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Can innovation increase the therapeutic options but accentuate the inequalities in the healthcare system?

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ABSTRACT

Melanoma is the most dangerous type of skin cancer, and pre 2011 the prognosis of metastatic melanoma was very poor. In developing countries, such as Brazil, a vast majority of patients do not have access to the opportunity of an early, curative melanoma approach and this leads to metastatic disease. In this sense, the purpose of this paper is to illustrate the distinct lack of access to innovative melanoma treatments, based on immunotherapy and target therapy, in the public and private health sectors in Brazil. We analyzed the Brazilian health regulatory system and the incorporation of health technologies in the public and private health settings. At present, for patients being treated within the public health system, only dacarbazine is available. Whereas, immune-oncology agents and target therapies are available for patients being treated within the private health sector. In this scenario, we concluded that the introduction of innovations could accentuate the existing inequalities in the delivery of healthcare in Brazil.

1. Introduction

Melanoma, although far less prevalent than non-melanoma skin cancers, is the primary cause of death from skin cancer and is more likely to be both reported and accurately diagnosed than non-melanoma skin cancers. [1] For decades, before the development of target therapies and immunotherapies, the only available treatment for metastatic melanoma (MM) was dacarbazine with the median overall survival of 6–10 months and a 5-year survival of 2–6 % [2,3]

The treatment landscape for advanced melanoma has been recently transformed by novel agents, such as immune-checkpoint inhibitors and molecular target drugs, which have significantly increased the survival benefit in MM patients [4]. FDA approved ipilimumab for metastatic setting in 2011. Since its approval, several targeted therapies have been approved by this regulatory agency. [5] Moreover, indeed, these numbers are much better after the approval of programmed cell death-1(PD-1) inhibitors, nivolumab and pembrozilumab [6]. The association of nivolumab and ipilimumab have also been shown to have complementary activity in MM. [7]

A variety of activating mutations have been described in melanoma. [8] Numerous target drugs have already been developed as BRAF and MEK inhibitors, isolated or combined, with a significant improvement in progression-free survival and overall survival [9]. This new technological platform, combined with drugs and knowledge, has actively helped MM patients in most developed countries, where the Health Management System (HMS) can afford such costly treatments. [10] In addition to this, most of these countries utilize effective melanoma awareness campaigns that have proven to improve early melanoma diagnosis and decrease the proportion of patients developing metastatic disease [11].

Unfortunately, in the vast majority of developing countries, including Brazil, most of the patients do not have the opportunity of an early and curative melanoma approach and they also suffer from absence of effective treatment options. The same health system that does not help the user at secondary prevention does not provide any effective treatment besides surgery in selected cases of metastatic disease. [12,13]

As these new technologies are implemented between the Brazilian public and private health systems in different ways and at varying speeds, the introduction of innovations can be accentuated and thus widen the gap of the already existing inequalities within the delivery of healthcare in Brazil. This research uses the regulatory journey in the

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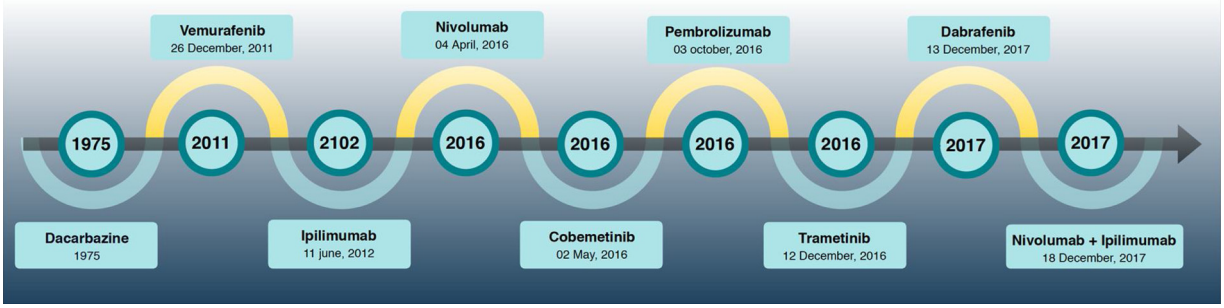

Fig. 1. Timeline of drugs approved by ANVISA for MM treatment.
Source: Data research

treatment of advanced melanoma to illustrate the differences in access to innovations in the public and private health systems in Brazil.

2. Brazilian health regulatory system

The Brazilian Health Regulatory Agency (Anvisa) is an autarchy of the Ministry of Health and acts as the coordinator of the Brazilian Health Regulatory System and is present throughout the national territory. The role of Anvisa is to promote the protection of the population's health by conducting sanitary control of the production, marketing and use of all products and services that are subject to health regulation. [14] It is the primary responsible agency for drug registration. Currently, the drugs registered by Anvisa for MM treatment are dacarbazine [3], vemurafenib [15], ipilimumab [16], cobimetinib [17], nivolumab [18], pembrolizumab [18], trametinib [19], and dabrafenib [20]. Fig. 1 shows the timeline of drugs approved by ANVISA for MM treatment.

