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Increasing Access to Immuno-Oncology Therapies in Brazil

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Highlights

- Immuno-oncology has become the fastest growing area in oncology
- In immune-oncology field there is a growing number of effective, but costly agents
- The entire Brazilian public health care system faces serious financial and organizational challenges
- In developing countries the overriding issue is the difficulty of assessing the true value of costly drugs
- We offer recommendations to health policy makers and stakeholders that may improve access and cost

Around the middle of the last century, a scientific understanding of the immune system began to develop. The ability to engineer antibodies and manipulate the molecules of the immune system led to an increasing understanding of how the immune system works [1]. This enabled the development of targeted therapeutic interventions and the rise of what today is termed immuno-oncology.

In recent years, immuno-oncology has become the fastest growing area in oncology and one of the most exciting areas of research and development in all of

science. In 2013, *Science* magazine declared cancer immunotherapy the breakthrough of the year [2]. The successes of the field have given rise to a growing number of pharmacologic agents to combat cancer. These drugs have had a promising effect on prolonging the life of many cancer patients who previously had few effective therapies. But while the near exploding growth of the field is transforming cancer care and portends huge promise, the access of immuno-oncologic products has given rise to many issues.

While the drug approval process has not been appreciably affected, in developing countries like Brazil the overriding issue is the difficulty of assessing the true value of these costly pharmaceuticals. Thus, the desire and ability of the public health system and payers to support the use of immuno-oncologic drugs has become a major subject of contention. The question is basically: What is the willingness-to-pay of the Brazilian society to improve universal, comprehensive and equitable health access, particularly in cancer prevention and treatment?

In the paper, we discuss the progress that has been made in the field of immuno-oncology and its impact on Brazil – a very large country with a complex health system, many competing health needs and limited resources – and offer suggestions for how access to immuno-oncology therapies may be enhanced.

Immuno-oncology

Over the past 25 years, research in cancer therapeutics has largely focused on two distinct lines of inquiry: understanding the underlying drivers of tumorigenesis and exploring the mechanisms of protective tumor immunity. This has resulted in an impressive array of molecular targeted therapies that harness the immune system to attack

malignant cells. Using the innate immune system to treat cancer has proven to be an invaluable treatment enabling complete, durable remissions for many cancer patients.

In brief, there are three steps that must be achieved to mount an effective antitumor immune response: dendritic cells (DCs) must process tumor antigens derived from dying tumor cells; tumor antigen-expressing DCs must generate protective T-cell responses in lymph nodes; and cancer-specific CD8⁺ cytotoxic T-cells must migrate through a potentially immunosuppressive environment to kill the tumor [3]. Researchers have attempted to intervene therapeutically at each of these steps.

Many immuno-oncology drugs have been approved and perhaps the most impactful have been the class of drugs termed checkpoint inhibitors. In 2011, the FDA approved ipilimumab [4], which was then approved in Brazil in 2012. Additionally, nivolumab [5] and pembrolizumab [6] were approved by the FDA in 2014, and both were approved in Brazil in 2016 and 2017, respectively; pembrolizumab, notably, was approved on the basis of a tumor-specific biomarker in some indications, which therefore resulted in highly specific therapy. Examples of immuno-oncologic therapies are shown in Table 1 and those that are available in the Brazilian public and private health care systems are indicated.

One growing trend in immuno-oncology development is an increase in studies on combination therapies, which have shown positive results in early trials. Immunotherapy modalities are being tested in combination with other chemotherapeutic agents, radiotherapy, other targeted therapies or with other immunotherapies. Meaningful synergistic effects are anticipated with such combination therapies [7]. The use of combination immunotherapies may convey long-term survival benefits that single-drug agents may not deliver.

It is clear that immuno-oncology is an evolving and essential treatment modality. Immuno-oncology agents have the potential to revolutionize cancer care and it is likely that they will continue to have an increasingly impactful role in cancer treatment. These medications have the potential to transform cancer into a controllable, or even curable, disease.

