

Cost Evaluation of Metastatic Colorectal Cancer Treatment in the Brazilian Public Healthcare System

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Abstract

Objective: The study aimed at evaluating and comparing healthcare-related costs for metastatic colorectal cancer treatment among patients receiving systemic (chemotherapy or biotherapy) therapy, considering both costs per treatment cycle and total costs per patient.

Methods: This was a cross-sectional, econometric study conducted in a public, tertiary referral hospital in Brazil, which is supported by national and state level funding. Data were collected between January 01, 2009 and October 31, 2013. Micro-costing method was employed to estimate costs related to medication, laboratory tests, imaging tests, drug preparation and administration.

Results: The XELOX plus bevacizumab therapy presented the highest average cost per cycle, 7,701 Brazilian reais, followed by FOLFIRI plus bevacizumab, with an average cost of 6,927 Brazilian reais. Costs of treatment regimens containing capecitabine and/or monoclonal antibody (capecitabine monotherapy, cetuximab, cetuximab plus irinotecan, FOLFIRI plus bevacizumab, XELIRI, XELIRI plus bevacizumab, XELOX and XELOX plus bevacizumab) had a greater impact on total cost of therapy. In the mFOLFOX6 and FOLFIRI regimens, the total cost of therapy was mostly influenced by the cost per cycle (51%) and the cost related to drug administration (50%).

Conclusions: the Brazilian universal healthcare system does not cover monoclonal antibody therapies and the chemotherapy regimens FOLFIRI and mFOLFOX6 for colorectal cancer, since they surpass the monthly reimbursement amounts provided by the system. On the other hand, XELOX regimen fits within the budget established by the system, representing a promising alternative for colorectal cancer treatment, especially taking into account current economic limitations.

Keywords: Colorectal neoplasms; Chemotherapy; Health care costs; Unified health system

Introduction

According to recent estimates, colorectal cancer (CRC) is the third most common type of cancer among men and the second among women, with 746 thousand and 614 thousand new cases diagnosed in 2012 [1]. For 2015, the estimated numbers of new cases of colorectal cancer are 15,070 among men and 17,530 among women in Brazil, corresponding to an estimated risk of 15.44 new cases per 100,000 men and 17.24 new cases per 100,000 women [2].

Although colorectal cancer is diagnosed at early stages in most cases, leading to the possibility of curative surgical procedure, nearly 20% of patients present metastatic disease at diagnosis [3]. In addition, 20%-40% of patients undergoing local and adjuvant therapy will present systemic recurrence during clinical follow-up [4].

In the past decade, significant improvements have been made in response rates, progression-free survival (PFS), and overall survival (OS) in the treatment of metastatic colorectal cancer (mCRC), due to the development of new chemotherapeutic combinations using specific target drugs [5,6], resulting in increased costs for the health system [7]. The standard treatment for mCRC includes chemotherapy with oxaliplatin, fluorouracil (5-FU) and folinic acid (FOLFOX), capecitabine monotherapy, 5-FU and folinic acid combined with irinotecan (FOLFIRI) and capecitabine and oxaliplatin combination therapy (XELOX).

A well-structured health financing system is essential for achieving and maintaining a universal coverage of a health system [8]. The

increase in health expenditure has been a problem faced by developed countries, and drug costs has been the largest component of such increase in Australia [9], Canada [10], United Kingdom [11] and the United States [12,13]. In Brazil, federal expenses on ambulatory and hospital care for cancer have been increasing year by year, from 1.92 billion Brazilian Reals (BRL) to 2.4 billion BRL in 2012 [14]. In light of this, the determination of total costs of cancer is crucial for estimating the economic burden of the disease and the impact of new prophylactic and therapeutic interventions [15].

Few studies have evaluated general costs of specific treatments for cancer in developed countries [16-18]. However, in Brazil, there is no study on the costs of oncology treatment for mCRC in the public health system. Therefore, the aim of this study was to investigate the real costs of health care in patients with a diagnosis of mCRC and receiving systemic therapy (chemotherapy or biotherapy), considering both costs per treatment cycle and total costs per patient [19].

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Received May 23, 2015; **Accepted** June 15, 2015; **Published** June 22, 2015

Citation: Ungari AQ, Pereira LRL, da Silva Castro Perdoná G, Bettim BB, Nunes AA, et al. (2015) Cost Evaluation of Metastatic Colorectal Cancer Treatment in the Brazilian Public Healthcare System. J Integr Oncol 4: 136. doi:10.4172/2329-6771.1000136

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Methods

Design and patients

This is a cross-sectional, economic study (cost of disease) conducted in the Clinical Hospital of the University of Sao Paulo Medical School, Ribeirão Preto, Brazil. This is a public, tertiary referral hospital in Brazil, supported by national and state level funding. The hospital has 875 beds and is qualified by the Brazilian Ministry of Health as a center for high-complexity care in Oncology. Also, the institution is nationwide known for promoting high quality health care, education and research.

