UNIVERSITY OF CALIFORNIA, SAN DIEGO
SAN DIEGO STATE UNIVERSITY

Access and Affordability of Cancer Drugs in International Settings

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Public Health (Global Health)

by

Raphael E. Cuomo

Committee in Charge:

University of California, San Diego

Professor Timothy Mackey, Co-Chair
Professor Cedric Garland
Professor Edward Gorham
Professor Lianne Urada

San Diego State University

Professor Thomas Novotny, Co-Chair
Professor Robert Seidman

2017

The Dissertation of Raphael E. Cuomo is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

_____

_____

_____

_____

_____
Co-Chair

_____
Co-Chair

University of California, San Diego

San Diego State University

2017

DEDICATION

I dedicate this dissertation to my father, who fought a painful battle with kidney cancer until his untimely death; to my wife, who has no equal in exceeding patience, grace, and beauty; and to my mentors, who have provided me with invaluable support and encouragement throughout this project.

EPIGRAPH

“To believe a thing impossible is to make it so.”

– French Proverb

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to acknowledge my dissertation co-chairs, Timothy K. Mackey and Thomas Novotny, for their steadfast perseverance and commitment to enriching me as a scholar of global public health. Their guidance has imbued me with a greatly expanded skillset and strong theoretical foundations, and I am immensely grateful for their considerable patience with me. I would also like to thank Cedric Garland and Edward Gorham, whose assiduous commitment to cancer epidemiology has served as a valuable model for my own aspiration to combat these diseases through pronounced creativity and sharp acumen. I would like to thank Robert Seidman for his inspirational introduction to health economics several years ago, and for his willingness to further guide me through the tumultuous sea of economic theory and practice. I would like to thank Lianne Urada, a valued mentor whose commitment to the edification of aspiring researchers is clearly apparent. I would like to thank David Strong, Kimberly Brouwer, Susan Kiene, and Elizabeth Reed for their electrifying commitment to guiding students and for their exemplary leadership of the PhD program in Public Health. Lastly, I would like to thank Freddie Bray, leader of the Section of Cancer Surveillance at the World Health Organization's International Agency for Research on Cancer (IARC), for taking me as his Trainee in 2014 and providing me with a valuable perspective into the wonderful research being conducted by IARC epidemiologists.

I would like to acknowledge UC San Diego's Frontiers of Innovation Scholars Program (FISP), which granted me a Pre-Doctoral Fellowship that allowed me to pursue much of the research in this dissertation. I would further like to thank the Naval Health Research Center (NHRC) at Naval Base Point Loma in San Diego, the American Cancer Society (ACS), and the National Cancer Institute (NCI) for the support they have provided for me through my doctoral studies.

Chapter 2, in full, is being prepared for submission to a journal with the citation: Cuomo, Raphael; Mackey, Timothy. The availability of essential cancer medication: An analysis of national formularies.

Chapter 3, in part, is being prepared for submission to a journal with the citation: Cuomo, Raphael; Mackey, Timothy; Seidman, Robert. Global inequality in purchase prices for essential cancer medications.

Chapter 4, in part, is being prepared for submission to a journal with the citation: Cuomo, Raphael; Mackey, Timothy. Policy-based approaches for facilitating access and affordability for essential cancer medications

VITA

2011	Bachelor of Science in Biology Lafayette College
2013	Master of Public Health in Health Management and Policy San Diego State University
2014	Professional Certificate in Sustainability Harvard University
2017	Doctor of Philosophy in Public Health (Global Health) University of California, San Diego & San Diego State University

PUBLICATIONS

1. Katsuki T, Mackey TK, **Cuomo RE**. (2016). Digital surveillance of prescription drug abuse: An accessible methodology for collecting and analyzing twitter NUPM data. *Annals of Global Health* 82(3): 590.

2. Katsuki T, Mackey TK, **Cuomo RE**. (2015). Establishing a link between prescription drug abuse and illicit online pharmacies: Analysis of twitter data. *Journal of Medical Internet Research* 17(12): e280.

3. **Cuomo RE**, Garland CF, Gorham ED, Mohr SB. (2015). Low cloud cover-adjusted ultraviolet B irradiance is associated with high incidence rates of leukemia: Study of 172 countries. *PLoS ONE* 10(12): e0144308.

4. **Cuomo RE**, Miner A, Mackey TK. (2015). Pricing and Sales Tax Collection Policies for E-Cigarette Starter Kits and Disposable Products Sold Online. *Drug and Alcohol Review* 35(1): 748-756.

5. Mackey TK, Miner A, **Cuomo RE**. (2015). Exploring the e-cigarette e-commerce marketplace: Identifying Internet e-cigarette marketing characteristics and regulatory gaps. *Drug and Alcohol Dependence* 156: 97-103.

6. Baggerly CA, **Cuomo RE**, French CB, Garland CF, Gorham ED, Grant WB, Heaney RP, Holick MF, Hollis BW, McDonnell SL, Pittaway M, Seaton P, Wagner CL, Wunsch A. (2015). Sunlight and vitamin D: Necessary for public health. *Journal of the American College of Nutrition* 34(4): 359-365.

7. Mackey TK, **Cuomo RE**, Liang BA. (2015). The rise of digital direct-to-consumer advertising?: Comparison of direct-to-consumer advertising expenditure trends from publicly available data sources and global policy implications. *BMC Health Services Research* 15(1): 236.

8. **Cuomo RE**, Mackey TK, Stigler P. (2015). The economics of counterfeit Avastin: A geospatial and statistical analysis of demographic correlates to FDA warning letters. *Pharmacoepidemiology & Drug Safety* 24(7): 748-756.

9. Garland CF, **Cuomo RE**, Gorham ED, Zeng K, Mohr SB. (2015). Cloud cover-adjusted ultraviolet B irradiance and pancreatic cancer incidence in 172 countries. *The Journal of Steroid Biochemistry and Molecular Biology* 155: 257-263.

10. **Cuomo RE**, Mackey TK. (2015). Determining demographic risk factors for receiving counterfeit cancer drugs. *Annals of Global Health* 81(1):65.

11. Mackey TK, **Cuomo RE**, Guerra C, Liang BA. (2015). After counterfeit Avastin®-what have we learned and what can be done? *Nature Reviews Clinical Oncology* 12:302-308.

12. Gorham ED, **Cuomo RE**, Mohr SB, Garland CF. (2014). Association between 25-hydroxyvitamin D and type 2 diabetes? *Lancet Diabetes & Endocrinology* 3(1):11.

13. Mohr SB, Gorham ED, Garland CF, Grant WB, Garland FC, **Cuomo RE**. (2014). Are low ultraviolet B and vitamin D associated with higher incidence of multiple myeloma? *The Journal of Steroid Biochemistry and Molecular Biology* 148: 245-252.

14. Mohr SB, Kim J, Hofflich H, **Cuomo RE**, Garland CF. (2014). Could vitamin D sufficiency improve the survival of colorectal cancer patients? *The Journal of Steroid Biochemistry and Molecular Biology* 148: 239-244.

15. **Cuomo RE**, Mackey TK. (2014). An exploration of counterfeit medicine surveillance strategies guided by geospatial analysis: lessons learned from counterfeit Avastin detection in the US drug supply chain. *BMJ Open* 4(12).

16. Mackey TK, Liang BA, **Cuomo RE**, Hafen R, Brouwer KC, Lee D. (2014). Emerging and re-emerging neglected tropical diseases: A review of key characteristics, risk factors, and the policy and innovation environment. *Clinical Microbiology Reviews* 27(4): 949-979.

17. **Cuomo RE**, Baek JD. (2014). The global association between maternal mortality and skilled health workers. *The Journal of Global Health Care Systems* 4(1).

18. **Cuomo RE**, Mohr SB, Gorham ED, Garland CF. (2013) What is the relationship between ultraviolet B irradiance and global incidence rates of colorectal cancer? *Dermato-Endocrinology* 5(1): 181-185.

ABSTRACT OF THE DISSERTATION

Access and Affordability of Cancer Drugs in International Settings

by

Raphael E. Cuomo

Doctor of Philosophy in Public Health (Global Health)

University of California, San Diego, 2017

San Diego State University, 2017

Professor Timothy K. Mackey, Co-Chair

Professor Thomas Novotny, Co-Chair

Background: The global burden of disease from cancer is rapidly increasing, especially in low- and middle-income countries (LMICs). The World Health Organization (WHO) publishes an Essential Medicines List (EML), which includes 48 medications in its “Antineoplastic and Immunosuppressives” category. The effectiveness of this list in promoting access and affordability of cancer medications in international settings should be assessed.

Methods: Medications listed on national formularies from 116 countries (mostly LMICs) were compared against cancer medications listed on the EML. Concordance between the two lists was compared with per capita gross domestic product (GDP) at purchasing power parity, per capita health expenditures, the human development index, the combined prevalence of overweight and obesity, and smoking prevalence. Purchase prices for cancer medications on the EML were collected and compared to one another, as well as across countries, regions, GDP, cancer incidence, formulation, generic status, medication category, and year of purchase.

Results: Fewer than half of cancer medications on the EML were present on most LMIC national formularies, with no country exhibiting full concordance. Concordance was positively associated with all indicators of economic development. Concordance was also positively associated with prevalence of overweight and obesity. Statistical tests found significant disparities in prices paid for essential cancer medication across countries, regions, individual medications, generic status, and medication categories.

Conclusion: Concordance was low in nearly all LMICs. Countries with greater economic development exhibited greater concordance. Cancer medications, on average, were much more expensive than medications in other categories, and several cancer medications exhibited median prices over $100 per package. On its own, the EML does not sufficiently ensure access and affordability of cancer drugs in international settings. Given that the expected prevalence of this already-pervasive disease will rapidly rise in the future, the

authors propose expanding the mandate of the International Agency for Research on Cancer (IARC) such that it can facilitate the affordable procurement of chemotherapy by LMICs.

CHAPTER 1: INTRODUCTION

It would contentiously appear that, throughout our history, we human beings have become ever more adept at cleverly mobilizing resources to overcome our biggest threats. High-income societies have had sufficient resources to undergo an “epidemiological transition,” where they shifted away from premature death due to famine, infant mortality, and infection [1]. Living longer lives, these societies began to observe new threats to human life characterized by behavioral habits and environmental factors. Throughout the 20th century, high-income countries (HICs) were increasingly plagued by non-communicable diseases, especially cardiovascular disease and cancer [2]. In the 21st century, HICs achieved steady declines in mortality rates from cardiovascular disease and cancer [3]. However, these declines have not been equal, with the mortality rate from cardiovascular disease declining much more rapidly than that of cancer [4]. Controversially, the etiology of cardiovascular disease was better understood than that of cancer, and for this reason, prevention and treatment for cardiovascular disease was much more successful. If this is indeed true, then successes against cancer required greater efforts in scientific investigation, prevention, screening, and treatment.

While the successes experienced in HICs against non-communicable diseases are indeed laudable, under one-fifth of the global human population currently lives in HICs [5]. While high-income society was strategizing about how to decrease mortality from non-communicable diseases, the low- and middle-income countries (LMICs), with about 6 billion people, began to undergo the

epidemiological transition. In 2012, 74% of the 38 million deaths in LMICs were from non-communicable diseases [6]. For cancer, this is expected to quickly worsen. Cancer cases in LMICs will rapidly ascend from 14 million cases in 2012 to 24 million cases in 2030 [7].

Cancer's expected high prevalence among LMICs poses a number of infrastructural challenges, not the least of which is how to supply treatment for this vast number of patients. Fortunately, with regard to chemotherapy, the World Health Organization (WHO) has organized a list of important medicines, the "Model List of Essential Medicines" (EML), which serves to inform LMIC health systems about which drugs should be prioritized as "essential" for their healthcare facilities [8]. Perhaps recognizing the impending challenge with cancer in LMICs, the 2015 version of the EML exhibited a 50% increase in the number of cancer drugs when compared to the previous version of the EML [9].

Little has been done to evaluate the degree to which LMIC health systems make available these "essential" chemotherapies. Fortunately, national governments publish formularies of drugs which they aspire to provide for their residents. In Paper 1 of this dissertation, I will assess national formularies to determine the proportion of essential chemotherapies that are listed in each available LMIC.

If a drug is listed on a country's formulary, it might be more available in that country than if the drug had not been listed on that country's formulary. However, if a listed drug has a very high price in a particular country, then that drug might still not be sufficiently accessible to cancer patients in that country. In

Paper 2 of this dissertation, I will assess the variation in cancer drug prices in LMICs.

Given that an already-pervasive disease is expected to rapidly increase in resource-deficient settings, policies can be formulated which alleviate issues in accessing drugs for that disease. In Paper 3 of this dissertation, I will assess the evidence generated in Paper 1 and Paper 2, and I will recommend global health policies that address issues in the access and affordability of cancer drugs in international settings.

REFERENCES

1. Omran AR. The epidemiologic transition: A theory of the epidemiology of population change. The Milbank memorial fund quarterly 1971;49:509-538.

2. Cutler D, Miller G. The role of public health improvements in health advances: The twentieth-century united states. Demography 2005;42:1-22.

3. Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, Abera SF*, et al.* Global, regional, and national disability-adjusted life years (dalys) for 306 diseases and injuries and healthy life expectancy (hale) for 188 countries, 1990-2013: Quantifying the epidemiological transition. Lancet 2015;386:2145-2191.

4. Heron M, Anderson RN. Changes in the leading cause of death: Recent patterns in heart disease and cancer mortality. Cancer 2016;400:600,000.

5. World Bank. The world bank databank. Washington D.C., World Bank Group, 2015

6. World Health Organization. Non-communicable diseases; in Centre M (ed), 2015

7. International Agency for Research on Cancer. Globocan 2012 database: Http://globocan.Iarc.Fr/. Accessed December 2013 2012

8. Robertson J, Magrini N, Barr R, Forte G, Ondari C. Medicines for cancers in children: The who model for selection of essential medicines. Pediatric blood & cancer 2015;62:1689-1693.

9. Jafarov A, Schneider T, Waning B, Hems S, van der Ham R, Ma E*, et al.* Comparative table of core and complementary medicines on the who essential medicines list from 1977–2011. Geneva, World Health Organization, 2012

CHAPTER 2: THE AVAILABILITY OF ESSENTIAL CANCER MEDICATION: AN ANALYSIS OF NATIONAL FORMULARIES

ABSTRACT

Objective: Compared to most other diseases, the total burden of common cancers is rapidly increasing in low- and middle-income countries (LMICs). The World Health Organization (WHO) publishes the Essential Medicines List, which provides guidance to countries in selecting which cancer medications should be prioritized for general public access. Countries commonly have formularies which are representative of the specific medications that the national government has prioritized for its populations.

Methods: National formularies were collected from 116 countries, and the quantification of essential cancer medication was computed using text-matching software. The proportion of essential cancer medications listed on national formularies (i.e. “concordance”) was compared to per capita gross domestic product, per capita healthcare expenditures, the human development index, smoking prevalence, and the combined prevalence of overweight and obesity.

Results: Median concordance with cancer drugs among low- and middle-income countries (LMICs) was 42.71%. In bivariate comparisons, concordance was significantly associated with per capita GDP at PPP ($p = 0.005$), per capita health expenditures ($p = 0.050$), the human development index ($p < 0.001$), and the combined prevalence of overweight and obesity ($p = 0.006$). However, concordance was not associated with smoking prevalence ($p = 0.292$).

Conclusion: With national formularies analyzed for over 80% of all LMICs, this study found that most LMICs listed under half of cancer medications considered by the WHO to be essential. LMIC decision-making for policies related to cancer drug access may be heavily influenced by economic development, as well as by the high prevalence of certain cancer risk factors. The results from this study suggest that LMICs are generally ill-prepared to adequately provide essential treatment for their rapidly rising numbers of cancer patients.

INTRODUCTION

The predominant disease burden in developing countries is notably shifting from infectious diseases to non-communicable diseases, especially cancers and cardiovascular disease [1]. Specifically, low- and middle-income countries (LMICs) are consistently seeing the most marked increases in cancer incidence [1]. Unlike heart disease, treatment for the advanced stages of cancer requires complex interventions, often involving multiple pharmaceutical treatment regimens and use of other advanced therapeutics [2]. Hence, access to cancer medications is a critical factor in decreasing cancer mortality and improving survivability for populations globally [3].