Health care in Brazil

Brazil is the fifth largest country in the world with a population of about 207 million [8] people dispersed over many cities and geographical areas with significant cultural, social and environmental differences. Healthcare is delivered by two distinct systems: one is the public health system that provides care to everyone and is funded by the government, the other is a private system that requires individuals or employers to purchase insurance and receive their care from specific institutions and health care providers.

Brazil has the largest universal public health system in the world. Known as SUS (Sistema Único de Saúde) after its initials in Portuguese, Brazil's public health system covers both citizens and non-citizens. Although the public system exists for all Brazilians, about 58% of healthcare spending is attributable to the cost of private health care [9], which provides services for about 25% of the population. Despite having full-coverage public health care, Brazil is the third-largest market for private health care insurance in the world, mainly because of wait times and the lack of widespread availability of newer technologies in the public system. The private system is known as the supplemental health sector and is regulated by a specific and separate agency, the National Regulatory Agency for Private Health Insurance and Plans, and has about 42.5 million members. Private health care insurance typically provides for the entire cost of

inpatient care. For outpatient care, the private system pays for all services, excluding any medications taken at home, with the exception of those oncology medications on a previously approved list [10].

Although total health care spending in Brazil is about 9% of gross domestic product (GDP), similar to the average of other countries in the Organization for Economic Cooperation and Development (OECD), only about half of this amount, as mentioned above, comes from public sources – a proportion that places Brazil far below the OECD average for the government's share of health expenditures [11]. Despite many accomplishments, the entire Brazilian public health care system faces serious financial and organizational challenges, increased by the demographic and epidemiological transition associated with an aging population, and the increased incidence and prevalence of non-communicable diseases [12].

The burden of cancer in Brazil

Approximately 600,000 people in 2016 were diagnosed with cancer in Brazil and it is the second leading cause of death. The most frequently diagnosed cancers in 2016, excluding non-melanoma skin cancers, are prostate cancer, accounting for about 61,000 cases of new cancers in men, and breast cancer, accounting for about 58,000 new cases in women. Lung and colorectal cancers are the next most common [13].

In 2015, R\$ 6.7 billion (US\$ 4.1 billion PPP*) of direct medical services were spent for cancer-associated care by the SUS. The estimated cost of cancer care for the private health care system was R\$ 9.2 billion (US\$ 5.7 billion PPP*) [14]. One should

* Brazilian costs were converted into US dollars during the analysis using a purchasing power parity basis (PPP 2015: US\$ 1 = R\$ 1.6) available in: <http://data.worldbank.org/indicator/PA.NUS.PPPC.RF>

remember that the private system provides care for only about 25% of the population yet spends about 30% more on cancer care than does the public health system.

The severity of cancers is often measured in number of deaths. However, number of years of life lost (YLL) is an indicator of the impact of cancer on society. Based on the total number of deaths at each age level, multiplied by the expected remaining years of life, an approximate total of 900,000 YLL for males and 670,000 YLL for females occurred in 2015. The cost YLL due to cancer was estimated to be R\$ 24 billion (US\$ 15 billion PPP*) in 2015 [15].

There appears to be no accurate data on the prevalence of various cancers in Brazil. In addition, it should be noted that given the socio-economic diversity of the population across geographical regions, and the variance with which the entire population has access to healthcare, the true prevalence of various cancers will fall within a wide range. Also, the unequal allocation of resources across the country, concentration of healthcare professionals in more developed urban centers, and altogether relatively low investments in equipment and infrastructure, result in great inequities in health care and outcomes. Of note, for some cancers the outcomes achieved from treatment in the private system were significantly better than what has been achieved in the public system, reflecting the existing inequalities in access [16].

Cancer care in Brazil

One of the greatest challenges currently facing oncology in Brazil is how to reconcile small, incremental and significant improvements in the management of cancer with the exponentially increasing cost of new treatments in a resource-constrained environment. With regard to cancer-specific medications, neither the public nor private sector provides all available drugs. The lack of availability of all effective and evidence-

based cancer-related drugs is a major problem. Equally important, immuno-oncology medications are not available in the public health system and only partially available in the private system. It is important to note that there are two categories of drug approval in Brazil: there is approval for the safety and efficacy of the drug that is given by ANVISA (Agência Nacional de Vigilância Sanitária), which we will refer to as “regulatory approval”, and there is approval for the actual use of the drug in the public health system, which we will term “access approval,” that is given by CONITEC (Comissão Nacional de Incorporação de Tecnologias).

