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REVIEW ARTICLE

Proposing Essential Medicines to Treat Cancer: Methodologies, Processes, and Outcomes

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ABSTRACT

Purpose

A great proportion of the world's cancer burden resides in low- and middle-income countries where cancer care infrastructure is often weak or absent. Although treatment of cancer is multidisciplinary, involving surgery, radiation, systemic therapies, pathology, radiology, and other specialties, selection of medicines that have impact and are affordable has been particularly challenging in resource-constrained settings. In 2014, at the invitation of the WHO, the Union for International Cancer Control convened experts to develop an approach to propose essential cancer medicines to be included in the WHO Model Essential Medicines Lists (EML) for Adults and for Children, as well as a resulting new list of cancer medicines.

Methods

Experts identified 29 cancer types with potential for maximal treatment impact, on the basis of incidence and benefit of systemic therapies. More than 90 oncology experts from all continents drafted and reviewed disease-based documents outlining epidemiology, diagnostic needs, treatment options, and benefits and toxicities.

Results

Briefing documents were created for each disease, along with associated standard treatment regimens, resulting in a list of 52 cancer medicines. A comprehensive application was submitted as a revision to the existing cancer medicines on the WHO Model Lists. In May 2015, the WHO announced the addition of 16 medicines to the Adult EML and nine medicines to the Children's EML.

Conclusion

The list of medications proposed, and the ability to link each recommended medicine to specific diseases, should allow public officials to apply resources most effectively in developing and supporting nascent or growing cancer treatment programs.

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INTRODUCTION

It is now well documented and widely recognized that the majority of the world's cancer patients reside in countries where options for treatment are limited, are sometimes only affordable by the wealthy, or do not exist at all.[1,2] Substantial gains have been made over the past four decades in improving outcomes for patients with cancer, but these largely benefit patients living in high-income countries. An improved understanding of the biology of cancer that accompanies advances in cancer surgery, radiation therapy, and systemic therapies has been responsible for this progress.[3-5]

The creation of a cancer treatment program is complex and multidisciplinary by nature. Tissue procurement, pathology capacity, cancer surgery, medical oncology, nursing oncology, radiology, and radiation oncology are all necessary for optimal treatment. The public sector in all countries must develop and nurture all of these disciplines to best support cancer care at the same time as they establish mechanisms for financing and resource procurement. Each of these layers of service delivery is elaborate, and, although more research is needed, there are a number of important articles delineating the process of overcoming such challenges in resource-constrained settings.[6-14]

When making decisions about establishing or strengthening a national cancer program, policy makers must have knowledge of the number of patients with each disease seen in their country and which types of cancer can be affected. This analysis can be time consuming, and a disease-based

decision-making platform is one way that countries have prioritized medicines for procurement when resources are limited. Nonetheless, among the many cancer medicines that have been developed over the years, there is wide variation in availability and access—a variation that that carries its own implications and one that often follows the fault lines of cost rather than efficacy.

Many have begun calling for the narrowing of the gap between the haves and the have-nots in global cancer medicine.[15-23] Indeed, a major development in this area recently was the invitation by the WHO to the Union for International Cancer Control to review the WHO Model List of Essential Medicines (EML), section 8.2, which recommends chemotherapeutic and hormonal agents for cancer treatment. The result of this review has been two-fold: an application to the WHO Essential Medicines Secretariat in December 2014 as well as a proposed methodology for regular revisions over time.

The overarching objectives of this exercise were not only to develop a comprehensive proposal, but also to describe and document guiding principles for the prioritization of systemic therapies that are most essential for cancer treatment. This article is not meant to diminish the importance of other components of cancer care—pathology, surgery, or radiation—but rather will focus on cancer medicines as one component of care. Similar analyses for the other aspects of cancer care would be highly complementary.

