ARTIGO ORIGINAL
ORIGINAL ARTICLE

Budgetary impact of oral chemotherapy incorporation in Brazil: a real world data analysis from the private payer perspective

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Keywords:
Health economics, budgetary Impact, chemotherapy, oral drugs

ABSTRACT

Background: In Brazil, health insurance companies (HIC) must, according to the law, offer coverage for intravenous chemotherapy drugs (IVChem), but not for oral chemotherapy drugs (OChem). We aimed to evaluate the incremental costs and the budgetary impact of the incorporation of OChem, using real world data, from the private payer perspective. **Methods:** We prospectively collected data during the year of 2008, on chemotherapy usage in 14 HIC, on a population of 2 million people from different regions in Brazil. First we calculated the costs of the IVChem actually used. After that, we indentified which patients would have formal indication for OChem either as a substitutive treatment or in association with IVChem. Then, we calculated the costs associated with this intervention. Later, the budgetary impact of using OChem for the eligible patients was calculated. Only drug acquisition costs were taken into account. We were conservative and assumed a "worst case scenario" approach as the base case, therefore skewing results against OChem. **Results:** During the one-year period, 1,322 patients that received intravenous chemotherapy also had formal indication to receive OChem. The cost of treatment given to these patients was US$ 19,630,000. If OChem were also used, the incremental cost would be an additional of approximately US$ 6,000,000 (US$ 5,982,656.00) or 30% of the total. The relative incremental cost associated with OChem is therefore US$ 3.00 per person insured per year or US$ 0.25 per person insured per month, in a worst case scenario approach. **Conclusion:** The budgetary impact linked with the adoption of OChem is of US$ 0.25 per person insured per month, in Brazil, according to this real world data analysis.

Introduction

The use of oral chemotherapy (OChem) for cancer treatment was adopted along recent years as an option for, or as an addition to, intravenous chemotherapy agents (IVChem) (O'Neill and Twelves, 2002).

OChem clearly became the standard therapy (Stupp, Hegi *et al.,* 2009) for some types of tumor and, occasionally their sole effective treatment (Stamatakos, Douzinas *et al.,* 2009). Patients usually prefer OChem over IVChem (O'Neill and Twelves, 2002).

In Brazil, 41 million people from its 190 million inhabitants have health insurance (Sistema de Informações de Beneficiários - ANS/MS - 03/2009, 2009). Companies offering any type of health insurance are legally bound to offer coverage for IVChem, but not for OChem (Presidência da República do Brasil 1998). This matter was extensively discussed in the past years, with an special focus on the financial capacity of the system to absorb OChem costs and how high would these costs be (Guandalini and Borsato 2008). However, as far as we know, no formal analysis was published, based on real data, estimating the OChem budgetary impact on the private health system in Brazil.

Methods

Our objective was to evaluate the incremental costs and the budgetary impact of the incorporation of OChem, in Brazil, through the payer's perspective.

Along the year of 2008, we prospectively collected data about the use of chemotherapy in 14 health plans based on

Recebido em 05/07/2012 – Aprovado para publicação em: 28/09/2012

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Competing interests: This study was supported in part by Roche Brazil. That support had no influence on the design, methodology or conduction of the study. OC – Received honoraria grants from Roche Brazil. LP – Received honoraria grants from Roche Brazil. None of the authors have stocks, patents or shares from any organizations that can benefit from these findings.

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Table 1 Table 1 - Oral drugs and indications considered for the analysis

OChem	Indication considered
Sunitinib	Metastatic Kidney Cancer
Sorafenib	Metastatic Kidney Cancer
Sorafenib	Hepatocellular Carcinoma
Temozolomide	Brain tumors - Anaplastic Astrocitoma/ Glioblastoma
Erlotinib	Second or Third Line Lung Cancer
Erlotinib	Advanced Pancreatic Cancer
Capecitabine	Adjuvant treatment and Advanced Colorectal Cancer
Capecitabine	Second or More line Metastatic Breast Cancer
Lapatinib	Metastatic breast Cancer Progressing while using Trastuzumab
Imatinib	Chronic Myelogenous Leukemia
Imatinib	Gastrointestinal Stromal Tumor
Dasatinib	Chronic Myelogenous Leukemia

four of the five Brazilian regions, comprising approximately two million users all together. That information was collected through a secure website exclusively dedicated to auditing and pooled in a searchable database. Data were supplied by the healthcare plans according to the confidentiality agreement term signed by both parties. The researchers had access only to electronic records with no possibility of identification of the identity of patients. The sponsors had no access to the raw data and all the analysis was performed independently.

