Access to lung cancer therapy in the Mexican population: opportunities for reducing inequity within the health system

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Abstract
Lung cancer is a major global public health problem, yet the disease is highly stigmatized, which impairs the opportunities to get optimal treatment for these patients. Globally, as well as locally in Mexico, lung cancer is the main cause of cancer-related deaths. Despite this, it is the only one among the five deadliest cancers in Mexico which is not covered by Popular Health Insurance. Lung cancer treatment is a complex algorithm, which requires fully trained personnel to assess each patient in order to determine standard-of-care therapy based on several factors associated with the molecular profile of the tumor, as well as patient characteristics and their financial capabilities. Coupled to this, in the recent decade, several breakthrough therapies have been launched, shifting the outlook for certain patient subgroups. However, none of these novel therapies are currently available to patients who have public-based health insurance. In this paper, we review

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Resumen
El cáncer de pulmón es un problema de salud pública a nivel global. Sin embargo, la enfermedad conlleva un gran nivel de estigma que disminuye las posibilidades de obtener un tratamiento óptimo para estos pacientes. El cáncer de pulmón es la causa principal de muertes relacionadas con cáncer, tanto en el mundo como localmente en México. A pesar de esto, en la lista de las cinco neoplasias con mayor mortalidad en México, el cáncer de pulmón es la única que no se encuentra cubierta por parte del *Seguro Popular*. El tratamiento del cáncer de pulmón es un algoritmo complejo, el cual requiere personal altamente calificado para la valoración de cada paciente y la determinación del estándar-de-cuidado, dependiendo de varios factores relacionados tanto con el perfil molecular del tumor como con las características del paciente y sus posibilidades económicas. Aunado a esto, en la década en curso ha surgido una gran cantidad de nuevas posibilidades terapéuticas que

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the inequities present in the Mexican health system and highlight the importance of addressing these opportunities.

Keywords: inequity; lung cancer; survival

cambian el pronóstico de ciertos subgrupos de pacientes. Sin embargo, estas terapias no están disponibles para pacientes que se encuentran asegurados por parte del sistema público de salud en México. En este trabajo se revisaron las inequidades que se presentan en el sistema de salud en México y se recalcó la importancia de actuar sobre estas áreas de oportunidad.

Palabras clave: inequidad; cáncer de pulmón; supervivencia

Lung cancer is a global public health problem. It represents the first cause of cancer-related deaths around the globe, both in developed as well as developing countries, and mortality in the future is expected to increase substantially.[1,2] Recently, lung cancer is reported to cause 2.07 million deaths each year; this amount is expected to almost double to three million by 2035. Importantly, 16% of the global deaths from lung cancer occur in the Americas region, a number which is also expected to double from 262 314 deaths reported in 2012, to 501 860 by 2035. These alarming figures highlight the need to battle this tendency.[3]

In Mexico the outlook is also somber; lung cancer claims more lives than any other malignant disease, with an average of 6 678 annual deaths.[4] In spite of the highly relevant burden of disease, globally as well as nationally, lung cancer patients still suffer from inequities in the access to healthcare. In this context, equity is understood as the absence of unfair or remediable differences among groups of people who vary in terms of social, economic, demographic or geographic determinants. As such, health equity therefore conceptualizes that everyone must have the same opportunity to achieve their full health potential. Further, health equity must be understood and measured as services provided (and not necessarily the population´s health condition). Therefore, health equity can be achieved when equal services are provided to the entire population.[5-7]

Overall, lung cancer programs face many challenges towards closing the inequity gap. For example, contrary to other common malignancies, there is currently no active public screening program for high-risk populations in Mexico; even though the main risk factors leading to this malignancy within the region, including tobacco and wood-smoke exposure, are well characterized.[8,9] High-risk subjects have the option of paying for screening studies, however these are costly and only available in certain centralized areas, creating a wide gap, due to demographic and economic determinants, in terms of achieving a timely diagnosis. Interestingly, in 2019 the government expects to collect a total revenue from tobacco taxation of 43 078.9 million (MXN), and these resources could very logically be directed towards this patient population.[10] On the contrary, lung cancer is the only high-mortality malignancy without coverage by the popular security insurance *Seguro Popular*. As such, lung cancer patients face late-stage diagnoses, due to a lack of screening, and restricted, if any, therapies available to them. Consequentially, lung cancer kills more people in Mexico than any other malignant disease.