METHODS

In January 2014, in response to the WHO invitation, the Union for International Cancer Control convened a group of oncology experts to review the existing pediatric and adult EMLs.[24,25] Although more information can be found on the WHO Web site and in the literature cited,[26,27] it is relevant to note here that applications for revisions to the Model List are accepted every 2 years (usually by agent, not by disease or disease category) and are deliberated on by a panel of invited experts in April of the given year. Full reviews of the cancer medicines on the WHO Model List were conducted in 1984,[28] 1994,[29] and, most recently, in 1999.[30]

This review was part of the regular cycle of applications to the WHO Expert Committee. Between January 2014 and December 2014, more than 90 individuals from all regions of the world contributed to the development of the 29 disease-based applications.[31] A working group of expert clinicians from around the world met at the WHO 1 month before submission to finalize the applications and identify the proposed medicines. As of the submission of this manuscript, the comprehensive proposal was under review by the WHO Expert Committee for deliberation in April 2015, with publication of decisions planned for the following month.

Choice of Diseases to Address

An initial series of in-person and telephone meetings defined which types of cancer should be addressed. Choices were based on a combination of disease burden (ie, incidence and prevalence) and the potential impact of systemic therapy (ie, medicines), mostly driven by impact rather than by disease burden. Breast cancer is an example of a disease with a high incidence and a high potential impact of systemic therapies. In wealthy countries, more than 80% of patients with breast cancer are long-term survivors.[32] Yet, estimates identify breast cancer as the leading cause of cancer death in women worldwide, which burdens health systems already strapped by minimal resources.[33] Non–small-cell lung cancer (NSCLC), conversely, is a high-incidence disease but one for which systemic therapy has a much more modest impact on survival, so it is included on the basis of disease burden.[34] Chronic myeloid leukemia (CML) is a rare disease but one for which oral therapy dramatically affects survival, so it is included on the basis of the impact of systemic therapy.[35] Diseases that were excluded from the analysis were based on low incidence, the lack of substantial impact of systemic therapies, or both.

Table 1. Diseases Included in the UICC Review and Proposal

Type of Cancer	
Adult	Pediatric
Acute myelogenous leukemia and acute promyelocytic leukemia (adult and pediatric)	Acute lymphoblastic leukemia
Chronic lymphocytic leukemia	Burkitt's lymphoma
Chronic myelogenous leukemia (adult and pediatric)	Ewing sarcoma
Diffuse large B-cell lymphoma	Hodgkin lymphoma
Early-stage breast cancer	Osteosarcoma
Early-stage cervical cancer	Retinoblastoma
Early-stage colon cancer	Rhabdomyosarcoma
Early-stage rectal cancer	Wilms tumor
Epithelial ovarian cancer	
Follicular lymphoma	
GI stromal tumor	
Gestational trophoblastic neoplasia	
Locally advanced squamous carcinoma of the head and neck	
Hodgkin lymphoma	
Kaposi's sarcoma	
Metastatic breast cancer	
Metastatic colorectal cancer	
Metastatic prostate cancer	
Nasopharyngeal carcinoma	
Non–small-cell lung cancer	
Ovarian germ cell tumors (adult and pediatric)	
Testicular germ cell tumors (adult and pediatric)	

Abbreviations: UICC, Union for International Cancer Control.

Traditionally, pediatric cancers have been considered separately from adult cancers in the WHO application process. Furthermore, disease-based recommendations already exist within the WHO for some childhood cancers. Thus, for the pediatric cancers that were considered to be a high burden and/or highly responsive to therapy, recommendations were made for revisions to the existing WHO Model List for Children and for additions to the Model List. Adult and pediatric diseases that were addressed are listed in Table 1.

Incidence of disease is a major contributor to public health relevance, together with other factors, such as age at diagnosis, cure rates, and potential for long-term remission. The data presented in these sections are derived from global estimates and are not country specific. Incidence of disease and age distribution is likely to vary geographically. Useful data sources include the International Agency for Research on Cancer, which maintains the GLOBOCAN database and includes national and regional data and projections.[18] In addition, the Institute for Health Metrics and Evaluation hosts a similar cancer data set: the Global Burden of Disease Study.[36] Although these repositories are a vital step toward our understanding of cancer burden worldwide, it remains optimal for policy makers to use national data, because regional projections may not be wholly reflective of cancer incidence or age distribution in a given country.

