Access to Cancer Therapeutics in Low- and Middle-Income Countries

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OVERVIEW

Cancer is rapidly becoming a major health care problem, especially in developing countries, where 60% of the world's total new cases are diagnosed. The success of new antineoplastic medicines and modern radiation devices to cure a good proportion of patients with cancer and to alleviate the suffering of many more has been achieved at a dramatic cost. Therefore, it has become mandatory for health care authorities and pharmaceutical companies to cooperate to use and develop resources in an efficient manner to improve health care delivery to patients with cancer worldwide. Regulatory harmonization is an important key to overcome delays in the approval process, whether for antineoplastic and pain control medicines or for essential medical devices. More emphasis on the significant role of opiates in pain control among patients with cancer is needed to overcome the ingrained belief in their potential for addiction. The World Health Organization (WHO) serves an important role in guiding priorities for health care and efficiently allocating resources by providing essential medicine lists (EMLs) and device lists. However, the financial challenge for access to health care is multi-tiered and requires collaboration between key stakeholders including pharmaceutical industry, local national health authorities, WHO, and other nonprofit, patient-oriented organizations.

Since the turn of the century, we have seen a paradigm shift in the way we treat cancer, with the advent of targeted therapies, especially monoclonal antibodies and small-molecule kinase inhibitors. Indeed the development of imatinib in chronic myeloid leukemia (CML) and rituximab in B-cell lymphomas have been considered among the greatest breakthroughs in cancer care in the past 50 years. Unfortunately, these and many other therapies that have significantly improved outcomes in patients with cancer are not available to everyone who needs them, especially in low- and middle-income countries (LMICs). The cost of new anticancer medicines is increasing, with the average monthly cost of some newly released molecules being over $12,000 per month for oral kinase inhibitors and $150,000 for a course of monoclonal antibodies. These costs have long been out of the range of most LMICs and are now becoming excessive even for European and North American patients.

The treatment of cancer has always been costly and difficult to access, be it surgery, radiation therapy, systemic medicines, or palliative care. Radiation machines are costly and limited in access in LMICs, whereas chemotherapy drugs have always been difficult to procure since they first became available in the 1950s. Surgical care is limited by lack of skills and facilities, whereas access to palliative medicines, especially for pain control, is limited by regulatory and legal restrictions, costs, and storage, as well as cultural attitudes to end-of-life issues. Radiation machines should be procured and maintained in LMICs at reasonable prices without sacrificing safety and efficacy, whereas surgical skills should be enhanced by improving local facilities and training cancer surgeons on site or at international centers.

There are no easy solutions to drug costs because pharmaceutical companies should make profits to be able to develop new medicines, knowing that not all medicines undergoing study come to market and that antineoplastic agents, especially biologic medicines, are difficult and costly to produce. The current model of oncology drug development, distribution, and marketing must change before it is too late. There must be collaboration between academia and individual pharmaceutical companies, as well as with regulatory authorities and governments, to avoid the situation being experienced in renal cancer, where we now have more than 10 agents on the market from multiple pharmaceutical companies. Collaboration with regulatory authorities can

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reduce research and development costs by streamlining the regulatory burden on clinical research and expediting registration of medicines with significant benefits over those with limited benefits. Development of medicines with limited benefits should be halted as early as possible. "Evergreening" (enhanced intellectual property protection) must also be prevented; extended patents are detrimental to underfunded patients in both high-income countries and LMICs. International collaboration in the development of good quality generics and biosimilars will help make these molecules available more rapidly to patients around the world. Development of EMLs, both in individual countries and internationally by WHO, will make the use of cancer medicines more cost effective and less wasteful.

Unless we all work together to find a solution, cancer care will only be available to the very wealthy. Indeed, we are seeing the development of more and more exciting treatments for fewer and fewer people.[1]

DRUG ACCESS AND APPROVAL IN LOW- AND MIDDLE-INCOME COUNTRIES

Cancer is rapidly becoming a major health care problem, especially in LMICs. The success of antineoplastic medicines to cure patients and alleviate their suffering has been achieved at a dramatic cost. Therefore, it has become mandatory for health care authorities to cooperate to use resources efficiently to improve health care delivery to patients with cancer worldwide.

