report File (DRF) that had been validated by the principal investigator against the Mexican Institute of Social Security (IMSS) patient files. DRFs were monitored for completeness and preciseness by a third-party monitor and transferred to an electronic database. Variables collected included patient demographics and clinical characteristics, treatment received, adverse events, hospitalization and outpatient visits, and resource utilization.

2.2 Outcomes

The primary outcomes of the analysis were defined as the demographic and clinical characteristics of the patient population in Mexico, the proportion of patients treated with each chemotherapy regimen per treatment line, and resource utilization, while secondary outcomes were defined as cost per patient-month and the distribution of cost per patient-month by category.

Start and end dates, as well as duration, were calculated using dates reported in the patient files. The number of days from diagnosis to treatment was calculated using the index date of diagnosis to the day of the first chemotherapy treatment in first-line. In order to include all resources used in each line of therapy, lines of treatment were calculated from the first day of treatment to the day before the following line of chemotherapy; for the first-line of treatment, this was defined as the first date of hospitalization, radiotherapy or chemotherapy following a diagnosis of advanced or metastatic GC. End of treatment was calculated by the last date registered before loss of follow-up, death, or the cut-off date of data capture.

Healthcare utilization rates were categorized by the type of medical resource service; specifically, acquisition of chemotherapy and premedication products, administration, adverse events, radiotherapy, inpatient hospitalization, outpatient visits, use of supportive care procedures and tests. Medicine use, both chemotherapy and premedication,

was calculated using the number of cycles multiplied by total milligrams per cycle, based on reported posology. Costs per milligram were used. Costs of administration, radiotherapy, and supportive care units were calculated by the reported number of sessions or units. The number of grade 3 and 4 adverse events was collected, and the cost of treatment was calculated by adding reported treatment and procedures. Hospitalization for adverse events was included in costs for inpatient hospitalization; inpatient hospitalization days were calculated according to reported admission and discharge dates only. Outpatient costs were calculated according to the reported type of visit, specifically emergency room (ER) visits, pain clinic, or oncology clinic/consultation. Supportive care resources included tests and procedures not captured in adverse events, but did not include medication as posology data were not captured for supportive care. Treatment prior to diagnosis of advanced or metastatic GC was not included in the analysis.

This study estimated direct medical costs from a payer perspective, from the index date to the recorded data point or to the end of data collection (8 August 2015). Cost estimates were calculated using resource utilization data and their corresponding unitary costs. Unit costs were taken from the IMSS unitary costs list for procedures (2015) [15], while the acquisition cost of medication was taken from the IMSS public tenders (2015) [16]. A limited number of supportive-care costs not published by the IMSS were taken from the National Institute of Cancer (INCAN) 2015 unitary costs list [17] ($n = 16$ variables); however, due to the number and general low cost of the affected variables, this had little impact on results. All estimated costs were in 2015 Mexican pesos (MXN\$) and then converted to 2015 US dollars (US\$). The exchange rate was 0.06317, calculated as the average exchange rate of 2015 from the database of the Bank of Mexico (1 January to 31 December).

2.3 Statistical Methods

Statistical analysis was descriptive due to the observational nature of the study, and was performed for all main variables collected. The mean, median, mode and standard deviation was calculated for continuous variables, and frequency and proportion were calculated for categorical variables. All measures were assessed using complete case analysis, with missing values being omitted in the final analysis of each variable. Descriptive analyses were completed in Excel 2010 (Microsoft Corporation, Redmond, WA, USA), and cost analysis was completed in STATA v11 (StataCorp LLC, College Station, TX, USA).

3 Results

3.1 Demographic and Clinical Characteristics

The final sample size of the study was 180, collected from three tertiary-level centers of investigation. Due to the low incidence, all patients meeting the inclusion criteria in the participating institutes were included. In the IMSS hospital, Centro Médico Nacional (CMN) Siglo XXI, patient files are organized according to consulting office; all patients who met the inclusion criteria of the two consulting offices were included.

