Costs to health systems for antineoplastic drugs acquired through lawsuits - a systematic review

Custos para os sistemas de saúde com medicamentos antineoplásicos adquiridos em ações judiciais - uma revisão sistemática

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ABSTRACT
Cancer, a rapidly increasing disease, imposes significant financial burdens on healthcare systems. This study investigates the costs incurred by health systems due to the legal processes involved in acquiring antineoplastic drugs. Conducted through a systematic literature review spanning January 2008 to March 2022, utilizing databases like Pubmed/Medline, LILACS, SciELO, and BIREME, 162 articles were initially identified. Ultimately, 15 retrospective studies were included, with a majority (53.3%) conducted in the United States. Despite implemented measures such as parity laws and financial assistance, cancer treatment costs persistently remain high. The study underscores the importance of a scientific foundation in health systems to assess the legal processes surrounding antineoplastic therapies, preventing unnecessary financial investments. To address these challenges, the study advocates for the development of public health strategies in pharmacoeconomics to democratize access to oncological treatment by reducing associated costs.

Keywords: Antineoplastic agents; Drug costs; Cancer; Right to health; Judicialization of health.

RESUMO
O câncer, uma doença em rápido crescimento, impõe encargos financeiros significativos aos sistemas de saúde. Este estudo investiga os custos incorridos pelos sistemas de saúde devido aos processos legais envolvidos na aquisição de medicamentos antineoplásticos. Realizada por meio de revisão sistemática da literatura no período de janeiro de 2008 a março de 2022, utilizando bases de dados como Pubmed/Medline, LILACS, SciELO e BIREME, foram identificados inicialmente 162 artigos. Ao final, foram incluídos 15 estudos retrospectivos, sendo a maioria (53,3%) realizada nos Estados Unidos. Apesar das medidas implementadas, como leis de paridade e assistência financeira, os custos do tratamento do câncer permanecem persistentemente elevados. O estudo ressalta a importância de uma base científica nos sistemas de saúde para avaliar os processos legais que envolvem as terapias antineoplásicas, evitando investimentos financeiros desnecessários. Para enfrentar estes desafios, o estudo defende o desenvolvimento de estratégias de saúde pública em farmacoeconomia para democratizar o acesso ao tratamento oncológico, reduzindo os custos associados.

Palavras-chave: Agentes antineoplásicos; Custos de medicamentos; Câncer; Direito à saúde; judicialização da saúde.
INTRODUCTION

The health system is defined as the part of society that has the specific purpose of “continuously improving the quantity and quality of life of citizens with regard to the health-disease phenomenon”. To fulfill its purpose, it has the essential function of carrying out health actions, at various levels, aimed at both people and the ecosystem. In terms of structure, the health system is fundamentally composed of three elements: the population, the provision of services and the benefits obtained. Added to these fundamental components are inputs (material and human resources) and restrictions (financial resources and political options) (Souza, Bahia, 2023).

There is a convergence of common elements between contemporary health systems, due to the demographic and epidemiological transition, cost pressures, technological incorporation and the dissemination of major policy guidelines by international organizations. However, important differences persist in the extension of social protection, financing and in the organization of services (Conill et al., 2023).

Thus, it is possible to group health systems into: national health system models (Beveridgean), in which everyone pays through taxes so that the entire population is covered; social health insurance (Bismarckian) which is funded through payroll deduction from employee paychecks with partial coverage; and residual, in which there are private services for those who pay directly, with the State being responsible for offering services to specific populations (Lobato, Giovanella, 2012).

Cancer, as with cardiovascular diseases, is part of the group of chronic non-communicable diseases responsible for high rates of morbidity and mortality at both national and international levels, and is currently one of the major public health problems (Brasil, 2021). Over the years, with the aging population and increased life expectancy, it is possible to observe an increase in the number of cancer cases both in Brazil and worldwide (Francisco et al., 2020).

A noteworthy global epidemiological study, carried out in 2018, indicated that the most common types of cancer worldwide are, respectively, lung cancer, in first place, and then breast, colon and rectum and prostate cancer, with rates of 2.1 million, 2.1 million, 1.8 million and 1.3 million individuals affected worldwide. Furthermore, from this study it is also possible to recognize that oncological diseases have an unequal distribution between the sexes, with a greater involvement, in general, of men when compared to women. Remaining in this context, it should be highlighted that, while, worldwide, lung
cancer is the most common cancer in males, among females, malignant neoplasms of the breast are the most epidemiologically relevant, from a quantitative perspective (Bray et al., 2018).