Process for Development and Completion of the Disease-Based Documents

More than 90 oncology specialists from all continents participated in the preparation of the disease-based documents. They were chosen on the basis of their areas of expertise and on geographic location, to gather a diversity of perspectives. A medical or pediatric oncologist who had specialized knowledge of the disease was engaged to produce the first draft of each disease-based document. He or she was asked to complete specific sections (Table 2) and could write these sections alone or recruit colleagues to help. Other consultants completed additional sections and documents (also in Table 2). A central team worked on collating information to put the documents into a consistent

Table 2. Disease-Based Documents

Section	Writer
Executive summary	Lead author(s)
Public health relevance	Staff
Requirements for diagnosis, treatment, and monitoring	Lead author(s)
Overview of regimens	Lead author(s)
Review of benefits and harms (including systematic reviews)	Lead author(s) and staff
Recommendations	Lead author(s)
Additions proposed for section 8.2 of EML	Lead author(s)
Supplementary documents	
Medicine prices from MSH price indicator guide (2014)	Staff
Costing scenarios	Staff
Regulatory information for recommended medicines	Staff
Patent status for recommended medicines	Staff
Granulocyte colony-stimulating factor	Lead author(s) and staff

Abbreviations: EML, Model List of Essential Medicines; MSH, Management Sciences for Health.

format. Each disease-based document was then reviewed by at least two additional disease specialists. On receiving each reviewed document, the central team synthesized the views of the different reviewers and created a consensus document. All disease-based documents were then, again, fully reviewed, evaluated, and discussed at an in-person meeting at the WHO headquarters in Geneva, Switzerland, in November 2014. Final documents were produced and submitted to the WHO in December 2014. The timeline for the work is shown in Table 3. It is important to note that there was enormous generosity and support by authors and reviewers, who received no compensation for the many hours devoted to this endeavor, which we believe reflects the groundswell of interest and commitment to global cancer medicine.[16]

Methodology to Evaluate Potential Impact of Systemic Agents

The value of systemic agents was assessed by reviewing treatment outcomes, including all therapeutic options—radiation, surgery, and regimens of systemic agents—and determining the relative contribution of single systemic agents and/or multidrug regimens in this context. Factors considered included the following: whether there was potential for long-term remission; whether the benefit was greater than a baseline benefit from surgery, as is the case with localized breast or colorectal cancer, versus a benefit entirely from systemic agents, such as with lymphomas; and the requirement or not of sophisticated pathology testing, such as genomic mutation analyses. The following hypothetical scenarios serve as examples of these different categories.

Large magnitude of treatment impact with medicines alone in a low- to moderate-incidence disease. Diffuse large B-cell lymphoma is a disease that is highly curable with medicines alone. Surgery offers no chance for cure (though biopsy is necessary to establish a diagnosis). Four old, relatively inexpensive medicines (ie, cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]), however, can cure approximately 55% of patients.[37] This represents an increase in the cure rate from 0% to 55% with CHOP alone. A newer biologic agent, the humanized monoclonal antibody rituximab, when added to CHOP, will increase the cure rate from 55% to greater than 70%.[22] Thus, rituximab increases the cure rate more than 15% from the cure rate of CHOP alone. Rituximab is much more costly than the four chemotherapy agents in CHOP and is more difficult to administer, so the improved cure rate comes with these costs. Our costing scenarios revealed that the cost of medicines in the CHOP with rituximab regimen are 30 times more expensive than CHOP, not including the additional costs related to administration of the agent (approximately $200 *v* $6,000 USD for six cycles of therapy).

Clinically relevant magnitude in cure rate with systemic therapy over surgery alone in a high-incidence disease. Early-stage breast cancer has a high cure rate in the developed world. Surgery is required for cure or long-term remission, with removal of the breast tumor and involved axillary lymph nodes. Without surgery, the chance for long-term remission is nil. A patient with stage II, estrogen receptor–positive, *HER2*-negative disease may have a cure rate of 70% with surgery alone (depending on the specifics of stage and biologic characteristics). Additional treatment with tamoxifen might increase the cure rate from 70% to 85%, therefore giving an incremental benefit of a 15% chance for cure versus surgery alone. The addition of chemotherapy to tamoxifen might increase the cure rate from 85% to 89%.[38,39] Because this is a high-burden disease in all parts of the world, the absolute number of saved lives with the addition of tamoxifen and chemotherapy would be substantial. Although not relevant to the recommendation for chemotherapy and tamoxifen, it is important to note that the medicines used to treat a woman with this disease profile could cost as little as $300 for the entire course of chemotherapy and 5 years of tamoxifen.