As the United Nation's international public health specialized agency, the World Health Organization (WHO) in 1977 began publishing a list of medicines that should be considered essential components of what health systems provide their constituents [4]. The selection of medications for this "Essential Medicines List" (EML) is conducted through a process overseen by the WHO, in

collaboration with leading experts, to recommend medicines based on disease prevalence, evidence of efficacy, evidence of safety, and comparative cost-effectiveness [5]. The most recent, 19th version of the EML was published in April 2015 and included a specific focus on cancer [6]. In this latest formulation, the WHO lists 48 cancer medications, which is a 50% increase over the 32 antineoplastic medications listed on the 18th EML.

However, despite its multilateral and multifaceted criteria, national governments are under no implicit legal requirement to provide access to cancer drugs listed on the EML. Instead, the EML serves as a guideline for sovereign states in deciding how to procure, finance and prioritize cancer drugs [7]. An indicator of whether the EML translates to national level pharmaceutical policy comes in the form of national drug formularies, which are generally published by individual governments and their health agencies. The impact of national formularies on patients' ability to access listed drugs may vary greatly between jurisdictions, depending on the extent of healthcare coverage, insurance schemes, resources, and financing, which varies country-to-country.

Though inclusion on a national formulary does not directly equate to availability of the drug domestically, it nevertheless indicates that the listed drug is recognized and prioritized as essential to its public health system. Therefore, in order to understand the degree to which essential cancer drugs are supported by national health policy, this study seeks to determine the agreement between national formularies and the WHO's global list for cancer medications. Specifically, this study primarily seeks to assess the variability in national

“concordance” with cancer medications on the WHO’s EML. We define the quantitative level of this agreement as “concordance,” denoted as a percentage of the drugs listed on a national formulary that are also listed on the EML.

Though variations in national concordance may exist, little has been done to determine the specific macroeconomic factors that influence LMICs in making decisions about the selection of essential cancer medications. This stems from the dearth of knowledge about national dialogue regarding decisions that impact the inclusion of cancer drugs on medical formularies, including specifically how national governments negotiate with manufacturers through selection processes [8]. Therefore, once variations in concordance have been assessed, this study will compare these variations with country-level data on economic development. The results of this study can inform international and domestic policymakers on decisions related to national development that may influence concordance of national formularies with cancer medications on the EML.

METHODS

We began this study by collating data from publicly available data sources, including the most recently updated EML [6]. The 19th global EML was obtained from the WHO’s website [6]. We then tabulated characteristics of antineoplastic drugs, including sub-category, formulation, and indication.

All national formularies made available on the WHO’s website [9] were included in this study. In the small number cases where the document provided by the WHO website clearly did not contain the full list of medicines, attempts

were then made to obtain the full national formulary through national government webpages. Only full national formularies that used characters from the Roman alphabet were included. Out of 101 total national formularies with characters from the Roman alphabet, 63 were in English, 21 were in French, 15 were in Spanish, and 2 were in Portuguese.

The sole outcome measure in this study is the proportion of essential cancer medications on national formularies. In order to calculate this metric, the number of essential cancer medications appearing in a national formulary must be counted and then divided by 48, which is the total number of essential medications in the “Antineoplastics and Immunosuppresives” category listed on the latest EML. As the developing world is expected to experience a rapid increase in cancer burden over the next century [10], this study prioritized the assessment of concordance among LMICs, which are currently defined by the World Bank as countries having a gross national income (GNI) of less than $12,476 per capita, based on the Atlas method [11]. For this reason, all statistical analyses are restricted to LMICs. Nevertheless, as the WHO provided formularies for a small set of high-income countries (HICs), the calculation of cancer concordance for the national formularies of these HICs are included in **Table 2.1**.

To determine country-level concordance with the 48 cancer medications listed on the WHO’s EML, QDA Miner, a software program for the analysis of textual data, was used to determine whether or not the document contained the EML medication name (i.e. the International Non-Proprietary Name) in any of the

four languages in which national formularies were published. Wildcard symbols were used in situations when special characters might have been involved, and searches were not case sensitive. For example, the search for calcium folinate was stylized as follows: “calcium folinate” OR “folinic acid” OR “*cido fol*nico” OR “folinate de calcium” OR “acide folinique” OR “folinique de calcium” OR “folinico de c*lcio” OR “leucovorin” OR “leucovorina.” In situations where the document did not provide machine-readable text (e.g., graphics embedded in Microsoft Word files), the documents were independently reviewed by the first author. Country-level rates of concordance were then depicted in a choropleth map, which was created using ArcGIS version 10.3.1 (Esri: Redlands, California).

Per capita gross domestic product (GDP) at purchasing power parity (PPP) and per capita health expenditures at PPP were obtained from the World Bank [12], and the human development index was obtained from the United Nations Development Programme (UNDP) [13]. As LMICs were the focus of this study, and this subset of countries may be particularly prone to issues deriving from financial scarcity, we selected indicators related to country-level economic development. As a common measure of country-level economic strength, per capita GDP was deemed an appropriate selection for determining the relationship between wealth and cancer concordance [14]. Concordance was further compared to per capita healthcare expenditures at PPP in order to specifically explore whether concordance was significantly associated with investment in national health systems [15]. Finally, we compared concordance with the human development index (HDI), a broad measurement of human

capability based on life expectancy, educational attainment, and per capita income [13].

Since differing levels of country-level wealth have broad impacts on the daily life of country residents [16], including employment choices and purchasing patterns, broad indicators for public health-related behaviors were chosen to elucidate the mechanism by which country-level wealth may impact concordance. We chose two covariates that broadly reflect public health-related behaviors: (1) the prevalence of tobacco consumption (among residents over age 14), and (2) the combined prevalence of overweight and obesity. These covariates are both widely considered to be major risk factors for many of the most highly-prevalent cancers and are broadly reflective of population-level habits affecting cancer risk [17]. These data were obtained from the World Health Organization [18].

Linear regression was used to quantify the association between concordance and national indicators for economic development and health-related behaviors. All statistical analyses were conducted in R version 3.2.3 (R Foundation for Statistical Computing: Vienna, Austria). Graphs showing trendlines were produced using JMP version 10 (SAS Institute: Cary, North Carolina).

RESULTS

The WHO's 19th EML includes 48 antineoplastic drugs, which are then subcategorized, in a mutually exclusive manner, as either immunosuppressive,

cytotoxic/adjuvant, or hormone/anti-hormone. These drugs were predominately cytotoxic/adjuvant (n=38; 79%) rather than hormone/anti-hormone (n=8; 17%) or immunosuppressive (n=2; 4%). Formulation and indication information was also provided within the WHO's EML documentation [6]. Specifically, 16 drugs were classified as tablets, 5 as capsules, and 34 as injectables. Furthermore, 26 were classified for treatment of blood cancers and 28 for treatment of organ cancers. It should be noted that these indications are neither mutually exclusive nor exhaustive, as some drugs like allopurinol or cyclosporine are primarily used for treatment of complications associated with cancer treatment; and some drugs like cyclophosphamide or vincristine can be used to treat either a blood cancer or an organ cancer.

Of the 116 countries that provided national formularies to the WHO web repository [9], 101 were available in a language with characters from the Roman alphabet. The median concordance among LMICs was 42.71% (n = 92 LMICs; Mean = 42.35%; Minimum = 2.08%; Maximum = 91.67%; Standard Deviation = 24.99%; **Figure 2.1**). Nine HICs provided formularies on the WHO web portal (Bahrain, Barbados, Chile, Malta, Nauru, Oman, Seychelles, Trinidad and Tobago, and Uruguay). Median concordance among HICs was much higher, at 64.58%.

Although no country was completely concordant with the WHO's list, Iran had the highest concordance (91.67%), and Colombia and Cambodia both had the lowest concordance (2.08%). We also assessed concordance of national formularies by the six WHO geographic office regions. This includes the regional

offices for Africa (AFRO), the Americas (PAHO), the Eastern Mediterranean (EMRO), Europe (EURO), South-East Asia (SEARO), and the Western Pacific (WPRO). Among LMICs, we found that median concordance was highest in PAHO (57.29%; n = 18), followed by EMRO (54.57%; n = 14), EURO (51.04%; n = 2), SEARO (50.00%; n = 11), AFRO (35.42%; n = 32), and WPRO (16.67%; n = 15).

Concordance was significantly positively associated with per capita GDP ($p = 0.005$; $R^2 = 0.09$; **Figure 2.2**), indicating that wealthier countries were more likely to include a greater number of essential cancer medications. Concordance also exhibited a statistically significant association with per capita healthcare expenditures ($p = 0.050$; $R^2 = 0.05$), thereby suggesting that country-level wealth, as measured by GDP, is an indicator for investment into the national health system, which itself is significantly associated with concordance between national formularies and the global EML. Finally, concordance exhibited a close, statistically significant association with HDI ($p < 0.001$; $R^2 = 0.14$; **Figure 2.3**).

As wealthier countries have more behavioral risk factors for highly prevalent cancers [16, 19-21], we sought to assess whether the significant relationship between concordance and per capita GDP exists because wealthier countries have greater cancer risk. To test this hypothesis, we compared concordance to country-level combined rates of overweight and obesity, and we found a significant positive relationship ($p = 0.006$; $R^2 = 0.09$). We also tested this hypothesis by comparing concordance with smoking prevalence. In this case, we found a no relationship ($p = 0.292$; $R^2 = 0.02$).

DISCUSSION

The sharp increase in the number of cancer medications listed on the 19th EML underscores the importance of preparing LMIC health systems to combat the rising threat of increasingly common cancers. The majority of antineoplastic drugs (79%) on the 19th EML was categorized as cytotoxic/adjuvant. Although the mechanisms of action for the listed cytotoxic drugs involve targeting different sub-cellular components, 20 (53%) of the drugs in the cytotoxic/adjuvant category were stated as indicated for treatment of at least 3 separate cancers. The preponderance of multiple-indication cytotoxic drugs on the 19th EML corresponds to the WHO's stated aim to support cost-efficacy [5], as this may provide guidance to countries for acquiring treatments for a greater number of cancers.

We found a significant association between concordance and several macroeconomic indicators of national development. This included a broad multi-faceted measure, the HDI. As the HDI is generally higher when life expectancy is higher, and there tends to be greater risk for cancer in those who have lived longer [22], the close relationship between concordance and the HDI may indicate that countries with already-high levels of cancer burden react to this challenge by listing a higher number of essential cancer medications on their formularies. Therefore, the HDI may capture a confluence of influential factors that prompt national governments to include more essential cancer drugs on their formularies.

Nevertheless, we found that concordance was not significantly associated with smoking prevalence, which itself bears an extremely close relationship with risk for lung cancer. Therefore, it may be that national governments are more receptive to listing more cancer drugs on formularies when the burden is high for specific types of cancer. Tobacco smoking exhibits especially close association with lung cancer [23], and it may be that high rates of lung cancer prompt policy initiatives advocating for smoking cessation or preventing uptake, and not policy initiatives revolving around drug procurement. Conversely, we found that concordance exhibited a statistically significant association with the combined prevalence of overweight and obesity. This globally-increasing risk factor, which may be considered by national governments to be less avoidable than tobacco consumption, may instead prompt policymakers to advocate for expanded cancer drug inclusion on national formularies [24].

Countries may look to historical data in guiding cancer policy, but may not take into account future projections when making these forms of health policy decisions. This is especially dangerous in the case of policies related to cancer drug access, as the cancer burden in LMICs is expected to rapidly worsen [10]. Furthermore, neglecting to institute adequate public health policy can be an important barrier toward preventing future national health emergencies [25]. In order to ensure adequate resources for providing sufficient standards of healthcare, it would be prudent for present policymaking to involve serious consideration of presently-available projections for future disease burden.

Conclusion

Exploring access variations allows for identification of decision-making factors related to policies that can impact access to essential medicines, as well as formulation of evidence-based policymaking to most effectively improve population health outcomes in response to the rise of cancer. This study builds upon and confirms prior analysis of the EML for cancer medicine inclusion [26]. This study analyzed over 80% of LMICs in the world and found that no country's national formulary contained all the cancer medications recommended by the WHO's EML. Among LMICs assessed in this study, the median concordance was 42.71%, which means that most countries analyzed had national formularies that listed less than half the recommended cancer medications in the WHO's most recent update to the EML. Though greater national wealth may encourage health ministries to invest in infrastructure related to non-communicable diseases, there is a dearth of information reported in the literature relating to possible reasons why one country would have more concordance with the cancer section of the WHO's EML than another country. Therefore, much more research is necessary on this topic, as there are few actionable, evidence-based choices that are presently available to global health experts for promoting the availability of cancer medications through these policy-based methods.

Limitations

The main limitation of this research is the variability of national governments in updating their formularies. Furthermore, this study addresses

national decisions to include certain quantities of essential cancer medications on national formularies, but it does not thoroughly explore the relative financial difficulty a health system may encounter when tasked with obtaining certain essential cancer medications.

Nonetheless, this study accessed national formularies directly from the WHO website at a single point in time, thereby providing a degree of control for the variability exhibited by countries in updating their formularies. Furthermore, this study uses concordance as a single metric that communicates the degree to which essential chemotherapy was found on national formularies. It therefore provides a clear snapshot of government support for a set of cancer medications vetted by a global health organization for efficacy, safety, and cost-effectiveness.

With the number of LMIC cancer cases expected to rapidly grow over the next twenty years, LMIC national governments should prioritize their support for policies that increase availability of essential chemotherapy. The listing of these drugs on national formularies may be one such way to promote availability in government healthcare facilities. However, the availability of a drug does not necessitate its affordability. A more in-depth exploration of prices for essential cancer drugs is conducted in a subsequent study.

ACKNOWLEDGEMENTS

I wish to express my gratitude and appreciation to Timothy Mackey, Cedric Garland, Edward Gorham, and Lianne Urada at the University of California, San Diego, and also to Thomas Novotny and Robert Seidman at San

Diego State University for their helpful input in designing this research. I would also like to express their appreciation to the Frontiers of Innovation Scholars Program at the University of California, San Diego for providing funding for this research.

Chapter 2, in full, is being prepared for submission to a journal with the citation: Cuomo, Raphael; Mackey, Timothy. The availability of essential cancer medication: An analysis of national formularies.

Table 2.1. Concordance with the WHO's most recent listing of essential cancer medicines, by country.

Country	Concordance with Cancer EML
Afghanistan	6.25%
Algeria	25.00%
Angola	4.17%
Argentina	79.17%
Armenia	52.08%
Bahrain	87.50%
Bangladesh	31.25%
Barbados	70.83%
Belize	43.75%
Bhutan	18.75%
Bolivia	54.17%
Botswana	43.75%
Brazil	77.08%
Burkina Faso	25.00%
Burundi	16.67%
Cambodia	2.08%
Cameroon	37.50%
Cape Verde	77.08%
Central African Republic	25.00%
Chad	22.92%
Chile	58.33%
China	6.25%
Colombia	2.08%
Congo, Democratic Republic of	33.33%
Congo, Republic of	52.08%
Cook Islands	16.67%
Cote d Ivoire	75.00%
Djibouti	8.33%
Dominican Republic	58.33%
Ecuador	72.92%
Egypt	33.33%
El Salvador	58.33%
Eritrea	41.67%
Ethiopia	29.17%
Fiji	47.92%
Gabon	22.92%
Georgia	50.00%
Ghana	52.08%
Guinea	8.33%
Guyana	27.08%
Haiti	14.58%
Honduras	83.33%
India	64.58%
Indonesia	50.00%
Iran	91.67%
Iraq	87.50%
Jamaica	56.25%
Jordan	79.17%
Kenya	54.17%
Kiribati	22.92%

Table 2.1 Continued. Concordance with the WHO's most recent listing of essential cancer medicines, by country.