The incidence of cancer has presented an exponential growth, particularly in countries under development, where it is expected that, by the year 2025, there will be an increase of 16 million new cases (Avellar et al., 2019). According to data from the National Cancer Institute (INCA), it is estimated that, each year between 2023 and 2025, 704 thousand new cases of cancer will appear in Brazil, and will be concentrated mainly in the South and Southeast regions of the country (Brasil, 2022a).

Cancer patients, in addition to care, need continuous monitoring, which involves expensive tests and medications, thereby contributing to the burden on public coffers and challenges to the health care system (Gomes et al., 2021). This information is corroborated by INCA estimates, according to which, around R$3.4 billion will be needed, in 2040, to invest in the oncological treatment of patients in the Brazilian Unified Health System (known as SUS), diagnosed with breast, colorectal and endometrium cancer, which could be avoided with investment in preventive policies (Brasil, 2022b).

Although the costs involved in purchasing medicines are lower when compared to the costs of the clinical and surgical management of cancer patients, understanding the costs of the drug treatment for cancer patients is extremely important in order to develop public health policies (Observatório de oncologia, 2018). With this in mind, strategic planning projects are already under development in order to implement programs that may reduce the value of oral antineoplastics to enable cancer patients to access these drugs and, therefore, carry on with their treatment (Stanz et al., 2021).

Furthermore, it is also valid to contemplate that in some countries, such as Canada, judicious cost-effectiveness measures have been adopted for the approval of new antineoplastic drugs. However, while these drugs have increased in price, there has been no statistically relevant beneficial return when considering the survival of patients who use new drugs, in comparison with substitute medications (Niraula, Nugent, 2018). Meanwhile, a study considering the reality of the United States (US) and Europe came to the conclusion that expenses in the US are higher than in European countries with regard to the drug treatment of cancer patients. Thus, it is feasible that medications of a less intense clinical benefit should be highlighted in price adjustments and, in addition, a much more flexible access to therapies that offer better results for patient health should be a priority in all nations (Vokinger et al., 2020).
As stated above, the present systematic review aims to analyze the price of antineoplastic drugs obtained through lawsuits and, from this, assist in the development of public health strategies, which enable preventive treatment in order to reduce the costs associated with the treatment of cancer patients and, therefore, make it more accessible.

MATERIAL AND METHODS

The following systematic review was structured based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2015). The search for scientific articles was conducted by independent researchers in the electronic databases MEDLINE (Pubmed), LILACS, SciELO and BIREME, restricted to the period between January 2008 and March 2022, including only studies in Portuguese, English and Spanish. The descriptors were selected from the Health Sciences Descriptors (DeCS) and Medical Subject Heading Terms (MeSH), considering the wide use of these tools by the scientific community to index articles in the PubMed database. The descriptors proposed for the study were: right to health, cost and cancer.

The bibliographic search was conducted using the PICOS strategy, an acronym for the terms: Population, Intervention, Comparison, Outcome and Study. Based on this, the inclusion criteria used for the search were studies that combined:

• Population: Patients undergoing cancer treatment who obtained payment for antineoplastic medications from health systems through lawsuits.
• Intervention: Costs of treatments obtained through lawsuits for the treatment of cancer.
• Comparison: Location and period of the study.
• Outcome: Costs and cost analysis. Analysis of related information.
• Types of study: Clinical, cross-sectional and cohort studies.

In this review, we included studies that contained information to answer the question: “What are the health costs for guaranteeing access to antineoplastic (oncological) medications through lawsuits?” Studies that analyzed the cost of antineoplastic drugs, laws for obtaining these drugs and obtaining them through extrajudicial means were included.

The study team, which consisted of 6 researchers, undertook a multi-step process in order to determine the final sample of articles that would be included in the review. In specific terms, at least two independent members of the study team examined all the titles
included in the initial search results, and then reviewed the abstracts of the articles. They then compared their results with those of other pairs in the team, and finally went on to read the complete versions of the articles so as to determine eligibility. The research team discussed and settled any discrepancies during the triage process. Table I presents the flowchart to identify the studies included in the review.