Table 3. Timeline for Cancer Medicines Review

Date	Process or Event
January-May 2014	Methodology and process determined by core group from the Dana-Farber Cancer Institute and UICC.
May 31, 2014	UICC held planning meeting with core group plus new contributors at the Annual Meeting of the American Society of Clinical Oncology in Chicago, IL.
June-August 2014	A total of 22 adult cancers (including adult and pediatric cancers) as well as seven pediatric-specific cancers were included in the 2014 review process. Authors and reviewers were identified for solicitation of disease-based briefings.
September-October 2014	Invited authors from all over the world prepared and submitted disease-based briefings (including regimens) for the adult and pediatric cancers.
October-November 2014	Peer reviewers from all over the world reviewed briefings, including the treatment regimens.
November 2014	Dana-Farber Cancer Institute and UICC group compiled final drafts of briefings and prepared supplementary documents (eg, regulatory information, costing and price information, patent status, G-CSF briefing).
November 17-19, 2014	Cancer Medicines Working Group meeting held in Geneva, Switzerland, with more than a dozen participants from around the world. Each cancer briefing was reviewed in detail, and all input was recorded in real time. Long-term solutions were also discussed.
November-December 2014	Disease briefings were revised according to working group input and finalized for submission; 52 cancer medicines were recommended in the review, and 22 of those medicines were not yet included in the current WHO Model List.
December 15, 2014	Application submitted to the WHO Medicines Secretariat.
January 7, 2015	Application posted online on WHO Web site for public comment.
April 20-24, 2015	WHO to host 20th Expert Committee meeting for the selection of medicines to the 2015 Model List of Essential Medicines.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; UICC, Union for International Cancer Control.

Large magnitude of palliative treatment impact in a low-incidence disease. CML is an uncommon disease and one that affects people of all ages, including children. Imatinib, an oral tyrosine kinase inhibitor of the *BCR-ABL* fusion protein, though not curative, offers a majority of patients long-term hematologic remission with acceptable toxicity and high quality of life—because many patients are young, productive life-years gained can be considerable. Though the incidence of CML is low, the prevalence becomes substantial with long-term disease control and life-long treatment with imatinib.[20] Imatinib should only be administered to patients whose leukemia cells contain the *BCR-ABL* fusion protein; therefore, access to molecular testing is required. The disease can be controlled before testing results with medications such as hydroxyurea.

Low to marginal magnitude of palliative treatment impact and extension of life in a high-incidence disease. NSCLC is one of the more common diseases worldwide and has a high mortality rate.[18,19] Even in wealthy parts of the world, most patients with NSCLC eventually die as a result of their disease; in the United States, the 5-year relative survival rate for NSCLC patients is approximately 15%.[40] Most patients present with metastatic disease—a disease that is never curable—and many patients who present with earlier-stage, potentially curable disease will have disease recurrence and will not survive.[41] For patients who present with metastatic NSCLC, the average survival without systemic therapy is approximately 6 months and increases to 10 to 12 months with doublet chemotherapy (eg, vinorelbine and cisplatin).[42] Despite the poor prognosis for most patients with NSCLC, chemotherapy does improve overall survival and should be available to patients in need.[43] When patients have tumor progression after first-line therapy, second-line chemotherapy offers only modest life extension[44,45]; in the context of this work, we often have not recommended use of second-line chemotherapy. Some patients with NSCLC will have targetable somatic mutations in their tumors, such as mutations in the epidermal growth factor receptor kinase region, or of anaplastic lymphoma kinase (*ALK*). In these instances, oral therapies can result in disease remission or stabilization, sometimes with long-term palliation and modest toxicity. Overall survival can be significantly prolonged and sometimes doubled, though no patients are cured.[46] In addition, the testing for these mutations currently is complex, not universally available, and expensive—though some are due to come off patent and should be more affordable in the near future.

