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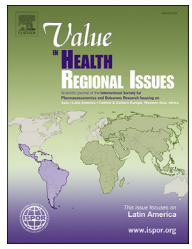

Policy Perspective

In the Era of Cost-Effectiveness Analysis, Affordability Is a Limiting Factor for Patients' Access to Innovative Cancer Treatments

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ABSTRACT

Background: Over the past 5 years, 55 new anticancer drugs have been launched worldwide. Considering the increasing costs of innovative treatments, both the number and the relevance of cost-effectiveness analyses have increased, meaningfully supporting decision making by stakeholders and policy makers. Notably, cost-effective treatments remain unavailable to patients because they are still unaffordable for a multitude of payers. **Objectives:** To discuss the differences between cost-effectiveness and affordability. **Methods:** We reviewed the most relevant data on the divergences between cost-effectiveness and affordability. In addition, we included our recommendations to improve patients' access to innovative cancer therapies. **Results:** The increasing costs of recently launched antineoplastic drugs, as high as $150 000 per year, represent a major barrier to patients' access to treatments globally. In Brazil, for example, patients' access to innovative treatments depends greatly on whether the individual has private health insurance. In the public health sector, patients' access to cost-effective innovative treatments varies according to the financial capacity of the facility, leading to inequalities within the same healthcare system. **Conclusions:** We conclude that because of the socioeconomic inequality mostly seen in lower and middle-income countries, it is difficult to define a cost-effectiveness threshold by region or a willingness-to-pay threshold affordable to the entire population. We consider that benchmark interventions might help to find an affordable willingness-to-pay threshold, and league table interventions might help policy makers, physicians, and the society to share the decision making.

Keywords: drug therapy, health policies, pharmacoeconomics

Introduction

The costs of anticancer drugs have risen steadily and have now become exorbitant. For example, inflation-adjusted analysis of all anticancer drugs covered by Medicare Part B showed that from 2010 to 2015 there was an increase in prices by 64% (the price of 12.7% of these anticancer drugs increased by more than 100% during this time frame).[1] Additional data analyzing 42 clinical trials showed that there has been a more than 5-fold increase in the costs of anticancer drugs from 2006 to 2015, with average drug costs increasing from roughly $30 000 to more than $160 000 per year, respectively.[2] As there continues to be a rise in the costs of anticancer drugs, tools such as cost-effectiveness analysis (CEA) and budget impact analysis (BIA) have become increasingly prevalent and relevant.

With the increase in the number of new anticancer drugs being developed and approved annually, there has been a growing interest and relevance in health economics research. This research and the emerging data are very important and informative for a multitude of cancers and other conditions. The key aspect that is often overlooked is that cost-effectiveness does not necessarily mean affordability. For instance, because of the tremendous cost burden of newly approved anticancer drugs, fewer than half are available to patients in, for example, Spain and Japan.[3] There is

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now a plethora of CEA studies published, yet many of them do not take into account the diverse social and economic status of varying countries. Specifically, when analyzing lower and upper middle-income countries such as Brazil, the applicability of a CEA diminishes when considering the nation's overall gross domestic product per capita (GDPPC). Goldstein et al[4] demonstrated that even though the costs of anticancer drugs are lower in countries other than the United States, their affordability in middle-income countries compared with high-income countries is lower as well because of lower purchasing power and greater disparities.

Cost-Effectiveness Analysis

CEA is a tool that assesses the relationship between the total expenditure for a treatment compared with the total efficacy of this treatment versus a control (often standard of care or placebo). In oncology, cost-utility analyses are commonly used, because they also consider the adverse events related to treatments. In cost-utility analyses, the cost and effectiveness are measured in monetary value (eg, US dollars) and quality-adjusted life-years (QALYs) or disability-adjusted life-years (DALYs) averted, respectively. The result is the incremental cost-effectiveness ratio (ICER), in other words, the incremental cost to improve 1 QALY or DALY averted. The value of these analyses is that they are straightforward and present concrete data. Like all statistical interpretations there are limitations to such analyses, because of primarily not taking into account the setting considered when assessing costs, drug toxicities, and quality of life after intervention.[5]

It is important to take a stepwise approach when reviewing a CEA critically. The first thing that should be apparent is the relevance of the treatment in current practice. A CEA must include information regarding the perspective considered, the indication of the treatment, inclusion criteria of patients, duration of treatment (eg, weeks, months, or indefinitely), further diagnostic evaluations (molecular tests, imaging studies, laboratory work, etc), and an outline of what alternative treatments (if any) are available in this setting. A key factor in evaluating a CEA is ascertaining whether it is generalizable and determining not only the efficaciousness (benefits to a trial population), but also the effectiveness (benefits to a global population). This basic schema to evaluate a CEA critically helps determine the value of the CEA, and it works to validate the idea of a threshold of benefit to the patient and population.[6]

Arguably, a critical factor in the decision-making process for the implementation of an intervention in this setting is the concept of a threshold value. For any health system, predefining a maximum cost per value will guide whether the system will endorse the intervention. Simply put, it is the willingness of a system to pay for a new treatment. Nevertheless, every country's health system has its own predetermined threshold based on its own economy and its capacity of carrying financial burden.