**Table 1. Stages of Articles Selection for the Review**

<table>
<thead>
<tr>
<th>Identification of studies via databases</th>
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<tr>
<td><strong>Identification</strong></td>
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<tr>
<td>Records identified through database search ((n = 162))</td>
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<tr>
<td>Records analysed through title and abstract reading ((n = 156))</td>
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<tr>
<td>Articles with full text analysed ((n = 29))</td>
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<td>Studies included in the systematic review ((n = 15))</td>
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<tr>
<td><strong>Screening</strong></td>
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<tr>
<td>Duplicated records removed ((n = 6))</td>
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<tr>
<td>Records removed through title and abstract reading ((n = 127))</td>
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<tr>
<td>Articles removed for not fitting the study’s objective</td>
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Source: authors’ own development; N = Number of studies
After the eligible studies were identified, the following data were extracted: authors, database, year of publication, country of origin, study objective, method used, drugs studied, study location, duration, number of people, main results and conclusion of the study.

MATERIAL AND METHODS

In order to determine which studies were eligible to be included in the research, the present study analyzed 29 articles in full, 14 of which were excluded because they failed to meet the objectives of the review. After the exclusions, 15 articles remained, and it was observed that, of these, 6 had been published between 2010 and 2015 and 9 between 2018 and 2021. With regard to the country of origin of the publications, 2 were from Europe, 2 from Asia, 3 from South America and 8 from the US. The 15 articles were retrospective, whereby some were quantitative and others qualitative.

It was observed that among the countries analyzed, different models of social protection had been adopted. In the US, the “residual model” predominated, in which social needs are resolved based on market possibilities, either on an individual basis or in small associative groups (Serapioni, Tesser, 2019). The United Kingdom (UK), Canada and Brazil follow the “Beveridge system”, based on the premise that the health care of the population is ensured by the State, which establishes taxes for this purpose. Germany and Switzerland highlighted the “Bismarck model”, in which only citizens who make a compulsory contribution are entitled to health protection (Rizerio, 2016).

The aim of most studies was to investigate and/or compare the cost of antineoplastic drugs prescribed in the health systems of different countries. They also assessed the impact of parity laws, and other regulations, on spending with oral anticancer drugs and health insurance. Among the studies that compared the prices of antineoplastics, one study in Switzerland aimed to compare the prices of antineoplastic drugs in countries such as the US, UK, Germany and Switzerland, and discovered that prices in the US were significantly higher.
Another study conducted in Canada using 60 new antineoplastic drugs confirmed that, despite showing an improvement in the effectiveness of anticancer drugs in the country, there was a simultaneous increase in the price of these medications. In Brazil, the studies assessed the compliance of lawsuits filed with the São Paulo State Department of Health that requested anticancer medications and also observed the attitudes of the legal system with regard to providing, through lawsuits, medications within the country’s health system - SUS. In addition, 3 studies assessed medical practice in prescribing medications, one of which assessed the opinion of US and Canadian oncologists on the costs of antineoplastic medications. While most US oncologists argued that patients should have the right to effective treatments regardless of cost, Canadian oncologists argued that the cost-benefit of treatment should be the main consideration. Furthermore, a large proportion of oncologists in both nations support state control over drug prices.

One of the studies carried out in the US analyzed whether the different state laws in Massachusetts were efficient in meeting the needs of parties involved in antineoplastic therapy and identified that some laws have contributed to an increase in commercial insurance costs. Moreover, another study conducted in Switzerland observed that of the 70 antineoplastic drugs that had been approved between 2009 to 2018, 80% were reimbursed by social health insurance. However, in 2018, patients waited an average of 463 days to be included in the country's "Special List", which therefore makes it difficult for individuals to receive treatment.

In relation to the impacts of parity laws on the cost and adherence to treatments, drugs such as Anastrozole, Exemestane, Letrozole and Tamoxifen were extensively analyzed. A study in the US, with 7778 patients undergoing treatment for breast cancer, identified that the higher the median monthly copayment, the greater the risk of non-adherence to medication. It was also identified that in states that had parity legislation, monthly copayments for Exemestane and Anastrozole decreased while copayments for Letrozole increased. In addition, another study, published in 2018, and carried out with 63,780 patients, concluded that adopting the state parity laws was associated with significant reductions in estimated monthly expenses for orally administered anticancer drugs, thereby improving the financial protection for many patients.

With regard to Medicaid, a survey carried out in the US demonstrated that patients residing in a state that does not adhere to the program had reduced access to critical treatment for breast cancer, which directly affected morbidity, mortality and quality of life. When analyzing the impacts of Medcare, another study also carried out in the US
identified that even after the end of changes in regulating the coverage of prescribed medicines on traditional healthcare insurance plans, costs for the beneficiaries who take these medicines remained high.