Country	Concordance with Cancer EML
Korea, Democratic Republic of	6.25%
Lebanon	66.67%
Lesotho	25.00%
Madagascar	31.25%
Malaysia	8.33%
Maldives	22.92%
Mali	54.17%
Malta	64.58%
Marshall Islands	12.50%
Mauritania	10.42%
Mexico	87.50%
Morocco	22.92%
Myanmar	70.83%
Namibia	58.33%
Nauru	14.58%
Nepal	58.33%
Nicaragua	52.08%
Nigeria	39.58%
Niue	8.33%
Oman	81.25%
Pakistan	50.00%
Palau	10.42%
Papua New Guinea	37.50%
Paraguay	47.92%
Peru	81.25%
Philippines	79.17%
Rwanda	22.92%
Senegal	37.50%
Seychelles	33.33%
Solomon Islands	37.50%
Somalia	6.25%
South African Republic	43.75%
Sri Lanka	79.17%
St Vincent and the Grenadines	50.00%
Sudan	66.67%
Syrian Arab Republic	81.25%
Tanzania	56.25%
Thailand	72.92%
Timor-Leste	16.67%
Togo	33.33%
Tonga	16.67%
Trinidad and Tobago	83.33%
Tunisia	58.33%
Tuvalu	27.08%
Uganda	29.17%
Uruguay	41.67%
Vanuatu	81.25%
Venezuela	62.50%
Yemen	14.58%
Zambia	62.50%
Zimbabwe	56.25%

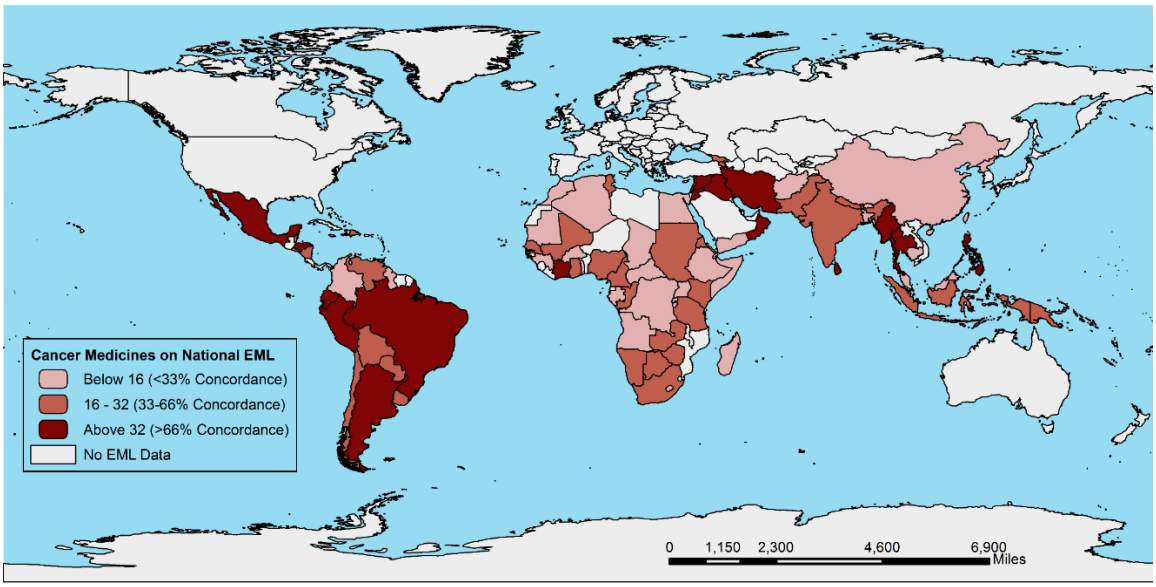

Figure 2.1. World map showing countries by level of concordance with cancer medicines listed on the WHO Essential Medicines List

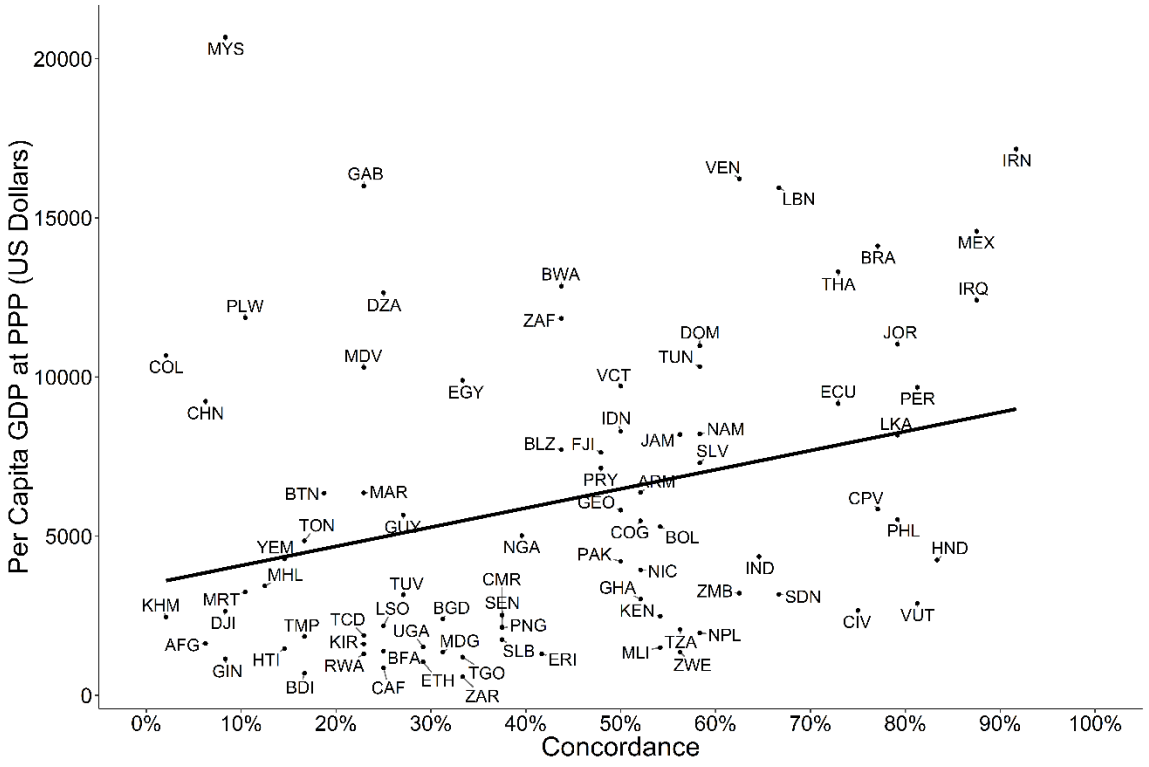

Figure 2.2. Comparison of concordance with per capita GDP in US Dollars (n = 84 LMICs; p = 0.005; R^2 = 0.09)

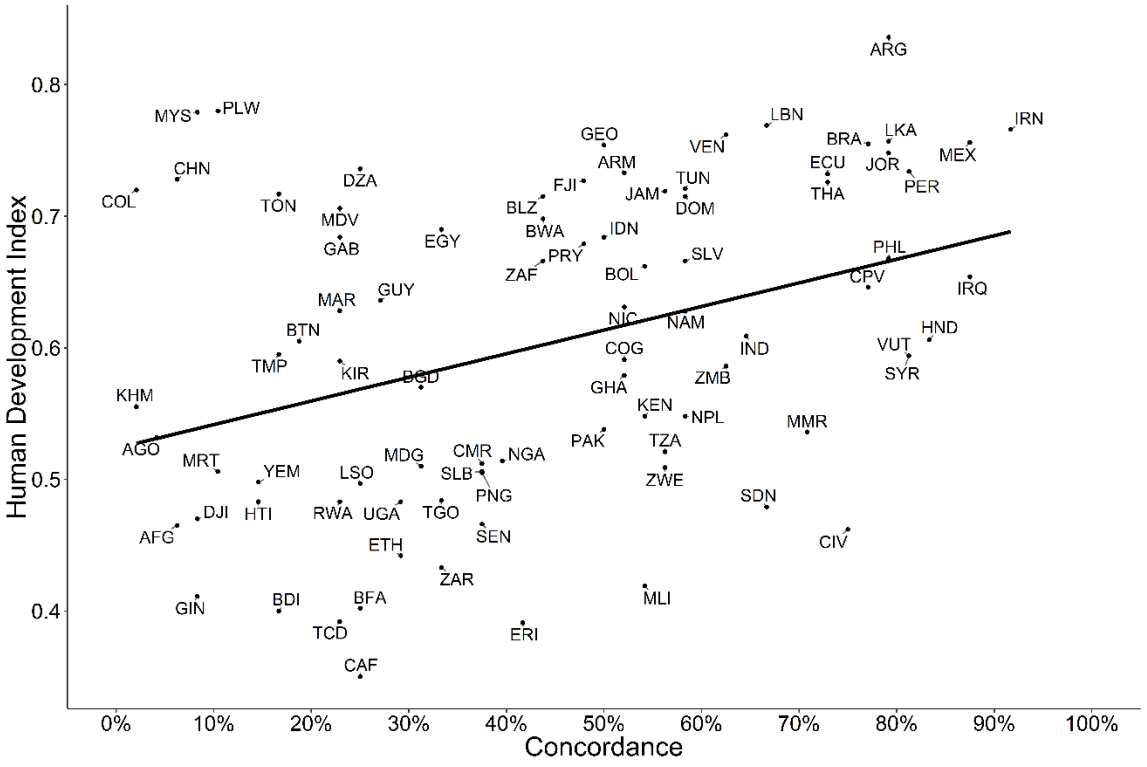

Figure 2.3. Comparison of concordance with the human development index (n = 85 LMICs; $p < 0.001$; $R^2 = 0.14$)

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet- Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians 2015;65:87-108.

2. Adelstein DJ, Rice TW, Becker M, Larto MA, Kirby TJ, Koka A*, et al.* Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. Cancer 1997;80:1011-1020.

3. de Lima Lopes G, de Souza JA, Barrios C. Access to cancer medications in low-and middle-income countries. Nature Reviews Clinical Oncology 2013;10:314-322.

4. Laing R, Waning B, Gray A, Ford N, Hoen Et. 25 years of the who essential medicines lists: Progress and challenges. The Lancet 2003;361:1723-1729.

5. Hogerzeil HV. The concept of essential medicines: Lessons for rich countries. BMJ 2004;329:1169-1172.

6. World Health Organization. 19th who model list of essential medicines. Geneva, Switzerland, 2015,

7. World Health Organization. Promoting rational use of medicines: Core components. 2002

8. Johnson JA, Bootman JL. Pharmacoeconomic analysis in formulary decisions: An international perspective. American Journal of Health-System Pharmacy 1994;51:2593-2598.

9. World Health Organization. National medicines list/formulary/standard treatment guidelines: Essential medicines selection. Geneva, Switzerland, 2015,

10. International Agency for Research on Cancer. Globocan 2012 database: Http://globocan.Iarc.Fr/. Accessed December 2013 2012

11. World Bank. World bank country and lending groups. 2015

12. World Bank. The world bank databank. Washington D.C., World Bank Group, 2015,

13. United Nations Development Programme (UNDP). Human development reports. 2016

14. Goossens Y, Mäkipää A. Alternative progress indicators to gross domestic product (gdp) as a means towards sustainable development. Beyond GDP 2007;305

15. Rogoff K. The purchasing power parity puzzle. Journal of Economic literature 1996;34:647-668.

16. Haase A, Steptoe A, Sallis JF, Wardle J. Leisure-time physical activity in university students from 23 countries: Associations with health beliefs, risk awareness, and national economic development. Preventive medicine 2004;39:182-190.

17. Prentice AM. The emerging epidemic of obesity in developing countries. International journal of epidemiology 2006;35:93-99.

18. World Health Organization. Who global infobase online Available from: http://wwwwhoint/ncd_surveillance/infobase/web/InfoBaseCommon/, accessed 10 July 2011

19. Muthuri SK, Wachira L-JM, Leblanc AG, Francis CE, Sampson M, Onywera VO*, et al.* Temporal trends and correlates of physical activity, sedentary behaviour, and physical fitness among school-aged children in sub-saharan africa: A systematic review. International journal of environmental research and public health 2014;11:3327-3359.

20. Katzmarzyk PT, Mason C. The physical activity transition. J Phys Act Health 2009;6:269-280.

21. Caballero B. A nutrition paradox—underweight and obesity in developing countries. n engl j med 2005;352:1514-1516.

22. Ames BN, Gold LS. Endogenous mutagens and the causes of aging and cancer. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 1991;250:3-16.

23. Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ*, et al.* Variations in lung cancer risk among smokers. Journal of the National Cancer Institute 2003;95:470-478.

24. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutrition reviews 2012;70:3-21.

25. Thomas MK, Murray R, Flockhart L, Pintar K, Pollari F, Fazil A*, et al.* Estimates of the burden of foodborne illness in canada for 30 specified

pathogens and unspecified agents, circa 2006. Foodborne pathogens and disease 2013;10:639-648.

26. Robertson J, Barr R, Shulman LN, Forte GB, Magrini N. Essential medicines for cancer: Who recommendations and national priorities. Medicine 2016;94

CHAPTER 3: GLOBAL INEQUALITY IN PURCHASE PRICES FOR ESSENTIAL CANCER MEDICATIONS

ABSTRACT

Background: Accessibility to essential cancer medication in low- and middle-income countries is especially threatened by insufficient availability and affordability. The objective of this study is to characterize variation in transactional prices for essential cancer medications across geographies, medications, and time.

Methods: Drug purchase prices for 19 national and international buyers (representing 29 total countries) between 2010 – 2014 were obtained from Management Sciences for Health. Median values for drug pricing were computed, to address outliers in the data. For comparing purchase prices across geographic units, medications, and over time; Mann-Whitney *U* tests were used to compare two groups, Kruskal Wallis *H* tests were used to compare more than two groups, and linear regression was used to compare across continuous independent variables.

Results: During the five-year data period examined, the median price paid for a package of essential cancer medication was $12.63. No significant differences in prices were found based on country-level wealth, country-level disease burden, drug formulation, or year when medication was purchased. Statistical tests found significant differences in prices paid across countries, regions, individual medications, and medication categories. Specifically, countries in the Africa

region tended to pay more for a package of essential cancer medication than countries in the Latin America region, and cancer medications tended to be more expensive than anti-infective medications and cardiovascular medications.

Conclusions: This study uncovered appreciable variation in prices paid by health systems to acquire cancer medication. Different prices are being paid by different countries for the same amount of the same drug, which may influence decision-making for drug acquisition and consequently drug accessibility for cancer patients.

INTRODUCTION

According to the World Health Organization (WHO), the “primary intent” of a health system is “to promote, restore or maintain health” [1]. For individuals with cancer, this goal is best served by efforts to increase tertiary prevention initiatives, which serve to reduce the worsening of disease. While advances in the modern era have allowed for the development of treatments with comparatively improved efficacy [2], little has been done to quantify the complex modalities in the context of accessibility and affordability which can lead to inefficiency in the delivery of cancer treatment.

Cancer itself is among the biggest modern threats to individual and population health [3]. The global cancer burden has been steadily increasing through the 20th and 21st centuries [4], and will likely continue to increase in the foreseeable future [5]. Consequently, the demand for cancer medications will also increase steadily [6]. In an effort to help meet the global demand for

medicines, the WHO has formulated a policy mechanism, the Essential Medicines List (EML), which is a list of medicines defined as drugs that “satisfy the priority health care needs of the population” [7]. Medications listed on the EML are supposed to meet a standard for efficacy, safety, and cost-effectiveness [8]. The EML standard for cost-effectiveness, in particular, is meant to ensure that domestic health agencies seeking to acquire an essential medication by including it on their national formularies would be able to do so without unreasonable financial burden [9]. Given that the prevalence of cancer is rising more rapidly in economically developing areas of the world than in high-income countries [4,10], it is critically important that research be conducted to shed light on whether essential cancer medications can actually be acquired at reasonable prices.

This study will attempt to address this important concern by exploring: (1) if some countries or regions pay more for essential cancer medications than others; (2) if countries with higher income or cancer burden pay more or less for essential cancer medication; (3) whether some essential cancer medications are more expensive than others; and (4) whether essential cancer medication is more expensive than other therapeutic categories of essential medicines. Characterizing the sources of financial variation in cancer drug pricing is valuable in the development of international policy as it may help to reduce the likelihood that price determinations result in barriers to acquire essential cancer medicine for at-risk populations [11]. Furthermore, this information may aid national governments in identifying and resolving issues in their pharmaceutical supply

chains that impede procurement of essential cancer medications [12]. This information may also be helpful for understanding variations in availability of treatment options for different cancers [13,14].

The ultimate goal of this research is to address low access to cancer treatment by characterizing affordability of essential cancer medications. Future policies that are informed by findings from this research may allow for improved international access to essential cancer medication or exploration of different policy mechanisms to enhance affordability, thereby improving the likelihood of survival for individuals with cancer who would otherwise be unable to access needed medication [11,15,16].

METHODS

Overview

In order to achieve the goals of this study, we conducted the following comparative analyses on *median* prices paid for essential cancer medications contained in a drug procurement dataset for 19 national and international buyers (representing 29 total countries) obtained from MSH for the period 2010 – 2014. Specifically, we made comparisons between median prices of essential cancer medications listed on the WHO EML by geography, cancer medication type, and date/time of procurement. Specific comparisons examined in this study are summarized in **Table 1**.