Under Brazilian law, before a drug can be marketed in the country, it is essential to obtain both the sanitary registration from Anvisa and the authorization of a maximum price by the Brazilian Drugs Market Regulation Chamber (CMED). The pricing methodology adopted by the CMED seeks to ensure that the maximum prices for new medicines are no higher than the lowest price when compared with the average price from nine other countries. However, this does not entail a higher treatment cost compared to the existing therapeutic alternatives for the same illness, unless superiority can be proven when compared.

After Anvisa has granted its registration and CMED has established price limits for a drug, the new drug is authorized to be marketed and sold throughout the country, but adequate access to the new technology or drug, in this case, is not yet guaranteed. At this stage the drug needs to be assessed before being integrated into the public and private health systems.

3. Brazilian incorporation of health technologies

Brazil has a population of over 207 million people [21] and it is estimated that approximately 20 % have access to Private Health Care, also known as Supplementary Health System, which provides more comprehensive access to a much wider range of procedures and medications when compard to the Public Health System. Private Health Care cover is generally financed by the individual or an employer [22].

The National Supplementary Health Agency (ANS) is the regulatory agency linked to the Ministry of Health responsible for the health insurance sector in Brazil. The ANS is responsible for defining the list of procedures that private health plans are required to cover, including the prevention, diagnosis, treatment, recovery, and rehabilitation of all diseases that make up the International Statistical Classification of Diseases and Related Health Problems (ICD), of the World Health Organization (WHO). [23]

ANS has conducted polls of various technologies, including immune-oncology agents ipilimumab, nivolumab, and pembrolizumab; and the target therapies vemurafenib, dabrafenib, and trametinib for MM treatment. [22]

The other 80 % of the population depend exclusively on the Unified Health System (SUS). SUS is a universal and free at the point of demand health system offered as a constitutional right to all Brazilians, immigrants and tourists. SUS is responsible for providing access to health care to the most vulnerable portion of the population. Faced with the current economic crisis, the current unemployment rate (which accounts for 12 % of the economically active population) and the recent economic growth, it is extremely unlikely that a vast majority of this some 165,000,000 people will ever convert thmselves from relying on SUS to a private health plans. [21,24,25]. This information emphasizes the relevance of a better understanding as to how new technologies or treatments should be incorporated within the SUS model.

The National Commission for the incorporation of Health Technologies (CONITEC) was established by The Brazilian Minister of Health (MoH) in 2011. The aim and purpose of CONITEC is to provide support and advice to the MoH during decision or policy making processes. This may include counsel relation to the incorporation, exclusion, or change of medicines, products, and procedures within the SUS, for example. It is also required to assist with any constitutional changes in the standard treatment guidelines and in updating the National List of Essential Medicines. The CONITEC analysis is based on evidence which is complied of aspects such as efficacy, accuracy, effectiveness, and safety of the technology, as well as comparative economic evaluation of benefits and costs of reagrding already existing technologies. It is also worth noting that any new products are required to be registered and approved by Anvisa prior to being evaluated by CONITEC. [26]

In order to offer an alternative to the lone-standing treatment of dacarbazine, for SUS's MM patients, the Brazilian Society of Clinical Oncology (SBOC) requested that CONITEC incorporate ipilimumab for systemic treatment as second-line monotherapy for adult patients with unresectable metastatic melanoma. Previous to this request from SBOC, dacarbazine was the only available immunotherapy registered for melanoma. The initial calculation of budget impact for the treatment of 346 patients was $50 million per year, but according to the analyses made, it is probable that this value was underestimated. Therefore, on 5th July 2018, the members of CONITEC ordered that the topic should be submitted to public consultation with preliminary recommendations unfavorable to the incorporation of ipilimumab for the treatment of patients with metastatic melanoma with progression after chemotherapy. The demanded treatment line was considered inadequate due to "*evidence too weak to subsidize the use of dacarbazine in the first line, existence of other immunotherapeutics with better-demonstrated efficacy in Randomized Clinical Trials, inadequate estimation of drug benefits, and underestimated in the incremental budgetary impact.*" [27]

Unfortunately, so far, CONITEC has not approved any targeted therapy or immunotherapy for MM. The only treatment for metastatic melanoma endorsed by CONITEC is still dacarbazine [28], to 165 millions Brazilians, even being well established at the guidelines for

MM treatment the use of target therapies and immunotherapy with an essential increase of response rate and overall survival compared to dacarbazine [5,29]

This situation reveals that the patients of SUS have no access to the recommended treatments, and oncologists are stuck in the 1970s, when only dacarbazine was available. Despite the efficacy of innovative treatments for MM, their high costs have led to disparities for 80 % of Brazilians. According to the Brazilian National Cancer Institute (INCA) in 2020, 8,450, new cases of melanoma are expected in the country [30], and 26.1 % of these cases are expected to be diagnosed at stage IV [12]. These numbers indicate 2205 MM patients, or in better context, 1697 SUS users.