The initial step in the process of access to antineoplastic medicines is a pharmaceutical company's application for approval by the responsible local health regulatory authorities. The expected revenues of a medicine depend on the volume of drug sold and the average income of targeted populations.[2] For cancer, expected revenues in LMICs may not justify investment because the target population's average income is low. This lack of incentive compelling regulation to register medicines results in excessive delays in access to newer medicines.

Once an application for a new medicine is filed, the complex regulatory approval process starts to ensure availability of high-quality, safe, and effective medicines.[3] Although some countries can assess a new drug themselves, based on the scientific dossier provided by the manufacturer (usually high-income countries), middle-income countries with varying levels of development and drug regulatory capabilities, or low-income countries with very limited or no drug regulatory capability cannot undertake full assessments of new pharmaceutical products. LMICs depend to differing extents on assessment made by a foreign drug regulatory authority, for example the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA). Drug approval by one of these major authorities provides a valid basis for marketing a product in these LMICs. In an attempt to facilitate drug registration in LMICs, WHO has developed a certification scheme to provide quality assurance for imported medicines by means of standard forms confirming the registration of the product in the country of manufacture (Certificate of Pharmaceutical Product [CPP]) and approval of good manufacturing practice conditions based on inspections and quality analysis of the product.[4,5] However, even after 2 decades of existence, the WHO certification scheme is not widely used. Regulatory procedures still vary significantly among nations, with certificate format, conditions, and wording varying from one country to another.[6] Each country requires different documentation, but almost all require at least one CPP from the manufacturing site, the packaging and release site, or both. The process for registering medicines remains complex and burdened with inefficiencies, duplications, delay, and, in some instances, corruption.[7,8] For instance, the manufacturing process may take place in several countries, complicating the process of obtaining a satisfactory CPP for the regulatory authorities in importing countries. This will potentially delay regulatory approval if the regulatory authority requests different CPPs than what was already provided. Some products are manufactured and approved in a certain country for export only, leading to concern that the competent authorities in the manufacturing country are less stringent with regard to products not to be used in their own territory. It is logical for some importing country's regulatory authority to request more reassuring documentation (e.g., formal declaration signed by the manufacturer's responsible good manufacturing practice person in addition to the Export CPP), to ensure follow-up on complaints from the importing country's authority regarding product defects or inaccuracy of the declaration's contents. Still, the regulatory authority could refuse to register that product.[9,10] To further illustrate the complexity of implementing the WHO certification scheme, assessment of quality of active pharmaceutical ingredients was also recommended by the International Conference of

KEY POINTS

- **The majority of patients with cancer reside in LMICs with limited access to essential medicines and services, resulting in a disproportionate increase in cancer mortality.**
- **Obstacles to cancer care are numerous and include costs, regulatory and cultural barriers, and limited availability of health care practitioners.**
- **The financial challenge for access to care is multi-tiered and requires collaboration between all stakeholders including the pharmaceutical industry, national and local health authorities, nongovernmental organizations, and the World Health Organization.**
- **Regulatory, financial, and cultural barriers limit access to chemotherapy agents, supportive care medicines, radiation therapy, and complementary and alternative medicines required for good cancer pain management in LMICs.**
- **Collaborative partnerships and regulatory harmonization can overcome delays in treatment access and approval and facilitate the development of quality cancer care delivery.**

Drug Regulatory Authorities.[7,11] Such recommendations added to the confusion and complexity of drug approval processes in LMICs, especially because many do not yet have the regulatory capacity required to fully implement the WHO certification scheme, let alone comply with those recommendations.[12]

After a medicine's approval by EMA or FDA, it takes a year or more to register that medicine in LMICs. Some countries adopt "fast-track" for the registration of priority medicines fulfilling an unmet medical need.[13] Even in North America, it was estimated that more than 250,000 life-years are lost per year of delay in access to drugs that were shown to prolong overall survival in phase III clinical trials.[14] Even more life-years are lost if we consider the possible estimate in LMICs where the delay is more of a challenge and the disease burden is escalating. Regulatory harmonization (i.e., either allowing for one centralized approval for drug registration in multiple countries, or mutual recognition once a drug has been registered in certain countries) is the key to using resources more efficiently and especially to speeding up the process to facilitate access to patients.[7]