Supportive Services

Administration of cancer medicines does not occur in isolation. A number of essential services must be available. Pathology is key for almost any cancer diagnosis. High-quality general histopathology contributes greatly as a first step, though it is often challenging in limited-resource settings.[12] Categorization of tumors as squamous cell carcinoma versus adenocarcinoma, versus lymphoma, is a critical first step but often insufficient. Immunohistochemistry can be important as in breast cancer, in which estrogen receptor status governs much of systemic therapy choices, as does *HER2* status if trastuzumab or similar medicines are available. Patients with suspected CML should have molecular confirmation of the BCR-ABL translocation before being prescribed imatinib, a costly medicine that will not be effective in patients whose leukemia cells lack this mutation. Novel and effective targeted biologic agents now utilized in NSCLC treatment, such as crizotinib, are only effective in patients whose tumors harbor specific mutations, such as *ALK*. Because only a small percentage of patients with NSCLC will have somatic *ALK* mutations, giving all patients with this disease a medicine such as crizotinib would be a poor use of resources and would add potential drug toxicity with no chance for benefit. Not all settings will have the ability to perform all tests; therefore, the procurement of drugs should be paired with the advancement of molecular diagnostic capacity.

Surgical resection of the primary tumor is required for potential cure of early-stage breast or colon cancer, for instance. Without the ability to perform safe and effective cancer surgery, adjuvant chemotherapy regimens will be palliative and not potentially curative. Authors point readers to an important and burgeoning set of literature on global surgical oncology in limited-resource settings.[47-50]

Stage IIB cervical cancer, for example, can be treated curatively with radiation and concurrent administration of cisplatin.[51] Cisplatin alone is not curative and in this circumstance likely works primarily as a radiation sensitizer. Therefore, procuring cisplatin to treat patients with stage IIB cervical cancer, if radiation is not available, is likely not to have a long-term impact on patients with this disease.

In regard to the use of systemic medicines, expertise in procurement, storage, supply chains, preparation, and administration is required, as is expertise in the monitoring of patients receiving these therapies. Capabilities for administration of parenteral medicines and necessary equipment, such as infusion pumps and monitoring devices, are required for safe and effective care. In addition, adequate blood product support is required for patients who receive intensive therapies, particularly those who have hematologic disorders, such as the acute leukemias.[52] The requirements differ depending on the treatment; therefore, specific recommendations are made in each disease-based document. Also, the contributors to this review who are clinical experts working in low-income settings provided unique reflections and responses to the realities of cancer care delivery within the disease briefings.

Choice of Regimens

Because each disease-based document was authored by one individual or a small group and reviewed and critiqued by at least two others, a variety of recommendations were taken into consideration. The core team collated all opinions, and, when necessary, obtained additional input from new experts; the result represents as much of a consensus as was possible. In all cases, there was input from multiple continents, and this wide geographic representation strengthened the process.

Finally, a standard regimen and, for many, alternative regimens, were agreed on for each disease. In the context of our application to the WHO, the word "standard" was applied after the regimen received its final review by the working group in November 2014; it is the result of as much consensus as could be achieved over the course of the 12-month review period. The disease-based documents, we hope, will allow policy makers to have more information to support decision-making processes within a specific national context. Criteria for choice included efficacy as well as toxicity. Cost was not a primary consideration for regimens with high levels of efficacy but was considered when benefit was marginal (as in NSCLC, for example).

Absolute and relative benefits were considered. As one example, a medicine might reduce the rate of relapse and death from 12% to 9%, which is a relative reduction of 25% but an absolute reduction of only 3%. For both patients and the EML decision-making process, the absolute figures are those that are most useful and more informative.

Systematic reviews of diseases and treatment options were utilized and referred to when possible and are referenced in the application. Key studies that provided strong support for use of one regimen versus another were also cited within the briefings (generally, large phase III trials).

Cost

Ideally, cost would not be a consideration when a person's well-being is concerned. However, even in wealthier countries such as the United States, cost now is becoming a major issue. For countries with relatively limited resources, cost is always a consideration. There is a wide spectrum of price for different medicines and, in some cases, the same medicine. Many of the older cytotoxic agents can be obtained relatively inexpensively, whereas newer biologic agents can be extremely expensive.