The majority of patients were treated in IMSS CMN Siglo XXI ($n = 167$; 92.8%), followed by the Secretary of the Navy (SEMAR) ($n = 7$; 3.9%), and patients found through the investigation center IBiomed ($n = 6$; 3.3%). The patient selection process is outlined in Fig. 1. The demographic and clinical characteristics of patients are summarized in Table 1.

The maximum level of education reported was generally low ($n = 137$): no schooling, 7.3%; primary school (age 6–12 years), 29.2%; secondary school (age 12–14 years), 27.0%; high-school, 21.9%; and completing university or postgraduate studies, 14.6%. The majority of patients (57.1%) reported no comorbidities, 14.9% reported diabetes, and 9.1% reported idiopathic hypertension; five patients had missing values. All other comorbidities impacted <5% of the sample. Smoking was associated with 52.0 and 3.5%, actively and formerly, respectively, of the 173 patients who reported on the variable.

Almost all patients included in the study were diagnosed with adenocarcinoma, totaling 98.9% of the 179 patients reporting data on the variable. Of the 173 patients with data, 96.1% were diagnosed with metastasis: approximately one-third of patients (28.9%) in two or more locations, 8.9% in three or more sites, and only 2.2% in four sites. Tumor characteristics of both the primary location and the

metastatic location are shown in Fig. 2. Patients had an average waiting time of 30.5 days [95% confidence interval (CI) 19.4–41.7] from diagnosis to first-line treatment.

3.2 Treatment Patterns

A total of 16 and 19 unique treatment regimens were identified for first- and second-line active treatment, respectively. Each of the five most used regimens in first-line therapy represented $\geq 10\%$ of the total population, summing to 93.9% of all selected therapies. Selection of second-line treatment showed each of the three most frequently used regimens representing $\geq 10\%$ of the overall population, and 64.9% of all regimens. Of the sample, 29 patients went on to receive BSC after first-line treatment, however, due to the small sample and lack of data on resource use, results for these patients are not presented.

No obvious tendency of cycle length per regimens could be observed, however due to the small sample size of each regimen, statistical differences were not tested for. Details for treatment characteristics and frequently used regimens are included in Tables 2 and 3.

3.3 Resource Utilization

The majority of hospitalization in first- and second-line treatment was associated with surgery. In second-line treatment, inpatient care was also linked to treatment of toxicity and adverse events. Supportive care was most associated with pain treatment (pain clinic and narcotics) and the use of endoscopies (see Table 4 for details).

Of the sample, 151 (84%) patients received two lines of chemotherapy, 51 (28.3%) received three lines, and <10% received more than three lines of active chemotherapy. The maximum lines of therapy received by a patient was seven. Estimated average costs per patient-month are presented in Table 5.

Fig. 1 Selection of patients entered in the study

Table 1 Characteristics of the patient population

Variable (<i>n</i>) ^a	Mean (SD)	95% CI	Min	Max
Age at diagnosis, years (180)	57.2 (12.4)	55.4–59.0	24.1	82.1
Height, cm (180)	160.4 (9.4)	159.0–161.8	120.0	191.0
Weight, kg (180)	62.7 (11.6)	61.0–64.4	40.0	101.0
BMI, kg/m ² (180)	24.4	23.7–25.0	13.4	47.9
Variable (<i>n</i>)	Category (<i>n</i>)	<i>n</i> (%)		
Sex (179)	Male	102 (57.0)		
<i>Helicobacter pylori</i> infection	Tested (180)	61 (33.9)		
	Positive (61)	23 (37.7)		
Family history of gastric cancer (160)	Positive	18 (11.3)		
Tumor stage at diagnosis of gastric cancer (180) ^b	IA	2 (1.1)		
	IB	1 (0.6)		
	IIA	2 (1.1)		
	IIB	4 (2.2)		
	IIIA	23 (12.8)		
	IIIB	58 (32.2)		
	IV	79 (43.9)		
	IIIA/IIIB	11 (6.1)		