Once a medicine is registered, access varies from one country to another. Rarely, registration entails availability for patients treated in public health care systems. In some countries, even if the medicine were to be available, it takes an additional 1 to 2 years to obtain.[13] In most countries, medicines will only be available for those who can pay out of pocket, creating a financial access obstacle, probably the most challenging in the access process. In many LMICs, as much as 90% of the population purchase medicines on an out-of-pocket basis,[15,16] with spending often disproportionate to personal or family income. The recently updated WHO EML for cancer could potentially serve as a valuable asset for advocacy to influence the local health authorities in LMICs to provide those medicines free of charge or make them available for patients at affordable cost.[17]

The financial access challenge creates another serious concern of drug quality. Many reports have described patients receiving substandard or counterfeit drugs.[18,19] This is mainly the result of importing cheaper, poorly manufactured "rogue generics." Although some governments have begun to promote the development of generic drug manufacturing capacity within their own borders—as in India, Brazil, South Africa, and, recently, Jordan—many countries rely solely on importing drugs. In its effort to combat this challenge faced in every field of medicine, WHO developed a prequalification program for pharmaceuticals and active pharmaceutical ingredients,[20] initially developed to help international procurement agencies, but lately used by LMICs to guide bulk purchase of medicines. Drugs passing quality control appear on the WHO prequalification website; however, antineoplastic medicines are not there yet. Conversely, delayed market entry of generics because of evergreening in countries that joined the World Trade Organization further increases cost.[21] Such countries should consider increasing spending on public health to offset the adverse impact on patients of strengthening its intellectual property protection relevant to medicines, in addition to long-term plans to control the price increase as a result of that commitment. Compulsory licensing "allowing generic versions of medications to be produced despite the existence of a patent" to provide medicines of need in a society at affordable prices, is a plausible policy already adopted in India, South Africa, and Thailand.[22]

Direct price control measures could help reduce the price by an average of 20%.[23] Control measures could be price setting included in registration and procurement through a central government agency. Because most of antineoplastic medicines are not procured centrally, they are only available in the private sector for out-of-pocket purchase at much higher prices.[7] If price is adjusted for affordability, LMICs pay a much higher price compared with high-income countries.[24] The prices set for the recently developed biologics are prohibitive not only for out-of-pocket purchase but also for central procurement, creating the case for differential international pricing. Concerns related to this approach (e.g., parallel trading and use in reference pricing) do seem legitimate, but the experience with HIV treatment does not support those concerns.[22] However, this differential pricing is beneficial if the different pricing levels indeed reflect the ability of the target population to pay. This is amplified by The World Bank's country income classification; although it was designed for World Bank lending decisions, its improper adoption to inform health-related decisions increases the cost of medicines. It does not reflect health system capacity of governments to invest more in health, and it does not take into account income inequality within a nation. Many countries have graduated to become upper-middle income resulting from statistical recalculations, although 15% to 55% live at or below national poverty lines.[25] This graduation will further complicate drug pricing policies and availability of expanded drug access programs for patients. Regulatory harmonization is the key to overcome delays in the approval process and efficiently use resources. The financial challenge for access is multitiered and requires collaboration between key stakeholders including pharmaceutical industry, local national health authorities, WHO, and other nonprofit, patient-oriented organizations.

CULTURAL AND REGULATORY BARRIERS TO PAIN MANAGEMENT INCLUDING ANTICANCER DRUGS, RADIOTHERAPY, AND SUPPORTIVE MEDICINES IN LOW- AND MIDDLE-INCOME COUNTRIES

More than half of all patients with cancer and more than three-quarters of patients with advanced disease will suffer from pain at some time in the course of the illness. The pain is usually moderate to severe, affecting the patient's quality of life, and it can become chronic in long-term cancer survivors.[26]

The management of cancer pain is a multidisciplinary process that has many barriers confronting patients and their families, as well as health care professionals. There are many difficult aspects to the management of cancer pain in

both high-income countries and LMICs developing. Despite the high prevalence of cancer pain, it is often poorly treated for several reasons. To manage cancer pain effectively, it is important to assess the type of pain and its effect on quality of life and to decide on a management plan using appropriate interventions, analgesics, and supportive care as required. Interventions can include disease-modifying therapies such as chemotherapy, radiotherapy, or surgery. Analgesics include nonopioid and opioid drugs, as well as co-analgesic (adjuvant) drugs for pain that is either not responsive or partially responsive to opioids. Interventions and analgesics have side effects, which should be treated with further medications. Many societies and cultures use traditional or complementary and alternative medications and nondrug measures to control pain.