Inclusion criteria

First, all patients aged greater than or equal 18 years with a diagnosis of malignant neoplasm of colon and/or rectosigmoid junction and/or rectum (International Classification of Diseases for Oncology codes C180-190, C19 and C20) were eligible. Second, we identified those patients with diagnosis of metastatic disease (clinical stage IV), presenting at least one measurable target lesion according to Response Evaluation Criteria In Solid Tumors (RECIST) [20]. Patients who had undergone previous chemotherapies were also included, i.e. one patient may have been included in more than one analysis, accordingly with different or subsequent chemotherapeutic regimens.

Data source

Data were collected from the electronic medical records of the hospital and the oncology center from January 01, 2009 to October 31, 2013. These systems provide information regarding patient's sociodemographic data, diagnosis, treatment and progression of malignant neoplasm cases, morphological and topographical description of tumors, as well as registration of date of utilization and all costs related to medications and laboratory and imaging tests, both in the outpatient and inpatient services per patient. Data regarding costs related to preparation and administration of infusion regimens were obtained from the pharmacy and nursing staff of the chemotherapy center respectively.

Measurement and valuation of cost

Treatment costs were calculated by the micro-costing method, which provides an accurate evaluation and estimates real costs for the health system. We adopted the perspective from a university hospital, for high-complexity care, supported by national and state level funding. The categories considered for the assessment of healthcare's real costs were: medications, laboratory tests, imaging tests, drug preparation by the pharmacy staff, and administration of the infusion solutions by the nursing staff, as follows:

Medications: We considered all medications in use by the patient during chemotherapy, including adjuvant drugs and medications used for the control of chemotherapy side effects, in outpatient and inpatient care. These values were adjusted by 5% per year in 2013.

The monetary values of medications were those registered in the electronic medical record of the hospital as used by the patient, and corresponded to the amount paid by the institution by means of a competitive, open, bidding processes. Bidding process is considered as one of the main criteria for allocation of public resources in Brazil, aiming at identifying the best offer among competitors and ensuring them equal conditions for participation [21].

Laboratory and imaging tests: Laboratory tests and imaging

tests performed during the treatment period were identified and the monetary cost of each test was established based on the hospital's financial expenses on consumer goods, equipment and human resources.

Drug preparation: We considered the total costs related to the material needed for the preparation of systemic therapy (chemotherapy or biotherapy) per treatment cycle. In addition, the average costs of compounding each chemotherapy infusion bag, apart from medications, including human resources, compensation and benefits, and facility-related costs, such as water, energy, and telephone use were also considered.

Drug administration: Costs related to the material needed for the infusion of chemotherapy were determined by the oncology nursing staff. For both outpatient and inpatient chemotherapy, we included the average cost per patient day, as well as costs related to human resources, compensation and benefits, and facility-related costs, such as cleaning and sanitizing, laundry service, and nutrition and dietetics services.

Capecitabine was taken orally by the patients at home, therefore, costs related to its administration was not registered.

For the mFOLFOX6 and FOLFIRI regimens during hospitalization, we added the cost of the long-term, totally implanted venous access system (230 BRL in 2013), since the catheter implant procedure was not fully described in the medical records.

For the laboratory and imaging tests, drug preparation and drug administration categories, the monetary values related to the year of 2013, and no inflation adjustments were necessary.

The costs were identified during the period from the first day of chemotherapy until the 30th day after its completion. This 30-day period was considered necessary by the medical staff for the possible occurrence of adverse effects to chemotherapy and performance of all laboratory and imaging tests.

Statistics analysis was performed by descriptive statistics for most of the variables. Results are presented as mean \pm standard deviation (SD) in frequency tables, and the nominal and quantitative variables are graphically depicted in a boxplot.

Ethical aspects

The study was approved by the Ethics Committee of the Clinical Hospital of the University of Sao Paulo Medical School, Ribeirão Preto, Brazil on April 17, 2013 (registration number 956/2013).

Results

Characteristics of patients and disease are presented in Table 1. Most patients were women (60.71%), of different age ranges (22-87 years), and tubular adenocarcinoma and rectal localization were the most common tumor types (56.03% and 36.14% respectively).