SD standard deviation, *CI* confidence interval, *Min* minimum, *Max* maximum, *BMI* body mass index, *AJCC* American Joint Committee on Cancer

^a Sample size of the variable

^b Tumor stage was defined using the AJCC TNM staging system 7th edition, *n* = 169; 6th edition, *n* = 3; unknown, *n* = 9

Fig. 2 Tumor characteristics.
a Primary gastric tumor location of the sample (*n* = 180),
b metastatic tumor sites of the sample (*n* = 173)

4 Discussion

Given the limited information that currently exists on patients diagnosed with advanced or metastatic GC in Mexico, this study was designed to better understand patient characteristics, real-world treatment patterns, and healthcare resource use. Additionally, this study estimated the average cost per patient-month.

The patient population of Mexico follows international tendencies for late- or advanced-stage diagnosis, with the majority of patients being diagnosed with stage III and IV GC. Of the study population, approximately 80% of patients started first-line treatment in Eastern Cooperative Oncology Group (ECOG) 1. While this number decreased to 56.6% in second-line treatment, this reflects patients who had ≥ 3 months of follow-up, and likely represents

Table 2 Treatment characteristics

	First-line therapy	Second-line therapy
Patients [<i>n</i> (%)]	180 (100.0)	151 (100.0)
ECOG score [<i>n</i> (%)]	176 (100.0)	145 (100.0)
1. Symptomatic but completely ambulatory	141 (80.1)	82 (56.6)
2. Symptomatic, <50% in bed during the day	31 (17.6)	50 (34.5)
3. Symptomatic, >50% in bed but not bed-bound	4 (2.3)	13 (9.0)
Duration of treatment period ^a		
Cycles [mean (95% CI)]	4.6 (3.6–5.5)	4.2 (3.6–4.8)
Duration of line of treatment ^b		
Months [mean (95% CI)]	5.5 (4.8–6.2)	4.5 (3.4–5.6)
Reason for ending treatment [<i>n</i> (%)]		
According to treatment protocol	49 (27.2)	36 (23.8)
Toxicity/intolerance	49 (27.2)	19 (12.6)
Tumor progression	30 (16.7)	31 (20.5)
Others	52 (28.9) ^c	65 (43.0) ^d

ECOG Eastern Cooperative Oncology Group, CI confidence interval

^a Duration of treatment was defined as time on active treatment; data available for *n* = 179 in the first-line therapy group, and *n* = 131 in the second-line therapy group

^b Duration of line of treatment was defined as time from the first day of chemotherapy until the day before the next line of chemotherapy; data available for *n* = 179 in the first-line therapy group, and *n* = 131 in the second-line therapy group

^c Including deterioration of patient health, improvement in tolerance for oral therapy, stable disease, partial response, programmed surgery

^d Including deterioration of patient health, stable disease, treatment still underway

patients who had a more positive response to treatment. Nonetheless, the data further suggest that few patients are treated once reaching ECOG 3.

The findings of this study show a wide variety of regimens used in both first- and second-line treatment, with a total of 16 and 19 unique treatment regimens, respectively. Variability in treatment patterns has been demonstrated to be an internationally consistent trait, as demonstrated in similar studies conducted in the US, Taiwan, and South Korea [18–20]. The variation in Mexico remains comparatively high, which may reflect the lack of hospital-specific guidelines for the institutions included in the analysis. However, the fact that the most frequently used regimens in first- and second-line therapy represent 93.9 and 64.9% of patients, respectively, suggests a level of conformity in the selection process. When the investigating physicians were consulted on the results, it was submitted that regimen selection is influenced primarily by the availability of specific chemotherapies in the hospital pharmacy at the time of prescription, and their form of administration.

The preference towards prescribing orally administered products may be a reflection of this latter variable; specifically, capecitabine was administered to 58.3 and 60.3% of patients in first- and second-line treatment, respectively. Patients were purposefully switched to capecitabine from first- to second-line therapy when the

viability of oral treatment was improved by first-line intravenous regimens.