Data from the MSH database included prices paid to purchase a package of specific essential cancer medication. With the exception of the comparative

analysis across essential medication categories (where prices were only available for 2014), all analyses were done on prices from 2010 to 2014, inclusive. Regarding the distribution of the number of package prices obtained across different years, it was observed that this distribution exhibited a skewness of -0.158 and a kurtosis of -1.411. These statistics support the uniformity of the distribution, thereby indicating that different time periods did not have very different levels of influence on the entire multi-year sample.

Data

Data for drug prices were obtained from the *International Drug Price Indicator Guide* (hereafter "***Guide")*** published by Management Sciences for Health (MSH), an international nonprofit focused on building programs to facilitate the improvement and strengthening of health systems. Pricing data are kept in a database maintained by the MSH Center for Pharmaceutical Management, a non-profit unit of MSH. MSH works with the WHO to obtain drug prices for the *Guide*. MSH primarily uses the latest version (April 2015) of the WHO's EML to determine which medications it will include in the *Guide*. [17].

Pricing data in the *Guide* are currently available for various formulations of nearly all cancer drugs included on the 19th edition (adopted in 2015) of the EML and provides data from 1996 - 2014 for 16 suppliers and 34 buyers. A supplier is a drug-selling entity that maintains a warehouse and provides a wide range of products, often including cancer drugs. A buyer is typically an agency within an individual national government (i.e., ministries of health), although some

international buyers exist which represent a group of countries [17]. There were two international buyers of essential cancer drugs included in this study: the Organization of Eastern Caribbean States Pharmaceutical Procurement Service (OECS) and the System of Central American Integration (SICA). The OECS represents seven countries (Antigua and Barbuda, Dominica, Grenada, Montserrat, Saint Kitts and Nevis, Saint Lucia, and Saint Vincent and the Grenadines) and the SICA represents eight countries (Belize, Costa Rica, the Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, and Panama). However, it should be noted that Costa Rica, the Dominican Republic, and Guatemala also purchase cancer drugs via their own national agencies.

The *Guide* states that buyer prices, unlike supplier prices, do not require adjustment for shipping charges. Furthermore, the country identity of the purchaser was only available for buyer prices, and not for supplier prices. For these reasons, buyer prices were used in this study. Furthermore, this study primarily used median values for measures of center, as the *Guide* recommends the use of median values for analytical purposes due to the propensity for outliers among provided medication pricing data [17].

Comparative Analyses

Three sets of comparative analyses were conducted. Data management and statistical testing was conducted in R version 3.2.3 (R Foundation for Statistical Computing: Vienna, Austria), and graphs were produced using JMP version 10 (SAS Institute: Cary, North Carolina).

Comparisons Across Geographies

First, the study sought to understand how the prices paid for essential cancer medications varied across different purchasing countries. We quantified the median price paid for all essential cancer medications for each buyer providing data. A Kruskal Wallis *H* test was conducted to test for a statistically significant difference in pricing data at the country level. International buyers were included in this comparative analysis.

Second, we sought to understand how the prices paid for essential cancer medications varied in different regions. We used country-level prices to compute a median value for each region. Therefore, countries and international buyers were attributed to regions. For this analysis, the United Nations Regional Groups classification scheme was used to categorize countries by region [18]. A Mann-Whitney *U* test was computed to test the null hypothesis that there was no statistically significant difference in prices between the two regions that emerged.

Third, we sought to understand whether there was an association between the prices that countries paid for essential cancer medications and the nominal GDP of those countries. We used linear regression to test the association between median country-level prices and country-level nominal GDP (from the International Monetary Fund [19]).

Finally, we sought to understand whether there was an association between the prices that countries paid for essential cancer medications and disease burden from cancer in those countries. We used linear regression to test

the association between median country-level prices and country-level all-cancer incidence. The all-cancer incidence rates for this study were obtained from the International Agency for Research on Cancer's (IARC) Global Cancer (GLOBOCAN) data from 2012 [20]. These data exclude incidence from non-melanoma skin cancer, given its disproportionate impact on cancer burden metrics [21].

Comparisons Across Medications

In this stage of analysis, we first sought to understand the variation in prices paid for different essential cancer medications. We quantified the median price for each cancer medication and assessed the range, midpoint, and distribution of median prices. A Kruskal Wallis *H* test was conducted to test for a statistically significant difference in prices among different cancer EML medications.

Second, we sought to understand how the prices paid for essential cancer medications may differ from the prices paid for essential medications in other therapeutic classes (i.e., that treat diseases other than cancer). We quantified the median price of essential cancer medication and the median price of essential medication in other categories, and then conducted a Kruskal Wallis *H* test to test the null hypothesis that no differences existed among category prices. The other categories chosen for comparison were those for cardiovascular disease and infectious disease. The cardiovascular medicines category was chosen to allow comparison of essential cancer medication pricing with that of another non-

communicable disease that shares a similar epidemiological prevalence across global regions [22]. Conversely, the infectious disease category was chosen so as to allow for comparison with a disease that has a very different etiology and global epidemiology [23]. For each category, the set of essential medications with data in the MSH database was cross-referenced with the set of essential medications in the 19th EML to ensure that the medication was categorized as "essential" in the WHO's latest EML, and also in order to determine the percentage of essential medications in each category with available pricing data.

We sought to understand if prices paid for injectable essential cancer medications were different from prices paid for orally administered essential cancer medications. The medication formulation was specified for each transaction (e.g. "vial," "tab-cap," "ampule," etc.) [17]. We used a Mann-Whitney *U* test to determine if the prices for injectable formulations were significantly different from the prices for oral formulations.

Finally, we sought to understand whether the prices paid for generic/biosimilar cancer drugs were significantly different than the prices paid for brand cancer drugs. Information regarding the dates of approval for generic versions of these drugs were obtained from DrugBank, an online bioinformatics and chemoinformatics resource [24]. For drugs transitioning to generic availability within the time frame, and when sample size permitted statistical analysis, Mann-Whitney *U* tests were used to compare the median price for packages sold before the generic/biosimilar approval date and the median price for packages sold after the generic/biosimilar approval date.

Comparison Across Time

We also sought to understand how prices paid for essential cancer medications varied over time. We quantified the median price for each essential cancer medication for each year with available data between 2010 and 2014. A Kruskal Wallis *H* test was used to determine if statistically significant differences in price existed across years. This was important to determine if there were significant price fluctuations experienced by countries in purchasing essential cancer medication over a five year time period.

RESULTS

A total of 949 transactions for essential cancer medication were recorded and analyzed from 2010 to 2014. The median price paid for a package of essential cancer medication was $12.63, with the lowest recorded price $0.03 and the highest recorded price $5,250.00. This indicates a high degree of variation in overall essential cancer medication pricing.

Comparisons Across Geographies

Prices were obtained for 19 buyers representing a total of 29 different countries. Results from a Kruskal Wallis *H* test suggest statistically significant differences in prices paid by different countries ($\chi^2 = 148.330$; $p < 0.001$). The median price paid for essential cancer medication by each country is available in **Table 2**. The highest median price was for transactions from Namibia (n = 119; *M*

= $27.75) and the lowest median price was for transactions from Ghana (n = 5; *M* = $1.10). While it is possible that comparisons between certain countries may be biased due to the specific cancer medications purchased, the statistically significant difference in pricing detected in this analysis is supported by situational observations with insufficient transactional data for statistical testing. For example, the Dominican Republic paid $4.56, on average, for 1 vial of cyclophosphamide in 2014 whereas Peru paid $9.52 for the same amount of the same drug in the same year. Similarly, Costa Rica paid $2.00 for 100 tablets of dexamethasone in 2010 whereas Namibia paid $7.96 for the same amount of the same drug in the same year. Many additional examples of the pricing disparity between countries for essential cancer medication are available from raw data in the MSH *Guide* [17].

A sub-analysis was carried out to further illustrate the disparity in transactional prices among buyers for individual cancer medications. This sub-analysis was conducted on cyclophosphamide (a cytotoxic drug used since 1959 for treatment of both blood cancers and solid tumors), which included the greatest number of package prices in the dataset during the five-year period between 2010 and 2014 (n=62). Additionally, cyclophosphamide was available as a generic during the study time frame and have been available since 1999 [24]. Buyers with less than five transactions recorded were excluded, leaving four buyers (Barbados, Namibia, the OECS multinational buyer, and South Africa) with 46 transactions. Purchases of tablets were excluded, allowing for the remaining 31 transactions to be normalized to the price per vial.

A Kruskall Wallis *H* test among these 31 transactions indicated a statistically significant difference in prices ($\chi^2 = 9.105$; $p = 0.028$), with the median price being $3.85 per vial for the OECS (n=5), $5.29 per vial for Barbados (n=5), $9.46 per vial for Namibia (n=12), and $10.00 per vial for South Africa (n=8). Further attempts to normalize to vial strength were limited due to sample size, resulting in insufficient statistical power for further testing. However, the 1-gram formulation provided the greatest number of transactions for these four countries, where we observed noteworthy variations in price per 1-gram vial: $3.85 per 1-gram vial for the OECS (n=5), $6.39 per 1-gram vial for Barbados (n=3), $11.17 per 1-gram vial for Namibia (n=4), and $13.02 per 1-gram vial for South Africa (n=4).

Transactions were recorded from 11 countries in the UN African region and 8 buyers (6 countries and 2 international organizations) in the UN Latin America region. Results from a Mann-Whitney *U* test suggest that transactions from African buyers exhibited a significantly higher price than transactions from Latin American buyers ($z = -3.468$; $p = 0.001$). The median price paid for essential cancer medication for an African buyer was $15.03 (n = 530), while the median price in these transactions for a Latin American buyer was $10.89 (n = 419). The significant difference in prices paid for essential cancer medication between these two regions further underscores a potential for pricing and procurement disparity based on a country's geographic region.

Linear regression found no statistically significant relationship between country-level GDP (nominal) and median prices paid for essential cancer

medication ($\beta = -4.778\times10^{-6}$; $p = 0.867$; $R^2 = 0.002$). Linear regression also found no statistically significant relationship between country-level all-cancer incidence and median prices paid for essential cancer medication ($\beta = 0.040$; $p = 0.347$; $R^2 = 0.059$).

Comparisons Across Medications

Results from a Kruskal Wallis *H* test suggest statistically significant differences in prices paid for different medications ($\chi^2 = 514.493$; $p < 0.001$). The median price paid for each essential cancer medication is available in **Table 3**. The lowest median price paid for an essential cancer medication was for allopurinol (n = 17; *M* = $6.40) and the highest median price paid for an essential cancer medication was for trastuzumab (n = 3; *M* = $1,800.00). Rituximab (n = 12; *M* = $413.53), capecitabine (n = 22; *M* = $354.04), and tioguanine (n = 6; *M* = $102.83) also exhibited median purchase prices exceeding $100 per package.

As these medications are intended to be considered essential for health systems, prices over $100 per package appear quite likely to put the medication out of reach for most people in most countries. Though efforts have been taken by some national governments to ameliorate the high price of trastuzumab [25,26], these efforts have been geographically limited [27], with generally insufficient options for residents of developing countries to gain access to this treatment. It is worth noting that trastuzumab is a treatment for HER2-positive breast cancer, a form of breast cancer diagnosed for several hundred thousand women each year [28].

Transactions were recorded for 43 of the 48 medications (90%) in the "Antineoplastic and Immunosuppressives" category of the 19th EML, 81 of the 167 medications (49%) in the "Anti-Infective Medicines" category, and 18 of the 28 medications (64%) in the "Cardiovascular Medicines" category. Results from a Kruskal Wallis *H* test suggest statistically significant differences in prices between categories ($\chi^2 = 108.421$; $p < 0.001$). The median price paid for a package of essential cancer medication in 2014 was $9.31 (n = 204), which is approximately 4 times higher than the median price paid in 2014 for a package of essential infectious disease medication (n = 457; *M* = $2.45) and 5 times higher than the median price paid for a package of essential cardiovascular disease medication (n = 129; *M* = $1.73). This analysis indicates that the median prices for acquiring essential infectious disease medication and essential cardiovascular disease medication are both much lower than the median price of acquiring essential cancer medication.

Results from a Mann-Whitney *U* test suggest that prices paid for injectable cancer medications were not significantly different than prices paid for oral cancer medications ($z = -0.205$; $p = 0.837$). The median price for a package of injectable medication was $12.17 (n = 610) and the median price for a package of oral medication was $13.31 (n = 339). About two-thirds (64.3%) of transactions were for injectable cancer medications.

We also investigated the role of generic/biosimilar availability on transactional prices of essential cancer drugs. Among the 43 drugs with available prices, 34 had generic versions available throughout the entire 5-year period

from 2010 through 2014 (median price = $10.62), 3 had no generic versions throughout this entire period (median price = $29.35), and the remaining 6 had a generic approved during the 5-year period. These drugs are anastrozole (generic available in 2010), gemcitabine (2010), docetaxel (2012), capecitabine (2012), rituximab (2013), and imatinib (2013). Only docetaxel and gemcitabine had greater than 5 package prices available in each of the following two categories: (1) the years from 2010 up through the generic approval year and (2) the years after the approval year. The year of approval was included in the "before" category, as this would allow for a short period of time for international buyers to adapt to ordering from new generic drug manufacturers. When using Mann-Whitney *U* tests to compare prices of these drugs before and after generic versions were approved, we found that docetaxel exhibited a statistically significant decrease in median price from $53.84 to $27.89 ($z$ = -2.134; p = 0.033) and capecitabine exhibited a non-significant decrease in median price from $362.84 to $209.68 ($z$ = -1.280; p = 0.201).

Comparison Across Time

Results from a Kruskal Wallis *H* test suggest that, between 2010 and 2014, prices paid for essential cancer medications did not significantly differ by year (χ^2 = 3.497; p = 0.478). Indeed, prices did not appear to exhibit a clear longitudinal trend, with the median price for essential cancer medication being $12.41 in 2010 (n = 216), $14.90 in 2011 (n = 150), $14.77 in 2012 (n = 131), $12.81 in 2013 (n = 248), and $9.31 in 2014 (n = 204).

DISCUSSION

Though preliminary and limited to pricing and procurement data available from the MSH dataset, the results of this study suggest that: (1) some countries pay significantly more for essential cancer medication than others; (2) some regions pay significantly more for essential cancer medication than others; (3) some essential cancer medications are significantly more expensive than others; (4) essential cancer medication is significantly more expensive than certain other categories of essential medications; and (5) prices for essential cancer medications may significantly decrease after generic/biosimilar approval.

As a global policy-based mechanism, the EML has the potential to have a broadly permeating downstream effect whereby national, subnational, and private-sector participants in the pharmaceutical supply chain react to EML medication inclusion by creating more market demand and potentially decreasing pricing due to increased volume that could lead to broader availability [29,30]. However, the longitudinal analysis in this study has uncovered no evidence that the EML has met its potential for a beneficial effect on medication affordability or availability through decreased prices.

While it is already known that the geographic location of a patient will likely have a notable impact on the patient's treatment options [31], and therefore the patient's ability to survive [31], the specific mechanisms by which location influences odds of survival have not been comprehensively enumerated. In this study, we have observed an appreciable variation in the prices paid by country-

level organizations in acquiring important medication for their cancer patients, thereby indicating that a mediator for the relationship between location and treatment quality is that different prices are being paid by different national health systems for the same drug. If a poorer country is unable to acquire an essential cancer medication at a lower price paid by a wealthier country or neighboring country, then the poorer country may decide to invest in inferior treatment options [32]. In this manner, variation in prices paid for cancer medication can introduce a geographic disparity in treatment quality, thereby presenting the potential to worsen existing geographic disparities in cancer survival [32].

The international drug pricing data observed in this study imply two characteristics about the current policies that affect the international market for essential cancer medications: (1) these policies do not emphasize the financial capacity to acquire drugs for cancer over drugs for other diseases, and (2) drug-related economic benefits from these policies are not equitably distributed across all countries. Larger-scale policies, such as those establishing free trade areas, group purchasing organizations/pooled procurement (to raise volume and negotiate lower pricing), and lowered tariffs may result in a drug supplier modifying the price offered for a given drug to customers in an affected country, relative to the price offered for that drug to customers in an unaffected country [33]. Consequently, a fundamentally ethical question raised is the appropriateness and equity of a country's trade policy to impact drug procurement prices for one country but not another [34-36]. This same question

is raised with regard to the impact of trade policies on the price of drugs for some disease classes but not drugs for other disease classes.

