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

Gilberto de Lima Lopes Jr, Jonas A. de Souza and Carlos Barrios

Abstract | Major breakthroughs have been realized in controlling cancer in the past five decades. However, for patients in low- and middle-income countries (LMICs), many of these advances are nothing but an aspiration and hope for the future. Indeed, the greatest challenge we face in oncology today is how to reconcile small, incremental and significant improvements in the management of cancer with the exponentially increasing costs of new treatments. Emerging economies are attempting to address this important issue of access to cancer medications. In this Review, we examine how LMICs are using generic and biosimilar drugs, expanding participation in clinical trials, implementing universal health-care schemes to pool resources, and using compulsory licensing schemes as well as increasing multiple-stakeholder public–private partnerships to increase access to cancer medications for their citizens. Any truly effective programme will require multiple stakeholder involvement—including governments, industry and civil society—to address the issue of access to medication. Only with the creation of a global entity to fight cancer that is supported by a global fund—for example, in the mould of the GAVI alliance and the International Finance Facility for Immunization—will we truly be able to improve cancer care in LMICs and drive down the high mortality rates in these regions.

Lopes, G. L. Jr *et al. Nat. Rev. Clin. Oncol.* **10**, 314–322 (2013); published online 9 April 2013; doi:10.1038/nrclinonc.2013.55

Introduction

In 2008, 63% of global deaths were attributed to noninfectious maladies, such as cancer. The vast majority of these deaths, 80% in fact, occurred in low- and middle-income countries (LMICs).[1] Recognizing this burden, the United Nations (UN) held a high-level summit on the prevention and control of noncommunicable diseases (NCDs) in September 2011.[1] As a result of that meeting, the UN General Assembly adopted resolution 66/2, which aimed to raise awareness and lead the efforts in combating NCDs in member nations.[2] Among NCDs, cancer causes more than 7.1 million deaths annually —exceeding those caused by tuberculosis, HIV/AIDS and malaria combined[3]—and is the most important cause of lost life years and productivity worldwide. Cancer had a total global economic impact of US$895 billion in 2008, which does not include direct costs of treatment, but rather economic loss from lost years and productivity, according to a study supported by the American Cancer Society and the LIVESTRONG foundation.[4] The economic toll of cancer was 19% higher than the second-most common cause (heart disease) and was equivalent to 1.5% of global gross domestic product (GDP).[4]

Major breakthroughs have been realized in the prevention and control of cancer in the past five decades. For example, marked improvements in the management of childhood cancer have improved typical 5-year survival rates to approximately 80% from <50% in the 1970s.[5] Moreover, since the 1990s, adjusted cancer death rates have decreased by nearly 21% in men and 12% in women in the USA because of expansive screening programmes (especially for prostate cancer and breast cancer), preventative measures and improved diagnostic accuracy, as well as treatment developments in specific malignancies, such as those of the breast, colon and lung.[6]

Even patients with noncurable metastatic diseases have benefited from considerable improvements in survival durations and quality of life with the introduction of systemic treatments with chemotherapeutic, hormonal and other targeted agents. For example, patients with colorectal and lung cancer now have median survivals of ≥1–2 years rather than just a few months.[7] According to the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, trends in 5-year survival rates in the USA improved 36% when comparing the periods of 1975–1977 to 1999–2006 over all tumour types.[7]

New therapies are certainly one of the explanations for these improved results. However, the resources needed to get an experimental agent past clinical trial and into the market are considerable; these costs are invariably passed down to the end payer (either the patient, insurance company or public health service). For example, monoclonal antibodies and tyrosine kinase inhibitors have been reported to cost $5,000–10,000 per month of treatment.[8] Given that LMICs bear the largest proportional burden of cancer mortality, how these nations address the burgeoning cost of cancer treatment is important. In this Review, we discuss how emerging economies are attempting to address the increasingly important issue of access to cancer medications (Table 1). We focus on how

The Johns Hopkins Singapore International Medical Centre of the Johns Hopkins University School of Medicine, 11 Jalan Tan Tock Seng, Level 1, Singapore 308433, Singapore (**G. L. Lopes Jr**). Department of Medicine, University of Chicago, 5841 South Maryland Avenue, MC 6092, Chicago, IL 60637, USA (**J. A. de Souza**). School of Medicine, Porto Alegre, Rio Grande do Sul, Avenue Ipiranga 6690, Predio 60, 3º andar, Porto Alegre, Rio Grande do Sul, Brazil 90610-000, Brazil (**C. Barrios**).

Correspondence to: G. L. Lopes Jr glopes@imc.jhmi.edu

Competing interests
The authors declare no competing interests.

to reconcile small, incremental, but significant improvements in the management of cancer with the exponentially increasing costs of new agents. We rely mostly on our experience and on past discussions with scores of colleagues and groups we have worked with and learned from over the years because no general consensus on the issue of access to drugs in LMICs exists or has been widely discussed.

Economic impact of cancer in LMICs

Of the new cases of cancer reported in 2008, approximately 60% occurred in LMICs; nearly two-thirds of cancer-related deaths occur in these nations.[1] These statistics demonstrate that LMICs are less able to meet the needs of patients than richer nations. Indeed, a 2009 study reported that approximately half of the total cost of cancer was attributable to treatment, whereas productivity loss accounted for one-quarter of the cost.[9] The report suggested that LMICs contributed only 6.2% of the total spent on cancer globally, but were responsible for a whopping 89% of the global cancer expenditure gap, which is the difference between the estimated cost incurred in each country and the cost that would have been incurred should the country match a global cancer expenditure standard.[9]

We calculated the economic burden of cancer per patient (using data from the LIVESTRONG foundation), including direct medical expenses, nonmedical expenses (such as transportation and home care) and productivity losses in South America ($7.92), China ($4.32) and India ($0.54). These values pale in comparison to the expense per patient in the UK ($183), Japan ($244) and USA ($460). Adjusting by income at current exchange rates, the amount spent on cancer care is equivalent to 0.12% of the per capita gross national income (GNI) in South America, 0.05% in India and 0.11% in China. In the UK, Japan and USA, the corresponding expenses were 0.51%, 0.6% and 1.02% of GNI, respectively (Figure 1).[10]

Current access to cancer treatments

LMICs face a dual challenge: while they must address long-term issues such as implementing preventive care and health education programmes for their populations, which are characteristic challenges of underdeveloped societies, they must also address how to finance and provide their population with increasingly expensive cancer therapies, which is a problem of the developed world. Limited data have been reported on the prevalence of the use of newer, innovative cancer medications in emerging markets.