In relation to the 2 studies carried out in Brazil, it was observed that the one carried out in the state of São Paulo demonstrated that 40 million BRL was spent to respond to lawsuits related to antineoplastic drugs, but that around 17% of the indications were not based on reliable scientific evidence, and generated approximately 6.8 million BRL in unnecessary expenses. The study carried out in the state of Pernambuco found that for antineoplastics and immune modulators, annual costs ranged from 37,000 to 193,000 BRL for acquiring each medication. Both studies reported the need for the prescription of a medicine to be based on scientific evidence in order to reduce public spending on medicines that have no scientific basis.

DISCUSSION

In this study, we have sought to analyze the extent of the cost to health systems for antineoplastic medicines acquired through lawsuits. Cancer is a disease with multifactorial etiology, and is on the rise among the world populations, especially due to an increase in life expectancy and, consequently, an increase in the number of older people (Francisco et al., 2020). The treatment of this condition requires the use of extremely specific drugs, which are considerably expensive, since their production requires a certain degree of technological complexity (Berry et al., 2010). It is known that the cost of purchasing anticancer drugs is extremely high and acquiring them within different health systems has a negative impact on patient treatment.

In Canada, a study conducted between 2011 and 2018 assessed 60 antineoplastic drugs, revealing that costs increased by a third per year (Niraula, Nugent, 2018). In China, research proposed analyzing the cost of treatment for colorectal cancer between 2009 and 2010, assessing the following medications: 5-Fluorouracil; Leucovorin; Oxaliplatin; Xeloda Roche; Avastin (Bevacizumab). The cost was calculated based on therapeutic prescriptions that combined different antineoplastic drugs. The FOLFOX regimen (12 cycles in 6 months) combined 5-fluorouracil, leucovorin and oxaliplatin, with an acquisition value of $8,926. The MAYO regimen (6 cycles in 6 months) combined 5-fluorouracil and leucovorin with an acquisition cost of $165. Lastly, the XELOX regimen included oxaliplatin, Xeloda and Roche Avastin (Bevacizumab) with a purchase cost of
$11,200 (Wong *et al*., 2012). The high investments to access antineoplastic therapy are a barrier to the therapeutic management of patients, therefore the implementation of legal measures that promote a reduction in the costs of this class of drugs is essential in order to democratize the acquisition of these medicines.

In Switzerland, research carried out between 2009 and 2018 mapped the time that 70 antineoplastic drugs took between being approved and included on the “Special List” by the Federal Secretariat of Public Health, so that when included, the acquisition value may be negotiated with the manufacturer. The average annual time for inclusion on the "Special List" has however increased over the years, with an average of 243 days in 2009 and 463 days in 2018 (Vokinger, Muehlematter, 2020).

In Chile, a study between 2012 and 2017 measured spending on 131 antineoplastic drugs in the public and private sector. In total, $398 million was spent, of which $234 million (84.2%) was provided by the public sector, $29 million (7.5%) through sales within the protocol and $34 million (8.3%) was spent by individuals purchasing medications outside the protocol. The per capita cost in Chile was $197 in 2017 for antineoplastic medications (Vargas *et al*., 2019). In China, it was observed a reduction in the Laspeyres index of antineoplastic medicines of 0.058 one year after the state began to regulate the prices of these substances, which did not change even after the government deregulated the prices of medicines (Guan *et al*., 2019).

In a study conducted in the US, the average cost of purchasing antineoplastic drugs for the treatment of lung cancer and colorectal cancer was compared across 21 drugs (Leucovorin; Avastin Bevacizumab; Carboplatin; Cetuximab; Cisplatin; Cyclophosphamide; Docetaxel; Etoposide; Fluorouracil; Gemcitabine; Irinotecan; Oxaliplatin; Paclitaxel; Premetrexed; Topotecan; Vinorelbine; Doxorubicin; Liposomal doxorubicin; Trastuzumab; Ifosfamide; Mitomycin) before and after the government measure to reduce service fees during the period 2004 and 2005. The cost of a daily dose among the medications ranged from $38.85 to $10,177.92 before the regulation (2004) and after it became effective (2005) from $15.82 to $9,239.13. The biggest difference in cost was observed for Paclitaxel which went from $1,244.52 to $134.55 with a difference of $1,109.97 before and after the regimen (Hornbrook *et al*., 2014). Although there was a decrease in costs after the policy, the cost of antineoplastic drugs remained high, requiring more effective policies. Another research also noted that, although parity laws aimed at oral antineoplastics are an important public health advance, they were inefficient
in reducing the personal expenses of patients for purchasing the medicines (Dusetzina et al., 2018).