Limitations

This study may not have comprehensively examined all independent variables which could explain variations in prices for essential cancer medication. It was also not possible to determine if data were gathered for the *Guide* in a non-random fashion. Furthermore, low sample sizes for the prices attributed to an individual drug did not permit for the comparison of median geographic prices to be stratified by drug. Similarly, low sample sizes for individual buyers did not permit comparison of median drug prices to be stratified by buyer.

Nonetheless, in order to support findings that showed significant differences in the aggregated price of cancer drugs across buyers, this study provided a sub-analysis comparing median prices of the cancer drug with the highest sample size (cyclophosphamide) across buyers with the highest numbers of recorded transactions. Also, in order to minimize the potential impact of omitted variable bias, we described the variation in cancer drug prices across a number of pharmacoeconomic factors. Furthermore, prices were gathered by the MSH via a systematic methodology, thereby theoretically providing a degree of control for sampling bias that would have otherwise differentially influenced buyers in the dataset.

The large range of chemotherapy prices observed in this study indicates that certain chemotherapies could be preferred over others in healthcare

facilities. This may lead to suboptimal treatment or to restrictions on the number of patients for which expensive chemotherapies may be provided. Significant associations uncovered in this study should be considered hypothesis generating, and further studies should be conducted that compare prices paid for essential medication between geographies, cancer medication categories, and individual classes of drugs. Better transparency and greater data availability are necessary in order to conduct analyses that yield more conclusive findings and provide a better overall picture of affordability and access to essential cancer medications.

CONCLUSIONS

Over one-fifth of essential chemotherapies assessed in this study cost over $50 per package. As over 50 countries have a per capita gross national income of under $2000 per person, essential chemotherapy may be too expensive to ensure global access. This study also found that countries with smaller economies were not being sold chemotherapy at lower prices than countries with larger economies. Global price barriers to chemotherapy access will likely be exacerbated in the future, as the number of cancer patients in low- and middle-income countries is expected to rapidly rise.

ACKNOWLEDGEMENTS

I wish to express my gratitude and appreciation to Timothy Mackey, Cedric Garland, Edward Gorham, and Lianne Urada at the University of

California, San Diego, and also to Thomas Novotny and Robert Seidman at San Diego State University for their helpful input in designing this research. I would also like to express their appreciation to the Frontiers of Innovation Scholars Program at the University of California, San Diego for providing funding for this research.

Chapter 3, in part, is being prepared for submission to a journal with the citation: Cuomo, Raphael; Mackey, Timothy; Seidman, Robert. Global inequality in purchase prices for essential cancer medications.

Table 3.1. Comparisons tested in this study. For all tests, the dependent variable was medication price.

Category of Analysis	Independent Variable	Test Performed	Number of Groups
Geographic	Buyers	Kruskal Wallis *H*	19
Geographic	Region*	Mann-Whitney *U*	2
Geographic	GDP (nominal)†	Linear Regression	N/A
Geographic	All-Cancer Incidence	Linear Regression	N/A
Medication	Essential Cancer Medications	Kruskal Wallis *H*	43
Medication	Essential Medication Categories	Kruskal Wallis *H*	3
Medication	Medication Formulations	Mann-Whitney *U*	2
Medication	Pre/Post Generic Approval Date§	Mann-Whitney *U*	2
Longitudinal	Year	Kruskal Wallis *H*	5

*Obtained from the United Nations

†Obtained from the International Monetary Fund

‡Obtained from the International Agency for Research on Cancer

§Obtained from DrugBank

Table 3.2. Median package prices of cancer medication for all included buyers, with other select characteristics.

Buyer	UN Region	Median Price	GDP (mil, nominal)	Cancer Incidence
Barbados	Latin America	$14.66	$4,498	263.1
Bolivia	Latin America	$4.94	$33,983	143.9
Botswana	Africa	$18.40	$12,701	107.6
Costa Rica	Latin America	$21.40	$56,908	179.3
Dominican Republic	Latin America	$6.15	$71,433	153.4
DR Congo	Africa	$9.60	$41,207	107.8
Ghana	Africa	$1.10	$38,171	91.7
Guatemala	Latin America	$6.24	$68,142	130.4
Lesotho	Africa	$6.28	$1,766	103
Namibia	Africa	$27.75	$11,210	82.7
OECS	Latin America	$9.00	-	-
Peru	Latin America	$7.89	$178,643	154.5
Rwanda	Africa	$11.45	$8,490	135.8
Senegal	Africa	$1.14	$14,572	101.2
SICA	Latin America	$8.15	-	-
South Africa	Africa	$14.27	$266,213	187.1
Sudan	Africa	$2.36	$93,729	91.1
Tanzania	Africa	$3.19	$45,899	123.7
Uganda	Africa	$12.17	$24,995	169.7

Table 3.3. Cancer medications in the 19th EML with median purchase price and formulations available.

Essential Cancer Drug	Median Price	Oral	Injectable
Allopurinol	$1.56	X	
All-Trans Retinoid Acid	*Not Available*	X	
Anastrazole	$6.40	X	
Asparaginase	$42.58		X
Azathioprine	$14.28	X	X
Bendamustine	*Not Available*		X
Bicalutamide	$17.61	X	
Bleomycin	$18.24		X
Calcium Folinate	$15.98	X	X
Capecitabine	$354.04	X	
Carboplatin	$26.49		X
Chlorambucil	$32.83	X	
Ciclosporin	$88.64	X	
Cisplatin	$8.47		X
Cyclophosphamide	$13.00	X	X
Cytarabine	$4.27		X
Dacarbazine	$14.50		X
Dactinomycin	$25.23		X
Daunorubicin	$6.08		X
Dexamethasone	$2.01		X
Docetaxel	$44.65		X
Doxorubicin	$7.53		X
Etoposide	$4.57	X	X
Filgrastim	$52.11		X
Fludarabine	$91.46	X	X
Fluorouracil	$1.86		X
Gemcitabine	$25.85		X
Hydrocortisone	$1.96		X
Hydroxycarbamide	$16.67	X	
Ifosfamide	$25.01		X
Imatinib	$75.41	X	
Irinotecan	*Not Available*		X
Leuprorelin	*Not Available*		X
Mercaptopurine	$55.90	X	
Mesna	$3.47	X	X
Methotrexate	$9.00	X	X
Methylprednisolone	$9.06		X
Oxaliplatin	$44.55		X
Paclitaxel	$14.85		X
Prednisolone	$7.18	X	
Procarbazine	*Not Available*	X	
Rituximab	$413.53		X
Tamoxifen	$5.24	X	
Tioguanine	$102.83	X	
Trastuzumab	$1,800.00		X
Vinblastine	$14.75		X
Vincristine	$3.53		X
Vinorelbine	$18.10		X

REFERENCES

1. Atrash K, Carpentier R. The evolving role of public health in the delivery of health care. Revista brasileira de crescimento e desenvolvimento humano 2012;22:396-399.

2. Skeel RT, Khleif SN. Handbook of cancer chemotherapy. Lippincott Williams & Wilkins, 2011.

3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V*, et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the global burden of disease study 2010. The Lancet 2013;380:2095-2128.

4. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians 2015;65:87-108.

5. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the human development index (2008–2030): A population-based study. The lancet oncology 2012;13:790-801.

6. Popat K, McQueen K, Feeley TW. The global burden of cancer. Best Practice & Research Clinical Anaesthesiology 2013;27:399-408.

7. World Health Organization Expert Committee. The selection and use of essential medicines: WHO Technical Report Series. Geneva, Switzerland, 2003,

8. Hogerzeil HV. The concept of essential medicines: Lessons for rich countries. BMJ 2004;329:1169-1172.

9. Magrini N, Robertson J, Forte G, Cappello B, Moja LP, de Joncheere K*, et al.* Tough decisions on essential medicines in 2015. Bulletin of the World Health Organization 2015;93:283-284.

10. López-Gómez M, Malmierca E, de Górgolas M, Casado E. Cancer in developing countries: The next most preventable pandemic. The global problem of cancer. Critical reviews in oncology/hematology 2013;88:117-122.

11. Zaidi S, Bigdeli M, Aleem N, Rashidian A. Access to essential medicines in pakistan: Policy and health systems research concerns. PloS one 2013;8:e63515.

12. Hogerzeil HV, Liberman J, Wirtz VJ, Kishore SP, Selvaraj S, Kiddell-Monroe R*, et al.* Promotion of access to essential medicines for non-

communicable diseases: Practical implications of the un political declaration. The Lancet 2013;381:680-689.

13. Shulman LN, Mpunga T, Tapela N, Wagner CM, Fadelu T, Binagwaho A. Bringing cancer care to the poor: Experiences from rwanda. Nature Reviews Cancer 2014;14:815-821.

14. O'Brien M, Mwangi-Powell F, Adewole IF, Soyannwo O, Amandua J, Ogaja E*, et al.* Improving access to analgesic drugs for patients with cancer in sub-saharan africa. The Lancet Oncology 2013;14:e176-e182.

15. Chalkidou K, Marquez P, Dhillon PK, Teerawattananon Y, Anothaisintawee T, Gadelha CAG*, et al.* Evidence-informed frameworks for cost-effective cancer care and prevention in low, middle, and high-income countries. The lancet oncology 2014;15:e119-e131.

16. de Lima Lopes G, de Souza JA, Barrios C. Access to cancer medications in low-and middle-income countries. Nature Reviews Clinical Oncology 2013;10:314-322.

17. Management Sciences for Health. International drug price indicator guide. Cambridge, MA,

18. United Nations Department for General Assembly and Conference Management. United nations regional groups of member states. 2014

19. International Monetary Fund. Imf data. 2016

20. International Agency for Research on Cancer. Globocan 2012 database: Http://globocan.Iarc.Fr/. Accessed December 2013 2012

21. Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. JAMA oncology 2015;1:505.

22. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H*, et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the global burden of disease study 2010. The lancet 2013;380:2224-2260.

23. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global burden of disease study. The Lancet 1997;349:1436-1442.

24. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P*, et al.* Drugbank: A comprehensive resource for in silico drug discovery and exploration. Nucleic acids research 2006;34:D668-672.

25. Pearson S-A, Ringland CL, Ward RL. Trastuzumab and metastatic breast cancer: Trastuzumab use in australia—monitoring the effect of an expensive medicine access program. Journal of Clinical Oncology 2007;25:3688-3693.

26. Limb M. Roche's decision to drop herceptin patent in india opens way for generics. BMJ 2013;347:f5197.

27. Nikolentzos A, Nolte E, Mays N. Paying for (expensive) drugs in the statutory system: An overview of experiences in 13 countries. London: London School of Hygiene & Tropical Medicine 2008

28. Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH*, et al.* Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of american pathologists clinical practice guideline update. Archives of Pathology and Laboratory Medicine 2013;138:241-256.

29. Li Y, Ying C, Sufang G, Brant P, Bin L, Hipgrave D. Evaluation, in three provinces, of the introduction and impact of china's national essential medicines scheme. Bulletin of the World Health Organization 2013;91:184-194.

30. Lu CY, Ross-Degnan D, Stephens P, Liu B, Wagner AK. Changes in use of antidiabetic medications following price regulations in china (1999–2009). Journal of Pharmaceutical Health Services Research 2013;4:3-11.

31. Kingham TP, Alatise OI, Vanderpuye V, Casper C, Abantanga FA, Kamara TB*, et al.* Treatment of cancer in sub-saharan africa. The Lancet Oncology 2013;14:e158-e167.

32. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (cml) is a reflection of the unsustainable prices of cancer drugs: From the perspective of a large group of cml experts. Blood 2013;121:4439-4442.

33. Gleeson D, Friel S. Emerging threats to public health from regional trade agreements. The Lancet 2013;381:1507-1509.

34. Shah AK, Warsh J, Kesselheim AS. The ethics of intellectual property rights in an era of globalization. The Journal of Law, Medicine & Ethics 2013;41:841-851.

35. Lopert R, Gleeson D. The high price of “free” trade: Us trade agreements and access to medicines. The Journal of Law, Medicine & Ethics 2013;41:199-223.

36. Dyck A. Ethical ramifications for a proposed fta between india and the eu. Perspectives on Global Development and Technology 2013;12:266-282.

CHAPTER 4: POLICY-BASED APPROACHES FOR FACILITATING ACCESS AND AFFORDABILITY FOR ESSENTIAL CANCER MEDICATIONS

ABSTRACT

Although cancer has existed for several thousands of years, its prevalence is now expected to rise dramatically in low- and middle-income countries (LMICs), which represent over 80% of the global population. Though treatment for cancer has rapidly advanced over the past century, these treatments remain inaccessible to most patients in LMICs. The most recent version of the WHO's Essential Medicines List (EML) has 48 drugs in its cancer category, and is designed as a policy mechanism to encourage countries to prioritize access to these drugs. However, analyses have shown a large disparity in the inclusion of these "essential" cancer drugs on national government formularies, and also that countries of similar income levels may be paying unequal prices. Though the EML was not intended to directly resolve issues in cancer medication access and affordability, we believe that such an approach has become necessary. In response, we propose that the International Agency for Research on Cancer (IARC) be empowered and transformed into a UN specialized agency, allowing it to act as a global leader and key governance instrument in the fight against cancer. This should include empowering the IARC to conduct research on cost and accessibility of cancer medications and to negotiate pooled procurement of cancer medication on behalf of LMICs.

BACKGROUND

Drug development has rapidly accelerated within the past century, but the fruits of innovation and investment in the science, discovery, manufacture, and supply of life-saving pharmaceutical products remains out of reach for most communities throughout the world [1-3]. This is a particular challenge for drugs that treat non-communicable diseases, which often require a consistent and sustained supply of treatment, and even more specifically for often-expensive forms of cancer medications (e.g., molecularly targeted therapy, angiogenesis inhibitors, and monoclonal antibodies) [4,5].

At its root, cancer is the proliferation of cells at such a rapid rate that it threatens harm to the multicellular organism [6]. This disease has afflicted human society for millennia, with the first recorded case occurring about four thousand years ago when a woman in ancient Egypt was diagnosed with a solid breast tumor [7,8].

Historically, all-cancer prevalence has been rising globally for at least the past one hundred years [9-12]. The causes of cancer's rising prevalence are many [13,14], and each risk factor is subject to its own level of inquiry and debate. Nevertheless, many decades and billions of dollars spent in scientific and medical efforts have failed to produce definitive cures for highly prevalent cancers [15]. Concomitantly, decades of public health interventions have similarly failed to prevent cancer and have yet to reverse all-cancer prevalence globally [16].

Consequently, cancer prevalence is expected to continue to rise for the foreseeable future [17,18]. However, prevalence is not expected to rise equally in all geographies. In 2016, the worldwide human population reached about 7.4 billion individuals, with the 2016 population of high-income countries (HICs; as defined by the World Bank [19]) being only about 1.2 billion individuals [20]. Therefore, about 84% of the world's population lives in a low- or middle-income country (LMIC).

Among this highly-populated set of LMICs, individuals currently tend to have lower life expectancies [20]. However, future demographic and behavioral changes, including longer life expectancy, are expected to result in a much more rapid increase in cancer prevalence in these jurisdictions [16,17]. Based on estimates from the International Agency for Research on Cancer (IARC), the number of cancer cases is predicted to increase from 14 million to 24 million cases between 2012 and 2030 [17]. Hence, the next century will present a new chapter in the fight against cancer, characterized by whether global health efforts will successfully tackle the increasing threat of cancer for the large population in developing countries.

In order to address the expected future challenges associated with cancer medication access among LMIC patients, this commentary will briefly review the history of cancer medication, examine the potential impact of current policy instruments to safeguard cancer medication access in LMICs, and finally propose policy solutions that may best resolve impediments faced by LMIC patients in obtaining cancer medication.

HISTORY OF CANCER TREATMENT

For nearly all of human history, there has been no viable medical treatment available for individuals suffering from the various types of cancers [21]. In the 19th century, the development of anesthesia and the discovery of x-rays facilitated the use of surgery and radiation to remove tumors and destroy cancer cells [22,23]. While later advances, such as radical dissection and the use of gamma radiation, would sometimes result in improved prognosis, these procedures exhibited vastly uneven success in prolonging life and survivability for those afflicted with cancer [24,25].

