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Concern over cost of and access to cancer treatments: A meta-narrative review of nivolumab and pembrolizumab studies

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ABSTRACT

Background: A better understanding of the modulation of the immune system has resulted in the development of new classes of antitumor agents such as nivolumab and pembrolizumab. Despite the proven effectiveness and tolerability of these new drugs for specific types of cancer, the high cost of treatment has affected their accessibility.

Objective: The aim of this study is to conduct a meta-narrative review of studies that have addressed the concerns that have been voiced regarding the cost of and access to nivolumab and pembrolizumab in oncology health care. This meta-narrative review attempts to answer the following questions: (1) which papers have considered this broad topic area?; (2) what are the main empirical/theoretical findings?; and (3) what insights can be drawn by combining and comparing findings from different papers?

Methods and data source: A meta-narrative review has been conducted in 5 research databases (Web of Science, Science Direct, Scopus, Embase and Pubmed) without time limitations up to January of 2017 to address concerns related to the cost of and access to nivolumab and pembrolizumab in oncology health care. From each research base, articles were selected that had a key word related to the theme of pharmacoeconomics and nivolumab or pembrolizumab in any field of scientific work. The research questions were analyzed through the application of a meta-narrative review approach and the use of a convergence-coding matrix to summarize similarities and differences directly related to the research topic between the different papers.

Key findings: The first contribution of this meta-narrative review is that it summarizes economic-based works on the use of nivolumab and pembrolizumab, particularly for three therapeutic indications: melanoma, NSCLC and RCC. In general, despite the clinical benefit of nivolumab and pembrolizumab being well accepted and proven by scientific works, the published studies show that there are contradictory results with regard to the cost-effectiveness of these anti-PD-1s. The regulatory, economic and epidemiological variations mean that healthcare costs for cancer patients vary greatly from country to country and according to the type of tumor. The second contribution has to do with the recommendations for the development of high quality process for pharmacoeconomic analyses, especially in the new field of immuno-oncology. Finally, the third contribution is with regard to recommendations for the sustainable use of immunotherapies.

Conclusions: Given the revolution in cancer therapy in recent years, the efficient allocation of existing resources is essential for healthcare systems to meet the evolving needs of populations and remain sustainable in the long term. The application of high quality information that stems from scientific evidence and economic modeling can help considerably to make the healthcare system sustainable over time mainly due to a higher number of therapeutic indications or more countries giving regulatory approval for the use of new and expensive cancer drugs.

Abbreviations: ASCO, American Society of Clinical Oncology; BRAF, B-raf proto-oncogene, serine/threonine kinase; CTLA4, cytotoxic T-lymphocyte associated protein 4; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; ICER, incremental cost-effectiveness ratio; LY, life year; NCCN, National Comprehensive Cancer Network; NICE, The National Institute of Health and Care Excellence; NSCLC, Non-Small Cell Lung Cancer; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; PFS, progression free survival; QALY, quality-adjusted life year; RCC, renal cell carcinoma

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1. Introduction

The incidence of cancer is growing all over the world (Ferlay et al., 2015). However, total mortality has been reduced in the last two decades because of a lot of strategies such as smoke fighting, vaccination campaigns, improvement in surgical and radiotherapy approaches (Gyawali et al., 2018), as well as early diagnosis of cancer and the introduction of new therapies (Zhang et al., 2016). There are currently over 700 different types of pharmacological treatments for cancer in the pipeline of the Food and Drug Administration (FDA) (Yu, 2016), and current knowledge of the biology of cancer means more promising therapeutic possibilities. A better understanding of the molecular mechanisms that propel the growth of tumor cells and advances in the modulation of the immune system have resulted in the development of new classes of antitumor agents.

Two therapeutic options recently approved in several countries have provided new efficacy data and different safety profile based on host immune response. Nivolumab and pembrolizumab are monoclonal antibodies with high affinity against the programmed cell death antibody (PD-1) present on the surface of activated T cells and B cells. By exerting double blockade by preventing the binding of PD-1 to the PD-L1 and PD-L2 programmed death receptors present on the surface of tumor cells, nivolumab and pembrolizumab impede the immune-suppressor effect that would allow the tumor to avoid destruction by the immune system (Marincola et al., 2000; Iwai et al., 2002). The anti-PD-1s, the designation of this new therapeutic class in immunotherapy, have been shown to restore the antitumor activity of the T lymphocytes and are an effective strategy against a range of cancers such as melanoma (Robert et al., 2015; Weber et al., 2015), non-small cell lung cancer (NSCLC) (Brahmer et al., 2015; Borghaei et al., 2015; Herbst et al., 2016) and renal cell carcinoma (RCC) (Motzer et al., 2015), the tumors type that received the first regulatory approvals of anti-PD-1s around the world. Other regulatory approvals have already been given or are pending.