For a new drug to be regulatory approved in Brazil, it must follow a strict process coordinated by ANVISA. Once registration is granted through this process, most drugs become available to patients in the private health system. For patients in the public system, however, an additional approval step is required, which consists of a health technology assessment (HTA) performed by CONITEC. Manufacturers, public health bodies and other stakeholders can submit applications for an HTA after a drug receives market authorization from ANVISA and has its maximum price set by an inter-ministerial commission. Most high-cost cancer-related medications evaluated by CONITEC have not been access approved for patients in the public system on the presumed basis of insufficient scientific evidence of benefit (despite ANVISA approval), perceived lack of cost-effectiveness, or presumed incomplete documentation.

The private system works on a “fee-for-service” model, while the public system provides a fixed budget per patient per month, based on the disease, stage and line of treatment. For the public healthcare system, this means that the incorporation of expensive new treatments is not possible since the budget does not take into account the escalating cost of new therapy. In addition, all states and cities within Brazil have their own healthcare budgets, which can also preclude the availability of a drug in the public

healthcare system independent of access approval by CONITEC. All these limiting factors raise serious concerns about the equity and quality of cancer care delivered to the Brazilian population receiving publicly funded health care. Other important parameters related to the status of cancer care in Brazil have been published in a Pan-American Health Organization report [17].

Availability and Accessibility in Brazil

Given the effectiveness of immune-oncology drugs, one might conclude that the therapies enjoy widespread use and availability throughout Brazil, not the least of which is because the Brazilian constitution states, “health is the right of all and the duty of the State” [18]. Unfortunately, however, the widespread use of immuno-therapeutics in Brazil has not occurred and will likely continue to be constrained. There are many reasons for this limited access. For example, for the most part the drugs are not affordable in the current Brazilian health care environment. Another reason is that the drugs require sophisticated knowledge on the part of health professionals, including health technology assessment capability. Third, it’s likely that many influential health policy makers are not aware of the impact and value of these newer agents. Fourth, in view of the given budget constraints, budget impact is likely the most important economic consideration in denying reimbursement.

An unfortunate, partial remedy to overcome some of these barriers to access has been that patients file lawsuits against payers (public and private), claiming that their right to health as enshrined in the constitution is being violated, or that their need for the drug exceeds any other concern [19]. Such lawsuits have resulted in many patients gaining access to drugs they never would otherwise get, but this remedy has been interpreted to apply to only the case in-hand and not to the entire population. Health

care litigation in Brazil is therefore making the public health system less fair and rational. Courts are creating a two-tier public health system: one for those who can litigate, and thus have access to any treatment irrespective of cost, and a second tier for the rest of the population. The legal system should not be used as a routine pathway to qualify for the use of a drug. In contrast, access to a drug must rely on evidence-based medicine and a careful balance between need, value and cost for the entire patient population.

Nonetheless, the price of immuno-oncologic pharmacotherapy is a major limiting factor. While we would expect the price for such drugs in developing countries would be lower than in higher-income countries, and such a price differential exists in Brazil, the price differential appears not to be fully proportional to differences in income or GDP. Thus, the price of these expensive pharmaceuticals, despite being lower than in developed countries, is still prohibitive [20].

To overcome some of the barriers, many initiatives have been implemented. One current initiative is that the Brazilian Society of Clinical Oncology has proactively petitioned CONITEC to decide the appropriateness of a pharmacological agent for the public healthcare system. This action encourages CONITEC to address the availability of a drug before they otherwise would [21]. The Society is also conducting professional education outreach programs to improve awareness and understanding of the value of immuno-oncological therapeutics.

Another approach has been to encourage more clinical trials related to drug approval to be conducted in Brazil on the safety and efficacy of immuno-oncologic agents, considering all the ethical issues required in clinical research. Such studies would, by their nature, enroll patients (in either arm of a trial) who might otherwise never receive these medications. However, this approach is hampered by the difficulty

of achieving government approval for initiating clinical trials in Brazil, and also presupposes that a drug not yet approved is indeed safe and effective for those who may be randomized to the experimental arm.