In a survey and focus group of medical oncologists and health-care policy experts from six Southeast Asian nations at the first Southeast Asian Cancer Care Access Network (SEACCAN) meeting in 2011, an estimated 15% of patients in LMICs in the region had access to an index of medications, which included oxaliplatin for the adjuvant treatment of patients with colorectal cancer, bevacizumab and cetuximab for palliative treatment in colorectal cancer, gefitinib or erlotinib for the treatment of patients with metastatic lung cancer who harbour *EGFR* mutations, sorafenib for the management of advanced-stage hepatocellular carcinoma and trastuzumab as an adjuvant therapy in patients with early HER2-positive breast cancer.[11] By contrast, 55% of patients in Singapore, a high income country in Southeast Asia, had access to these treatments.

We validated these data using sales figures from IMS Health (London, UK) and calculated the expenditure per capita on the same index of drugs to be $0.49 in Thailand, $0.48 in Malaysia, $0.12 in the Philippines, $0.11 in Vietnam and $0.04 in Indonesia; in Singapore and the USA the expenditures per captia on this drug index were $6 and $20, respectively. Unsurprisingly, access to these drugs correlated strongly with GNI per capita ($r^2 = 0.99$) and, interestingly, with cost-effectiveness ($r^2 = 0.7$), even though only Thailand routinely uses health-economic evaluations when deciding on therapeutic coverage in the region.[11] Intuitively, lowering the cost of effective treatments can help increase access to cancer in LMICs and improve outcomes for these patients, and a number of mechanisms can be leveraged by these nations to achieve improved access.

Key points

- Approximately 80% of global cancer-related deaths occur in low and middle-income countries (LMICs), which might reflect poor access to oncology therapies—including drugs—in these regions
- LMICs can drive down the costs of drugs by, for example, buying generic or biosimilar drugs, expanding their involvement in clinical trials and implementing universal health-care schemes to pool resources
- Compulsory licensing schemes, sanctioned by the World Trade Organization, can be put in place to permit the production of generic medications while intellectual property rights are still in effect
- Furthermore, multiple-stakeholder public–private partnerships can be leveraged to finance drug distribution schemes in LMICs

Improving access to care

Universal coverage for health care in LMICs

With the goal of improving access to health care, universal insurance coverage—the fundamental element of functional health-care systems that pools resources and provides financial protection from the costs of illness[12]—is increasingly common in emerging Asian and Latin American countries. For example, Brazil, Chile, Colombia, Costa Rica, Mexico, Malaysia, South Korea, Taiwan, Thailand and others have enacted legislation creating comprehensive insurance systems over the past few decades. Notably, the definitions of universal coverage vary widely between countries and, even when enacted, systems struggle to increase the breadth of coverage, the proportion of a population that is insured, the extent of benefits that are offered and the proportion of expenses that are covered.[13] Although universal coverage is needed for adequate access to cancer medications in LMICs, its establishment requires political will to manage myriad challenges.

The majority of LMICs, many of which are in Africa, still lack a universal coverage programme. A survey of 192 nations revealed that although 75 countries had a mandate for universal access to health care, only 58 of these met the stricter criteria of ≥90% of the population having access to skilled birth attendance (doctors,

Table 1 | Improving access to cancer medications in LMICs

Initiative	Description	Benefits	Challenges
Access to care			
Universal health-care coverage	The provision of insurance coverage for the whole population of a country or region	Pooling of resources Financial protection	Financing through taxation or contribution in areas with low resources Rising health-care costs and expenditures once enacted Lawsuits against the state or government when drugs are not supplied
Generic drugs and biosimilars	Pharmaceutical products that are produced without a license once the patent or exclusive rights expire	Lower cost of drugs through increased competition Increased access	Public and health-care worker perception on quality Regulatory pathways for biosimilars are still uncertain in many jurisdictions
Compulsory licensing	WTO Trade-Related Aspects of Intellectual Property Rights agreement permits governments to issue compulsory licenses on the grounds of public interest, without the consent of a patent holder, to permit the production of generic medications while intellectual property rights remain in effect	Early introduction of generic drug competition	Might lead to trade sanctions and decreased incentives for innovation
Research			
Participation in clinical trials and research	Participation in industry-funded, government-funded or otherwise-funded clinical studies	Access to standard and research medications and treatments that might not be widely available because of high cost	Ethical issues include the adequacy of informed consent, independent review and oversight, ethnic differences and conflicts of interest
Drug development in emerging markets	Pharmaceutical development of agents for exclusive use in LMICs	Lower cost of development might lead to cheaper medications and increased access	Regulatory scrutiny seems less rigorous Efficacy and safety issues
New payment methods			
Price discrimination	Practice of charging different prices for the same product in different markets based on the ability to pay and elasticity of demand	Companies expand the number of customers who are able to afford its products Successful distribution of medications in the developing world	Parallel imports can lead to decreased profits in higher paying markets, political backlash because of lower prices in other jurisdictions and perceived inequity
Access programmes	Industry-led price discrimination in the form of rebates or discounts or in extra products	Companies expand the number of customers who are able to afford its products	Parallel importing
Risk-sharing agreements	Payment method in which the provider company only gets paid if certain conditions are met	Decreases overall costs as no payment is made for patients who do not benefit from drug	Complexity, lack of consensus on adequate surrogate end point and definition of benefit
Cooperation among stakeholders			
Health technology assessments	The use of formal economic techniques to assess the cost-effectiveness of health care Set insurance coverage and product pricing based on clinical and economic value	Pricing process for a new medications is objective and attuned to its clinical and economic benefit	Complexity, lack of agreement for universal willingness-to-pay threshold
Public–private partnerships and philanthropy	Schemes that are funded and operated through a combination of government and private entities and charities	Multiple stakeholder involvement and sources of finance	Often haphazard, leading to wasted efforts Sometimes unsustainable in the long term