The characteristics of the lung cancer epidemic in Mexico have been characterized in previous studies, and therefore this paper will focus on the important subject of access to lung cancer therapy for Mexican patients, highlighting opportunities for greater equity within the health system.

The Mexican public healthcare sector

Mexico's healthcare system is a complex subset of institutions, mostly derived from public policies, though a private sector also exists. The Ministry of Health (MoH) is in charge of governance, health policies, public health, financing and highly specialized healthcare, and oversees the actions taken by the local health secretariats of the MoH which serve in each of the 32 Mexican states. Under the MoH governance, several institutions exist, which affiliate the individuals according to their job status (employed in the formal market or not), rather than by their health needs (not their economic necessity). Though it certainly has achieved several public health milestones, this fragmented system has often proven to be complex, unequal and many times inefficient in dealing with non-transmissible diseases. Subjects might be affiliated to several systems at the same time, and real-time electronic patient records are still unavailable, making cross-talk between previous and current physicians challenging, to say the least.[11] Further, Mexico is lagging behind in terms of compiling a robust database with the objective of

registering the cancer cases diagnosed throughout the country. On July, 2018 the Federation's Official Newsletter released information regarding the nascent program for a national cancer registry, which would have the objective of integrating cancer cases information in order to provide consistent, complete and opportune information for use in research, resource allocation and development of public policies in this matter. Results will be published online yearly by the National Cancer Institute (INCan), and it is certain that this information will improve our current understanding of cancer epidemiology in the nation, helping to assess the problematic through a unified perspective. Public sector healthcare providers and programs include, in order of highest-to-lowest affiliated members, the *Instituto Mexicano del Seguro Social* (IMSS), *Seguro Popular* (SPS), *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado* (ISSSTE), *Petróleos Mexicanos* (Pemex), *Secretaría de la Defensa* (Sedena), and *Secretaría de Marina* (Semar).[12] Increasing the complexity of the matter, each dependency has a master catalogue of approved medications, each with their particular indications and presentations, therefore therapeutic schemes might vary across the healthcare system due to lack of the proper supplies or the means to enforce adherence, which impedes the establishment of nation-wide standards of care for this particular neoplasm. Altogether, the structure of the healthcare system as it currently is makes it difficult to promote the provision of equitable services for lung cancer patients.

Basic interinstitutional catalogue of medications

The General Health Counsel is a multidisciplinary organism, which is in charge of creating, updating and publishing the basic list of supplies for the first, second and third level of attention. Through eight specific committees, this counsel incorporates scientific and technologic advances in medicine, in the form of a master "Essential Interinstituional Catalogue of Medications", in order to encourage the rational use of quality supplies in the public institutions of the National Health System. In 2016, an updated version of the master catalogue for basic and higher-level care medications was released by this interinstitutional committee in an effort to harmonize the catalogues from the different institutions. In this document, the 17th group is comprised of Oncologic medications, including 114 currently approved and available drugs throughout the different health providing institutions. Interestingly, lung cancer has only 14 drugs as therapeutic options. Moreover, among these 14 drugs, four of them are obsolete in the current guidelines for the management of lung cancer patients, due to lack of efficacy and high toxicity profiles (cyclophosphamide, doxorubicin, ifosphamide and mitomycin). This leaves only 10 options, among which two are standard first line treatment options for Non-small cell lung cancer (NSCLC) (carboplatin/pemetrexed) and four other are second line NSCLC options (Docetaxel, gemcitabine, vincristine, vinorelbine), there is one treatment option for small cell lung cancer (etoposide). All the above-mentioned treatments are based on chemotherapy and are recommended for patients with advanced-stage disease who do not have actionable mutations or who are not candidates for immune checkpoint inhibitors. Meanwhile, only three drugs included in this catalogue are targeted therapy agents, including one tyrosine kinase inhibitor (TKI) for patients with rearrangements in the Anaplastic Lymphoma Kinase gene (ALKr), and two TKIs for patients with sensitizing mutations in the Epidermal Growth Factor Receptor gene (EGFR). Unfortunately, all these targeted therapies (crizotinib, erlotinib and gefitinib) are first-generation drugs, which have considerable limitations in terms of their long-term effectiveness and pharmacokinetic profile (such as central nervous system penetration). Meanwhile, second and third generation drugs, including afatinib, osimertinib, alectinib among others, have managed to circumvent these limitations and offer patients better survival outcomes, however none of these are included in the catalogue.[13]