Because the purpose of this initiative was to determine the essential cancer medicines in a way that could be useful to policy makers, cost was a factor that was not ignored. A complete financial analysis of all recommended medicines in the standard regimen was beyond the scope of this work in the timeframe available. In addition, any costing data presented referred only to the cost of the antineoplastic medicines and did not take into consideration the cost of ancillary medications, such as antiemetics, or the cost of provision of care or other components of care, such as surgery or radiation, all of which are important as well. This area of research has received scant attention, and more investigation is highly needed,[53-55] as

Table 4. List of Recommended Medicines for Included Diseases

Medicine	Disease
Allopurinol	Supportive care
Anastrozole* (class)	Early-stage breast cancer, metastatic breast cancer
Arsenic trioxide*	Acute promyelocytic leukemia
Asparaginase	Acute lymphoblastic leukemia
ATRA*	Acute promyelocytic leukemia
Bendamustine*	Follicular lymphoma, chronic lymphocytic leukemia
Bicalutamide*	Metastatic prostate cancer
Bleomycin	Testicular germ cell tumor, ovarian germ cell tumor, Hodgkin lymphoma, Kaposi's sarcoma
Calcium folinate	Early-stage colon cancer, early-stage rectal cancer, gestational trophoblastic neoplasia, metastatic colorectal cancer
Capecitabine*	Early-stage colon cancer, early-stage rectal cancer, metastatic colorectal cancer, metastatic breast cancer
Carboplatin	Epithelial ovarian cancer, early-stage breast cancer, metastatic breast cancer, nasopharyngeal cancer, non–small-cell lung cancer, ovarian germ cell tumor, osteosarcoma, retinoblastoma
Chlorambucil	Chronic lymphocytic leukemia
Cisplatin*	Epithelial ovarian cancer, early-stage cervical cancer, head and neck cancer, testicular germ cell tumor, ovarian germ cell tumor, nasopharyngeal cancer, non–small-cell lung cancer, osteosarcoma
Cyclophosphamide	Chronic lymphocytic leukemia, diffuse large B-cell lymphoma, early-stage breast cancer, metastatic breast cancer, gestational trophoblastic neoplasia, Hodgkin lymphoma, follicular lymphoma, Burkitt's lymphoma, rhabdomyosarcoma, Ewing sarcoma, acute lymphoblastic leukemia
Cytarabine	Acute myelogenous leukemia, acute promyelocytic leukemia, acute lymphoblastic leukemia, Burkitt's lymphoma
Dacarbazine	Hodgkin lymphoma
Dactinomycin	Gestational trophoblastic neoplasia, rhabdomyosarcoma, Ewing sarcoma, Wilms tumor
Dasatinib*	Chronic myelogenous leukemia
Daunorubicin	Acute myelogenous leukemia, acute promyelocytic leukemia, acute lymphoblastic leukemia
Dexamethasone	Metastatic prostate cancer, ovarian germ cell tumor, acute lymphocytic leukemia
Diethylstilbesterol*	Metastatic prostate cancer
Docetaxel	Early-stage breast cancer, metastatic breast cancer, metastatic prostate cancer
Doxorubicin	Epithelial ovarian cancer, diffuse large B-cell lymphoma, early-stage breast cancer, Hodgkin lymphoma, Kaposi's sarcoma, follicular lymphoma, metastatic breast cancer, osteosarcoma, Ewing sarcoma, acute lymphoblastic leukemia, Wilms tumor, Burkitt's lymphoma
Erlotinib*	Non–small-cell lung cancer
Etoposide	Epithelial ovarian cancer, testicular germ cell tumor, gestational trophoblastic neoplasia, Hodgkin lymphoma, non–small-cell lung cancer, ovarian germ cell tumor, retinoblastoma, Ewing sarcoma, acute lymphoblastic leukemia, Burkitt's lymphoma
Fludarabine*	Chronic lymphocytic leukemia
Fluorouracil	Early-stage breast cancer, early-stage colon cancer, early-stage rectal cancer, metastatic colorectal cancer, nasopharyngeal cancer
G-CSF*	Supportive care
Gefitinib*	Non–small-cell lung cancer
Gemcitabine*	Epithelial ovarian cancer, non–small-cell lung cancer, metastatic breast cancer
Hydrocortisone	Acute lymphoblastic leukemia
Hydroxycarbamide	Chronic myeloid leukemia
Ifosfamide	Testicular germ cell tumor, ovarian germ cell tumor, osteosarcoma, Rhabdomyosarcoma, Ewing sarcoma
Imatinib*	Chronic myeloid leukemia, GI stromal tumor
Irinotecan*	Metastatic colorectal cancer
Leuprolide* (class)	Metastatic prostate cancer
Mercaptopurine	Acute lymphoblastic leukemia, acute promyelocytic leukemia
Mesna	Testicular germ cell tumor, ovarian germ cell tumor, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma
Methotrexate	Early-stage breast cancer, gestational trophoblastic neoplasia, osteosarcoma, acute lymphocytic leukemia, acute promyelocytic leukemia
Methylprednisolone	Acute lymphocytic leukemia
Nilotinib*	Chronic myeloid leukemia
Oxaliplatin*	Early-stage colon cancer, early-stage rectal cancer, metastatic colorectal cancer
Paclitaxel	Epithelial ovarian cancer, early-stage breast cancer, metastatic breast cancer, Kaposi's sarcoma, nasopharyngeal cancer, non–small-cell lung cancer, ovarian germ cell tumor
Prednisolone	Chronic lymphocytic leukemia, diffuse large B-cell lymphoma, Hodgkin lymphoma, follicular lymphoma, acute lymphoblastic leukemia, Burkitt's lymphoma
Procarbazine	Hodgkin lymphoma
Rituximab*	Diffuse large B-cell lymphoma, chronic lymphocytic leukemia, follicular lymphoma
Tamoxifen	Early-stage breast cancer, metastatic breast cancer
Thioguanine	Acute lymphoblastic leukemia
Trastuzumab*	Early-stage breast cancer, metastatic breast cancer
Vinblastine	Hodgkin lymphoma, Kaposi's sarcoma
Vincristine	Chronic lymphocytic leukemia, diffuse large B-cell lymphoma, gestational trophoblastic neoplasia, Hodgkin lymphoma, Kaposi's sarcoma, follicular lymphoma, retinoblastoma, rhabdomyosarcoma, Ewing sarcoma, acute lymphoblastic leukemia, Wilms tumor, Burkitt's lymphoma
Vinorelbine*	Non–small-cell lung cancer, metastatic breast cancer