Abbreviations: LMICs, low- and middle-income countries; WTO, World Trade Organization.

midwives or both) and insurance.[14] Although poverty *per se* (that is, income of <$1 per day) is an obstacle to universal coverage, it is not an insurmountable one. For example, many countries, including Germany and Panama, enacted universal coverage when their income per capita was <$5,000.[14] The mean GNI per capita reported in the aforementioned survey was $13,000 (inflation adjusted) across the 75 countries when universal coverage was established.[14] Encouragingly, large middle-income countries that still lack universal coverage are working towards it. For example, Indonesia passed legislation in 2012 establishing the first steps towards comprehensive health-care coverage for its citizens and China is on target to cover most of its population in the coming years.[15,16]

Universal coverage brings not only the opportunities of improved care for citizens, but also challenges, such as increased public expenditure (that is, increased taxation) and increased bureaucratic and administrative demands. In China, for instance, public expenditure accounted for nearly 60% of the total health-care spending in 2012, a marked increased from 35.6% in 2001.[17] Moreover, in low-resource settings, institutions might be weaker and problems with management and accountability

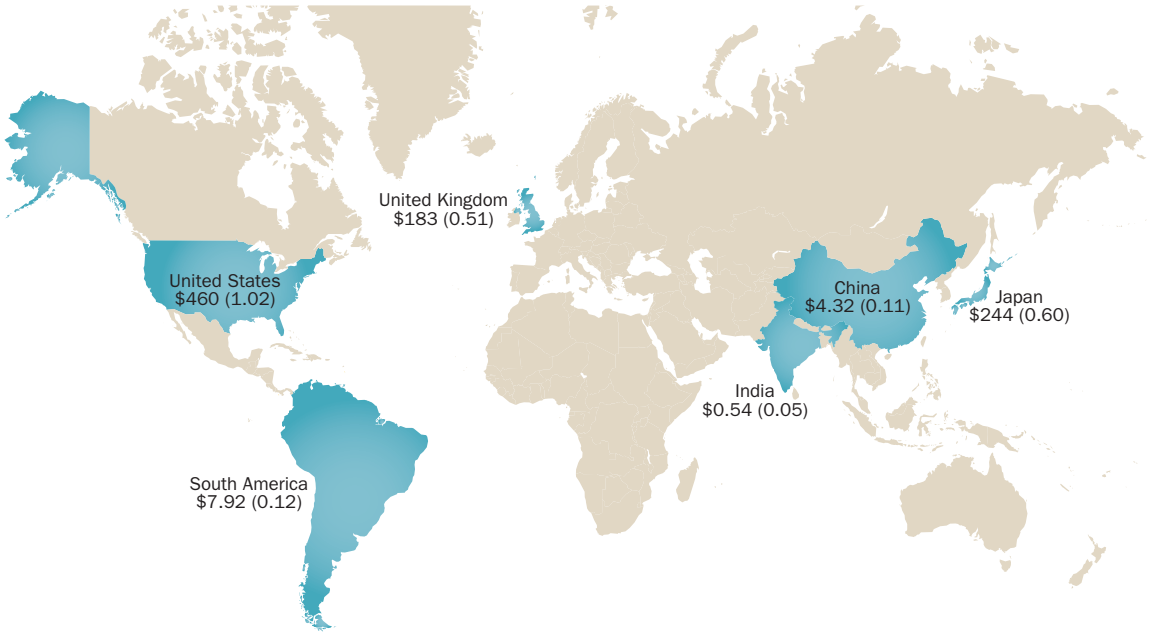

Figure 1 | The economic burden of cancer in selected countries and regions, as indicated by expenditure per patient in US dollars and as a percentage of gross national income per capita (in brackets). The economic burden includes direct medical costs of treatment, nonmedical costs and productivity losses. Medical costs include medical procedures, hospitalization, outpatient visits and prescription drugs. Nonmedical costs include transportation, complementary and alternative treatments for cancer and care-giving costs. Productivity losses include the economic value of time and output lost or foregone by patients with cancer because of treatment or disability.[9]

might be prevalent, leading to corruption and perverse incentives that result in underfunding and misallocation of expenditures.

In many Latin American countries, increased democratization, universal coverage and right-to-health guarantees in the national constitutions led to many lawsuits being brought against the state by individuals who were denied access to expensive treatments that were otherwise available to fellow, privately insured citizens. At least in Brazil and Colombia, most patients who sued their governments were awarded favourable verdicts by the courts. According to the Brazilian National Justice Council, >240,000 cases of this kind were heard at the federal and state levels in 2011.[18] In 2010, the Brazilian federal government spent $72 million to settle judicial claims—a 64-fold increase from the $1.12 million spent in 2005. However, these judicial cases do not necessarily favour those most in need; approximately 60% of the claims came from two of Brazil's richest states, Rio Grande do Sul and São Paulo.[18] Importantly, a court-mandated verdict forces the government to purchase the drugs at the market rate; critics have argued that, if the government included the medications in the public plan initially, a better price could be negotiated with the provider companies. That is, if these medications were considered as part of a strategic plan that recognized the potential number of patients who would require each specific therapy, the state would save a considerable amount of money when compared with settling single cases.