Oral chemotherapy may also be a demonstration of cost-constraining policies being implemented in the main hospital of the study, i.e. IMSS, as an attempt by doctors to reduce hospital visits. Administration of chemotherapy was identified as the main cost driver of this analysis, and a reduction of visits for this purpose would have an important impact on overall costs. Additionally, the study estimated that, on average, patients wait 30.5 days from diagnosis of metastatic GC to treatment. This may be another cost-constraining effort as the IMSS manages a global budget and a delay in treatment may increase cashflow flexibility for administrators. However, it is important to note that this may be institute-specific as wait times for elective services are reported as highly variable across and within institutes [21]. Finally, the study saw a lack of follow-up in tertiary-level care institutes for patients receiving BSC as the demand for resources by the high-volume IMSS hospital requires that these patients move to primary care units for follow-up care.

In terms of overall cost estimates, the administration schedule of the selected regimen had the largest impact on the average cost per patient, representing 35–48% of total costs in first- and second-lines of treatments. This,

Table 3 Frequently used treatment regimens in first- and second-line therapy

Regimen	Percent of population	Agent	Mean cycles	95% CI
<i>First-line therapy</i>				
EOX	32.2	Epirubicin Oxaliplatin Capecitabine	5.7	2.9–8.5
XELOX	23.3	Capecitabine Oxaliplatin	4.4	3.6–5.1
ECF	14.4	Epirubicin Cisplatin 5-FU	2.4	1.8–3.0
FLOX	13.9	5-FU Folinic acid Oxaliplatin	5.2	3.8–6.6
FUP	10.0	5-FU Cisplatin	3.3	2.2–4.5
Other ^a				
<i>Second-line therapy</i>				
CAP	34.4	Capecitabine	4.3	3.3–5.3
DOC	16.6	Docetaxel	3.9	2.7–5.0
XELOX	13.9	Capecitabine Oxaliplatin	4.4	2.1–6.7
Other ^b				

5-FU 5-fluorouracil, CI confidence interval, CAP capecitabine, DOC docetaxel, EOX (epirubicin/oxaliplatin/capecitabine), ECF (epirubicin/cisplatin/5-FU), FLOX (5-FU/folinic acid/oxaliplatin), FUP (5-FU/cisplatin), XELOX (capecitabine/oxaliplatin)

^a Cisplatin/5-FU/paclitaxel; DCF (doxorubicin/cisplatin/5-FU); EOF (epirubicin/oxaliplatin/5-FU); DOX (docetaxel/oxaliplatin/capecitabine); carboplatin/5-FU; carboplatin/5-FU/paclitaxel; DCX (doxorubicin/cisplatin/capecitabine); oxaliplatin/capecitabine/trastuzumab/doxorubicin; DCX/trastuzumab; capecitabine/cisplatin; DOF (doxorubicin/oxaliplatin/5-FU)

^b Paclitaxel/carboplatin; EOX; FLOX; paclitaxel; FUP; ECX (epirubicin/cisplatin/capecitabine); ECF; carboplatin; DOX (doxorubicin/oxaliplatin/capecitabine); EOF; capecitabine/cisplatin; capecitabine/cisplatin/docetaxel/trastuzumab; irinotecan; FOLFIRI (5-FU/leucovorin/irinotecan); FLOT (5-FU/leucovorin/oxaliplatin/docetaxel); radiotherapy

compared with the 14–21% for the cost of drug acquisition, highlights the generic status of the products used. Inpatient hospitalization and supportive care used a comparable proportion of resources as medication. Supportive care medication and outpatient care were minimal and were primarily associated with analgesics and narcotics (morphine, buprenorphine, and tramadol), as well as nutritional support.