Distribution of the number of cycles by chemotherapy regimen is depicted in Figure 1. In the biotherapy consisted of cetuximab in a weekly or fortnightly schedule, 9-30 cycles were observed per patient, whereas in the capecitabine chemotherapy in a monthly schedule, most patients underwent 1-3 cycles.

Table 2 presents descriptive measures of costs per cycle, and the impact of each category on the therapy regimen is presented in Table 3. The XELOX plus bevacizumab therapy presented the highest average cost per cycle (7,701 BRL), followed by FOLFIRI plus bevacizumab (6,927 BRL). In addition, the highest cost per cycle (11,900 BRL) was

Characteristics	N=166	%
Sex		
Male	75	39.29
Female	91	60.71
Age range		
22 - 50 years	44	26.5
51 - 59 years	39	23.5
60 - 68 years	42	25.3
69 - 87 years	41	24.7
Morphology		
Tubulovillous Adenocarcinoma	1	0.6
Mucinous Adenocarcinoma	12	7.23
Tubular Adenocarcinoma	93	56.03
Non-specific Adenocarcinoma	60	36.14
Topography		
Cecum	4	2.4
Ascending Colon	14	8.43
Descending Colon	8	4.8
Sigmoid Colon	25	15.1
Transverse Colon	9	5.42
Colon, non-specific	19	11.44
Ileum	1	0.6
Rectosigmoid junction	26	15.67
Rectum	60	36.14

Table 1: Sociodemographic characteristics of patients (n=166) and morphological and topographical description of disease.

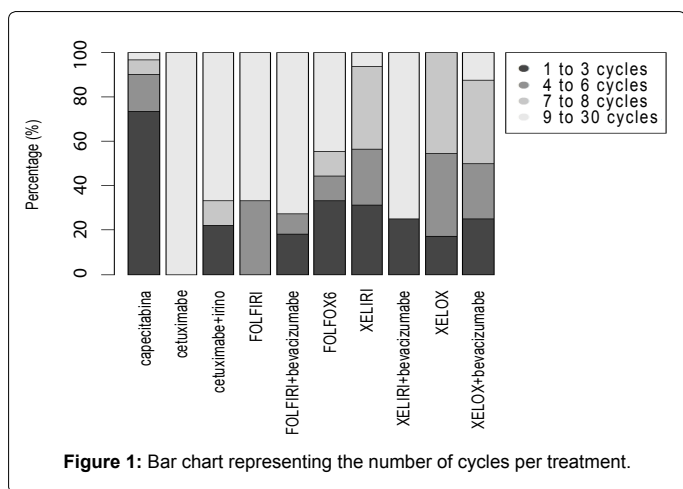


Figure 1: Bar chart representing the number of cycles per treatment.

observed in the XELOX plus bevacizumab therapy and the lowest in the capecitabine monotherapy.

Figure 2 shows descriptive measures of total cost by therapy regimen. Monoclonal antibody therapies (biotherapies) are the most expensive, and FOLFIRI plus bevacizumab combination therapy presented the highest average cost (65,460 BRL).

Discussion

According to current available literature, this is the first study to estimate the real costs (cost of the disease) of systemic therapy (chemotherapy or biotherapy) for mCRC from the perspective of the Brazilian public health system, using accurate cost-related data.

The results of this investigation show that cost of the medications have the greatest impact on the regimens containing capecitabine and/or monoclonal antibody (capecitabine monotherapy, cetuximab, cetuximab + irinotecan, FOLFIRI + bevacizumab, XELIRI, XELIRI + bevacizumab, XELOX and XELOX + bevacizumab). Oral capecitabine, with demonstrated clinical efficacy and safety, may be a suitable alternative in the treatment of mCRC, resulting in fewer sessions of intravenous chemotherapy and more comfort for the patient [18]. Frequently, the administration of chemotherapeutic drugs during hospitalizations is not ensured by the public health system in Brazil, due to the limited number of beds, and the number of ambulatory infusion pumps available for use in the home is also insufficient, which can cause a delay in the commencement of chemotherapy. This fact explains why most patients in our study were undergoing the XELOX (capecitabine plus oxaliplatin) regimen.

Most studies on treatment costs of mCRC compared the costs of XELOX with FOLFOX6 regimens, since it is suggested that both therapies are similar in terms of efficacy and safety. A cost-minimization study conducted in Australia has demonstrated that the use of XELOX in first line and second line treatment for mCRC reduced the average cost by \$9,110 and \$7,113 respectively, as compared with mFOLFOX [22]. From the French health insurance perspective, as compared with mFOLFOX6, XELOX resulted in lower costs related to drug acquisition and shorter hospitalizations per patient [17]. In our study, we observed statistically similar values of average cost per therapy cycle between XELOX, mFOLFOX6 and FOLFIRI.