Generic and biosimilar off-patent medications

Drug development is a long and expensive process, taking at least 10 years and investments of nearly $1.8 billion to bring a new medication to market.[19] Accordingly, nations and the international community grant patents that give manufacturers a period of exclusive rights to sell a new drug as an incentive for innovation. Once a patent expires, other companies are allowed to make and market a once exclusively branded agent as long as they can demonstrate bioequivalence.[20] Once generic competition sets in, the price of medications can drop considerably, often by 80% or more.[21] Several chemotherapy drugs are included in the WHO list of essential drugs, which are selected based on disease prevalence, efficacy, safety and comparative cost-effectiveness (Box 1).

A systematic review and meta-analysis of 38 randomized controlled trials comparing generic and branded cardiovascular drugs confirmed their clinical equivalence.[22] However, little has been published on the prevalence of use, safety, efficacy and economic implications of generic oncology medications, especially in LMICs. Using data from a retrospective series of patients who were treated with generic oxaliplatin and irinotecan in India,[23] we could not identify any evidence of decreased clinical outcomes, but estimated yearly cost savings of nearly $64 million. Such a cost reduction is considerable in a country with a per capita GNI of <$1,500 per year (at current exchange rates) and that had expenditures of only $54 per capita on health care in 2010.[23]

Major challenges for the increased penetration of generic drugs include public and health-care worker perception and quality issues. For example, in a survey of 839 physicians in the USA, nearly 25% of responders had a negative perception of the efficacy and 50% of the quality of generic medications.[24] In some cases,

Box 1 | Anticancer medications*

- Allopurinol
- Asparaginase
- Bleomycin
- Calcium folinate
- Carboplatin
- Chlorambucil
- Cyclophosphamide
- Cytarabine
- Dacarbazine
- Dactinomycin
- Daunorubicin
- Docetaxel
- Doxorubicin
- Etoposide
- Fluorouracil
- Hydroxycarbamide
- Ifosfamide
- Mercaptopurine
- Mesna
- Methotrexate
- Paclitaxel
- Procarbazine
- Tamoxifen
- Thioguanine
- Vinblastine
- Vincristine

*Included in WHO Model List of Essential Medicines[58]

the concern is warranted. For example, a study in Iraq showed that approximately one-third of patients with chronic myeloid leukaemia lost haematological, cytogenetic and molecular control after switching from branded to generic imatinib.[25] Quality assurance, good manufacturing practices and adequate supervision by regulatory authorities are of paramount importance to ensure bioequivalence and, therefore, the safety and efficacy of generic medications.

The WHO defines biosimilars as biotherapeutic products that are similar in quality, safety and efficacy to licensed reference biological agents.[26] Although versions of supportive medications are currently approved, 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 widely available. Biosimilars are typically monoclonal antibodies, which are bigger and more complex molecules than small-molecule generic drugs; minor changes such as glycosylation patterns could change the molecular conformation of the biosimilars and affect the efficacy and safety of the drug compared with the original agent. Accordingly, these substitutes must undergo assessment by clinical trial and are likely to be relatively more expensive and less accessible than generic small-molecule drugs. Furthermore, the particular manufacturing difficulties related to biosimilars suggest that, at best, only a 30% decrease in prices relative to the original biological agent will be achieved. Several prospective randomized clinical trials of biosimilars are currently being planned or conducted (NCT01419665, NCT01534949, NCT01764022, NCT01763645), and specific legislation and pathways regarding the development and introduction of biosimilars are being extensively discussed in the USA and Europe. These discussions seek to address preclinical and clinical efficacy as well as safety, extrapolation and pharmacovigilance.[27]

Notably, in India, pharmaceutical companies lacked patent protection until the country's accession to the WTO in 1995. Accordingly, the intellectual property legislation differs from most other nations and many anticancer generic drugs, including biosimilars (such as a monoclonal antibody that targets CD20 that is similar to rituximab), are widely available. Indeed, this example might serve as a model to be evaluated (or followed) by other developing nations that are seeking to expand their access to cancer drugs.

Compulsory licensing

The WTO Trade-Related Aspects of Intellectual Property Rights agreement (TRIPS) went into effect in January 1995.[28] TRIPS enables any country to issue compulsory licenses on grounds of public interest—without the consent of a patent holder—to permit the production of generic medications while intellectual property rights are still in effect. The Doha Declaration of November 2001 introduced provisions for the least-developed countries (and those that do not have drug production capabilities) to export medications produced under compulsory licensing.[28] The patent owner, which is usually a pharmaceutical company in the case of medications, still holds the rights to its invention and is entitled to compensation under TRIPS; governments will usually request a voluntary license before issuing a compulsory one.[29,30] Many countries, including Brazil and South Africa, have issued compulsory licenses to increase access to HIV medications in recent decades.[31] The US government considered using compulsory licenses to help stockpile ciprofloxacin during the anthrax scares that followed the 11 September 2001 attacks.[31]

In oncology, a well-studied example of compulsory licensing comes from Thailand. The Thai government issued compulsory licenses for docetaxel, letrozole, erlotinib and imatinib in 2008 (the latter was cancelled after an access programme was agreed on with Novartis, which manufactures imatinib). A budget impact study suggested savings in excess of $140 million in the use of these three anticancer medications over 5 years.[32] Recently, India has followed suit and issued a compulsory license for sorafenib.[33]

Although some critics have suggested that failing to uphold intellectual property rights will decrease incentives for innovation and, therefore, lead to fewer new medications in the future, evidence in support of this notion is scant. However, countries that do issue compulsory licenses might be subject to pressure from industry and trade partners. For example, when Egypt issued a compulsory license for sildenafil (a phosphodiesterase type 5 inhibitor used to treat erectile dysfunction) in 2002, Pfizer announced it would rethink its investment in a modern production facility in the country.[34] Despite this isolated case, the use of compulsory licenses does

not seem to lead to an overall decrease in foreign direct investment in countries that adopt the scheme. For example, Brazil has benefited from considerable investments despite its issuance of compulsory licenses for HIV medications.[35] Returning to the Thai example, even though the Office of the US Trade Representative withdrew duty-free access to the US market for the generic Thai products in response to the compulsory licenses issued for docetaxel, letrozole and erlotinib, a net economic benefit for Thailand was observed (for example, the saving of $140 million over 5 years). Furthermore, no relationship could be found between the use of the compulsory licenses and foreign direct investment inflows in the country between 2002 and 2008.[36]

Compulsory licensing is clearly an important instrument of policies related to access to medications. Despite its controversies, countries are increasingly using the approach as a negotiating 'chip' when discussing drug prices with industry. Indeed, the pharmaceutical industry has responded with a series of price discrimination strategies to increase sales as well as access to medications in LMICs.