It is imperative to be able to compare cost-effectiveness and affordability for a system in the decision-making process to be able to identify an "ideal threshold" for any given health system.

The most cited and used CEA threshold is that of the World Health Organization (WHO), which deems treatments with incremental costs for 1 additional QALY or DALY averted of less than 3 times the GDPPC to be considered "cost-effective." Moreover, those with an ICER of less than 1 GDPPC are considered "very cost-effective."[7,8] The threshold represents how the drug cost will compare with the value at which a healthy citizen would produce capital of the same increment. The limitation of a set threshold is that it has been arbitrarily defined and frequently does not suit distinctions between assessment and appraisal.[9]

Table 1 – Differences between CEA and BIA.

Parameter	CEA	BIA
Inputs	Cost and clinical benefit	Cost for a population
Endpoint	ICER	Budget impact
Perspective	System or society	Payers
Time frame	Lifelong term	Short term
Threshold	ICER below the WTP	Cost affordable

BIA indicates budget impact analysis; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; WTP, willingness to pay.

Alternatives to the fixed WHO GDPPC threshold include the following:

- *An ability-to-pay/willingness-to-pay relationship index*, which could realistically reflect the relationship between a given nation's wealth and health expenditure.
- *ICER region-specific* threshold adjusted to countries' GDPPC.

To address different diseases and expand countries' perspectives, WHO had proposed 3 distinct approaches in 2015[10]:

1. *Thresholds based on* per capita *incomes*—the former WHO threshold of 1 to the 3 GDPPC threshold, as mentioned earlier.
2. *Benchmark interventions*—to use a benchmark intervention that a given country has already adopted as the reference for a cost-effective comparator to future analysis.
3. *League table interventions*—to define high-impact health interventions, rank them into a table according to their ICERs, and adopt them following the established sequence.

Budget Impact Analysis

The BIA addresses the affordability of a treatment by approximating the short-term costs for the payer.[11] The value in using this analysis simultaneously with a CEA is that a BIA allows you to determine the affordability of an intervention independently of cost-effectiveness and can help determine whether a set threshold is at an appropriate value. Unlike CEAs that are measured in a ratio unit, BIAs are measured solely in absolute monetary value, such as dollars.

Interpreting a BIA is very intuitive and straightforward. Lower costs equate to more affordability of a treatment. A BIA assesses the cost of an intervention multiplied by the total number of individuals in the population who will need or use this intervention to estimate a total cost.

Nevertheless, a BIA could also lead to misinterpretation because lower costs are not always linked to more affordability of a treatment. To note, lower middle-income countries frequently exhibit household economic disparities. Whenever a BIA is based on GDP, it does not address this economical gap and could mask differences in affordability across diverse socioeconomic strata, as shown by Goldstein et al.[4] Table 1 summarizes the differences between CEA and BIA.

There is a great deal of potential value of using both a CEA and a BIA in the decision-making process of whether to potentially implement a new intervention. The increasing popularity in studies published on CEA and BIA is intriguing and sheds light on many financial challenges that many countries face. The value in combining the use of both analyses for an intervention helps to

find a balance of both the most cost-effective and the one that is affordable.

Disparities in Brazil

Brazil is an upper middle-income country where the unaffordability of novel antineoplastic drugs hinders patients' access to novel antineoplastic therapies from both private and public health systems.