Also in the US, the regulation change in part D (coverage of prescription drugs) promoted by the “Affordable Care Act” aimed to reduce the costs of 23 antineoplastic medications (Abiraterone acetate; Afatinib; Axitinib; Cabozantinib; Crizotinib; Dabrafenib; Dasatinib; Enzalutamide; Erlotinib; Everolimus; Imatinib; Lapatinib; Lenalidomide; Nilotinib; Pazopanib; Pomalidomide; Regorafenib; Sorafenib; Sunitinib; Trametinib; Vandetanib; Vemurafenib; Vorinostat). In 2010, the cost varied between $6,456 for Dabrafenib and $12,160 for Sunitinib. In 2020, assuming that the value of drugs does not vary, it is estimated that the average will be $5,663 across all products, which is equivalent to a reduction of $2,550 per year. Despite the significant decrease in the average amount paid by patients within the implemented regime, it is noted that the cost of purchasing medications remains high (Dusetzina, Keating, 2016). Also in the US, a study reported that the value of the monthly copayment for antineoplastic drugs varied directly proportional to patient non-adherence to medication, especially in copayments that exceeded the $20 mark per month (Chin, Bentley, Pollom, 2019). This reality is extremely worrying, since the discontinuation of treatment directly implies a lower prospect of a cure for individuals with cancer.

A study carried out in Brazil assessed lawsuits for acquiring antineoplastic drugs (Capecitabine; Bevacizumab; Erlotinib; Rituximab; Cetuximab; Imatinib and Temozolomide) in São Paulo between 2006 and 2007. There was a significant increase in investment by the São Paulo Health Department (SES-SP) regarding the supply of these medicines. In terms of the total cost of anticancer drugs, there was a significant increase from 27,646,287.3 BRL to 54,694,305.3 BRL during this period of time, particularly Imatinib, the corresponding annual value of which for SES-SP increased by 3,051,384.35 BRL to 16,640,915.7 BRL. However, one relevant fact covered in the study is that the use of lawsuits in acquiring certain antineoplastic drugs, whose effectiveness and clinical use have no scientific basis, caused a financial expenditure equivalent to $ 13,383,878.40 BRL for SES-SP (Lopes et al., 2010).

As a limitation of the present work, we would highlight the small number of studies in the current literature related to the topic. It should also be noted that the lack of solid data regarding the exact values of antineoplastic medications in different countries before and after the judicialization process is characterized as another obstacle to broaden
our findings. Therefore, it is extremely necessary for more research to be carried out within this spectrum.

CONCLUSION

Based on the data presented in the article, it may be concluded that the high cost of antineoplastic drugs is a significant challenge for healthcare systems and patients worldwide. The increasing incidence of cancer, together with the aging population, has contributed to an increase in the number of cases and the need for effective treatments. However, the high costs may make access to these medications difficult and negatively impact patient treatment.

The systematic review has demonstrated that different countries face similar challenges when it comes to the costs of antineoplastic drugs. Countries such as Canada, Switzerland, Chile and the US have seen significant increases in the costs of these drugs over time. Furthermore, the acquisition of these medicines through lawsuits has become a common practice in several countries, which highlights the need for more effective strategies to make these treatments more accessible.

Parity laws, which seek to equalize the costs of antineoplastic drugs, have been implemented in a number of countries, such as the US. However, although these laws have brought benefits in terms of reducing personal expenses for the patients, costs still remain high. It is also observed that when costs are shared between the State and the patient, there is low adherence to treatment.

In relation to judicialization, the need for scientific basis in prescribing antineoplastic drugs acquired through lawsuits is particularly outstanding. The study carried out in Brazil revealed that a significant percentage of lawsuits were not based on reliable scientific evidence, which resulted in unnecessary expenses for the healthcare system. It should also be added that in universal, free healthcare systems, such as that in Brazil, failure to comply with cost-effectiveness, also due to the lack of scientific basis for prescribing innovative medicines, contributes to excessive financial expenditure for the State.

In conclusion, the article has highlighted the importance of developing public health strategies that aim to reduce the costs associated with antineoplastic medications and make treatment more accessible to cancer patients. This requires implementing effective policies, such as a thorough assessment of lawsuits, based on reliable scientific
evidence. Furthermore, it is of fundamental importance to conduct more research in this area to broaden our understanding of the costs of antineoplastic drugs and identify innovative approaches to address this global public health challenge.

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