Drug development in 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. For example, BetaPharma (Branford, CT), in combination with Zhejiang Beta Pharma (Beijing, China) have developed icotinib, an EGFR inhibitor that is noninferior to gefitinib in the treatment of patients with lung cancer who have failed to respond to palliative chemotherapy. As drug development is 10–40-fold cheaper in China—with reported costs of <$1 million, $2–3 million and $3–7 million for phase I, II and III trials, respectively—than in the USA, icotinib is a cheaper alternative to erlotinib and gefitinib. Indeed, icotinib costs approximately 30% less than gefinitib.[37] Since the Chinese Food and Drug Administration (SFDA) approved sales in June 2011, over 7,000 patients have received the drug, with sales reaching $15 million as of June 2012. Annual sales are expected to reach $158 million and the Chinese Ministry of Health is currently considering adding icotinib to its basic drug list. The company plans to apply for marketing approval in the USA as well.[37–39]

Another example is Nanoxel™, a nanoparticle-based paclitaxel formulation developed by Dabur Pharma, which is an Indian company that was acquired by the German health-care company Fresenius Kabi. Based on the results of a randomized controlled trial, the Indian drug regulatory authority approved its use as an alternative to cremophor-based paclitaxel in 2006. The drug is currently available in several countries in Asia and Latin America; in India, Nanoxel™ is cheaper than branded paclitaxel (for example, Taxol®, which is manufactured by Bristol–Myers Squibb). As it does not require premedication (for example, to prevent nausea) and is not associated with infusion reactions (based on our review of 562 infusions), we estimate that Nanoxel™ is $400 cheaper to administer per cycle than paclitaxel. Despite this finding, the lack of adequately sized randomized controlled trials in other countries that compare Nanoxel™ to paclitaxel and nab-paclitaxel (the albumin-bound form of the drug) have hindered its approval in other markets.[40]

Finally, nimotuzumab is a monoclonal antibody that targets the EGFR that was initially developed at the Center for Molecular Immunology in Havana, Cuba. It is approved for use and is currently marketed in several countries in Latin America and Southeast Asia, based on early randomized clinical trials showing potential benefits in head-and-neck cancer and glioma.[41,42]

Although these developments go some way to driving down the costs of medications, several caveats must be raised. Firstly, scrutiny of new medications in LMICs seems to be less rigorous than in the USA and Europe, which raises the possibility of safety and efficacy concerns. For example, clinical trials that led to the approval of icotinib in China and Nanoxel™ in India have not yet been published in peer-reviewed journals. Secondly, as companies take these drugs to larger and more lucrative markets in high-income countries, their development costs will likely increase in the future. Finally, that a significant number of new drugs will come through this route is unlikely because pharmaceutical and biotech companies in developed nations are still more likely to generate the largest number of new clinically significant compounds.

Involvement in clinical research

Physicians and patients in LIMCs often choose to participate in clinical trials as a means of accessing medications that would otherwise not be covered in their low-resource health-care systems. The share of global clinical trials enrolling patients in countries other than those in North America and Western Europe increased from <5% in 1997 to approximately 30% in 2007, which are the latest statistics available.[43] A review of 300 clinical trials published in 2009 showed that the number of countries in which clinical trials are conducted doubled between 1995 and 2005.[44]

Although this positive effect of increasing clinical trial participation is evident in emerging markets, many challenges must be addressed. These issues include ethical matters—such as the adequacy of informed consent, financial compensation and potential conflicts of interest for all involved in the trial—as well as potential lack of adequate oversight from regulatory authorities and potential ethnic differences in treatment results.[17] Another issue is cost; for example, the cost per trial case in India can be 90% lower than that in academic centres in the USA, for reasons that might include cheaper labour and less-restrictive regulations.[45] However, whether a decrease in the cost of running clinical trials eventually translates into lower costs for drugs in LMICs remains to be seen. Furthermore, the issue of incentives for academic centres in LMICs must be addressed: the active participation in the development of certain drugs does not guarantee that those drugs will be available to the large majority of patients that seek care in the same institution once approval is granted because of a lack of insurance coverage.

New payment systems

LMICs can also gain access to expensive drugs through price discrimination, which is (despite its inequitable-sounding name) an important concept in economics and business that consists of charging different prices for the same product in different markets or segments of a market. This discrimination is usually based on consumers' ability to pay and on the elasticity of demand. Also called differential, tiered or equity pricing, price discrimination is common practice in most industries outside health care, in which discounts and rebates are common place, and enables companies to expand the number of customers who are able to afford its products.

Price discrimination policies have, for example, facilitated the successful distribution of lower-cost vaccines and AIDS medications throughout the developing world.[46] However, this achievement has not been replicated in oncology. For instance, using data from IMS Health, we identified little (<20%) variation in the price per unit of a basket of drugs (containing oxaliplatin, bevacizumab, cetuximab, trastuzumab, sorafenib, erlotinib and gefitinib) in Southeast Asian markets despite the GNI per capita varying between countries by a factor of ≥30.[10] However, the threat of compulsory licensing and rising overall health-care costs have spurred an increasing number of pilot projects in price discrimination in LMICs. GlaxoSmithKline, for example, has instituted a price-tier policy for its oncology products worldwide, lowering the prices of some medications (such as pazopanib) in low-income countries by up to 70% compared with its US prices.[47] Other companies, such as Eli Lilly and Sanofi, have used price discrimination for selected products as well.