According to Quintiles IMS Holdings, Inc, of the 55 new approved drugs worldwide between 2012 and 2017, 12 were approved in Brazil with a delay of 2 years to the first global approval. Also, another 12 new drugs were approved for use in Brazil in 2017.[12]

Unfortunately, a new drug approved in Brazil does not mean it is going to be available to patients. According to the Brazilian Society of Clinical Oncology (*Sociedade Brasileira de Oncologia Clínica*), none of the 24 new drugs approved in Brazil have been used in the Brazilian public health system (*Sistema Único de Saúde*). In addition, only 5 of the 24 new drugs are available to patients with private health insurance.[13]

In the private health sector, new oral drugs must be included in the National Health Agency (*Agência Nacional de Saúde* [ANS]) list to be covered by health insurance companies. Only 20% of novel oral drugs are covered by private health insurance in Brazil, because of the 2-year wait period for updates to the ANS drug list.[13]

ANS argues that the 2-year interval helps health insurance companies plan their expenses and take into consideration the high costs of these new drugs. In other words, the mandatory coverage list may not only help the insurance companies to plan their budgets but could also endorse a resource constraint policy that does not necessarily focus on patient needs.

As a consequence, Brazil has experienced an unprecedented litigious environment in which many patients sue insurance companies and the government to obtain the treatments that are included in the ANS drugs list. This has led to an increase in the number of judicial processes for antineoplastic treatments, where oral drugs account for most of the lawsuits (31.4%), followed by monoclonal antibodies (17.1%).[14]

With reference to the Brazilian public health system, access to new antineoplastic drugs plays a critical role. As mentioned earlier, as of 2012 none of the 24 newly approved drugs in Brazil have been available in the public health system. This is due to a myriad of reasons including, but not limited to, slow and comprehensive analysis process, unbalanced demand, low human resources capacity, and limited resources, among others.

Brazilian Technical Chamber of Technology Inc (*Câmara Técnica de Incorporação de Tecnologias* [CONITEC]) from the Brazilian Health Ministry analyzes efficacy, safety, cost-effectiveness, and budgetary impact of new health technologies, including medicines, before their incorporation into the Brazilian public health system, which includes 77% of the Brazilian population.[15] Considering both Brazilian GDPPC and the WHO threshold, a cost-effective treatment can cost as much as $25 000 per QALY in Brazil. Nevertheless, a cost-effective treatment can have an overwhelming budget impact, making it more difficult to incorporate it in the Brazilian drug landscape.

Not to mention, a law recently made healthcare investment in Brazil immutable until 2038, a challenge considering the epidemiological aspects and the economic crisis the country has faced over the past 5 years.

Moreover, it is difficult to find a threshold for cost-effectiveness in Brazil because of the economic and social inequalities.[4] What is cost-effective in a country where 1% of the population concentrates 28% of the GDP[16]?

Brazilian and UK health technology assessment agencies, namely, CONITEC and the National Institute for Health and Care Excellence, are frequently compared; there is, however, a crucial difference. Even though CONITEC performs both CEA and BIA, price negotiation, discounts, and market-sharing policies are not under the health technology assessment scope when negotiating a new drug's maximum and acceptable price to be paid, whereas these are taken into consideration in the National Institute for Health and Care Excellence.

Trastuzumab has recently been incorporated into CONITEC's list after an 18-year interval from its approval in Brazil. The process was possible because of the Ministry of Health's centered purchasing policy, which negotiated on a price discount, estimated up to 80%.

In other cases, the CONITEC approval does not mean availability for patients' treatment. The Brazilian Ministry of Health reimburses the service providers according to the diagnosis. For example, in metastatic lung cancer, there is a fund of $300 per month; it does not matter what type of treatment is received. This value must be enough to purchase drugs, pay taxes, and reimburse local employees. Tyrosine kinase inhibitors used in the treatment of metastatic lung cancer with epidermal growth factor receptor (EGFR) gene mutations have an average cost of $1000 per month. They are the criterion standard for patients with EGFR-mutated advanced lung cancer around the world. In the Brazilian public health system, although the recommendation to use EGFR tyrosine kinase inhibitors is indicated, the reimbursement is the same and the hospital is forced to incur the balance.[17]

Thus, patients with the same pathology at different cancer care institutions receive different treatments, further perpetuating the disparity within regionalization, hierarchy, universality, and equity principles that should guide the Brazilian public healthcare policy.

Recommendations

To note, the myriad of national and regional socioeconomic perspectives challenges one who aims to admit a specific threshold. The inequalities not only among different countries but also within the same country may determine heterogeneous affordability. We propose 2 approaches to tackle this problem:

1. Benchmark interventions that take into account previous adopted technologies to set up an affordable WTP.
2. League table interventions to support the decision-making process among the society, namely, policy makers, physicians, and advocacy groups, to prioritize the access to innovative treatments for the patients who will benefit the most.

Conclusions

Even though cost-effective, some treatments are not widely available because of their unaffordable budget impact. Further efforts need to be made to translate cost-effectiveness studies into current clinical setting.

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