Another important limitation in the currently approved list of medications is the lack of immunoncology (IO) agents, which are changing the paradigm of advanced lung cancer treatment in the current age. Several large-scale clinical trials have found that in a subgroup of advanced NSCLC patients, the use of IO increases progression-free and overall survival, reducing the risk of death by more than 40% compared to chemotherapy.[14] Aside from their improved survival outcomes, studies have assessed the cost-effectiveness of these agents, finding them cost-effective in the United Kingdom, however such data within Mexico's regional setting is lacking.[15]

Last, it is important to highlight that many of the medications which are covered by this catalogue and applied at most of the public health institutions are free of charge, and there is no copayment at the point of care. This is particularly important when considering the costs associated with lung cancer care for patients in Mexico, which ranges from 47 858.00 to 393 934.06 MXN, varying depending on disease

Table I
AVAILABILITY OF LUNG CANCER NEEDS WITHIN THE MAJOR PUBLIC HEALTH SUBSYSTEMS IN MEXICO

Resource	*IMSS*	*ISSSTE*	*Pemex, Sedena, Semar*	*SPS*	*Private*	*Incan*
Screening program	No	No	No	No	No	Pending resource allocation
First-line chemotherapy	Yes	Yes	Yes	No	Yes	Only for women
Second-line chemotherapy	Yes	Yes	Yes	No	Yes	Only for women
Genotyping (hospital-based)	No	No	No	No	Yes	Yes
Genotyping (surrogate by pharma)	Yes	Yes	Yes	Yes	Yes	Yes
ALK-TKI	No	No	Yes	No	No	Yes
EGFR-TKI	Yes*	Yes*	Yes	No	Yes	Yes
Bevacizumab	No	No	Yes	No	Yes	Yes
Immunoncology	Yes*	No	Yes	No	Yes	Only for patients in clinical trials
Palliative care	Yes	Yes	Yes	Yes	Yes	Yes

*Gefitinib and Pembrolizumab have recently been approved for inclusion in the Basic Medication Catalogue of IMSS.
IMSS: Instituto Mexicano del Seguro Social; ISSSTE: Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado; Pemex: Petróleos Mexicanos; Sedena: Secretaría de la Defensa Nacional; Semar: Secretaría de Marina; SPS: Seguro Popular; Incan: Instituto Nacional de Cancerología; ALK: anaplastic lymphoma kinase; TKI: tyrosine kinase inhibitor; EGFR: epidermal grouth factor receptor

stage. All of these costs are therefore absorbed by the institution when the patient is insured by IMSS, ISSSTE, PEMEX, Sedena or Semar. For patients who are not affiliated to the previous institutions, or who have SPS, costs associated with this disease imply a catastrophic expenditure, and therefore it is imperative that government instances solve the issue of access to treatment for these patients, who most of the time do not have the economic resources required for therapy.

Discrepancies in lung cancer care across health institutions

As previously mentioned lung cancer *de facto* standard-of-care varies in Mexico and depends on the health institution to which each patient is affiliated. In table I a short overview of some of the most important needs to be met by a lung cancer oncology service are listed, and then reviewed by their availability within the major health institutions in the country. We review availability also in the private sector and the National Cancer Institute (Incan), as well, which is a nation-wide reference center for this malignancy.

The information presented here can be interpreted in myriad ways, however one of the most straightforward affirmations that can be made from this table is the fact that the sector of the population most well-equipped for facing a lung cancer case is that which holds a private medical insurance service. Unfortunately, in Mexico, less than 7% of the population has private health insurance. On the other hand, the most vulnerable population in terms of lung cancer care is that which is affiliated to *Seguro Popular*, or popular health insurance (PHI) which arose as an initiative that sought, in a period of seven years, to offer health insurance to over 50 million people who at the time where not affiliated to any health service.[16] Currently, over 54 million Mexicans have PHI, and though this ambitious initiative has managed to reduce catastrophic health expenditure in homes nationwide by up to 46.5%,[17] the program has some severe limitations. Ultimately, what is perhaps the most pressing concern is the fact that standard-of-care for lung cancer patients should be dictated by the scientific literature available, in order to produce the most state-of-the art guidelines for these patients. Counter to this, in the practical sense lung cancer care in Mexico is currently dictated by the institution which affiliates the patient, the available resources for treatment, and the access to the facilities which have the infrastructure and personnel to treat this