In March of 2009, we listed all oral chemotherapy drugs available in Brazil and their indications. We considered the "on label" indication according to the national regulatory entity – National Agency of Sanitary Surveillance (ANVISA) or, when existing, published Phase III trials demonstrating clinical improvement associated to the OChem use (Table 1) (Druker, Talpaz *et al.,* 2001; Hori, Kodama *et al.,* 2001; Scheithauer, McKendrick *et al.,* 2003; Shepherd, Rodrigues Pereira *et al.,* 2005; Escudier, Eisen *et al.,* 2007; Kantarjian, Pasquini *et al.,* 2007; Moore, Goldstein *et al.,* 2007; Motzer, Hutson *et al.,* 2007; Arkenau, Arnold *et al.,* 2008; Blanke, Rankin *et al.,* 2008; Cameron, Casey *et al.,* 2008; Llovet, Ricci *et al.,* 2008; Moehler, Sprinzl *et al.,* 2009; Stupp, Hegi *et al.,* 2009).

On the database, we identified the registry of patients that received IVChem for cancers where the use of OChem could be possible. All cycles of chemotherapy administered during 2008 were considered in this analysis regardless of the date of diagnosis. We retrieved the names and doses of the medications administered, as well as anthropometric data and treatment duration. We calculated the costs of the IVChem used for each cycle and for the treatment those patients received during that year. We included only direct costs of chemotherapy drugs, but when 5fluorouracil infusion was used, we also considered the infusion pump costs. We used the price listed at the Brazilian official list SIMPRO, with an 18% added tax rate value (2009). In some isolated cases (Chronic Myelogenous Leukemia and Gastrointestinal Stromal Tumors, mainly), patients were receiving OChem supplied by the government. In such cases we assumed that the private payer would take over these costs. We did not add the cost of materials and medications such as antiemetic drugs to our calculations. We used anthropometric measures of each patient to calculate the dose to be adopted if OChem would be administered; then, we totaled the costs associated with this intervention for each eligible patient and for the whole population.

Different approaches to calculate the costs were used, considering each treatment particularities:

1) OChem fully or partially substitutes IVChem (substitutive option)
    a. Example: Capecitabine substitutes 5fluorouracil/ leucovorin to treat colon neoplasm (Arkenau, Arnold *et al.,* 2008; Moehler, Sprinzl *et al.,* 2009).
    b. We assumed equal treatment duration for both parenteral and oral group.
2) OChem adds an additional treatment line (additive option)
    a. Example: Lapatinib adds a second line of treatment in patients with HER2+ breast cancer, whose disease progresses during treatment with Trastuzumab (Cameron, Casey *et al.,* 2008).
    b. We assumed that the additional line of treatment would have the same duration of treatment of the previous one.
3) OChem is used concomitantly with IVChem (associative option)
    a. Example: Erlotinib associated to Gemcitabine to treat pancreas cancer (Moore, Goldstein *et al.,* 2007).
    b. We considered that oral chemotherapy would be used in all cycles, together with parenteral chemotherapy.

In those cases in which the administration of oral chemotherapy was possible in different situations, (Erlotinib can be used in second or third line to treat lung cancer) (Shepherd, Rodrigues Pereira *et al.,* 2005), we calculated the costs for both and used the highest one for OChem in the final analysis (Table 2). In the particular case of Erlotinib used as third line in lung cancer, we assumed that 60% of the patients submitted to a second line treatment would also receive a third line (Cancer Research UK, 2005). For the kidney cancer analysis, we projected 100% of the treatments with the more expensive drug - Sunitinib. If any type of OChem presented

Table 2 Parenteral chemotherapy and associated oral chemotherapy costs used for a population of two million users