ORTHODOX MEDICINES

Cancer chemotherapy plays a critical role in reducing pain in patients with cancer by shrinking and, in certain malignancies, curing the cancer. As mentioned before, access to cancer chemotherapy has always been limited by costs and by slow regulatory approval in many LMICs. In South Africa, approval of a new chemical entity or generic medicine may take as many as 3 years unless a fast-track status is obtained, owing to an unmet medical need or public health requirement, which will reduce the time to about 18 months. Dossiers for registration have to go through three to four committees, including the Naming and Scheduling Committee, the Pharmaceutical and Analytic Committee, the Central Clinical Committee, and, in some cases, the Biologic Committee, all of which are understaffed. Many doctors in LMICs are reluctant to refer patients for chemotherapy because of myths concerning the side effects, and patients themselves have similar views often perpetuated by the media.

Opioid analgesics are the mainstay of cancer pain control but are frequently inadequately used because of doctors' and patients' fears concerning addiction and abuse. Longer-acting opioids including slow-release morphine and fentanyl patches are limited by slow regulatory approval of generics and high costs of the originator. Opiophobia is a significant barrier to pain control with opioid analgesics in LMICs.[27] Patient-related factors include fear of psychological dependence and stigma related to opioid use, especially where opioids are associated with criminal activity and gang violence.[28,29] Health professional–related opiophobia, including beliefs that opioids cause addiction, tolerance, or difficult-to-control side effects, is also a significant barrier to adequate pain treatment with opioids.[30]

Tricyclics, anticonvulsants, and particularly $\alpha 2\delta$ ligands gabapentin and pregabalin play an important role in the treatment of neuropathic pain but are often not available in LMICs because of slow regulation of generics and high costs of originators.

Osteoclast inhibitors including bisphosphonates and RANK-ligand inhibitors play an important role in the management of bone pain. Unfortunately, their availability is also limited by slow regulatory approvals and high costs (Sidebar).

SIDEBAR. Medicines Used for Management of Cancer Pain

Disease-Modifying Agents
- Chemotherapeutic agents

Analgesics
- Paracetamol
- Nonsteroidal anti-inflammatory drugs
- Weak opioids: codeine, tramadol.
- Strong opioids: morphine, fentanyl
- Local anesthesia

Co-analgesics (Adjuvants)
- Tricyclic antidepressants
- Anticonvulsants
- $\alpha 2\delta$ ligands: gabapentin and pregabalin
- Baclofen
- Benzodiazepines

Other Essential Medications
- Laxatives
- Antiemetics
- Proton-pump inhibitors
- Corticosteroids
- Bisphosphonates and RANK-ligand inhibitors

RADIATION THERAPY FACILITIES: LINEAR ACCELERATOR VERSUS COBALT 60

Linear accelerator access is limited by high up-front and maintenance costs, with less effective but low maintenance and cheaper cobalt 60 being supported in some LMICs by the International Atomic Energy Agency. In addition, cultural beliefs and use of traditional medicines likely affect the acceptability of radiation therapy for patients in LMICs. A study in San Francisco found that Chinese and other Asian women received less radiation or other adjuvant treatment of breast cancer than Japanese or white women, most likely because of cultural beliefs about disease and death, body image, medical decision making, and use of alternative medicines.[31]

TRADITIONAL OR COMPLEMENTARY AND ALTERNATIVE MEDICINES

The use of traditional or complementary and alternative medicines (TCAMs) varies across the world from 7% to 64%.[32] In LMICs, TCAMs are a natural element of traditional health practice. TCAMs are categorized by the National Centre for Complementary and Alternative Medicine in the United States (Table 1).[33]

There is limited evidence for the effectiveness of TCAMS in treating cancer pain. Differing responses to multidisciplinary pain programs have been noted where the mood symptoms improved in all patient groups but improvement in pain was culturally determined.[34] The effectiveness of TCAMs in managing cancer pain is dependent on cultural beliefs and expectations. However, reliance on TCAMs and resistance to

TABLE 1. Categories of Traditional or Complementary and Alternative Medicines

Category	Example
Alternative medical systems	Traditional Chinese, Ayurvedic, and African traditional medicine
Mind-body (spirit) interventions	Meditation, prayer, faith healing, support groups, music therapy, and hypnosis
Biologically based therapies	Herbal medicines, dietary supplements, vitamins
Manipulation and body-based therapies	TENS, acupuncture massage, chiropractic, osteopathy, and reflexology
Energy therapies	Qi Gong, Reiki, and magnetic field therapy

conventional interventions and opioids may exacerbate pain in LMICs.