The total average cost per patient-month of first- and second-line care were very similar, at US\$1230 and US\$1192, which is significantly lower than the US\$10,653 per patient-month published by Knopf et al. for patients diagnosed with GC in the US [9]. In comparison, Yabroff et al. estimated that the last year of patient care for a patient with GC in the US was US\$7435 [11]. This may be comparable with the results of a recently published paper in Mexico that estimated the cost per patient-year of late-stage breast cancer in the IMSS for stages III and IV of

MXN\$154,018 and MXN\$199,274, respectively, equivalent to US\$9729 and US\$12,587, respectively, using the previously stated 2015 average exchange rate [22]. While firm conclusions are hard to make given the different time horizons of the analysis, if considering the short overall survival of GC patients it may be expected that the overall spending on advanced GC in Mexico is similar to that of breast cancer.

This is the first Health Resource Utilization study completed in Mexico focusing on the standard care of treatment of patients diagnosed with advanced and metastatic GC, and can be seen as a step towards providing information regarding treatment patterns and estimating the overall costs of these patients. This is of particular importance in a field where the majority of treatment options remain generic and the recent and future development of innovative products will increase overall treatment costs for public providers.

Table 4 Patient supportive care and hospitalization by phase of therapy [17]

	First-line therapy (<i>n</i> = 180)	Second-line therapy (<i>n</i> = 151)
Supportive care [<i>n</i> (%)]		
Analgesics	135 (75)	109 (72.2)
Diuretics	4 (2.2)	2 (1.3)
Antidepressants	1 (0.6)	0 (0)
Granulocyte colony-stimulating factors	9 (5)	6 (4.0)
Pain interventions ^a	22 (12.2)	12 (7.9)
Erythropoiesis-stimulating agents	1 (0.6)	1 (0.7)
Granulocyte/macrophage colony-stimulating factor	1 (0.6)	2 (1.3)
Blood transfusion	24 (13.3)	16 (10.6)
Endoscopy	161 (89.4)	78 (51.7)
Radiotherapy ^b	11 (6.1)	25 (16.6)
Nutritional support, patients with information available [<i>n</i> (%)]		
Nutritional support clinic	2 (1.1)	0 (0)
Total parenteral nutrition + nonspecified nutritional support	6 (3.3)	2 (1.3)
Inpatient hospitalization		
Hospitalization per patient (<i>n</i>)	0.27	0.18
At least one inpatient stay [<i>n</i> (%)]	40 (22.2)	22 (14.6)
Length of stay/hospitalization (days) [<i>n</i> (95% CI)]	7.0 (4.9–9.1)	7.1 (4.6–9.6)
Main reasons for visit [<i>n</i> (%)]	49	28
Disease symptom management	7 (14.3)	5 (17.9)
Gastric cancer-related surgery	31 (63.3)	11 (39.3)
Adverse events/toxicity	3 (6.1)	8 (28.6)
Others	8 (16.3)	4 (14.3)
Outpatient care, patients with information available		
Mean visits/all patients (<i>n</i>)	0.25	0.27
Patients with at least one visit [<i>n</i> (%)]	26 (14.4)	14 (9.3)
Mean visits/patient requiring outpatient care (<i>n</i>)	1.7	2.9

CI confidence interval

^a Pain interventions include use of the pain clinic and use of narcotics, including morphine, buprenorphine and tramadol^b The radiotherapy data presented in this paper differ from the poster presented on the same study (Jones et al. [23]); differences were found between the reporting of posology, necessary for the cost calculations included in this paper, and general resource use included in the poster. This paper decided to report resource use using posology data due to the greater level of detail presented and in order to maintain consistency of data between resource use and costs. Differences are potentially due to capture error (transfer from paper Data Report File to electronic database) and patients who received radiotherapy but did not have posology details on file

Healthcare in Mexico is provided by multiple public institutes that deliver full or subsidized care depending on employment status. However, provision of care between institutes is not equal; each institute makes its own decision on the benefits and products to be provided, given the available resources. The results presented in this study are primarily a reflection of treatment practices and costs in the IMSS, the largest public healthcare provider in Mexico, which covers private sector employees and their dependents. The IMSS provides free care at the point of access, spending an estimated MXN\$2909/US\$184 per patient, on average (data from 2013); this in comparison to MXN\$3326/US\$210 and MXN\$16,772/US\$1059 for

Institute of Social Security and Services of Employees of the State (ISSSTE) and Mexican Petroleums (PEMEX), and MXN\$1262.42/US\$80 for the Seguro Popular [24]. These differences in spending are accounted for by the social/economic difference of the contributing population.