Tumor	Most commonly used parenteral chemo	OChem	Oral chemo use situation	Number of cases	Incremental cost (US$)	Mean incremental cost/ patient (US$)
Kidney	Interferon	Sunitinib or Sorafenib	Substitution	18	486,036.00	27,002.00
Glioblastoma	BCNU (carmustine)/ Irinotecan	Temozolomide	Substitution	38	272,064.00	7,160.00
Colorectal*	FOLFOX/FOLFIRI (+ Bevacizumab†)	Capecitabine	5Fu/leucovorin substitution	315	0.00	0
Metastatic Breast Cancer HER2+	N/A – additive strategy	Lapatinib	Additional line after Trastuzumab failure	83	1,868,139.00	22,508.00
Pancreas	Gemcitabine	Erlotinib	Associated to Gemcitabine	28	240,324.00	8,583.00
Rare tumors (hepatocarcinoma/ GIST/ CML)	N/A	Sorafenib/ Imatinib/ Dasatinib	Substitution	37	804,601.00	21,746.00
Lung*	N/A – additive strategy	Erlotinib	Addition of a 3rd. line	285	544,478.00	1,910.00
Metastatic breast*	N/A – additive strategy	Capecitabine	Extra line addition	518	1,767,014.00	3,411.00
Total				1322	5,982,656.00	

N/A - not apply; FOLFOX- 5fluorouracil, Leucovorin, Oxaliplatin; FOLFIRI - 5Fluorouracil, Leucovorin, Irinotecam; * Other analysis were possible (see Table 3); † Use of Bevaciumab when appliable

a lower final cost than the correspondent IVChem, we didn't consider it as an economy, but as a null budgetary impact.

Costs of OChem that were calculated but not considered in the final analysis, due to the existence of a most expensive option, are described in Table 3.

Costs were converted from the Brazilian currency (Real) to US Dollars considering the exchange rate of R$ 2.00/ US$ 1.00.

A sensitivity analysis was undertaken considering three situations:

1) Use of *market price* instead of the *official list price*.
2) Replacement of Sunitinib for Sorafenib in the treatment of kidney cancer (100% of the cases).
3) Exclusion of Temozolomide of the analysis, as an IV presentation may be available in the Brazilian market in the first semester of 2010. The price of both, IV and oral presentations, are expected to be the same.

Results

In 2008 we identified on the database, 1,322 cancer patients treated with IVChem that might have an indication for OChem (Table 1). The actual drug costs to treat them using IVChem was almost 20 million Dollars (US$ 19,630,000.00).

If OChem were to be used in this population, there would be an increase in costs of about six million Dollars (US$ 5,982,656.00) or 30% of the total expended in a worst case scenario for OChem, from an economic point of view (Table 2). The incremental cost per capita for the insured population of two million covered by these HIC would be US$ 3.0/per person/per year or US$ 0.25/per person/per month.

Most of this increase is derived from the indication of OChem as additive option. The use of Lapatinib and Capecitabine for metastatic breast cancer and Erlotinib as third line in lung cancer were jointly responsible for 69.9% of this impact (Table 2). The substitutive option was responsible for 26.1% of the costs and the associative option for 4%. According to the tumor site, approximately 60% of the cost increase comes from breast cancer.

When replacing 5fluorouracil/Leucovorin with Capecitabine for colon and rectal cancer, the OChem cost was lower than the IVChem. Therefore, as stated in the methods, the considered budgetary impact was null in the final analysis.

Sensitivity analysis performed demonstrated that these results could be largely affected according to the price source. If the costs were calculated using market price, the incremental cost could be as low as US$ 0.16 per insured person per month (36% less) for the same scenario. The other two sensitivity analysis did not significantly change the costs. If parenteral Temozolomide reaches the market at the same price of the oral presentation, the incremental cost of OChem would be US$ 0.24 or one cent less than originally estimated. Also, the substitution of Sunitinib for Sorafenib would have a virtually zero impact in the global analysis - the cost of OChem would be US$ 0.2472.

Table 3 Scenarios not considered in the final analysis

Tumor	Most commonly used parenteral chemo	OChem	Situation for oral chemo use	Costs saved (US$)	Worst case analysis scenario considered
Metastatic breast, second line	Paclitaxel/Docetaxel/ Gemcitabine	Capecitabine	Substitution of all parenteral chemo	2,791,026.00	Extra line addition chemotherapy considered
Lung, second line	Pemetrexede/ Docetaxel	Erlotinib	Substitution of all parenteral chemo	1,041,005.00	Third line addition considered
Colorectal	FOLFOX/ FOLFIRI (+bevacizumabe)	Capecitabine (+bevacizumabe)	5Fu/leucovorin substitution	368,363.00	Considered as null impact

Discussion

This study showed that in a worst case scenario analysis, the coverage for oral chemotherapy would be associated with an incremental cost of approximately US$ 0.25 per month per person insured, representing less than 1% of the monthly payment for a healthcare plan in Brazil (Agência Nacional de Saúde Suplementar, 2009).