Nearly 80% of cancer patients are treated by the Brazilian universal healthcare system. This system encompasses a subsystem for Authorization of High Complexity Procedures (AHCP), in which data regarding sociodemographic information, diagnosis, histology and

Chemotherapy regimens	N	Minimum	1° Quartile	Median	Mean	Standard Deviation	3° Quartile	Maximum
Capecitabine	30	898	1,334	1,661	2,088	1441.25	2,154	8,644
Cetuximab	6	2,369	3,227	3,383	3,273	485.74	3,507	3,782
Cetuximab + Irinotecan	9	3,003	4,182	6,090	5,469	1,690.73	6,347	7,733
FOLFIRI	3	1,925	2,053	2,182	2,164	230.55	2,283	2,385
FOLFIRI + Bevacizumab	11	2,967	6,106	6,597	6,927	2,340.95	8,032	10,990
mFOLFOX6	9	1,486	1,792	1,833	2,137	656.99	2,248	3,468
XELIRI	16	1,463	1,611	1,890	2,018	521.02	2,445	3,069
XELIRI + Bevacizumab	4	3,811	5,314	6,410	6,532	2,375.05	7,627	9,495
XELOX	140	1,310	1,827	1,988	2,064	405.05	2,295	3,615
XELOX+Bevacizumab	8	4,961	5,787	7,028	7,701	2,535.25	9,110	11,900

Abbreviations: FOLFIRI: 5-Fluorouracil plus folinic acid plus irinotecan; mFOLFOX6: 5-Fluorouracil plus folinic acid plus oxaliplatin; XELIRI: capecitabine plus irinotecan; XELOX: capecitabine plus oxaliplatin

Table 2: Descriptive measures of costs per cycle by therapy regimen, in Brazilian reais.

Chemotherapy regimens	Medication cost		Preparation cost		Administration cost		Cost of laboratory tests		Cost of imaging tests		Catheter cost	
	BRL	%	BRL	%	BRL	%	BRL	%	BRL	%	BRL	%
Capecitabine	1,667	79.84	0	0	0	0	65.69	3.16	355.3	17	0	0
Cetuximab	2,824	85.01	34.77	1.05	319.2	9.6	42.32	1.28	101.5	3.06	0	0
Cetuximab+Irinotecan	4,898	89.56	42.65	0.78	358	6.54	41.57	0.76	128.8	2.36	0	28.27
FOLFIRI	721.3	33.34	45.03	2.08	1,088	50.29	68.18	3.15	212.7	9.83	28.27	1.31
FOLFIRI+Bevacizumab	5,035	72.68	56.62	0.82	1,089	15.72	203.8	2.94	484.3	6.99	59.02	0.85
mFOLFOX6	671.2	31.42	51.87	2.43	1,888	50.92	48.19	2.25	199.3	9.33	77.97	3.65
XELIRI	1,456	72.13	11.37	0.56	145.2	7.19	70.16	3.48	335.7	16.64	0	0
XELIRI+Bevacizumab	5,429	83.11	21.08	0.32	251.6	3.85	134	2.05	696.4	10.67	0	0
XELOX	1,607	77.86	20.31	0.98	145.2	7.03	66.37	3.21	225.2	10.92	0	0
XELOX+Bevacizumab	6,898	89.57	30.02	0.39	251.6	3.27	91.75	1.19	430	5.58	0	0

Abbreviations: FOLFIRI: 5-Fluorouracil plus folinic acid plus irinotecan; mFOLFOX6: 5-Fluorouracil plus folinic acid plus oxaliplatin; XELIRI: capecitabine plus irinotecan; XELOX: capecitabine plus oxaliplatin.

Table 3: Average cost (in Brazilian reais, BRL) and percentage (%) of each category, component of the cost per cycle by chemotherapy regimens.