Besides the underfunding of SUS, most medicines are not sold in competitive commodity markets in Brazil. Specifically for MM, the pharmaceutical market is oligopolistic with few competitors who are able to drive up prices given the informational asymmetry that exists between themselves and their purchasers. [31] The financial determinants of access to medicines, including its price and its impact on household budgets and the financing of the health care system are becoming of considerable importance to the country [32]. By volume, Brazilian companies hold around 70 % of the pharmaceutical market in Brazil; however, Big Pharma controls about one-half of the market [33]. This figure underestimates its presence as multinational pharmaceutical corporations have been active in mergers and acquisitions of domestic companies. In the present context of an economic recession, the government is attempting to impose spending controls through centralization of purchases and strengthening regulation of pharmaceutical prices, for instance, ANVISA's denials to provide some high-cost prescription drugs not included in its guidelines [34].

The degree to which price regulation is valid differs from country to country with differences in effectiveness. In Brazil, some criteria for direct regulation of medicine prices have been applied based on therapeutic use, economic assessments, the cost of alternative treatments available on the market for the same diseases/conditions, and/or on international price comparisons. [32]

A report from a Brazilian Parliament committee suggested that drugs reach Brazilian consumers at prices many times above the cost of production. Shipping, packaging, and distribution costs, as well as taxation, contribute to the final retail price of a drug. Nonetheless, these expenses do not in anyway explain nor justify a 13-fold increase over the International Drug Price Indicator Guide mean prices. Price composition data supplied by pharmaceutical companies to Brazil's Parliament indicated that the cost of production comprises 42.6 % of the retail price. [35]

A Brazilian study showed that retail prices for essential drugs in Brazil are almost twice as much as they in Sweden, and taking into account that Brazil's average income level is ten times lower than that of Sweden. Certainly, high prices, without doubt, are restricting access to essential drugs for low-income Brazilians. [36] These low-income Brazilians are, as we already established, SUS users.

Whereas direct price regulation has been the traditional strategy applied to impact the price of medicines, international experience indicates that other effective alternatives are available. Indirect controls such as those in force in the United Kingdom may target areas other than price, such as placing a maximum cap on what a pharmaceutical company can invoice the public health system. [32]

The medicine pricing situation, as described above considering with the fact that SUS is chronically underfunded, has ignited the need to satisfy health requirements and the growing demands for new technologies. It has triggered the phenomenon of health litigation for the provision of therapies that have not been incorporated into SUS. Many of these legal cases seek to ensure the right of access for patients to expensive medicines, that they would otherwise not be able to access, on SUS. [37,38]

In this scenario, we have three different profiles of MM patients in Brazil. Firstly, one that represents 20 % of the population is covered by Private Healthcare Insurance and has access to all the same innovative treatments as most developed countries. Second, 80 % of patients covered only by SUS that have no access to immunotherapy and target drugs, just dacarbazine. Finally a thirdly, among SUS users: patients that can afford lawyers to sue the government to receive these treatments. Typically, the government lossing at the end must pay for drug costs and even lawsuit expenses.

A study covering Unions, states, and municipalities found that Brazil's spending on health lawsuits in 2015 was R$ 1 billion, an increase of more than 1,300 % over the previous seven years. This data could be underestimated as there is no data collection for processing and routine analyses that allow the design of the health judiciary to support decision making. [39]

There is another possibility of access to innovative treatments. Clinical Trials could potentially allow patients to access medicines that would otherwise not be available to them due to their high cost or difficult access. Unfortunately, in Brazil, clinical trials face many challenges, including lengthy start-up time which can severely impact a patient's prospects of treatment and recovery [40].

4. Conclusion

The access to optimal treatment for patients with MM in Brazil is far from acceptable and the collated information shows, clearly, a situation that is considerably worse for patients from a low socioeconomic status. The flow of information nowadays is free and fast, even including medical results for lawyers. It is an awful situation where a population has the ability to access to all of the necessary information but cannot understand why they are not able to access to it. This plight is not yet evident even to health professionals as it is yet to be fully established.

Declaration of Interest Statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from claudimar.veiga@gmail.com.

Compliance with ethical standards

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Data analysis and interpretation: All authors

Manuscript writing: All authors

Accountable for all aspects of the work: All authors

All authors read the manuscript, provided critical feedback, and approved the final version

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