The major problems with price discrimination include the risk of parallel importing of drugs from low-cost to high-cost countries, political backlash in nations where prices are higher and the fact that even price-adjusted medications might not be cheap enough in low-income countries.[48] To counteract the first two issues, industry has implemented control mechanisms and devised ways of providing price discrimination without open discounts through access-sharing and risk-sharing programmes. For example, Novartis, has a worldwide access programme for imatinib, which has helped tens of thousands of patients gain access to the medication in >80 countries.[49,50] Roche has begun marketing some of its products under different brand names in India in hopes of decreasing parallel imports and political backlash while increasing overall sales.[51] Although challenging, these problems can be overcome—using HIV medication payment and distribution schemes as a prime example—to increase access to cancer medications in LMICs. At least initially, the international community will need to support countries that cannot afford the drugs (even at the lowered, price-tiered prices) through assisting and developing public–private partnerships.

Health technology assessments

Just as in Canada and Western Europe, LMICs that implemented a policy of universal health-care coverage have struggled with rising health-care and medication costs. This stress has led to the creation of agencies or groups that provide formal and informal health technology assessments, one dimension of which is cost-effectiveness. In the past two decades, Malaysia, Indonesia, Taiwan, South Korea, Vietnam, Argentina, Brazil, Chile and others have conducted economic evaluations of new health interventions (for example, drugs, diagnostic methods and medical devices), which have become an integral part of coverage decisions in national health-care and other-payer systems. Although the main reasons for establishing these agencies or groups are similar around the world—that is, the creation of an objective and transparent means of assessing alternative interventions in the setting of limited resources, aiming to improve health-care quality—LMICs struggle more with a lack of resources, human capital and knowledge of the subject.[52]

At the same time, LMICs can leverage health-care systems that promote 'value' in oncology, which might eventuate in the wake of health technology assessments 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 dollars. Value-based insurance design and pricing schemes use the basic premise that an intervention's cost should be linked to the benefit it provides, which could potentially bring the cost of new medications closer to thresholds that would be considered cost-effective because medications that are not considered value-for-money would not be covered. This scheme would also avoid rationing of more-effective and life-saving medications because of high costs. Importantly, value-based insurance programmes can also help industry and payers establish price discrimination policies as cost-effectiveness thresholds vary according to national per capita income.[53]

Public–private partnerships and philanthropy

The challenge of access to cancer medications in LMICs can only be effectively addressed through a combination of public and private efforts. Throughout the world a growing number of such entities are aiming to improve health-care financing and delivery. The most relevant example to this commentary is that of the GAVI Alliance and its International Finance Facility for Immunisation.[54]

The GAVI Alliance, formerly the Global Alliance for Vaccines and Immunization, is a public–private partnership that has made considerable 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 important stakeholders—including industry, donor and recipient governments, The UN Children's Fund (UNICEF), the 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 $0.18 and $5 from $24–43 and $96–135, respectively.[53]

Most importantly, the Alliance provides a model to draw inspiration from and build upon. Through engagement and goal setting, recipient countries have incentives to create and develop their health and human capital infrastructures with adequate technical support from the Alliance's technical partners.[54] Additionally, through the provision of funding, the Alliance creates a functioning market of 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 of the International Finance Facility for Immunization in 2006, which issues bonds in capital markets that are leveraged by guarantees of future donations. The facility, which is funded by many donor countries—including Australia, France, Italy, The Netherlands, Norway, South Africa, Spain, Sweden and the UK—has the World Bank as its treasurer and has raised >$3.5 billion in capital markets, effectively more than doubling the amount of funds available to GAVI to pursue its endevours.[55]

Box 2 | Global fund, international finance facility and alliance to fight cancer?

We propose creating a global fund to fight cancer, an international finance facility for cancer control and an alliance organization that will bring together international donors, philanthropic entities, governments, nongovernmental organizations, WHO and the International Atomic Energy Agency.

Modelled on the Global Fund to Fight Malaria, AIDS and Tuberculosis, GAVI and the International Finance Facility for Immunization, this organization will—through engagement, goal setting and multiple-stakeholder involvement—provide recipient countries with incentives to create and develop their health and human capital infrastructures with adequate technical support. The alliance of funding and technical partners will unify efforts, support the creation and implementation of cancer control plans and make available cancer interventions in a stepwise fashion, led in the most cost-effective way. The alliance could also help create a functioning market for the provision of low-cost interventions where none exists today, fostering innovation and lowering costs. Furthermore, we envisage that the alliance will support negotiations with industry to facilitate the implementation of tiered pricing schemes in low-income countries. An international finance facility would make funds available upfront through the securitization of donor pledges, supporting the activities of the alliance.