CANNABINOIDS

Historically, the use of cannabis as medicine dates back to before the Christian era in Asia and spread to the Middle East in the 10th century, to Africa in the 15th century, to South America in the 16th century, and to Europe and the United States in the 19th century.[35] A meta-analysis of several controlled clinical trials supports the use of cannabinoids (dronabinol and nabilone) for chemotherapy-induced nausea and vomiting, but not for pain. There is no good evidence supporting the use of inhaled or oral extracts of cannabis for any cancer-related side effects.[36] Country- and state-specific barriers to legalizing cannabis for symptom control exist largely because of lack of adequate controls and concerns about abuse.

CULTURAL BARRIERS TO CANCER PAIN MANAGEMENT IN LOW- AND MIDDLE-INCOME COUNTRIES

Many studies on cultural barriers, reported in English, are largely associated with pain management in Western countries with cultural minorities, usually of ethnic groups originating from LMICs. These minority groups are often marginalized and from lower socioeconomic levels, which may confound the results because these groups often do not have equitable access to health care. In these countries, language barriers may also play a role in inaccurate pain assessment. It has been shown that nurses who share the same language as Arabic patients when assessing pain usually assigned similar ratings to the patients compared with non-Arabic–speaking nurses.[37] However, with this in mind, these studies may provide a proxy for studying cultural aspects of cancer pain management in LMICs.

Two reviews of ethnic and cultural differences in pain and pain management by Kwok and Bhuvanakrishna[38] and by Campbell and Edwards[34] reveal the following potential cultural barriers to pain management: (1) differences in perception of pain, health beliefs, and the meaning of pain with normalizing of the cancer experience; (2) reluctance to report pain because of negative stigma associated with cancer progression and fatalism, and a belief in accepting pain with stoicism; and (3) different coping practices with belief in traditional remedies, faith healing, prayer, or positive thinking.

There appear to be differences in the experience of physical pain, in the reporting of pain, and in the emotional response to pain, which may reflect differences in the meaning of pain in different cultures. There are cultural taboos and fears that limit access to pain-relieving medications, but there are also traditional practices that are used to manage pain. Although it is important to ensure that pain medications and modalities to treat pain are accessible to all, it is important to consider different cultural attitudes toward illness and pain and its management.

WORLD HEALTH ORGANIZATION LIST OF ESSENTIAL MEDICINES AND DEVICES: MAXIMIZING CANCER CARE VALUE AND SUPPORTING THE DEVELOPMENT OF CANCER DELIVERY PROGRAMS

Cancer is a group of very disparate malignant diseases, with the diagnostics and treatment varying widely among them. In addition, many patients require sophisticated surgery, radiation, and systemic therapies. High-quality pathology is required to make accurate diagnoses in almost all patients, and imaging is frequently necessary for cancer staging and assessment of treatment response and follow-up. There are many essential cancer medications with different cancers requiring different noninterchangeable agents. Many countries and ministries of health face daunting obstacles in establishing functional and quality services in all of these areas. Toward this end, the WHO has several processes aimed at aiding countries in the establishment and enhancement of cancer services.

The Essential Medicines List

In 1977 WHO published its first EML addressing medicines felt to be critical to treating many diseases, including cancer. In the intervening years, additional medicines were evaluated and added to the EML. In the case of cancer medicines, agents were added one at a time, without clear instruction about where the benefit for the medication existed. In 2012, the Union International for Cancer Control and the Dana-Farber Cancer Institute filed applications with WHO to add trastuzumab and imatinib to the EML for cancer. At that time, there were no targeted therapies or on-patent drugs on the EML for cancer. The applications argued that these two medicines dramatically alter the outcomes and survival rates for patients with HER2-positive breast cancer and CML, respectively, and that there were no less-costly alternatives having similar benefits. WHO deferred judgment and asked Union International for Cancer Control and Dana-Farber

Cancer Institute to lead a comprehensive review of the cancer EML.