Microscopic observations of cancer cells led Paul Ehrlich in 1907 to devise his “chemotherapia specifica” theory, wherein certain chemicals would be able to specifically target certain types of cells [26]. Observations of the biological effect of mustard gas in the First World War led to the development of nitrogen mustard (INN chlormethine) as a lymphoma chemotherapy [27]. The later use of aminopterin by Sidney Farber in 1947 and mercaptopurine by Joseph Burchenal in 1954 would lead to a revolution in cancer treatment involving the discovery of many new chemotherapeutic agents and the introduction of combination/adjuvant chemotherapy [28-30]. The approval of trastuzumab in 1998 [31] and imatinib [32] in 2001 resulted in fervent interest surrounding molecularly targeted chemotherapy [33], which was further amplified by the completion of the Human Genome Project in 2003 [34]. Recent advances in genomics, accompanied by

progress in proteomics and metabolomics, offer to advance the efficacy of cancer treatment by enhancing the precision medicine approach [35].

While progress in scientific and clinical discovery of cancer treatment may be the first step to alleviating the global burden of disease from cancer, a critical next step is to include these medicines in global policy instruments in order to provide guidance regarding their inclusion on national formularies. These linkages serve to create policy and financing frameworks that can facilitate their access and availability.

DISCUSSION

The Essential Medicines List and National Formularies

Penicillin was beginning to be used successfully in the 1940s, and with the subsequent introduction of the Salk polio vaccine in the 1950s, chemical compounds gained greater attention and policy support during the formative years of the World Health Organization (WHO), the specialized international public health agency of the United Nations. [36]. In 1977, the WHO published its first list of “essential medicines,” defined as drugs that “satisfy the priority health care needs of the population” [37]. Known officially as the Model List of Essential Medicines (EML), drugs (and drug combinations) listed on the EML are supposed to be chosen on standards of disease prevalence, evidence of efficacy/safety, and comparative cost-effectiveness [38]. The broad purpose of the EML is to provide technical assistance to countries and provide guidance on what medicines are minimally necessary for a functioning health system.

The first EML had 207 total drugs. Though 23 of the 48 current medicines in the “Antineoplastics and Immunosuppresives” category were available in 1977, only 7 were present in the first EML [39]. The number of medicines in the cancer category of the EML grew steadily to 32 in 2013 [39]. However, in 2015, the 19th version of the EML would include a spike in the number of cancer medications listed, reaching 48 total medications in the cancer category, including two immunosuppresive drugs, 38 cytotoxic drugs, and eight hormone/antihormone drugs [37].

In parallel to the WHO’s formulation of the EML, many drug formularies have been published by national, subnational, and private-sector bodies [40]. Formularies from these bodies may have a great deal of action-oriented support from their issuing organization. These formularies list drugs that are approved for prescribing and are used for reimbursement activities in national health systems. The listing of a drug may imply that the government or private body intends to ensure the availability of that drug and include it in its standard of care to treat a disease [40,41].

If a drug is prescribed but not listed on a government formulary, it may still be acquirable by the patient through means of a third party, such as a private insurer [40,42]. Conversely, if a drug is prescribed which is listed on a formulary, the affordability of the drug is not necessarily guaranteed by that government or insurer, as a variable proportion of the drug cost may be passed to the patient (for example, though a co-pay or other cost-sharing mechanism) [43]. Even though a drug may be affordable at one point in time, market fluctuations, patent

and exclusivity status, or manufacturer decisions may result in increased drug prices [44], which may or may not be passed on to the patient. For some high-cost cancer drugs, additional programs have existed whereby the cancer patient (or the patient's physician) can apply for some of the cost to be forgiven, subsidized, or reimbursed by the drug manufacturer or government entity [45].

As national formularies generally imply that the authoring government body will make some effort to ensure the availability of a listed drug, it is reasonable to suspect that if a formulary has an insufficient number of drugs indicated for a particular disease, this may result in treatment that is inaccessible [46]. Conversely, listing all available drugs for a particular indication on a national formulary would be prohibitively expensive for most middle-income or low-income countries, and the likelihood that these drugs could be procured due to constraints on national health budgets is also questionable. However, the inclusion of a cancer drug on a government formulary may provide leverage to negotiate lower prices with manufacturers. Nevertheless, health ministries must often be selective in choosing drugs to be listed on their government formularies in order to avoid issues regarding over-inclusion and limits in budgets and procurement [47]. Therefore, the WHO's EML is intended, in part, to provide guidance on what specific "essential" drugs should be prioritized for inclusion in national formularies [48].

A recent study from the WHO revealed a statistically significant relationship between per capita gross national income (GNI) and the number of medications on the 18th EML (published in 2013) which appeared in national

formularies [49]. In a separate analysis, this same study found a statistically significant relationship between per capita GNI and newly-added cancer medications to the 19th EML (published in 2015) which appeared on national formularies [49]. In a similar study, Cuomo et al. compared cancer medications in the 19th EML with 101 national formularies made available in the WHO's Internet repository (who.int/selection_medicines/country_lists/), finding that the median LMIC formulary listed only 43% of the 48 drugs listed in the "Antineoplastics and Immunosuppresives" category of the 19th EML [50]. Over 80% of all LMICs were included in this study. By contrast, HICs assessed in this study exhibited much higher agreement with the EML, with 65% of EML cancer drugs on the median HIC formulary. This study assessed each country for "concordance" with the cancer section of the EML, which was defined as the proportion of essential cancer medications appearing on the country's national formulary. No country formulary reviewed had full concordance with the cancer drugs listed in the 19th EML.

Though little is known about the specific mechanisms by which cancer drugs are commonly chosen to be included on national formularies [51], it would appear that the WHO's EML does not directly translate to national formulary inclusion, as there appears to be a great deal of variation in concordance, especially among LMICs. Furthermore, additional analysis has found that countries with more essential cancer medication on their formularies were significantly associated with greater gross domestic product (GDP) per capita. Importantly, this analysis also found that the number of essential cancer

medications listed on national formularies was associated with the combined prevalence of overweight and obesity. However, this study did not uncover a statistically significant relationship with country-level smoking prevalence. This pattern of associations between cancer risk and EML cancer medicine inclusion suggest that LMIC health ministries may react to the high preponderance of specific cancer risk factors by expanding drug access policies.

Essential Cancer Medication Pricing

Based on Article 1 of its constitution, the WHO's objective is "the attainment by all peoples of the highest possible level of health" [52]. Therefore, the EML is intended to not only provide guidance on a minimum standard of care, but to do so with health equity in mind. Perhaps as a result, a key factor for selection of a drug in the WHO's EML is cost-effectiveness [53]. The number of considerations falling under the umbrella of "cost-effectiveness" may reasonably be very broad. The intention to control the cost of a drug implies attempts to make the drug affordable [54]. The affordability of a drug depends on both the transactional price of the drug and the strength of the country's healthcare financing to procure/afford the drug [55].

Many factors determine the extent and usage of healthcare funds in a country; these differ considerably between countries (including countries in the same income classification), and may include such factors as corporate taxation, trade policy (import and export tariffs), development assistance for health, remittances, and many others [56]. However, as the majority of LMICs spend

within a narrow range (between 3% and 6%) of their gross domestic products (GPDs) on healthcare, countries with lower national wealth generally have a smaller reservoir of resources to spend on domestic health financing [20,57]. Every LMIC also has its own health insurance scheme (or lack thereof) which differentially impacts decisions on domestic healthcare spending, including procurement and dispensing of medicines [57]. However, national health insurance programs in many LMICs may cover only specific types of residents (such as those who can contribute through payroll taxes) or they may have been designed to emphasize coverage for only specific diseases, especially infectious diseases such as malaria, tuberculosis, and HIV/AIDS [58,59]. Furthermore, the large out-of-pocket expense required for LMIC patients to receive healthcare services is a reality that complicates the delivery of treatment in already-challenging settings [60,61].

Several policy experts have decried the high price of cancer medication as a barrier for patients in LMICs [4,62-64]. While a study comprehensively providing quantitative analyses of variation in prices for essential cancer medications in LMICs has not been conducted, such analyses in high income markets have revealed a large degree of variation in the price of cancer medications [65,66]. Cuomo *et al.* assessed publically-available data from Management Sciences for Health [67], a nonprofit organization working with the WHO, to determine the variation in prices for packages of essential cancer medications purchased by 19 buyers (16 LMICs, 1 HIC, and 2 multinational buyers) during the five-year period between 2010 and 2014, inclusive [68]. They

discovered that, although some countries spent significantly more than others on packages of cancer medication, there was no relationship between country-level wealth and prices paid for essential cancer medication. The researchers also discovered large variance in transactional prices for the medications themselves, with the median package price of allopurinol (the least expensive essential cancer medication) being only $1.56 while the median package price of trastuzumab (the most expensive essential cancer medication) being $1,800.00.

As relatively expensive drugs are purchased at the same price by two countries at different income levels, it is plausible that the lower income country may have its health insurance scheme only cover these more expensive treatment options for fewer residents. In this way, if two countries are acquiring essential cancer medications at similar prices, the insurance scheme of the poorer country is likely to produce more disparity than the insurance scheme of the wealthier country. In summary, the lack of a positive association between country-level wealth and transactional price indicates that pricing is not adjusted in the context of national healthcare financing, which serves to magnify disparities in cancer medication access in poorer countries.

Financing Chemotherapy

There is no global financing mechanism allowing LMIC cancer patients to acquire chemotherapy [69]. These patients rely entirely on the generosity of their national/subnational governments or drug manufacturers. Some national governments and drug manufacturers have made efforts to increase

chemotherapy access to cancer patients in LMICs, though these efforts are limited and uneven.

In 2012, India issued a compulsory license to Natco Pharma for the production of Sorafenib, a chemotherapy drug used to treat kidney cancer and liver cancer [70]. Under the World Trade Organization's (WTO's) Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement and the subsequent Doha Declaration, a country can issue a compulsory license to compel access to medicines when it constitutes a public health concern [71]. A compulsory license allows for the use of a patent protected product by an entity other than the original rights-holder. When India issued its compulsory license, the price of a one-month supply of Sorafenib dropped 97%, from $4,200 to $130 [69]. This marks the only time that an LMIC government has issued a compulsory license for a cancer drug. However, government use licenses (GULs), which are similar to compulsory licenses and only allow for the government to use the intellectual property (IP), were issued by Thailand for four cancer drugs: letrozole, docetaxel, erlotinib, and imatinib [72]. Thailand eventually rescinded its GUL for imatinib after negotiations with Novartis, the patent holder for imatinib. Analyses have indicated that these policies are likely to have allowed the Thai government to provide more cost-effective access to these cancer medications [73].

Though limited, some efforts have been made by drug manufacturers to make cancer medications more affordable for LMIC patients. Roche, which manufactures trastuzumab (the most expensive cancer medication on the EML), does not apply for new patents in low-income countries for any of their drugs

[69]. In the Philippines, Roche allows physicians to refer cancer patients to its "Roche Patient Access Programme," in which a third party evaluates the patient's personal finances and Roche provides medication to the patient at a discounted price. Novartis, which manufactures imatinib (Glivec), has the "Glivec International Patient Assistance Program" [74], which helps to provide imatinib in over 80 LMICs to patients who do not have insurance and cannot otherwise pay.

NOVEL POLICY SOLUTIONS

The EML was intended to inform national governments on which medicines to prioritize in providing treatment for their populations, in order to enhance public health outcomes [75]. However, the EML, though not specifically intended to improve access to cancer medicines, appears to have had little tangible downstream positive impact on ensuring the availability and affordability of essential cancer medications in LMICs, where cancer prevalence is expected to greatly increase in the near future. Hence, more direct policy interventions are needed to increase access and affordability to essential cancer medications, especially in LMICs. While limited, the EML serves as a valuable stepping stone toward an effective policy framework, in that it leverages medical expertise to identify the specific chemical compounds that should exhibit universal accessibility to combat cancers. Several policy initiatives should be explored to supplement the EML's initial efforts to encourage global accessibility for essential chemotherapy medications.

Expanding the Research Mandate for the International Agency for Research on Cancer

The WHO established the IARC in 1965. The roots of this organization can be traced to Emmanuel d'Astier de la Vigerie, a French journalist who, in 1963, published an article expressing his sadness about a letter he had received from his friend, Yves Poggioli, who described his wife's suffering from cancer [76,77]. In response, d'Astier de la Vigerie petitioned the President of France, and after some years of political exchanges and strategic maneuvering, the IARC was founded with its objective being "to promote international collaboration in cancer research" [76]. The IARC, which is an agency of the WHO, is the only cancer-focused intergovernmental agency organization with global reach and support, providing technical assistance from a multidisciplinary array of cancer experts. However, over fifty years since the founding of the IARC, the fruits of much cancer research have arguably failed to benefit many people, especially those in LMICs. Therefore, given the evident deficiencies today in the global battle against cancer, it may be time for IARC's guiding objective to be amended so that its *raison d'être* now encapsulates ensuring access to a minimum standard of cancer care for persons with presently-inadequate support from their national governments.

A first step toward safeguarding a minimum standard of cancer care for LMIC cancer patients would be to expand the IARC's research mandate to encompass issues that more directly address treatment access for cancer patients. The IARC has a history of compelling advances in cancer research [77].

Additional research is urgently needed to provide thorough and accurate characterizations of the variations in cancer mediation pricing and to identify and suggest solutions to barriers to access in different markets. Furthermore, analyses are needed that use predictive modeling and other econometric techniques to aid the politico-economic community in understanding the relationship between money spent on cancer treatment programs and consequent impacts on the global burden of cancer. The IARC should be fully empowered to fulfill the aims of an expanded research portfolio that includes these much-needed analyses on cancer treatment accessibility and affordability.

Pooled Procurement of Cancer Medications

It is proposed that the IARC be expanded to spearhead pooled procurement of cancer medications on behalf of LMICs. Pooled procurement has been used by other UN organs such as the UN Children's Fund (UNICEF), a UN specialized agency within the UNDG, to acquire vaccinations for LMICs; and the global health initiative UNITAID (that uses airline ticket levies to finance programs addressing HIV/AIDS, tuberculosis, and malaria) for developing countries [78,79]. This type of arrangement would allow the IARC to purchase EML cancer drugs from drug manufacturers on behalf of groups of LMICs, thereby leveraging economies of scale in order to acquire a bulk order of medication at a lower price per unit. Pooled procurement has been shown to lead to lower pricing and increased access when compared to other policy mechanisms, such as issuing compulsory licenses [80].

Additionally, as part of this effort to facilitate the lowering of chemotherapy costs for developing economies, the IARC could form strategic partnership with pharmaceutical manufacturers, distributors, and innovators to coordinate on corporate policies, supply chain issues, and pricing strategies to better ensure equitable access while also expanding market share. This could include linking private sector patient access programs with corporate social responsibility programs for larger segments of LMIC populations, and facilitating registration in access programs for populations in LMICs.

Enhanced IARC Financing

An expanded role for the IARC would require additional financing. We propose that the IARC be moved up in the UN hierarchy, thereby allowing it to function as a UN specialized agency within the UN Development Group (UNDG). If the IARC became part of this group, it may benefit from being able to engage in greater financing, including fundraising activities similar to that of other international, national, and local cancer civil society organizations. This expanded governance function might include negotiation with national governments, partnerships with philanthropic groups, and sponsorships with private organizations. Similar arrangements and designation as a disease-specific UN specialized agency has proven beneficial for the Joint UN Programme on HIV/AIDS (UNAIDS), which conducts a large scope of fundraising operations to finance its wide-ranging strategies to combat HIV/AIDS [79]. These

operations include bilateral commitments, private philanthropy, and partnership with non-governmental organizations.

The promotion of a disease-focused agency to a more independently-functioning role might require substantial advocacy by world leaders and public health organizations. We foresee this requirement as a major barrier to ensuring that the IARC is adequately enabled to safeguard chemotherapy access in the developing world. While the majority of cancer cases occur in less developed countries [81], public perception may wrongly consider the burden of disease in these countries to be mostly infectious-related [82,83]. Perhaps as a result, cancer is currently not being sufficiently prioritized among existing global health agencies that primarily focus on the major infectious diseases of HIV/AIDS, tuberculosis and malaria, maternal child health, and other traditional global health programs that do not include non-communicable diseases. In order to correct public perception, global health organizations and LMIC governments should reframe cancer prevention, screening, and treatment as priority public health issues.

