ISSUES IN ACCESS TO CANCER MEDICATIONS IN LOW- AND MIDDLE-INCOME COUNTRIES

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In the last five decades major breakthroughs have been realized in the treatment of cancer but, mainly due to the high cost of new drugs, for those of us who practice in low- and middle-income countries (LMIC) many of these advances are but an aspiration and hope for the future. LMIC account for about 60% of new cancer cases and nearly two thirds of related deaths, demonstrating the lower ability these nations have to address the disease; yet emerging economies incur a paltry 6.2% of the global cancer cost and are responsible for a whopping 89% of the global cancer expenditure gap.

Cost of cancer in low- and middle-income countries

We have calculated the economic burden of cancer per patient, including direct medical costs, non-medical costs and productivity losses, in South America, China and India to be US$7.92, US$4.32 and US$0.54, respectively, which is little when compared to US$183, US$244 and US$460 in the United Kingdom, Japan and the United States, in that order. Adjusting by income at current exchange rates, the cost of cancer care represents 0.12% of gross national income per capita (GNI) in South America, 0.05% in India and 0.11% in China. In the United Kingdom, Japan and United States the corresponding cost was 0.51%, 0.6% and 1.02% of GNI per capita, respectively.

Access to cancer medications in low- and middle-income countries

Little data has been presented or published on the prevalence of use of cancer medications in emerging markets. In a survey and focus group of medical oncologists and health care policy experts from six South-east Asian nations at the first Southeast Asian Cancer Care Access Network (SEACCAN) meeting in 2011, we estimated that approximately 15% of patients in low- and middle-income countries in the region had access to an index of medications which included oxaliplatin in the adjuvant treatment of colon cancer, bevacizumab and cetuximab in the palliative treatment of colorectal cancer; gefitinib or erlotinib in the treatment of patients with metastatic lung cancer who harbour epidermal growth factor receptor mutations; sorafenib in the management of advanced hepatocellular carcinoma; and trastuzumab in the adjuvant therapy of early HER2/neu over-expressing breast cancer. This contrasted to 55% of patients in Singapore, a high-income country in south-east Asia. Moreover, we validated these results using sales data from IMS Health and calculated the expenditure per capita on the same index of drugs to be US$0.49 in Thailand, US$0.48 in Malaysia, US$0.12 in the Philippines, US$0.11 in Vietnam and US$0.04 in Indonesia as compared to US$6 in Singapore and US$20 in the United States. Not surprisingly, access correlated strongly with GNI per capita (R2=0.99) and, interestingly, with cost-effectiveness (R2=0.7), even though only Thailand routinely uses health economics evaluations when deciding on therapeutic coverage in the region.

This paper is a summary version of a more comprehensive and detailed manuscript which will be published in an upcoming issue of *Nature Reviews Clinical Oncology*.

Universal coverage for health care in emerging economies

With the goal of improving access to health care, universal insurance coverage, the fundamental element of functional health care systems as it pools resources and provides financial protection from the costs of illness, is increasingly common in emerging Asian and Latin American countries. However, the majority of countries, many of which are in Africa, still lack universal coverage. Encouragingly, large middle-income countries which still lack universal coverage are working towards it. Indonesia recently passed legislation establishing the first steps towards comprehensive coverage and China's efforts are well under way and on target to cover

most of its population in coming years.

Use of generics and biosimilars for off-patent medications

Once generic competition sets in, the price of medications can drop significantly, often by 80% or more. Several, mostly older, chemotherapy drugs are included in the WHO's Essential Drugs List. These are selected based on disease prevalence, efficacy, safety and comparative cost-effectiveness. Major challenges for the greater penetration of generics include public and health care worker perception and quality issues.

WHO defines Biosimilars as biotherapeutic products that are similar in quality, safety and efficacy to licensed reference biotherapeutic products. While there are currently approved versions of supportive medications such as granulocyte and erythrocyte colony stimulating factors, prospective randomized clinical trials will be needed before biosimilars of monoclonal antibodies such as bevacizumab, cetuximab, rituximab and trastuzumab become more extensively available, likely making these substitutes more expensive and therefore less accessible than regular generics.

Compulsory licensing

The World Trade Organization's (WTO) Trade-Related Aspects of Intellectual Property Rights agreement (TRIPS) went into effect in January 1995, allowing countries to issue compulsory licenses on grounds of public interest, without the consent of a patent holder, and permitting the production of generic medications while intellectual property rights are still in effect. The Doha Declaration in November 2001 introduced provisions for least developed countries and for those that do not have drug production capacity, allowing the export of medications produced under compulsory licensing in specific situations. The patent owner, in the case of medications usually a pharmaceutical company, still holds rights to its invention and is entitled to compensation under TRIPS; governments will usually request a voluntary license before issuing a compulsory one. Many countries, including Brazil and South Africa for instance, issued compulsory licenses to increase access to HIV medications in the last couple of decades and the United States considered using it to create stockpiles of ciprofloxacin during the Anthrax scares which followed the 11 September, 2001 attacks.

Drug development geared exclusively towards emerging markets

A number of pharmaceutical companies in emerging markets have started to develop drugs that are not intended, at least initially, to be sold in high-income economies. Examples include icotinib, an epidermal growth factor receptor inhibitor, which was approved by the Chinese Food and Drug Administration (SFDA) in June 2011; and Nanoxel™, a nano-particle based paclitaxel formulation, developed by Darbur Pharma, an Indian company that has since been acquired by Fresenius Kabi, a German health care company. Several caveats have to be raised however. First, scrutiny of new medications in low- and middle-income countries may be less rigorous than in the United States and Europe, raising the possibility of safety and efficacy issues and second, it is unlikely that a significant number of important new drugs will be developed solely for emerging markets.