In 2014, a process was undertaken to identify cancers where systemic therapies had significant impact. Cancers were chosen if they were of high burden, if systemic therapies had at least some benefit (such as non–small cell lung cancer) and if they had lower disease burden (such as CML), and if systemic therapies (e.g., imatinib) had a major impact on survival. In all, 27 diseases were evaluated, with separate applications for early-stage and metastatic disease for breast cancer and colorectal cancer. Nearly 100 oncologists from all continents were recruited to help in the process. For each disease, a document was created that included: (1) an executive summary; (2) public health relevance; (3) requirements for diagnosis, treatment, and monitoring; (4) overview of regimens; (5) review of benefits and harms (including references and systematic reviews); and (6) recommendations for additions to the EML.

Each disease-based document was initially written by a cancer expert or team of experts and reviewed and critiqued by at least two other experts or teams. A central committee then collated the work of all three groups to form a consensus-based document. The central committee added the section on public health relevance and references focusing on important phase III studies and systematic reviews, and in some cases costing information. Importantly, each document contained a section on diagnostics and specific needs for treatment and monitoring of patients. The documents were designed to provide critical information to governments and ministries to understand better what was needed to treat the particular disease and make administration of the listed medications safe and effective.

The approach in each document was regimen-based, rather than based on individual medications. For some diseases, such as CML, the regimen was a single drug; in this case imatinib, but for many diseases the regimen consisted of multiple drugs such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for Hodgkin lymphoma. In addition, the incremental benefit of the medicines was quantitated. As an example for diffuse large B-cell lymphoma, where surgery is required for biopsy and diagnosis but does not add at all to remission or cure rates, the medicines alone accounted for all benefits. In this case, the administration of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) would result in a 55% long-term remission rate, whereas the addition of rituximab to this regimen (*R*-CHOP) would provide an incremental benefit of 15%, bringing the long-term remission rate to 70%. In the case of early-stage breast cancer, where surgery is required and will result in cure for many patients, the medicines would have incremental benefit above surgery. In a hypothetical patient with node-negative, estrogen receptor–positive, HER2-negative breast cancer, surgery alone might result in a long-term remission rate of 70%. The addition of hormone therapy such as tamoxifen might give 15% incremental benefit to the long-term remission rate, bringing it to 85%, and the addition of adjuvant chemotherapy might add 5% more to the long-term remission rate, bringing it to 90%.

The disease-based documents contained specific information on dosing of each medication as well as schedule and duration of therapy. With this information, ministries of health could estimate annual drug needs by knowing the number of patients with each disease and the dose of each drug needed to treat a patient.

Drafts of the 29 disease-based documents were reviewed by an expert committee at an in-person meeting at WHO in November 2014, and finalized documents were submitted to WHO in December 2014. They were posted on the WHO website for public comment in January 2015. In April 2015, a WHO Expert Committee reviewed all documents, and in May 2015 made public their decisions. The documents had provided support for the 30 existing medications on the EML and recommended the addition of 22 medicines. WHO approved the 30 existing medications and added 16 new medicines to the list, whereas six were rejected. Approved medications included, for the first time, patented, costly agents (i.e., trastuzumab and imatinib). The rejected medicines included two second-generation tyrosine kinase inhibitors for CML (insufficient data to support them as more essential than imatinib), two EGFR antagonists for the treatment of non–small cell lung cancer (molecular testing frequently unavailable with modest incremental benefit), arsenic trioxide for the treatment of acute promyelocytic leukemia (insufficient data to support it as an essential medication), and diethylstilbestrol for the treatment of metastatic prostate cancer (mostly unavailable and toxic).[39]

The final documents and the revised EML for cancer are now available on the WHO website. Each medicine on the EML can be referenced back to a disease-based document supporting and delineating its contribution to treatment of the disease, something not previously available on the EML. Planning is underway to develop a mechanism for periodic reviews of the EML for cancer as new scientific data become available.

ESSENTIAL MEDICAL DEVICES FOR CANCER

In April 2015, WHO convened a group of experts with the goal of detailing needs for services critical to the diagnosis, evaluation, and treatment of patients with cancer. Based on the advice of this group, a steering committee of experts was formed and met at WHO in September 2015 to better outline a plan to accomplish the work. Committees were formed to delineate needs for pathology and laboratory services, radiology services, surgical services, administration of systemic therapies, and radiation therapy. Committee members were recommended by the steering committee and met via teleconference throughout 2015.

This work is also disease-based, using a subset of cancers to complete lists of essential medical devices for each of the categories listed before. The work is still underway, with plans to complete the lists in the first half of 2016.