Conclusion

If a woman in a rural region of a low-income country were to be diagnosed with breast cancer, the EML appears to do little to ensure this woman will receive appropriate treatment, as it neither directly encourages the low-income country to make drugs available nor does it ensure the affordability of those drugs. Though addressing this fundamental challenge in access to medicines seems complex,

such a problem has been successfully addressed in the case of HIV/AIDS. For HIV/AIDS, UNAIDS was established in part to fill the gap in providing treatment for the global epidemic of HIV/AIDS. Similarly, the policy proposals outlined here empower IARC to fill the gap in treatment for cancer. Nevertheless, broadened versions of the policy proposals here may be warranted in order to adequately address insufficiencies in LMIC chemotherapy access. For example, the IARC could be empowered to intervene in the supply chain management of chemotherapy, perhaps extending to the logistics of warehousing and distribution, should other governance reforms to empower IARC to fight global cancer prove successful.

In summary, we believe that the IARC is well positioned to serve an enhanced role in global governance for the purposes of better enabling access to minimum standards of cancer treatment. In order to accomplish this mission effectively, the IARC should be expanded in three key ways: (1) broadening of its research portfolio to include analysis of medication pricing and access; (2) enabling the IARC to engage in pooled procurement for LMICs; and (3) expanding the IARC's mission, operational design, and financing by transforming it into a UN-specialized agency under UNDG membership. Though admittedly challenging, broad collaboration at a global level is a powerful tool that may indeed resolve issues in chemotherapy access for the many future cases of cancer in economically marginalized countries.

ACKNOWLEDGEMENTS

I wish to express my gratitude and appreciation to Timothy Mackey, Cedric Garland, Edward Gorham, and Lianne Urada at the University of California, San Diego, and also to Thomas Novotny and Robert Seidman at San Diego State University for their helpful input in designing this research. I would also like to express their appreciation to the Frontiers of Innovation Scholars Program at the University of California, San Diego for providing funding for this research.

Chapter 4, in part, is being prepared for submission to a journal with the citation: Cuomo, Raphael; Mackey, Timothy. Policy-based approaches for facilitating access and affordability for essential cancer medications

REFERENCES

1. Cohen-Kohler JC. The morally uncomfortable global drug gap. Clinical pharmacology and therapeutics 2007;82:610-614.

2. Zucker H, Rago L. Access to essential medicines for children: The world health organization's global response. Clinical pharmacology and therapeutics 2007;82:503-505.

3. Chawla N, Kepka DL, Heckman-Stoddard BM, Horne HN, Felix AS, Luhn P*, et al.* Health disparities around the world: Perspectives from the 2012 principles and practice of cancer prevention and control course at the national cancer institute. J Oncol Pract 2013;9:e284-289.

4. Farmer P, Frenk J, Knaul FM, Shulman LN, Alleyne G, Armstrong L*, et al.* Expansion of cancer care and control in countries of low and middle income: A call to action. The Lancet 2010;376:1186-1193.

5. Adelstein DJ, Rice TW, Becker M, Larto MA, Kirby TJ, Koka A*, et al.* Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. Cancer 1997;80:1011-1020.

6. Huber O, Petersen I. 150th anniversary series: Desmosomes and the hallmarks of cancer. Cell communication & adhesion 2015;22:15-28.

7. Kelly J, Mahalingam S. Surgical treatment of head and neck cancers in the ancient world. The Journal of laryngology and otology 2015;129:535-539.

8. Rebecca VW, Sondak VK, Smalley KS. A brief history of melanoma: From mummies to mutations. Melanoma research 2012;22:114-122.

9. Lortet-Tieulent J, Soerjomataram I, Ferlay J, Rutherford M, Weiderpass E, Bray F. International trends in lung cancer incidence by histological subtype: Adenocarcinoma stabilizing in men but still increasing in women. Lung cancer (Amsterdam, Netherlands) 2014;84:13-22.

10. Zhou CK, Check DP, Lortet-Tieulent J, Laversanne M, Jemal A, Ferlay J*, et al.* Prostate cancer incidence in 43 populations worldwide: An analysis of time trends overall and by age group. Int J Cancer 2016;138:1388-1400.

11. Erdmann F, Lortet-Tieulent J, Schuz J, Zeeb H, Greinert R, Breitbart EW*, et al.* International trends in the incidence of malignant melanoma 1953-2008--are recent generations at higher or lower risk? Int J Cancer 2013;132:385-400.

12. Zhang Y, Ren JS, Shi JF, Li N, Wang YT, Qu C*, et al.* International trends in primary liver cancer incidence from 1973 to 2007. BMC Cancer 2015;15:94.

13. Bal DG. Cancer and social justice: A demographic, economic, historic, sociocultural, and ethical perspective. Cancer 2005;104:2891-2894.

14. Armon R. From pathology to chemistry and back: James w. Cook and early chemical carcinogenesis research. Ambix 2012;59:152-169.

15. Eckhouse S, Lewison G, Sullivan R. Trends in the global funding and activity of cancer research. Molecular oncology 2008;2:20-32.

16. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends--an update. Cancer Epidemiol Biomarkers Prev 2016;25:16-27.

17. International Agency for Research on Cancer. Globocan 2012 database: Http://globocan.Iarc.Fr/. Accessed December 2013 2012

18. Bray F. The evolving scale and profile of cancer worldwide: Much ado about everything. Cancer Epidemiol Biomarkers Prev 2016;25:3-5.

19. World Bank. World bank country and lending groups. 2015

20. World Bank. The world bank databank. Washington D.C., World Bank Group, 2015,

21. Morrison WB. Cancer chemotherapy: An annotated history. Journal of veterinary internal medicine 2010;24:1249-1262.

22. Sakorafas GH, Safioleas M. Breast cancer surgery: An historical narrative. Part iii. From the sunset of the 19th to the dawn of the 21st century. European journal of cancer care 2010;19:145-166.

23. Akram M, Siddiqui SA. Breast cancer management: Past, present and evolving. Indian J Cancer 2012;49:277-282.

24. Aronowitz JN. Partial breast irradiation by brachytherapy, 1927. Brachytherapy 2011;10:427-431.

25. Pascual JM, Prieto R, Castro-Dufourny I, Carrasco R, Strauss S, Barrios L. Development of intracranial approaches for craniopharyngiomas: An analysis of the first 160 historical procedures. Neurosurgical focus 2014;36:E13.

26. Strebhardt K, Ullrich A. Paul ehrlich's magic bullet concept: 100 years of progress. Nat Rev Cancer 2008;8:473-480.

27. Inoue Y, Kusunoki M. Advances and directions in chemotherapy using implantable port systems for colorectal cancer: A historical review. Surgery today 2014;44:1406-1414.

28. Lichtman MA. Battling the hematological malignancies: The 200 years' war. The oncologist 2008;13:126-138.

29. Goeckenjan G. [lung cancer - historical development, current status, future prospects]. Pneumologie (Stuttgart, Germany) 2010;64:555-559.

30. Chabner BA, Roberts TG, Jr. Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer 2005;5:65-72.

31. Shepard HM, Jin P, Slamon DJ, Pirot Z, Maneval DC. Herceptin. Handbook of experimental pharmacology 2008:183-219.

32. Muller BA. Imatinib and its successors--how modern chemistry has changed drug development. Current pharmaceutical design 2009;15:120-133.

33. Mizuki M, Kanakura Y. [the development history and future perspective of molecularly targeted therapy]. Nihon rinsho Japanese journal of clinical medicine 2014;72:997-1003.

34. Wild CP, Bucher JR, de Jong BW, Dillner J, von Gertten C, Groopman JD*, et al.* Translational cancer research: Balancing prevention and treatment to combat cancer globally. J Natl Cancer Inst 2015;107:353.

35. Perroud B, Lee J, Valkova N, Dhirapong A, Lin P-Y, Fiehn O*, et al.* Pathway analysis of kidney cancer using proteomics and metabolic profiling. Molecular cancer 2006;5:1.

36. Chirac P. Translating the essential drugs concept into the context of the year 2000. Transactions of the Royal Society of Tropical Medicine and Hygiene 2003;97:10-12.

37. Robertson J, Magrini N, Barr R, Forte G, Ondari C. Medicines for cancers in children: The who model for selection of essential medicines. Pediatric blood & cancer 2015;62:1689-1693.

38. Robertson J, Hill SR. The essential medicines list for a global patient population. Clinical pharmacology and therapeutics 2007;82:498-500.

39. Jafarov A, Schneider T, Waning B, Hems S, van der Ham R, Ma E*, et al.* Comparative table of core and complementary medicines on the who essential medicines list from 1977–2011. Geneva, World Health Organization, 2012,

40. Seigfried RJ, Corbo T, Saltzberg MT, Reitz J, Bennett DA. Deciding which drugs get onto the formulary: A value-based approach. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2013;16:901-906.

41. Santangelo M. Historical perspective on adding drugs to medicare. Health care financing review 2005;27:25-33.

42. Newhouse JP, Seiguer E, Frank RG. Was part d a giveaway to the pharmaceutical industry? Inquiry : a journal of medical care organization, provision and financing 2007;44:15-25.

43. Khan S, Sylvester R, Scott D, Pitts B. Physicians' opinions about responsibility for patient out-of-pocket costs and formulary prescribing in two midwestern states. Journal of managed care pharmacy : JMCP 2008;14:780-789.

44. Wang J, Liu X, Wang S, Chen H, Wang X, Zhou W*, et al.* Short-term differences in drug prices after implementation of the national essential medicines system: A case study in rural jiangxi province, china. Indian journal of pharmacology 2015;47:535-539.

45. Mackenzie R, Chapman S, Salkeld G, Holding S. Media influence on herceptin subsidization in australia: Application of the rule of rescue? Journal of the Royal Society of Medicine 2008;101:305-312.

46. Anis AH, Guh D, Wang X-h. A dog's breakfast: Prescription drug coverage varies widely across canada. Medical care 2001;39:315-326.

47. Drummond M. Cost-effectiveness guidelines for reimbursement of pharmaceuticals: Is economic evaluation ready for its enhanced status? Health economics 1992;1:85-92.

48. Laing R, Waning B, Gray A, Ford N, Hoen Et. 25 years of the who essential medicines lists: Progress and challenges. The Lancet 2003;361:1723-1729.

49. Robertson J, Barr R, Shulman LN, Forte GB, Magrini N. Essential medicines for cancer: Who recommendations and national priorities. Medicine 2016;94

50. Cuomo R, Mackey T, Novotny T, Seidman R, Garland C, Gorham E*, et al.* The availability of essential cancer medication: An analysis of national formularies. In Progress 2016

51. Johnson JA, Bootman JL. Pharmacoeconomic analysis in formulary decisions: An international perspective. American Journal of Health-System Pharmacy 1994;51:2593-2598.

52. World Health Organization. Constitution. 1989

53. Hogerzeil HV. The concept of essential medicines: Lessons for rich countries. BMJ 2004;329:1169-1172.

54. Kelly RJ, Smith TJ. Delivering maximum clinical benefit at an affordable price: Engaging stakeholders in cancer care. The lancet oncology 2014;15:e112-e118.

55. Bigdeli M, Jacobs B, Tomson G, Laing R, Ghaffar A, Dujardin B*, et al.* Access to medicines from a health system perspective. Health Policy and Planning 2012;1:13.

56. Fryatt R, Mills A, Nordstrom A. Financing of health systems to achieve the health millennium development goals in low-income countries. The Lancet 2010;375:419-426.

57. Schieber G, Maeda A. Health care financing and delivery in developing countries. Health Affairs 1999;18:193-205.

58. Lagomarsino G, Garabrant A, Adyas A, Muga R, Otoo N. Moving towards universal health coverage: Health insurance reforms in nine developing countries in africa and asia. The Lancet 2012;380:933-943.

59. Sarpong N, Loag W, Fobil J, Meyer CG, Adu-Sarkodie Y, May J*, et al.* National health insurance coverage and socio- economic status in a rural district of ghana. Tropical medicine & international health 2010;15:191-197.

60. Leive A, Xu K. Coping with out-of-pocket health payments: Empirical evidence from 15 african countries. Bulletin of the World Health Organization 2008;86:849-856C.

61. Damme WV, Leemput LV, Hardeman W, Meessen B. Out-of-pocket health expenditure and debt in poor households: Evidence from cambodia. Tropical Medicine & International Health 2004;9:273-280.

62. Mellstedt H. Cancer initiatives in developing countries. Annals of Oncology 2006;17:viii24-viii31.

63. Kerr DJ, Midgley R. Can we treat cancer for a dollar a day? Guidelines for low-income countries. New England Journal of Medicine 2010;363:801-803.

64. Kingham TP, Alatise OI, Vanderpuye V, Casper C, Abantanga FA, Kamara TB*, et al.* Treatment of cancer in sub-saharan africa. The Lancet Oncology 2013;14:e158-e167.

65. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (cml) is a reflection of the unsustainable prices of cancer drugs: From the perspective of a large group of cml experts. Blood 2013;121:4439-4442.

66. Lucarelli C, Nicholson S. A quality-adjusted price index for colorectal cancer drugs, National Bureau of Economic Research, 2009,

67. Management Sciences for Health. International drug price indicator guide. Cambridge, MA,

68. Cuomo R, Mackey T, Novotny T, Seidman R, Garland C, Gorham E*, et al.* Global inequality in purchase prices for essential cancer medications. In Progress 2016

69. Hoen E. Access to cancer treatment: A study of medicine pricing issues with recommendations for improving access to cancer medication, OXFAM International, 2014,

70. Mudur G. Indian health groups welcome country's first compulsory licence. BMJ 2012;344:e2132.

71. Abbott FM. The doha declaration on the trips agreement and public health: Lighting a dark corner at the wto. Journal of International Economic Law 2002;5:469.

72. Yamabhai I, Mohara A, Tantivess S, Chaisiri K, Teerawattananon Y. Government use licenses in thailand: An assessment of the health and economic impacts. Globalization and health 2011;7:1.

73. Mohara A, Yamabhai I, Chaisiri K, Tantivess S, Teerawattananon Y. Impact of the introduction of government use licenses on the drug expenditure on seven medicines in thailand. Value in Health 2012;15:S95-S99.

74. Lassarat S, Jootar S. Ongoing challenges of a global international patient assistance program. Annals of Oncology 2006;17:viii43-viii46.

75. World Health Organization. Promoting rational use of medicines: Core components. 2002

76. Sohier R, Sutherland AGB. The origin of the international agency for research on cancer. Lyon, International Agency for Research on Cancer, 2015.

77. Saracci R, Wild CP. International agency for research on cancer: The first 50 years, 1965–2015. Lyon, International Agency for Research on Cancer,, 2015.

78. Batson A. The problems and promise of vaccine markets in developing countries. Health Affairs 2005;24:690-693.

79. Kates J, Lief E, Avila C. Financing the response to aids in low-and middle-income countries: International assistance from the g8, european commission and other donor governments, 2008. Henry J. Kaiser Family Foundation, 2009.

80. Beall RF, Kuhn R, Attaran A. Compulsory licensing often did not produce lower prices for antiretrovirals compared to international procurement. Health affairs (Project Hope) 2015;34:493-501.

81. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. Journal of clinical oncology 2006;24:2137-2150.

82. Boffetta P, Parkin DM. Cancer in developing countries. CA: a cancer journal for clinicians 1994;44:81-90.

83. Igene H. Global health inequalities and breast cancer: An impending public health problem for developing countries. The breast journal 2008;14:428-434.

CHAPTER 5: DISCUSSION

In Chapter 1 of this dissertation, we introduced the central problem that necessitated an assessment of chemotherapy access in low- and middle-income countries (LMICs): the rapid impending increase in LMIC cancer cases. Specifically, LMICs will exhibit 10 million more cancer cases in 2030 than they did in 2012 [1]. Therefore, in order to better understand future exacerbations to chemotherapy access in LMICs, we set out to use available data on national formularies and chemotherapy prices in order to assess current barriers to access for chemotherapies deemed “essential” by the World Health Organization (WHO).

In Chapter 2 of this dissertation, we observed that the majority of LMICs listed under half of the essential chemotherapies. This finding indicates that quite a large number of cancer patients in LMICs may be receiving treatment that is beneath the minimal standard set forth by the WHO.

In Chapter 3 of this dissertation, we observed nine essential cancer drugs whose median price exceeded $50 per package. This finding indicates that a sizable proportion of important chemotherapy may be out of reach for a very large number of cancer patients in LMICs.