A third approach has been an attempt to demonstrate to policy makers that the very successful outcomes from the use of immuno-oncology drugs warrants that they become a healthcare priority, and that this be done as quickly as possible to remedy increasing inequity between the private and public healthcare sectors [10]. The approval of multiple cost-effective options in a therapeutic class may lead to greater price competition, thereby lowering prices and increasing accessibility.

Brazil also has many opportunities to stimulate the use of new immuno-oncologic agents. The country has a publically funded universal health system, which signifies a commitment to providing healthcare to an entire population on a cost-effective basis. A second attribute is Brazil's very large population, which itself encourages the introduction of new drugs that would be prescribed to a large number of patients. A third attribute of the Brazilian market is that it has a large industrial base that already enjoys the presence of public-private partnerships, and thus the country has the experience to facilitate the expansion of such partnerships into the pharmaceutical sphere. A fourth attribute is that there is considerable investment in Brazil, and the health economic-industrial complex is well-entrenched and growing, and thus has a growing infrastructure to expand greatly into immuno-oncology products [22]. Finally, the country has adopted the perspective that improved health is a major national strategic area for development, including an emphasis on translational research and HTA studies, both of which have the potential to improve the effectiveness of the healthcare system while expanding drug affordability.

Faced with these opportunities, the following five recommendations are suggested as a strategy to increase innovation and access to technology in the field of immunotherapy.

One recommendation is to emphasize to all stakeholders that the cost of a drug directly impacts access; the link between price and access must be publicly recognized and a strategy must be put in place to directly link the cost of the drug with the ability of industry to sell the drug in the country. Although a reduction in price may first appear to decrease pharmaceutical profits, the resulting increase in access, and thus an increase in the number of patients treated, would result in an overall increase in both economic and health outcomes for all stakeholders. As a result, it is vital that the government directly and transparently deal with the issue of price and access.

A second recommendation relates to the ongoing debate about value-based delivery and reimbursement in oncology. For example, should the same drug have different prices for different indications if the outcomes are not the same? A new pricing paradigm would force pharmaceutical manufacturers to compete on prices and outcomes.

The pricing of pharmacologic products in Brazil is a complex topic, involving three main parts: the fundamental cost of producing the drug, the taxes applied to the product and the profits that are made. The latter two costs overwhelmingly contribute to the final price and are two areas that must be urgently addressed.

Thus, our third recommendation is related to price, involving three challenges: First, the government should direct the existing high-level commissions to address the ethical issues surrounding the extent to which an essential health-related pharmaceutical should generate high profit margins and also be taxed. Is it possible a mutual commitment between industry and government to reduce taxes and profit margins? The

recent experience of Productive Production Partnership shows that this consensus is feasible [23]. Second, industry should examine the potential implementation of value-based pricing. Must profit margins (after research and other expenses are accounted for) be what they are given that many drugs are essential for the basic right of health?

Pricing is a complex process given the imperatives of capitalism and of health as a social and individual right. Thus, the third challenge of this recommendation is that government can and should develop incentives and regulations that impart novel ways to influence the price of drugs. Here, too, the existing commission comprised of public and private members (e.g. health professionals, civil society organization, consumers, and industry representatives) should urgently address this issue and provide reasonable and enforceable recommendations for change.

A fourth recommendation is to use the strength and size of local institutions and enterprises to increase competitive pressure between companies selling immuno-oncology products. By stimulating start-up and increased local production by established pharmaceutical companies, providing tax and financial incentives, obtaining access to the public market to offer health strategic products and to have priority in the regulatory process or approving more cost-effective drugs for use in the public health system, may foster a more competitive environment.

A fifth recommendation is to create more public-private partnerships whereby the government provides resources that support and encourage pharmaceutical companies in Brazil to enter the immuno-oncologic field. In addition, the government should encourage more private-private partnerships so that the private Brazilian pharmaceutical industry gains expertise, experience, and training that will eventually lead to a more robust local pharmaceutical industry. The benefit for the Brazilian and non-Brazilian pharmaceutical industry may be increased access to the Brazilian market.