THE ROLE OF WHO IN DEVELOPMENT OF CANCER TREATMENT PROGRAMS

WHO exists to serve its member states in the arena of health care. In many LMICs, ministries of health struggle with health care priorities as advances in control of infectious diseases and other important areas such as maternal-child health, noncommunicable diseases become increasing health burdens. In acknowledgment of this, the United Nations convened a high-level meeting in September 2011 to address the needs of noncommunicable diseases. The work of WHO flows from the recommendations of this meeting and follow-up meetings.

THE ROLE OF COUNTRIES AND MINISTRIES

WHO is providing guidance to countries and ministries on essential medicines and devices for the diagnosis and treatment of cancer. It remains, though, for individual countries to develop cancer plans specific to their needs and environment. In some LMICs, this is well underway, and in others, much remains to be done. Many countries have little or no in-country cancer care expertise—few, if any, pathologists, medical oncologists, radiation oncologists, and skilled nurses. Many countries have very limited resources and must prioritize their needs as best they can. Partnerships between cancer specialists from high-income countries and LMICs can help. External funding would help immensely to move the global cancer agenda forward, funding such as was raised for the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

All of this work aims at bringing affordable and high-quality cancer care to those who currently have little or no access. Patients who have treatable cancers with a high likelihood for cure in high-income countries are, in many locations, dying without treatment or with inadequate and poor-quality treatment. We should work together to erase this social and medical inequity.

CONCLUSION

Improving patient outcomes is not only achieved by the success of medicines or procedures in large phase III clinical trials. It is achieved when patients worldwide have ready access to those successful interventions and the infrastructure and human capacity to use those interventions safely and effectively. The challenges to such access are many, with regulatory, financial, and cultural barriers among the most important barriers to overcome. Success can only be accomplished by constant collaboration between key stakeholders, including the pharmaceutical industry, local and national health authorities, the WHO, and other nonprofit, patient-oriented organizations. The oncology community in high-income countries should have a humanitarian obligation to accompany those in LMICs to achieve these goals to the betterment of all.

References

1. Ruff P. Achieving treatment for all. ASCO Connection: The Best of ASCO Connection Commentary 2015; Special Edition 2014-2015: 35.
2. Villa S, Compagni A, Reich MR. Orphan drug legislation: lessons for neglected tropical diseases. *Int J Health Plann Manage*. 2009;24:27-42.
3. World Health Organization. Policy Perspectives on Medicine. http://whqlibdoc.who.int/hq/2003/WHO_EDM_2003.2.pdf. Accessed January 5, 2016.
4. World Health Organization. Model Certificate of a Pharmaceutical Product. http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/modelcertificate/en/. Accessed January 5, 2016.
5. World Health Organization. Certification scheme on the quality of pharmaceutical products moving in international commerce. http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/. Accessed January 5, 2016.
6. World Health Organization. Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce. http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index1.html. Accessed January 5, 2016.
7. World Health Organization. The World Medicines Situation 2011. http://apps.who.int/medicinedocs/en/m/abstract/Js20054en/. Accessed January 5, 2016.
8. World Health Organization. Measuring transparency in medicines registration, selection and procurement: four country assessment studies. http://www.who.int/medicines/areas/policy/goodgovernance/Transparency4CountryStudy.pdf. Accessed January 6, 2016.
9. Ministry of Public Health. Guidelines on Good Storage and Distribution Practices of Pharmaceutical Products in Lebanon. http://www.moph.gov.lb/Drugs/Documents/Guidelines-GSDPLebanon%28English%29.pdf. Accessed January 10, 2016.
10. World Health Organization. Proceedings of the Ninth International Conference of Drug Regulatory Authorities (ICDRA) - Berlin, Germany 25-April 29, 1999. http://apps.who.int/medicinedocs/en/d/Js4925e/. Accessed January 10, 2016.
11. World Health Organization. 15th International Conference of Drug Regulatory Authorities (ICDRA) - Tallinn, Estonia, 23-October 26, 2012, http://apps.who.int/medicinedocs/documents/s20142en/s20142en.pdf. Accessed January 10, 2016.
12. Doua JY, Van Geertruyden JP. Registering medicines for low-income countries: How suitable are the stringent review procedures of the World Health Organisation, the US Food and Drug Administration and the European Medicines Agency? Tropic Med Int Health. 2014;19:23-36.
13. Registration Requirements of the Pharmaceutical Products with Jordan FDA. http://www.nobles.com.jo/PharmaceuticalProducts/FormNo2-1Product/reg_req_of_the_pharmacutical_products_2-1.pdf. Accessed January 8, 2016.
14. Stewart DJ, Stewart AA, Wheatley-Price P, et al. Impact of time to drug approval on potential years of life lost: The compelling need for improved trial and regulatory efficiency. *16th World Conference on Lung Cancer*. Presented September 7, 2015.
15. Cameron A, Ewen M, Ross-Degnan D, et al. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet*. 2009;373:240-249.