Clinical research and participation in clinical trials

Physicians and patients in low- and middle-income countries often choose to participate in clinical trials as a means of accessing medications that would otherwise not be covered in health systems with limited resources. While there are clearly positive effects of increasing clinical trial participation in emerging markets, it is important to note that there are also challenges. Authors often cite difficulties with ethical matters such as the adequacy of informed consent, financial compensation and potential conflicts of interest, as well as potential lack of adequate oversight from regulatory authorities, and potential ethnic differences in treatment results.

Newer payment systems: Tiered pricing, access programmes, risk-sharing agreements

Price discrimination, which despite its inequitable sounding name is an important concept in economics and business, consists of charging different prices for the same product in different markets or segments of a market, usually based on the consumer's ability to pay and on elasticity of demand. Also called differential, tiered or equity pricing, it is a common practice in most industries outside health care, where discounts and rebates are common place, allowing companies to expand the number of customers who are able to afford its products. Price discrimination policies have allowed for successful distribution of lower-cost vaccines and AIDS medications in the developing world. The main problems with price discrimination include the risk of parallel importing from low to high cost countries, political backlash in nations where prices are higher and the fact that even cheaper medications may not be cheap enough in low-income countries.

Health technology assessment, cost-effectiveness and value-based insurance design and pricing

Just as in Canada and Western Europe, low- and middle-income countries that enabled universal coverage have struggled with rising health care and medication costs, often leading to the

creation of agencies or groups that provide formal and informal health technology assessment, one dimension of which is cost-effectiveness. While the main reasons for establishing these agencies or groups are similar around the world, namely the creation of an objective and transparent way of assessing alternative interventions in the setting of limited resources, aiming to improve health care quality, low- and middle-income countries struggle even more with lack of resources, human capital and knowledge of the subject.

At the same time, low- and middle-income countries may leverage from health systems that promote value in oncology. Value-based insurance design and pricing may eventually follow in the wake of health technology assessment and cost-effectiveness evaluations. Many new drugs in oncology improve median overall survival by just a few months at a cost of thousands or tens of thousands of US dollars. Value-based insurance design and pricing, with a basic premise that an intervention's cost should be linked to the benefit it provides, could potentially bring the cost of new medications closer to thresholds in which these would be considered cost-effective. This would also avoid the rationing of more effective and life-saving medications due to high costs. These can also help industry and payers establish price discrimination policies as cost-effectiveness thresholds vary according to national per capita income.

Public-private partnerships and philanthropy: The GAVI Alliance and the international financing facility for immunization

The challenge of access to cancer medications in low- and middle income countries can only be effectively addressed through a combination of public and private efforts. Throughout the world there are a growing number of such entities aiming to improve health care financing and delivery in low- and middle-income countries. The most relevant example to this commentary is that of the GAVI Alliance and the International Financing Facility for Immunization.

The GAVI Alliance, formerly the Global Alliance for Vaccines and Immunization, is a public-private partnership that has made significant strides in increasing access to vaccines, including those that prevent cancer, such as human papillomavirus [HPV] and Hepatitis B, in low-income countries. Bringing together all significant stakeholders, including industry, donor and recipient governments, UNICEF, WHO, The World Bank, The Bill and Melinda Gates Foundation and other philanthropists, research and technical agencies and representatives from civil society groups, the Alliance has helped immunize an additional 325 million children and likely helped avert 5.5 million future deaths since its foundation in 2000. In cancer care, GAVI has been able to lead negotiations in decreasing the cost of cancer preventing vaccines in low-income countries, bringing the price per dose of hepatitis B and HPV vaccines down to US$0.18 and US$5, respectively.

Most importantly, the Alliance provides a model that those of us interested in increasing access to cancer medications in low- and middle-income countries can draw inspiration from and build upon. Through engagement and goal setting, recipient countries have incentives to create and develop their health and human capital infrastructure with adequate technical support from the Alliance's technical partners; second, through the provision of funding, the Alliance creates a functioning market in vaccines for low-income countries, generating interest and solutions from private players. Finally, GAVI has been the test case for a new approach in innovative funding models, through the creation in 2006 of the International Finance Facility for Immunization, which issues bonds in capital markets, leveraged by guarantees of future donations. The Facility, which is funded by many donor countries such as Australia, France, Italy, the Netherlands, Norway, South Africa, Spain, Sweden, and the United Kingdom and has the World Bank as its treasurer, has raised in excess of US$3.5 billion in capital markets, effectively more than doubling the amount of funds available to GAVI.

Looking forward

It will take the whole world to control cancer in low- and middle-income countries. Only through multiple stakeholder involvement, including governments, industry and civil society, and through the creation of a global entity to fight cancer, supported by a global fund in the mould of the GAVI Alliance and the International Finance Facility for Immunization will we truly be able to win the fight against the disease. Finally, it is of paramount importance to note that, while in this perspective the author has focused on access to medications, effective cancer control plans have to be culturally appropriate, comprehensive and holistic, involving data gathering, health education, prevention, screening, early detection, surgical and radiotherapeutic treatments in addition to access to anti-cancer drugs. •

(The author welcomes comments and would like to invite readers to contribute with stories and their experience by emailing us or posting them at "Access to Cancer Care in Low and Middle Income Countries", a webpage which is available at http://www.facebook.com/CancerControlInLowAndMiddleIncomeCountries?ref=hl)