Abbreviations: ATRA, all-trans-retinoic acid; G-CSF, granulocyte colony-stimulating factor.
*New medication.

we learned and are still learning in the case of HIV/AIDS and tuberculosis treatment cost analyses.[56-58]

Although some of the medicines recommended for addition to the EML are currently under patent protection and are only sold at a high price, there are some good examples of initiatives to expand the availability of such medicines to lower-income settings at an affordable price. To acknowledge that there is both a human rights imperative and a financial imperative to avail cancer medicines to patients with cancer worldwide, the authors believe inclusion on the WHO Model List as a critical step in the right direction to improve affordability, as was a widely held view for antiretroviral therapy. In addition, some medicines currently under patent will shortly come off of patent and are likely to be available at much lower prices (eg, gefitinib and imatinib).

Generation of a Proposal to Include New Cancer Medicines on the WHO EML

Each disease-based document lists required medicines. The application lists all proposed drugs together, including agents on the 2013 list and newly proposed agents. In the list of medicines, each agent refers back to diseases for which it is indicated. For example, a medicine such as cyclophosphamide has 11 diseases listed next to it, whereas an asparaginase only lists acute lymphocytic leukemia. We believe that this approach could be beneficial to all who use the EML.

Classes of medicines exist in parts of the WHO EML for many diseases. For cancer medicines, there are times when any medicine in a particular class would be acceptable. One example is aromatase inhibitors as treatment for breast cancer, for which it was recommended that anastrozole be added to the EML; letrozole and exemestane were considered in the same class and can be included on this basis. The platinum medicines, however, are examples of a class of medicine for which interchange is not always permissible. Oxaliplatin is efficacious in colon cancer but not in lung or ovarian cancer, in which carboplatin and cisplatin do have utility. Cisplatin is efficacious in combination with radiation therapy for stage II cervical cancer, but carboplatin and oxaliplatin are not acceptable replacements. The medicines within a class that are not interchangeable are listed specifically, and class inclusion is not implied. Thus, important recommendations were made to the WHO to separate the platinum medicines instead of listing them as a class.