While the study provides an important starting point for data collection in GC in Mexico, it is important to note certain limitations. In particular, the small sample size combined with the range of regimens identified in both first- and second-line therapy limited the ability to estimate costs per regimen and to compare results across regimens. Furthermore, the generalization of these results to all public institutes is limited. While the IMSS is the largest

Table 5 Average cost per patient-month and distribution of costs of patients treated for metastatic gastric cancer

Total cost per patient-month ^a (95% CI)	First-line therapy					Second-line therapy					Total				
	1230 (1034–1425)					1192 (913–1471)					1292 (1044–1541)				
Resources	<i>n</i>	Mean cost	%	95% CI (low)	95% CI (high)	<i>n</i>	Mean cost	%	95% CI (low)	95% CI (high)	<i>n</i>	Mean cost	%	95% CI (low)	95% CI (high)
Drug acquisition ^b	171	174	14.1	131	218	128	244	20.5	171	316	120	250	19.3	173	327
Administration	179	586	47.6	478	695	131	421	35.3	270	5720	180	627	48.5	466	789
Adverse events	179	5	0.4	2	8	131	2	0.2	1	3	180	10	0.8	0	19
Radiotherapy	179	9	0.7	2	15	131	139	11.7	75	202	180	55	4.3	38	73
Hospitalization (inpatient)	179	185	15.0	80	289	131	247	20.7	92	403	180	227	17.6	95	360
Outpatient visits ^c	179	51	4.1	–5	106	131	14	1.2	–3	30	180	26	2.0	13	39
Supportive care ^d	179	200	16.3	154	245	131	152	12.8	110	194	180	279	21.6	174	384

CI confidence interval

^a To calculate the cost per patient-month per line of treatment, patients who had missing values in any of the variables were eliminated: first-line therapy, $n = 171$; second-line therapy, $n = 128$; all lines, $n = 120$; first-line therapy costs start at the first input of chemotherapy, radiation, or hospitalization

^b The sample size between the drug acquisition cost and the remaining costs is different due to the missing values in the number of cycles received or the dose, which made it impossible to estimate the total milligrams received, and to therefore calculate a cost. Given that the number of cycles and the dose are clinical patient-dependent variables, it was considered that no statistical method exists to appropriately reflect the missing values

^c Outpatient care: emergency room visits, rehabilitation and auxiliary units visits

^d Supportive care includes tests and procedures, but does not include medications as posology data were not captured for supportive care

public institute in Mexico (insuring approximately 32% of the population [25]), as can be inferred by the different levels of expenditure between institutes, treatment patterns may vary across institutes. The treatment patterns presented here illustrate the IMSS as an institute rather than the national tendencies. Similarly, the unitary costs are representative of the IMSS, and care should be taken when applying to other institutes with different cost structures. A direct comparison between the price lists of the IMSS and the Secretariat of Health shows that the costs published for INCAN and the National Institute of Medical Science and Nutrition Salvador Zubirán (INCMNSZ) are approximately 5 and 12% of the cost of the IMSS. This difference has the potential to change both the total costs and the distribution of costs, even while resource use remains constant across institutes.

Importantly, the protocol planned for the possible loss of patients to the system and included a criterion of a minimum of 3 months of follow-up in cases where more than one-third of all patients were lost before 3 months. This prioritized the capture of resource utilization of patients treated in tertiary care hospitals over the calculation of the percentage of patients treated in second-line with an active chemotherapy, and proved an important bias as patients are frequently sent to local health units to receive BSC. As a result, these patients were not captured in the study and it

was not possible to calculate the proportion of patients treated with active care in second-line versus BSC.