On the other hand, the price of the new cancer drugs has increased faster than the benefits that they offer (Howard et al., 2015). The introduction of new drugs, especially cancer drugs, is a double-edge sword, resulting in a time of commemorations of scientific progress, but also the huge challenges of maintaining a sustainable healthcare system, even in high-income countries. The costs involved in cancer treatment are higher than for other chronic medical conditions (Bernard et al., 2011) and have affected governments, insurance companies and patients (Goldstein et al., 2016). It is estimated that the cost of care in the United States will increase from one hundred and twenty-five billion dollars in 2010 to two hundred and six billion dollars in 2020 (Mariotto et al., 2011). In Europe, the cost of medicine alone for cancer treatment rose from seven billion, six hundred million euros in 2005 to nineteen billion, one hundred million in 2014 (Jönsson et al., 2016). This new reality of limited resources and the rising cost of care for cancer patients has forced doctors and patients to make decisions on treatment based on accessibility and availability of financial resources to pay for better results (Meropol, 2013).

Obviously, the current economic problem facing healthcare systems is the result of multiple factors, but the most significant is the growing cost of new generations of drugs (Tartari et al., 2016). Anti-PD-1s have especially had an adverse effect on the situation because they reach the market with a high price tag, they can be approved for a range of treatments (including being used in combination with other therapies), and the patients can use the product for a long time. Therefore, ever since nivolumab and pembrolizumab were first given regulatory approval and became part of the onerous plan for cancer treatment, cost has been constantly discussed at conferences and in scientific articles. In this sense, the aim of this study is to conduct a meta-narrative review of studies that have addressed the concerns that have been voiced regarding the cost of and access to nivolumab and pembrolizumab in oncology health care. This meta-narrative review attempts to answer the following questions: (1) which papers have considered this broad topic area?; (2) what are the main empirical/theoretical findings?; and (3) what insights can be drawn by combining and comparing findings from different papers? These questions will be analyzed through the application of a meta-narrative review approach and the use of a convergence-coding matrix to summarize similarities and differences directly related to the research topic between the different papers.

The outputs of qualitative aggregation of the main papers and the narrative summary of the main findings make three important contributions to the topic. The first contribution of this meta-narrative review is that it summarizes the heath economic works on the use of nivolumab and pembrolizumab, particularly regarding three therapeutic indications: melanoma, NSCLC and RCC. The second contribution has to do with recommendations for the development of high quality processes for pharmacoeconomic analyses, especially in the field of immune-oncology. Finally, the third contribution involves four recommendations for the sustainable use of immunotherapies.

2. Materials and methods

The meta-narrative review was considered the most appropriate method for this systematic review because it is the best suited for studying topic areas that have been differently conceptualized and studied by different groups (Wong et al., 2013). The review seeks first to identify and understand as many as possible of the potentially important different research traditions, which have a bearing on the topic. This answers the question concerning which papers have considered this broad topic area, addressed in subsections: 2.1 Data Sources: Identification, and 2.2 Screening and eligibility criteria. In addition to identifying and selecting data from primary sources, in the second phase, this work compared and contrasted findings from these different traditions to build a rich picture of the topic area from multiple angles. This answers the questions on the main empirical/theoretical findings and the insights that can be drawn by combining and comparing findings from different papers. This topic was addressed in subsection: 2.3 Convergence coding matrix. The result of the second phase is predominantly descriptive, but recognizes the potential for analytical, theory-building insights (Greenhald et al., 2005).

2.1. Data sources: identification

One of the main challenges in meta-narrative review is to identify a sufficiently broad range of sources in order to build as comprehensive a map as possible of the research undertaken on the topic. A literature review was conducted to identify the publications that addressed concerns related to the cost of and access to nivolumab and pembrolizumab in oncology health care. The research was conducted from 02 to 15 January 2017 in 5 different databases, following the criteria outlined in Table 1. The databases were chosen to enable a wider range of research involving the field of health and social sciences, particularly econometrics and decision science (Andalia et al., 2015; Falagas et al., 2008). From each database, articles were selected that had a key word related to the theme of pharmacoeconomics (Group 1) and nivolumab or pembrolizumab (Group 2) in any field of scientific work within an unlimited period of time.

2.2. Screening and eligibility criteria

The search of the five databases resulted in a total of 306 articles, considering overlapping of the platforms. All the bases were practical to use and provided research facilities in their article selection criteria. It is important to highlight that despite the overlap, 77% of the selected works (234 articles) were available in only one database, demonstrating that meta-narrative review should not to be limited to a single research platform.

The selected articles were reviewed by title, abstract and full text to