16. O'Donnell O, van Doorslaer E, Rannan-Eliya RP, et al. Who pays for health care in Asia? *J Health Econ*. 2008;27:460-475.

17. World Health Organization. WHO Model List of Essential Medicines. 2015; http://www.who.int/entity/medicines/publications/essential-medicines/en/index.html. Accessed January 15, 2016.

18. Caudron JM, Ford N, Henkens M, et al. Substandard medicines in resource-poor settings: a problem that can no longer be ignored. *Trop Med Int Health*. 2008;13:1062-1072.

19. Gautam CS, Utreja A, Singal GL. Spurious and counterfeit drugs: a growing industry in the developing world. *Postgrad Med J*. 2009;85: 251-256.

20. World Health Organization. Prequalification Programme. A United Nations Programme Managed by WHO. http://apps.who.int/prequal/. Accessed January 4, 2016.

21. Abbott RB, Bader R, Bajjali L, et al. The price of medicines in Jordan: the cost of trade-based intellectual property. *J Generic Med.* 2012;9: 75-85.

22. Hoen Et, Law L-M. Access to cancer treatment. http://apps.who.int/medicinedocs/documents/s21758en/s21758en.pdf. Accessed March 2, 2016.

23. Schut FT, Van Bergeijk PA. International price discrimination: the pharmaceutical industry. *World Dev*. 1986;14:1141-1150.

24. Machado M, O'Brodovich R, Krahn M, et al. International drug price comparisons: quality assessment. *Rev Panam Salud Publica*. 2011;29:46-51.

25. The World Bank. Data. http://data.worldbank.org/country. Accessed January 10, 2016.

26. Blanchard C, Chetty S, Ganca L, et al. Guide to the treatment of cancer pain in South Africa. http://dx.doi.org/10.6084/m9.figshare.1612170. Accessed March 2, 2016.

27. Krakauer EL, Wenk R, Buitrago R, et al. Opioid inaccessibility and its human consequences: reports from the field. *J Pain Palliat Care Pharmacother*. 2010;24:239-243.

28. Bağçivan G, Tosun N, Kömürcü S, et al. Analysis of patient-related barriers in cancer pain management in Turkish patients. *J Pain Symptom Manage*. 2009;38:727-737.

29. Kim YC, Ahn JS, Calimag MM, et al; ACHEON Working Group. Current practices in cancer pain management in Asia: a survey of patients and physicians across 10 countries. *Cancer Med*. 2015;4:1196-1204.

30. Peker L, Celebi N, Canbay O, et al. Doctors' opinions, knowledge and attitudes towards cancer pain management in a university hospital. *Agri*. 2008;20:20-30.

31. Prehn AW, Topol B, Stewart S, et al. Differences in treatment patterns for localized breast carcinoma among Asian/Pacific islander women. *Cancer*. 2002;95:2268-2275.

32. Cassileth BR. Complementary therapies: overview and state of the art. *Cancer Nurs*. 1999;22:85-90.

33. Molassiotis A, Fernadez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol*. 2005;16:655-663.

34. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag*. 2012;2:219-230.

35. Zuardi AW. History of *cannabis* as a medicine: a review. *Rev Bras Psiquiatr*. 2006;28:153-157.

36. National Cancer Institute. Cannabis and Cannabinoids–Health Professional Version http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq. Accessed January 23, 2016.

37. Al-Atiyyat N. Cultural diversity and cancer pain. *J Hosp Palliat Nurs*. 2009;11:154-164.

38. Kwok W, Bhuvanakrishna T. The relationship between ethnicity and the pain experience of cancer patients: a systematic review. *Indian J Palliat Care*. 2014;20:194-200.

39. Shulman LN, Wagner CM, Barr R, et al. Proposing essential medicines to treat cancer: Methodologies, processes, and outcomes. *J Clin Oncol*. 2016;34:69-75.