Finally, future investigations should look to expand the objective patient population to all patients, increase the study size, and include additional public institutes of interest in order to calculate more universally applicable results.

5 Conclusion

To our knowledge, this is the first study to look at patient management and resource use for patients with advanced or metastatic GC in Mexico, with results showing considerable variation in first- and second-line chemotherapy regimens. Understanding GC treatment patterns in Mexico will help measure the impact of new innovations in treatment practice and create opportunities to harmonize treatment options.

Acknowledgements The authors would like to thank Barbara Monroy Cruz for assistance with the statistical analysis conducted in the study, although any errors are our own.

Author Contributions MQ: Substantial contributions to conception and design of the study; acquisition, analysis, and interpretation of data; critically revising the manuscript for important intellectual

content; provided final approval of the version to be published. JAT: Substantial contributions to conception and design of the study; acquisition, analysis, and interpretation of data; drafting and critically revising the manuscript for important intellectual content; provided final approval of the version to be published. DN: Substantial contributions to conception and design of the study; acquisition, analysis, and interpretation of data; critically revising the manuscript for important intellectual content; provided final approval of the version to be published. KJ: Substantial contributions to conception and design of the study; acquisition, analysis, and interpretation of data; drafting the manuscript; provided final approval of the version to be published. BSB: Substantial contributions to conception and design of the study; acquisition, analysis and interpretation of data; critically revising the manuscript for important intellectual content; provided final approval of the version to be published. JAS: Substantial contributions to conception and design of the study; acquisition of data; critically revising the manuscript for important intellectual content; provided final approval of the version to be published.

Compliance with Ethical Standards

Data availability statement The data are not made available at this time as they are currently being analyzed for further publications.

Ethical statement Ethics approval was obtained from each of the participating institutes. Approval letters are available for review in PDF format. (1) IMSS: Comisión Nacional de Investigación Científica: # de Registro: 2014-785- 083. (2) iBiomed Aguascalientes: Comité de Ética en Investigación de Investigación Biomédica para el Desarrollo de Fármacos (12 June 2015; oficio: 0000004). (3) iBiomed Queretero: Comité de Ética en Investigación de Investigación Biomédica para el Desarrollo de Fármacos (12 June 2015; oficio: 0000003). (4) SEMAR: Comité de Bioética e Investigación (24 July 2015). Patient consent was not required as the study was a retrospective, observational, patient chart review.

Consent for publication Data capture respected international patient privacy regulations. Data that allowed for patient identification were not collected.

Funding Funding for this study was provided by Eli Lilly and Company.