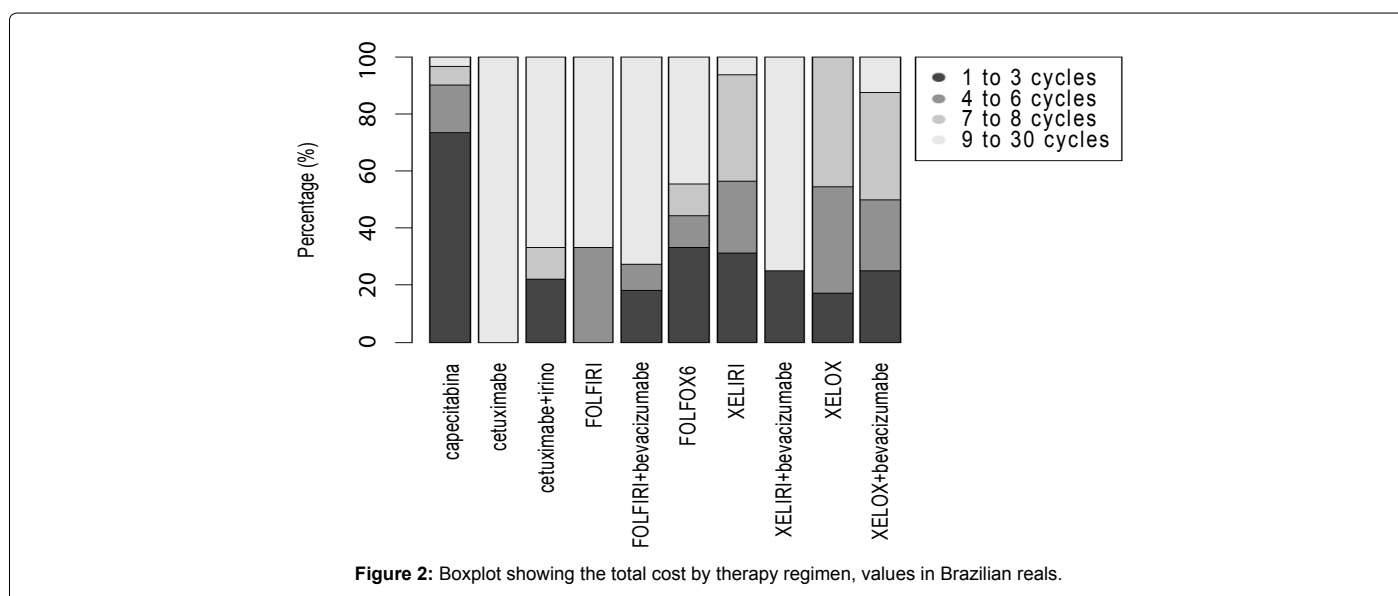


Figure 2: Boxplot showing the total cost by therapy regimen, values in Brazilian reais.

clinical staging, treatment intent (palliative or curative), and previous systemic therapies are registered. These data are used as reference for establishing the value reimbursed to the health institutions [23]. The AHCP system does not discriminate the list of medications to be used for the treatments, which is decided by the medical staff of the clinical oncology teams, based on local protocols and international guidelines.

According to the AHCP, for first line and second line palliative chemotherapy for colon and rectum adenocarcinoma (locally-regionally advanced, metastatic or recurrence), an amount of 2,224 BRL is repaid to the institutions by monthly reimbursement [24]. The duration of a cycle of XELOX treatment is 21 days [5], and 14 days for mFOLFOX6 and FOLFIRI (two cycles a month) [25]. In our study, the drug administration category had the greatest impact on the costs of both mFOLFOX6 and FOLFIRI, which indicates that ambulatory infusion pump may be an appropriate alternative to reduce costs and to fit within the budget established by APAC. Tampellini [26] compared the administration of FOLFIRI and FOLFOX in day-hospital care with outpatient care (ambulatory infusion pump), and found that at least five times more patients can be treated by using the ambulatory infusion pump system than the traditional system (day-hospital care) in the same time period and using the same resources.

A number of limitations need to be considered. First, the number of patients is considerably different between the groups. This difference was caused by the preference for prescribing oral rather than intravenous chemotherapy, due to restricted number of beds for hospitalization, and was mitigated by sample calculation and statistical analysis. Second, patient-related indirect costs such as lost working days and transportation were not included, since these data were not available for this analysis.

However, this study offers a comprehensive overview of the costs of treatment of mCRC by the Brazilian universal healthcare system, considering not only the price of medications, but also other categories that may affect total costs of disease and its treatment. Also, we believe that this study may serve as a base for future pharmacoeconomic studies.

Conclusions

This study has shown that the Authorization of High Complexity Procedures (AHCP) subsystem of the Brazilian universal healthcare system does not allow the inclusion of monoclonal antibody therapies and some chemotherapy regimens (FOLFIRI and mFOLFOX6), since they surpass the monthly reimbursement amounts. On the other hand,

XELOX regimen fits within the budget established by the system, representing a promising alternative for colorectal cancer treatment, especially taking into account economic issues faced by patients treated in the public healthcare system.

Acknowledgments

The authors gratefully acknowledge Carlos Roberto de Castro, Gislaine Rodrigues Guimarães and Rosimeire Aparecida de Oliveira de Carvalho (HCFMRP-USP) for provision of data.

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