With either approach, upon approval, immuno-oncologic drugs may have a lower price and therefore be more accessible. Also, an incentive for partnerships can be a government commitment to purchase the resulting products.

Finally, there should be some mechanism for all stakeholders – international and local pharmaceutical companies, government, policy makers and regulators, healthcare providers, patient advocacy, medical societies - to interact and develop strategies, such as what is occurring in the Health Industrial Complex Executive Group and Forum (GECIS), that will foster the appreciation and utilization of new technologies in the immuno-oncology area [24].

In fact, the discussion on access to costly cancer drugs is global. Alternative pricing, marketing and reimbursement models are warranted. More than that, a new model for interaction between government, pharmaceutical industry, healthcare providers and society should be established if we are to move from a standard capitalism-based pricing model towards value-based oncology care. Despite well-known limitations on the delivery of standard health care across the country, Brazil has a sophisticated regulatory system and has recently implemented policies and incentives for encouraging private-private and Productive Development Partnerships, demonstrating that new ways to organize and deliver health care are feasible [23]. There is certainly room for a new drug production and pricing model to be tested. Moreover, despite differences in healthcare systems across distinct countries, the Brazilian experience and initiatives may well be applicable to other countries.

Summary

Immuno-therapeutics have revolutionized the field of oncology. The Brazilian cancer population would unquestionably benefit from an increase in the availability of

cost-effective immuno-oncologic drugs. The challenge is how to incorporate these into the toolbox of health professionals, given the complexity and inequities of the Brazilian healthcare system, limiting financial resources and numerous health needs. We provide a series of recommendations that are likely to improve access and reduce the cost of these important medications. Nonetheless, there are numerous challenges that must be overcome if the entire Brazilian cancer population is to benefit from this remarkable advancement in health care.

Declaration of interest:

NONE

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Modality	General use or utility	Limitations	Examples	Availability	
				Public	Private
Vaccines	Prime patient immune response to tumor-specific antigens	Heterogeneous tumor antigen composition and expression; prone to be hampered by mechanisms of immune suppression	Vaccines against targets such as gp100, MUC1, MAGEA3	None	None
Recombinant cytokines	Agonism or blockade of protein-protein immune pathways	Antigenicity; poor pharmacokinetics; high toxicity	GM-CSF, IL-7, IL-12, IL-15, IL-18, IL-21, IL-2, IFN- α	IFN- α	IL-2, IFN- α , GM-CSF
mAbs	Highly selective agonism or blockade of extracellular protein-protein immune pathways; long half-life; non-immunogenic (human or humanized)	Expensive and time-consuming manufacturing and development costs; challenges in achieving high tumor exposures	mAbs targeted against CTLA4, PD1, PDL1, (T-cell checkpoint blockers)	None	Anti-CTLA4, anti-PD1
Autologous T cells	Tumor-targeted cytotoxicity of extracellular and intracellular tumor-specific antigens	Heterogeneous tumor antigen composition and expression; on-target, off-tumor toxicity	CAR T cells, TCRT cells	None	None
Small molecules	Uniquely suited for intracellular targets, but also equally applicable to cell surface or extracellular targets	Off-target activities; dose-limiting; ineffective at blocking protein-protein interactions; require daily dosing	IDO1 and COX2 inhibitors, TLR agonist and chemokine antagonist	None	TLR agonists

Table 1. Therapeutic modalities targeting immune regulation of cancer

CAR, chimeric antigen receptor; COX2, cyclooxygenase 2; CTLA4, cytotoxic T lymphocyte-associated antigen 4; GM-CSF, granulocyte-macrophage-colony-stimulating factor; IDO1, indoleamine 2,3-dioxygenase 1; IFN- α , interferon- α ; IL, interleukin; MAGEA3, melanoma-associated antigen 3; MUC1, mucin 1; PD1, programmed cell death protein 1; PDL1, programmed cell death 1 ligand 1; TCR, T cell receptor; TLR, Toll-like receptor.