The current and proposed list of medicines is shown in Table 4, together with the diseases for which they are the proposed treatment.

Utility of the WHO EML for Governments and Ministries of Health

Historically, the purpose of having a comprehensively updated WHO EML for cancer was to provide public officials guidance on purchase and procurement prioritization. It is the hope of the authors that a list that reflects drugs used to treat diseases for which systemic therapy has a high impact and/or diseases that are high burden will support national cancer programs. In addition, our application details dosing and scheduling for each regimen, which, if appended to the 2015 EML, could ease volume determination and supply chain planning and strengthening.

Keeping the EML Current

Cancer medicine is evolving rapidly. Studies are being presented and published that give us more accurate information about the optimal treatment for a particular disease, and new medicines are frequently being approved by regulatory agencies. An EML for cancer medicines, thus, is also likely to need regular review and revision. Organizations such as the National Comprehensive Cancer Network, which has developed treatment guidelines for many cancers, has a formal process to review and update guidelines on an annual basis. We would propose that a similar process be put into place for the EML for cancer, and we offer our support to the WHO and the Expert Committee on the selection and use of essential medicines and on potential mechanisms to do so. This new mechanism would be concerned with the addition of new types of cancer for therapy consideration and, thus, medicine addition, possible deletion if a medicine is superseded by another, and additional lines of treatment for current and added disease types.

In conclusion, a large and growing portion of the world's patients with cancer live in low- and middle-income countries. Many of these patients have cancers that are potentially curable or amenable to long-term remission with surgery, radiation, and systemic therapies. As policy makers and program managers strategize to develop and scale-up cancer treatment programs, it can be a challenging task to select systemic therapies that will have a major impact on patients in a national setting. The work described in this article is an attempt to provide some relevant and applicable guidance that, we hope, results in improved outcomes for patients around the world. The proposed list of recommended systemic therapies in the applications to WHO is provided in Table 4 along with the diseases for which they are included. The authors believe this effort to be just one component of the major movement required, and happening, in global cancer medicine as the world advances toward the dual aims of lowering cancer incidence and increasing access to cancer therapies.

Addendum

The World Health Organization Rules on EML. On May 8, 2015 (after the development of this manuscript), the WHO published its 2015 Model List of Essential Medicines for Adults, in which 16 of the 22 proposed new cancer medicines were included, bringing the total of approved cancer medicines to 46. The 2015 EML for Children included nine new medicines, eight of which had been approved for adults but not yet children. These new medicines for adults and children affect treatment regimen options for 26 different types of cancer, of the 29 cancer types considered. Furthermore, the WHO EMLs now include the disease-based regimens that are associated with each medicine, facilitating national formula development, procurement decisions, and supply chains.

The six medicines that were not approved were arsenic trioxide (acute promyelocytic leukemia), dasatinib and nilotinib (CML), diethylstilbesterol (prostate cancer), and erlotinib and gefitinib (NSCLC). The following limitations in the applications were observed that resulted in these medicines not being added to the 2015 list: the clinical impact of arsenic trioxide was not significant enough in treatment-naïve patients, and the price of the drug was extremely high; second-line CML therapy with nilotinib and dasatinib was not supported because of inadequate data demonstrating impact beyond existing treatment options; diethylstilbesterol's side effects are notably hazardous, and it had negligible to no advantage compared with alternative treatment options for prostate cancer; last, neither gefitinib nor erlotinib were included because of relatively modest impact of therapy coupled with infrastructural complexities and financial considerations surrounding molecular testing for *EGFR* mutations in patients with NSCLC. In addition, although oxaliplatin was approved for early-stage colon cancer and metastatic colorectal cancer, its use was not approved for early stage rectal cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Proposing Essential Medicines to Treat Cancer: Methodologies, Processes, and Outcomes

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