Table II
Point-of-care cost by disease stage and mutation status

Event	*I* *$MXN*	*II* *$MXN*	*III* *$MXN*	*IV mut-* *$MXN*	*IV mut+* *$MXN*
Diagnosis	19 353.00	30 766.92	57 156.42	83 545.93	83 545.93
Hospitalization		32 058.33	49 822.03	67 585.72	67 585.72
Surgery	9 722.00	9 722.00	9 722.00		
Intensive therapy			14 392.69	28 785.38	28 785.38
Molecular tumor profile				3 055.00	3 055.00
Chemotherapy		39 686.33	30 191.99		
Systemic treatment (mut +)					137 279.03
Systemic treatment (mut -)				46 948.28	
Radiotherapy		57 495.00	57 495.00	57 495.00	57 495.00
Monitoring	18 783.00	5 396.00	5 396.00	8 094.00	16 188.00
Total	47 858.00	175 124.57	224 176.13	295 509.31	393 934.06

Mut +: mutation positive; Mut -: mutation negative.

disease. Currently, the first five causes of cancer-related deaths in Mexico include, in descending order, lung, breast, colon, prostate, cervix. Even though lung cancer tops this list, this is the only one out of the five malignancies that is not covered by the FPGC (Fund for protection against catastrophic expenditures) of the PHI. Also, other sources of financing must be available in order to treat cancer, including current costs, infrastructure, surgery, diagnostic supplies and other costs (table II), which are covered by the MoH.[18] This is a severe impairment, especially when considering that lung cancer treatment costs are usually associated with catastrophic health expenditure when patients are not covered by health insurance.[19] Furthermore, previous studies have determined that in NSCLC there is a direct association between expenditure allowance and survival, in which patients have a significantly reduced risk of dying when they have access to a greater fund in order to treat the disease. In contrast, such association has not been found in the case of breast or renal carcinoma, nor in chronic myeloid leukemia.[20]

Opportunities and adversities to tackle

A new era for cancer treatment emerged in 2011, transforming patient therapy through a deeper understanding of tumor biology and novel drugs which target specific pathways within or around the tumor cells. All these factors, in addition to improved diagnosis and access to treatment, have produced a steady decline in cancer mortality within developed nations, including France, Japan, and the United States. Life expectancy for lung cancer patients has therefore benefitted from these advances in molecular biology and technology, positively impacting the outlook for a population which at many times is economically productive. Nonetheless, this declining mortality is also related to access to treatment, and therefore developing nations with less availability of novel therapeutic options might be lagging behind.[21] Since 2011, 11 new drugs have been launched globally for the treatment of lung cancer, encompassing agents for actionable mutations (TKIs) and immune checkpoint

inhibitors. The use of novel therapies has forever changed the outlook for lung cancer patients, providing durable responses and better safety profiles, and is expected to further improve as new drugs emerge from the pipeline and as current ones gain approval within the first-line setting.[21] Furthermore, ongoing clinical trials are stratifying patients in order to adequately find the subgroup which might reap the most benefit from each new agent, emphasizing the transition towards the era of personalized medicine. The question will now be: Who will have access to these therapies? In a resource-limited setting, such as Mexico and Latin America, the answer will likely be those wealthy enough to have costly private health insurance services. Our most economically vulnerable population will continue to rely on their very scarce financial resources, and will therefore not reap any benefit from all this wealth of knowledge and options. In a country which states that health is a constitutional right, it is difficult to not find this disturbing. The current pipeline for oncology drug development is overwhelmed by target molecules and target biologic agents, both of which remain underrepresented within our public health system even though they bring the best outcomes and have been shown to be cost-effective.[22-24] The challenges and opportunities now facing Mexico's health system in terms of lung cancer must be addressed—it is ever so important that we tackle the issue of treatment inequity, and work to reverse the fact that more than 90% of the country's population will not benefit any time soon from the latest breakthroughs in lung cancer science. In addition to the lack of last-generation therapies, Mexico's bureaucracy many times delays the approval and implementation of clinical trial protocols which could admit patients and offer them options unavailable to them otherwise. Such barriers must be sorted in order to make this system more efficient and therefore benefit from recruiting clinical studies. In addition, this would also help increase the representation of Hispanic patients throughout the current body of scientific knowledge, optimizing the safe implementation of therapies which are generally approved with data from Caucasian or Asian patients. Another important opportunity is the creation of unified treatment guidelines, facilitating patient management and decreasing associated costs and complexity. This is highly relevant as oncologists are more than ever dealing with chronicity and such trend is expected to continue in the nearby future. Government policy makers must realize the widening breach which faces lung cancer patients from different socioeconomic backgrounds. The poorest of our country should not have to be in danger of dying from lung cancer.

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