Current major challenges to the creation of such a programme include the complexities involved, compounded by a lack of political awareness and, therefore, interest and support from industry and other stakeholders. We urge you to discuss this idea in your country and community and encourage joining our discussion online.[57]

Conclusions

The major breakthroughs in the management of cancer over the past several decades have been out of reach for most patients and health-care professionals in LMICs. Indeed, middle-income countries are better positioned than low-income ones to address the access challenge and most have started to develop and improve their health-care systems and can now provide basic, and even sometimes advanced, cancer treatments to their citizens. These countries also have the opportunity to learn from prior experiences in their richer counterparts. The strategies most likely to be effective in increasing access to cancer medications in LMICs are the increased use of quality generics, price discrimination policies and value-based insurance design (public and private) and pricing policies. One can argue that, in any health system in which resources are limited, some degree of prioritization should occur. Accordingly, the medical and scientific community should work towards creating resource-appropriate guidelines that list health interventions according to their cost-effectiveness to aid such prioritization.[7]

Through multiple stakeholder involvement—including the participation of governments, industry and the public—and through the creation of a global entity to fight cancer, supported by a global fund in the mould of the GAVI Alliance, will we truly be able to control cancer globally. The appropriate use of oncology drugs requires adequate training and infrastructure, including complementary laboratory and pharmacy services, physicians and nurses. Although access to medications has been the focus of this Review, any adequate programme for oncology care in LMICs should make provision for surgical and radiotherapeutic services, without which the impact of drug therapy is limited. Furthermore, effective cancer control plans have to be culturally appropriate, comprehensive and holistic, involve data gathering, health education, prevention, screening and early detection programmes. Notably, in settings where resources are severely curtailed, palliative care and pain control might be the only potential cost-effective intervention available to patients with cancer.

We propose establishing a global fund to fight cancer (Box 2) in the mould of the Global Fund to Fight Malaria.[56] We welcome comments and would like to invite readers to contribute with stories and experiences by e-mailing us or posting them on the Cancer Control in Low and Middle Income Countries webpage.[58]

Review criteria

Searches of the PubMed, Embase and Google Scholar databases as well as searches of the reviewed abstracts of the ASCO and ESMO conferences were conducted using the terms "cancer", "control", "access", "medications" and "low and middle income countries" in various permutations. Articles published in English, Spanish and Portuguese between 1 January 2000 and 1 January 2013 were considered. The authors also used information from discussions with colleagues from around the world who have an interest in the subject.

1. WHO. United Nations high level meeting on noncomunicable disease prevention and control (WHO, 2011).
2. The General Assembly. Resolution 66/2: Political declaration of the high-level meeting of the General Assembly on the prevention and control of non-communicable diseases (United Nations, 2011).
3. Mathers, C. D. & Loncar, D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* **3**, e442 (2006).
4. LiveStrong foundation and American Cancer Society, 2012. The global economic cost of cancer. *The American Cancer Society* [online], http://www.cancer.org/aboutus/globalhealth/global-economic-cost-of-cancer-report (2010).
5. National Cancer Institute. A snapshot of pediatric cancers: incidence and mortality rate trends. *The American Cancer Society* [online], http://www.cancer.gov/aboutnci/servingpeople/snapshots/pediatric.pdf (2011).