In Chapter 4 of this dissertation, we evaluated the evidence presented in Chapter 2 and Chapter 3, and we formulated a policy initiative that may alleviate issues in access to chemotherapy for cancer patients in LMICs. This initiative bolstered the role of the International Agency for Research on Cancer (IARC) via

multiple policies: (1) the IARC will be empowered to collect better data on chemotherapy access, and will conduct analyses on these access data; (2) the IARC will spearhead pooled procurement of cancer medications on behalf of LMICs; and (2) the IARC will become a United Nations (UN) specialized agency within the UN Development Group (UNDG).

As mentioned in the first sentence of this dissertation, it would appear that human society has become more proficient in mobilizing resources to overcome major challenges. A large part of this success may derive from our increased capacity for broad-scale collaboration, which itself can be said to have allowed for many global health initiatives, including the WHO and the IARC. As our global society increasingly deals with the ever-growing threat that cancer poses to human life, the capacity for broad collaboration on a global scale will be an ever-more valuable tool for solving challenges from this pervasive disease.

This dissertation research illustrates the potential for global health policy to tackle *tertiary prevention*, which focuses on how to decrease problems resulting from insufficient or improper medical treatment [2]. Policies instituted by global organizations can also be useful in undertaking initiatives for *primary prevention* and *secondary prevention*, which respectively focus on the prevention of disease and the screening of disease. Much research has been done on population-level initiatives that prevent cancer and detect cancer, and global health organizations would do well to closely consider these bodies of research when considering broad anticancer policies.

With regard to cancer treatment, this dissertation very specifically considers *chemotherapy* in the broadest sense of the word. This is to say that this dissertation is concerned with the ability of LMIC cancer patients to access *chemical therapies* for cancer. Cancer treatment with surgery and radiation also have great value in the treatment of common cancers, and access issues among LMIC cancer patients in obtaining surgery and radiation therapy should also be examined.

The diagnostic capacity of healthcare in LMICs was not thoroughly explored as part of this research project. If a healthcare practitioner is unable to properly diagnose a patient with cancer, this itself can be considered a barrier to chemotherapy access. In other words, if a healthcare practitioner incorrectly diagnoses a cancer, the cancer patient may receive chemotherapy that is either ineffective or sub-optimal (which might have the same consequence as if the optimal chemotherapy were unavailable or unaffordable). Data on oncological diagnostic capacity in LMICs is not publically available, and our policy recommendation for the IARC to expand its research portfolio is, in part, meant to address this. However, this issue was otherwise outside the scope of this dissertation.

It is also important to note that this dissertation was not intended to evaluate the medical effectiveness of essential chemotherapies. The range for these drugs being approved by the Food and Drug Administration (FDA) range from 1958 to 2008 (see **Appendix A**), and therefore may represent a broad degree of medical advancement in the chemotherapeutic treatment of cancer.

Nevertheless, while these drugs were evaluated for efficacy by the WHO in their construction of the Essential Medicines List (EML) [3], scrutiny by third parties may be appropriate.

It is worth noting that the medical effectiveness of many chemotherapies may be bolstered by early-stage cancer detection, and that early detection may be bolstered by improved diagnostic capacity. Therefore, when considering the best anticancer global health approaches, many of these issues become inexorably linked. It is my hope that the discipline of Global Health begins to consider cancer as a top priority, and that initiatives to alleviate chemotherapy access converge upon solutions akin to the policies recommended in this dissertation project. Nevertheless, I also encourage Global Health practitioners to consider the important issues that were outside the scope of this dissertation, including primary and secondary prevention, non-chemotherapy forms of treatment, LMIC diagnostic capacity, and the effectiveness of individual chemotherapies.

REFERENCES

1. International Agency for Research on Cancer. Globocan 2012 database: http://globocan.iarc.fr/. Accessed December 2013 2012

2. Katz D, Ali A. Preventive medicine, integrative medicine & the health of the public. Commissioned for the iom summit on integrative medicine and the health of the public. Institute of Medicine (IOM), Washington, DC 2009

3. Robertson J, Hill SR. The essential medicines list for a global patient population. Clinical pharmacology and therapeutics 2007;82:498-500.

APPENDIX A: APPROVAL DATES AND MECHANISMS OF ACTION FOR ESSENTIAL CANCER MEDICATIONS

Preface

The 19th, most recent, version of the EML was published in 2015 and includes 48 medications in its "Antineoplastic and Immunosuppressives" category [1]. Drug approval dates, indications, and mechanisms of action were obtained from DrugBank, an online bioinformatics and chemoinformatics resource [2].

Antineoplastic and Immunosuppressives

Allopurinol

First approved by the FDA in 1966, allopurinol lowers serum levels of uric acid by disrupting its production via purine metabolism. It is typically used to manage hyperuricemia resulting either from blood cancers or their treatment.

All-Trans Retinoid Acid

Approved to treat leukemia in 1995, all-trans retinoid acid is drug used to treat leukemia. It operates via an unknown mechanism of action to cause cancer cells to differentiate into a cell type that will subsequently undergo apoptosis.

Anastrozole

First approved in 1995, anastrozole is a breast cancer treatment that reversibly binds to aromatase, an adrenal enzyme that synthesizes estrogens. As a result, anastrozole inhibits the formation of estrogens, which consequently decreases the growth of breast tumors.

Asparaginase

Discovered to be a cancer treatment in 1953, asparaginase is an enzyme produced by various microorganisms (primarily *E. coli*) that can be used for treating leukemia. By metabolizing circulating asparagine, it is suspected to cause the death of leukemia cells, which rely heavily on circulating asparagine.

Azathioprine

First approved in 1968, azathioprine is an immunosuppressant that works through the actions of its metabolite, meraptopurine, which inhibits amidophosphoribosyltransferase from synthesizing purines. It is primarily used to combat rejection after organ transplantation.

Bendamustine

First approved by the FDA in 2008, bendamustine is a blood cancer treatment whose hypothesized mechanism of action involves the addition of alkyl groups to DNA, thereby resulting in double-stranded DNA breaks and apoptosis of cancer cells.

Bicalutamide

First approved by the FDA in 1995, bicalutamide treats prostate cancer by blocking androgen receptors. This consequently prevents testosterone from effecting cellular metabolism, which ultimately decreases the growth of prostate tumors.

Bleomycin

First approved by the FDA in 1973, bleomycin is a peptide that treats various cancers through an unconfirmed mechanism which causes strand breaks in DNA. Several hypothesized mechanisms free radical oxidation.

Calcium Folinate

First approved for medical use in 1952, calcium folinate is typically used in combination with the chemotherapy drug methotrexate. Methotrexate blocks the enzyme necessary for cells to use folic acid, and calcium folinate is able to bypass this enzyme to provide cells with folic acid derivatives.

Capecitabine

First approved by the FDA in 1998, capecitabine is primarily used for treating of breast and colorectal cancers. It combats these cancers by converting to 5-fluorouracil, which blocks thymidylate synthase and consequently deprives cancer cells of the deoxythymidine monophosphate they need in order to survive.

Carboplatin

First approved by the FDA in 1989, carboplatin is a platinum-containing chemotherapy drug most commonly used for treatment of ovarian cancer. The most commonly accepted hypothesized mechanism involves the interaction of platinum with water molecules to disrupt DNA repair.

Chlorambucil

First approved by the FDA in 1957, chlorambucil is a treatment for blood cancers that works by alkylating DNA, which results in DNA breaks and cell death.

Ciclosporin

First approved by the FDA in 1983, ciclosporin is an immunosuppressant which is administered to prevent organ rejection. It suppresses the immune system by binding to cytosolic proteins in T cells and consequently decreasing transcription of certain cytokines.

Cisplatin

First approved by the FDA in 1978, cisplatin is a platinum-containing chemotherapy drug for treating sarcomas and carcinomas in various organs. As with carboplatin, cisplatin damages DNA through the binding of platinum.

Cyclophosphamide

First approved by the FDA in 1959, cyclophosphamide treats both blood cancers and solid tumors by adding alkyl groups to DNA at guanine bases, thereby causing DNA damage and subsequent cell death.

Cytarabine

First approved by the FDA in 1969, cytarabine is a treatment for blood cancers that works through the incorporation of its metabolite into DNA, thereby blocking mitosis.

Dacarbazine

First approved by the FDA in 1975, dacarbazine has been used to treat a wide array of a cancers, including melanoma, lymphoma, sarcoma, and carcinoma. It works by adding an alkyl group to guanine bases on DNA, which results in subsequent cell death.

Dactinomycin

First approved by the FDA in 1964, dactinomycin is a peptide derived from *Streptomyces* bacteria for treatment of various solid tumors. The mechanism of action for dactinomycin involves binding of DNA at specific sites for inhibition of transcription.

Daunorubicin

First approved by the FDA in 1979, daunorubicin is derived from *Streptomyces* bacteria for treatment of leukemia. Like dactinomycin (another *Streptomyces*-derived anthracycline), daunorubicin prevents the growth of cancer cells by preventing transcription by binding to DNA at specific sites.

Dexamethasone

First approved by the FDA in 1958, dexamethasone is a steroid typically used for treatment of brain swelling for those with brain cancer or for direct chemotherapeutic treatment of multiple myeloma. In both cases, dexamethasone works by binding to cytoplasmic glucocorticoid receptors, thereby regulating transcription.

Docetaxel

First approved by the FDA in 1996, docetaxel is used to treat a variety of solid cancers. Docetaxel binds to microtubules in a high-affinity manner so as to promote their assembly and prevent their disassembly, thereby inhibiting mitosis and facilitating cell death.

Doxorubicin

First approved by the FDA in 1974, doxorubicin is used for treatment of both blood cancers and organ cancers. Doxorubicin works by binding to DNA at specific sites to inhibit transcription.

Etoposide

First approved by the FDA in 1983, etoposide is used for treatment of various cancers. Etoposide causes apoptosis of cancer cells by forming a complex with both DNA and topoisomerase II, thereby resulting in DNA breaks.

Filgrastim

First approved by the FDA in 1991, filgrastim is a glycoprotein used to treat neutropenia (low levels of certain white blood cells) resulting from chemotherapy. It promotes the production of white blood cells in bone marrow by binding to the granulocyte colony-stimulating factor (G-CSF) receptor.

Fludarabine

First approved by the FDA in 1991, fludarabine is a purine analog used to treat blood cancers. A metabolite of fludarabine interacts with several enzymes needed for DNA synthesis, thereby inhibiting DNA replication.

Fluorouracil

First approved by the FDA in 1962, fluorouracil is a pyrimidine analog used to treat a number of cancers. Fluorouracil blocks thymidylate synthase, which results in decreased levels of deoxythymidine monophosphate, a molecule needed for cellular division.

Gemcitabine

First approved by the FDA in 1996, gemcitabine is a pyrmidine analog used primarily for the treatment of organ cancer. As with fluorouracil (another pyrmidine analog), gemcitabine induces apoptosis by inhibiting thymidylate synthetase.

Hydrocortisone

First approved by the FDA in 1952, hydrocortisone is a glucocorticoid used to decrease inflammation in various applications, including after organ transplantation. As with other glucocorticoids, hydrocortisone binds to cytoplasmic receptors, thereby regulating transcription.

Hydroxycarbamide

First approved by the FDA in 1967, hydroxycarbamide is used for a variety of blood cancers. It is converted to nitric oxide, which then inactivates ribonucleotide reductase, thereby inhibiting DNA synthesis and promoting cell death.

Ifosfamide

First approved by the FDA in 1988, ifosfamide is used to treat a wide variety of both blood cancers and organ cancers. As with other alkylating agents, ifosfamide’s mechanism of action is to introduce an alkyl group to DNA, thereby causing DNA breaks and subsequent cell death.

Imatinib

First approved by the FDA in 2001, imatinib is a tyrosine-kinase inhibitor used to treat several cancers, especially leukemia. Imatinib blocks the action of

specific tyrosine kinases, thereby preventing the chemical signaling required for tumors to grow.

Irinotecan

First approved by the FDA in 1996, irinotecan is a semisynthetic analog of camptothecin (from the tree *Camptotheca acuminata*) used for treating colorectal cancer. Its metabolite inhibits topoisomerase I, thereby preventing DNA transcription and ultimately resulting in cell death.

Leuprorelin

First approved by the FDA in 1985, leuprorelin is a peptide used primarily to treat prostate cancer and breast cancer. Leuprorelin binds to receptors in the pituitary gland to inhibit gonadotropin secretion, thereby resulting in decreased levels of estrogen and testosterone.

Mercaptopurine

First approved by the FDA in 1953, mercaptopurine is an immunosuppressive medication used primarily for treatment of leukemia. Mercaptopurine inhibits amidophosphoribosyltransferase from synthesizing purines, which consequently hinders DNA synthesis.

Mesna

First approved by the FDA in 1988, mesna is typically used to prevent hemorrhagic cystitis (bleeding of the bladder) resulting from administration of ifosfamide or cyclophosphamide. It binds to acrolein, a highly-reactive, toxic compound which accumulates in the bladder following administration of ifosfamide or cyclophosphamide.

Methotrexate

First approved by the FDA in 1953, methotrexate is used for treatment of various cancer types. Methotrexate blocks a critical enzyme in the synthesis of thymidine, thereby preventing DNA synthesis and promoting cell death.

Methylprednisolone

First approved by the FDA in 1957, methylprednisolone is a steroid used for treating complications that arise from cancer treatment and for direct chemotherapy of certain blood cancers. As with dexamethasone (another glucocorticoid used in cancer treatment), methylprednisolone regulates transcription by binding to cytoplasmic glucocorticoid receptors.

Oxaliplatin

First approved by the FDA in 2002, oxaliplatin is a platinum-containing drug primarily used for treatment of colorectal cancer. As with other platinum-containing chemotherapies, oxaliplatin damages DNA through the binding of platinum.

Paclitaxel

First approved by the FDA in 1992, paclitaxel is used to treat various solid tumors and also Kaposi's sarcoma. As with docetaxel (another taxane cancer drug), paclitaxel facilitates cell death by binding to microtubules so as to prevent the disassembly of tubulin structures.

Prednisolone

First approved by the FDA in 1955, prednisolone is a steroid used for treating chemotherapy side-effects and for direct chemotherapy of certain blood

cancers. As with other glucocorticoids used in cancer treatment, prednisolone's mechanism of action involves binding to glucocorticoid receptors in cellular cytoplasm, consequently regulating transcription.

Procarbazine

First approved by the FDA in 1969, procarbazine is used for treatment of brain cancer and Hodgkin's lymphoma. While the exact mechanisms are unknown, procarbazine is thought to exhibit its cytotoxic effect by inhibiting the formation of transfer RNA, thereby preventing synthesis of the proteins needed for DNA replication.

Rituximab

First approved by the FDA in 1997, rituximab is a monoclonal antibody used to treat several blood cancers. Rituximab binds to CD20 antigens on B cells, thereby signaling natural killer (NK) cells to destroy those B cells.

Tamoxifen

First approved by the FDA in 1977, tamoxifen is a drug used for both treating and preventing breast cancer. Tamoxifen and its metabolites bind to estrogen receptors, thereby preventing them from binding with estrogen.

Tioguanine

First approved by the FDA in 1966, tioguanine is used primarily for treatment of leukemia. Like azathioprine and mercaptopurine (other antimetabolic purine analogs), tioguanine exerts its cytotoxic effect by binding to enzymes which are involved in purine synthesis.

Trastuzumab

First approved by the FDA in 1998, trastuzumab is a monoclonal antibody used primarily for treatment of HER2-positive breast cancer. Trastuzumab exhibits cytotoxicity through various mechanisms, including suppression of angiogenesis, activation of tumor suppressors, and cell-mediated cytotoxicity.

Vinblastine

First approved by the FDA in 1965, vinblastine is an extract from the flowering plant *Catharanthus roseus* that is used to treat a wide variety of cancers. Vinblastine causes cell death by binding to tubulin and inhibiting mitosis.

Vincristine

First approved by the FDA in 1963, vincristine is also an extract from the flowering plant *Catharanthus roseus* that is used to treat a wide variety of cancers. Like vinblastine (another vinca alkaloid derived from the *Catharanthus roseus* plant), vincristine also exerts its cytotoxic effect by inhibiting mitosis via tubulin binding.

Vinorelbine

First approved by the FDA in 1994, vinorelbine is another extract from *Catharanthus roseus* that is used in the treatment of several cancers. Like other vinca alkaloids, vinorelbine binds to tubulin proteins, thereby inhibiting mitosis and ultimately causing cell death.

REFERENCES

1. World Health Organization. 19th who model list of essential medicines. Geneva, Switzerland, 2015,

2. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. Drugbank: A comprehensive resource for in silico drug discovery and exploration. Nucleic acids research 2006;34:D668-672.