One of our main concerns was to avoid underestimation of the costs of OChem, so, all calculations were performed using a worst case scenario. It is likely that in reality the costs would be even lower than in this study. The same reasoning applies to the calculation of drug costs as we used the official list price without any discounts. It is the usual practice here to offer substantive discounts for clinics that buy in bulk. The sensitivity analysis performed showed that the pricing of OChem is a major determinant of the increase in costs.

The facts that these data were prospectively collected and that the extraction was previously planned, diminish but do not exclude the chances of sub-notification of eligible cases to OChem. This chance is, however, inherent to this research methodology (Chumney and Simpson, 2006). To double check for any inconsistencies, we compared our findings with data from the Brazilian National Cancer Institute (INCA) (Instituto Nacional do Câncer - INCA, 2007) and found no differences in the expected number of cases for the main pathologies reported herein (breast, colon and lung). The number of cases found for a population of two million individuals seems to be in accordance to the expectations of the country official statistics. However, we couldn't make this check for rare tumors, due to the lack of official data (Table 4).

Future developments can change this scenario in several ways, sometimes making the relative cost of OChem lower, sometimes higher. For example, the approval of Temsirolimus (Hudes, Carducci *et al.,* 2007) expected in Brazil for the next year, has the potential to dramatically change the costs of renal cancer treatment. Being a parenteral medication much more expensive than Interferon, it will widely decrease the incremental cost associated to the use of Sorafenib or Sunitinib. On the other hand, new oral chemotherapy agents are expected for several indications, therefore increasing the incremental cost of OChem (Motzer, Escudier *et al.,* 2008).

Table 4 Expected number of tumors according to Brazil official statistics for a population of 2.000.000 of people and the number of cases identified in the database

Tumor	Number of cases identifies in the database	Expected number for the studied population
Breast	518	555
Colon	315	300
Lung	285	320

As our costs analysis was restricted to the use "on label" or to indications based on solid Phase III studies, these results do not apply to the "off label" use.

It must be also considered that there is a repressed demand and the number of actual cases can be initially higher than those expected. Also, for health insurance companies with a smaller population the statistical predictions are prone to a larger probability of error.

The costs of cancer treatment have risen sharply in the last years (Corral, Clopes *et al.,* 2007), in worldwide. While some analysis point to a relatively low cost per year of life saved with these new treatments (Martin, Rice *et al.,* 2008), most annalists are concerned about the budgetary impact of these technologies and the ability of the institutions to pay for them (Corral, Clopes *et al.,* 2007; Camps, Caballero *et al.,* 2008). In Spain, for instance, the impact of new therapies for colon cancer is calculated to be over 35 millions of Euros in Cataluña only. In Germany, the adoption of Docetaxel in the adjuvant treatment of breast cancer is associated to an increase of more than 60% in costs (Braun, Jacobs *et al.,* 2009).

Although adding costs for the cancer treatment, the adoption of OChem in Brazil is not as high as one could expect. Considering that the monthly payment made by each insured person in Brazil is approximately US$ 35.00 (Agência Nacional de Saúde Suplementar, 2009), the percentage increase for the adoption of this technology would be lower than 1% of the total premium.

Conclusion

The budgetary impact of oral chemotherapy in the private sector in Brazil is associated to an incremental cost of US$ 0.25/person insured/month.

Authors contributions:

Clark O – Planned and designed the study, analyzed data and wrote the final manuscript.
Alves AF– Designed the methods for data extraction, extracted and analyzed data.
Castro AP - Designed the methods for data extraction, extracted and analyzed data.
Santos F – Designed the database, extracted data and gave technology support during all the study.
Faleiros E – Supervised the process of data extraction, designed the database structure, analyzed data.
Clark L – Analyzed data, wrote the final manuscript and supervised the data extraction.
Paladini L – Analyzed and extracted data.
Engel T – Analyzed and extracted data.
Pegoretti B – Analyzed and extracted data.

All authors took part in discussions about the interpretation of the findings, approved the final manuscript and gave inputs on how to design the database.

Acknowledgement

The authors thanks to Valéria Clemente, Luciana Vasconcelos, Mário Saggia e Eduardo Santos, from Roche do Brasil for the support and valorous inputs during the conduction of this research. We also thanks to Roche do Brasil for the financial support that was provided to this study, and to the 14 Health Insurance Companies that allowed the use of their data.

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