6. Jemal, A., Ward, E. & Thun, M. Declining death rates reflect progress against cancer. *PLoS ONE* **5**, e9584 (2010).
7. Howlader, N. *et al.* (eds) SEER Cancer Statistics Review, 1975–2007 (Vintage 2009 Populations), *National Cancer Institute* [online], http://seer.cancer.gov/csr/1975_2009_pops09/ (2010).
8. Smith, T. & Hillner, B. E. Bending the cost curve in cancer care. *N. Engl. J. Med.* **364**, 2060–2065 (2011).
9. Economist Intelligence Unit. Breakaway: The global burden of cancer – challenges and opportunities. *LIVESTRONG* [online], http://www.livestrong.org/pdfs/GlobalEconomicImpact (2009).
10. Goss, P. *et al.* Cost of cancer care in Latin America and future challenges. *Lancet Oncol*. (in press).
11. Lopes, G. The new front in the war on cancer. Presented at the First South East Asia Cancer Care Access Network Meeting, Singapore. http://www.ispor.org/regional_chapters/Singapore/documents/presentation%20of-the-SE-Asia-Cancer-Care-Access-Network.pdf (2011).
12. Clements, B., Coady, D. & Gupta, S. *The Economics of Public Health Care Reform in Advanced and Emerging Economies* (International Monetary Fund, 2012).
13. WHO. Advancing and sustaining universal coverage. *Primary health care – now more than ever*. *The World Health Report 2008* [online], http://www.who.int/whr/2008/whr08_en.pdf (2009).
14. Stuckler, D., Feigl, A. B., Basu, S. & McKee, M. The political economy of universal health coverage. Background paper for the global symposium on health systems research (WHO, 2010).
15. [No authors listed] Health care reform: heroes dare to cross. *The Economist* (21 Jul. 2012).
16. Primanita, A. & Sagita, D. SBY plants seed for universal health care in Indonesia. *The Jakarta Globe* [online], http://www.thejakartaglobe.com/news/sby-plants-seed-for-universal-health-care-in-indonesia/534584 (2012).
17. The World Bank. Health expenditure, public (percentage of total expenditure). *The World Bank* [online], http://data.worldbank.org/indicator/SH.XPD.PUBL?page=1 (2012).
18. Cavalcanti, H. Brasil tem mais de 240 mil processos na área da Saúde. *Conselho Nacional de Justiça* [online], http://www.cnj.jus.br/noticias/cnj/14096-brasil-tem-mais-de-240-mil-processos-na-area-de-saude (2011).
19. Paul, S. M. *et al.* How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* **9**, 203–214 (2010).
20. U.S. Food and Drug Administration. Understanding generic drugs. *U.S. Food and Drug Administration* [online], http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm (2013).
21. Generic Pharmaceutical Association. Generic Medicines. *Generic Pharmaceutical Association* [online], http://www.gphaonline.org/about-gpha/about-generics (no date listed).
22. Kesselheim, A. S. *et al*. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA* **300**, 2514–2526 (2008).
23. Lopes, G. Cost comparison and economic implications of commonly used originator and generic drugs in India. Submitted for presentation at the 2013 American Society of Clinical Oncology Annual Meeting.
24. Shrank, W. S. *et al.* Physician perceptions about generic drugs. *Ann. Pharmacother.* **45**, 31–38 (2011).
25. Alwan, F., Alshami, A., Hatim, A. & Ali, A. Impact of switching therapy from imatinib mesylate to generic copy of imatinib on hematologic response in patients with chronic phase chronic myeloid leukemia: single center study [abstract 1219]. *Haematologica* **96**, a1219 (2011).
26. WHO. *Medicines: Biosimilars* [online], http://www.who.int/medicines/services/inn/inn_bio/en/index.html (2006).
27. Mullard, A. Can next-generation antibodies offset biosimilar competition? *Nat. Rev. Drug Discov.* **11**, 426–428 (2012).
28. WHO. *Trade-related aspects of intellectual property rights* [online], http://www.wto.org/english/tratop_e/trips_e/trips_e.htm (2013).
29. WTO. Compulsory licensing of pharmaceuticals and TRIPS. *World Trade Organization* [online], http://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm (2006).
30. WHO. Trade, foreign policy, diplomacy and health. *World Health Organization* [online], http://www.who.int/trade/glossary/story063/en/index.html (2013).
31. Berman, D. AIDS, essential medicines, and compulsory licensing. *J. Int. Assoc. Physicians AIDS Care* **5**, 24–25 (1999).
32. 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 Health* **15** (Suppl. 1), 95–99 (2012).
33. [No authors listed] Drugs and emerging markets: tripped up. *The Economist* (8 Sep. 2012).
34. McGill, A. M. Compulsory licensing of patented pharmaceuticals: why a WTO administrative body should determine what constitutes a public health crisis under the Doha Declaration. *Wake Forest Intell. Prop. L. J.* **10**, 69–97 (2009).
35. Bird, R. C. Developing nations and the compulsory license: maximizing access to essential medicines while minimizing investment side effects. *J. Law Med. Ethics* **37**, 209–221 (2009).
36. Yamabhai, I., Mohara, A., Tantivess, S., Chaisiri, K. & Teerawattananon, Y. Government use licenses in Thailand: an assessment of the health and economic impacts. *Global Health* **7**, 32 (2011).
37. BetaPharma. Welcome to BetaPharma – company information. *BetaPharma* [online], http://www.betapharma.com/index.html (2012).
38. Sun, Y. *et al.* A randomized, double-blind phase III study of icotinib versus gefitinib in patients with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy (ICOGEN) [abstract]. *J. Clin. Oncol.* **29** (Suppl.), a7522 (2011).
39. Liu, C. BIO 2012: development cost comparison, China vs. US. *Bioentrepreneur* [online], http://blogs.nature.com/tradesecrets/2012/07/02/bio-2012-development-cost-comparison-china-vs-us (2012).
40. Ranade, A. A. *et al.* A novel, cremophor-free, polymeric nanoparticle paclitaxel (do/ndr/02) multicenter study in advanced/metastatic breast cancer [abstract]. *J. Clin. Oncol.* **26** (Suppl.), a1115 (2008).
41. Westphal, M. & Bach, F. Final results of a randomized phase III trial of nimotuzumab for the treatment of newly diagnosed glioblastoma in addition to standard radiation and chemotherapy with temozolomide versus standard radiation and temozolomide [abstract]. *J. Clin. Oncol.* **30** (Suppl.), a2033 (2012).
42. Rodríguez, M. *et al.* Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck. *Cancer Biol. Ther.* **9**, 343–349 (2010).
43. Ahlstrom, D. & Bruton, G. D. *International Management: Strategy and Culture in the Emerging World* (Cengage Learning, 2010).
44. Glickman, S. W. *et al.* Ethical and scientific implications of the globalization of clinical research. *N. Engl. J. Med.* **360**, 816–823 (2009).
45. Garnier, J. P. Rebuilding the R&D engine in big pharma. *Harv. Bus. Rev.* **86**, 68–76 (2008).
46. Hornbeck, R. A. Price discrimination and smuggling of *AIDS* drugs. *Top. Econ. Anal. Pol.* **5**, Article 16 (2005).
47. [No authors listed] GlaxoSmithKline launches two cancer drugs at reduced prices. *The Hindu Business Line* [online], http://www.thehindubusinessline.com/companies/article2285697.ece (2011).
48. Darrow, J. J. Recent developments in health law. Essential medicines: why international price discrimination may increasingly be the wrong solution to a global drug problem. *J. Law Med. Ethics* **39**, 291–296 (2011).
49. The Max Foundation. What is GIPAP? *The Max Foundation* [online], http://www.themaxfoundation.org/GIPAP/Answers.aspx?q=13 (2010).
50. The Max Foundation. Glivec® International Patient Assistance Program (GIPAP). *The Max Foundation* [online], http://www.themaxfoundation.org/gipap/Default.aspx (2010).
51. Kollewe, J. Roche to offer discounted cancer drugs in India. *The Guardian* (23 Mar. 2012).
52. Rajan, A., Gutierrez-Ibarluzea, I. & Moharra, M. Addressing issues in health technology assessment promotion: motives, enablers, and barriers. *Int. J. Technol. Assess. Health Care* **27**, 55–63 (2011).
53. de Souza, J. A., Polite, B. N., Manning, W. G., Fendrick, A. M. & Ratain, M. J. Value-based insurance design in oncology. *Lancet Oncol.* **12**, 321–323 (2012).
54. The GAVI Alliance. *The GAVI Alliance* [online], http://www.gavialliance.org (2013).
55. International Finance Facility for Immunization. *IFFIm* [online], http://www.iffim.org/ (2013).
56. The Global Fund to Fight AIDS, Tuberculosis and Malaria. *The Global Fund to Fight AIDS, Tuberculosis and Malaria* [online], http://www.theglobalfund.org/ (2013).
57. [No authors listed] Cancer control in low and middle income countries. *Facebook* [online], http://www.facebook.com/CancerControlInLowAndMiddleIncomeCountries?ref=hl) (2013).
58. WHO. WHO model list of essential medicines (WHO, 2011).

Author contributions

All authors researched the data for the article, contributed to the discussion of the manuscript's content, wrote the manuscript and edited it before submission.