Conflict of interest Miguel Quintana has received professional fees as a speaker on issues of GC for Eli Lilly and Company in Mexico. Diego Novick declares he is an employee of and owns stock in Eli Lilly and Company. Kyla Jones has received professional fees to conduct both the current study and additional studies for Eli Lilly and Company. Brenda S. Botello is an ex-employee of Eli Lilly and Company who was employed during data acquisition, analysis and development of the manuscript. She has no current competing interests.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Roder D. The epidemiology of gastric cancer. *Gastric Cancer*. 2002;5(Suppl 1):5–11.
- Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon: International Agency for Research on Cancer; 2013. <http://globocan.iarc.fr>. Accessed 3 Dec 2015.
- Stewart BW, Kleihues P, editors. World cancer report. Lyon: IARC Press; 2003.
- Kanavos P. The rising burden of cancer in the developing world. *Ann Oncol*. 2006;17(Suppl 8):viii15–23.
- Torpy JM, Cassio L, Glass RM. Stomach cancer. *JAMA*. 2010;303(17):1771.
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: gastric cancer version 1.2014. NCCN; 2014.
- Waddel T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO–ESSO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi57–63.
- Association Japanese Gastric Cancer. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer*. 2011;14:113–23.
- Knopf KB, Smith DB, Doan JF, Munakata J. Estimating the economic burden of gastric cancer in the United States (abstract no. e16589). *J Clin Oncol*. 2011;29(15 Suppl). doi:10.1200/jco.2011.29.15_suppl.e16589.
- Mariotto AB, Yabroff R, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst*. 2011;103:117–28.
- 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(1):14–23.
- Oñate-Ocaña LF. Gastric cancer in Mexico. *Gastric Cancer*. 2001;4:162–4.
- Sampieri CL, Mora M. Gastric cancer research in Mexico: a public health priority. *World J Gastroenterol*. 2014;10(16):4491–502.
- Vieira FMAC, Victorin APOS, Cubero DIG, Beato CAM, Minowa E, Julian GS, et al. Real world treatment patterns in metastatic and/or unresectable gastric cancer patients in Brazil (abstract no. PCN308). ISPOR 19th annual European conference, Vienna. 29 Oct–2 Nov 2016.
- Tabla que contiene los Costos Unitarios por Nivel de Atención Médica actualizados al 2015. DOF: 11/02/2015 ACUERDO ACDO.AS3.HCT.280115/7.P.DF. Instituto Mexicano del Seguro Social; 2015. http://www.dof.gob.mx/nota_detalle.php?codigo=5381602&fecha=11/02/2015. Accessed 8 Jul 2015.
- Búsqueda Productos. Portal de Compras del IMSS. http://compras.imss.gob.mx/?P=search_alt. Accessed Jul 2015.
- Instituto Nacional de Cancerología Tabulador Autorizado de Cuotas de Recuperación. Oficio No. 349-B-032. Subsecretaría de Ingresos: Unidad de Política de Ingresos no Tributarios. Mexico D.F., 30 Jan 2015.
- Karve S, Lorenzo M, Liepa AM, Hess L, Kaye J, Calingaert B. 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. *J Gastric Cancer*. 2015;15(2):87–104.
- Cuyun Carter G, Kaltenboeck A, Ivanova J, Liepa AM, San Roman A, Koh M, et al. Treatment patterns in patients with advanced gastric cancer in Taiwan. *Asia Pac J Clin Oncol*. 2017;13(3):185–94.
- Cuyun Carter G, Kaltenboeck A, Ivanova J, Liepa AM, San Roman A, Koh M, et al. Real-world treatment patterns among patients with advanced gastric cancer in South Korea. *Cancer Res Treat*. 2017;49(3):578–87. doi:10.4143/crt.2016.001.

21. Contreras-Loya D, Gómez-Dantés O, Puentes E, Garrido-Latorre F, Castro-Tinoco M, Fajardo-Dolci G. Waiting times for surgical and diagnostic procedures in public hospitals in Mexico. *Salud Pública Méx.* 2015;57:29–37.
22. Knaut FM, Arreola-Ornelas H, Velázquez E, Dorantes J, Méndez O, Ávila-Burgos L. El costo de la atención médica del cáncer mamario: el caso del Instituto Mexicano del Seguro Social. *Salud Publica Mex.* 2009;5(Suppl 2):S286–95.
23. Jones K, Silva JA, Novick D, Botello BS, Monroy Cruz B, Iglesia-Chiesa J, et al. Real world treatment patterns of previously treated advanced gastric and gastroesophageal junction adenocarcinoma (GC) in Mexico (abstract no. 143). *J Clin Oncol.* 2016;34(Suppl):4S.
24. Estado actual de la Seguridad Social en México. 2013. Centro de Investigación Económica y Presupuestaria; 6 Nov 2016. Centro de Investigación Económica y Presupuestaria. <http://ciep.mx/estado-actual-de-la-seguridad-social-en-mexico-2013>. Accessed 17 Sept 2016.
25. Gutiérrez JP, Hernández-Ávila M. Cobertura de protección en salud y perfil de la población sin protección en México, 2000-2012. *Salud Publica Mex.* 2013;55(Suppl 2):S83–90.