

SPECIAL REPORT

Medicines for Cancers in Children: The WHO Model for Selection of Essential Medicines

Jane Robertson, BPharm, MMed Sc, PhD,¹ Nicola Magrini, MD,^{1*} Ronald Barr, MB, ChB, MD,² Gilles Forte, BPharm, PhD,¹ and Clive Ondari, BPharm, PhD, MBA¹

Pressures to include more cancer medicines in the WHO Model List of Essential Medicines (EML) pose challenges for the Expert Committee responsible for recommending changes to the list. How do medicines for cancer fit within a definition of essential medicines as those meeting the priority health needs of the population? Will identifying a medicine as “essential” offer some leverage to improve access to effective cancer medicines in low and middle-income countries (LMICs)? The addition of a number of medicines for the treatment of cancers in children to the Model List of Essential Medicines for Children (EMLc) in 2011 provides important insights into previous Expert Committee decision-making and offers a platform for future deliberations. As combination chemotherapy is required for effective treatment of many malignancies, a disease-

based approach makes more sense than an agent-based approach. Inadequate financing to purchase essential medicines is a reality in many LMICs, thus a consideration of health impact is central to decisions on the selection and procurement of medicines. Inclusion in national EMLs should identify medicines that have priority for procurement in the public sector. This article will discuss some of the factors taken into account by the Expert Committee in developing the WHO EMLc. We argue that the disease-based approach coupled with the assessment of the magnitude of the clinical benefit provides an appropriate approach for considering further additions of medicines for pediatric cancers and for the review of the adult cancer section of the Model List. *Pediatr Blood Cancer* 2015;62:1689–1693. © 2015 World Health Organization

Key words: essential medicines; pediatric cancers; WHO model list

INTRODUCTION

The World Health Organization (WHO) strategy on access to medicines is based on the principles of evidence-based selection of a limited range of essential medicines, efficient procurement of quality-assured products, prices affordable to the health system and patients, effective distribution networks to ensure equitable access to needed medicines, and appropriate and responsible use of these agents in practice as elements of national pharmaceutical policies. These inter-related activities within the pharmaceutical sector must be addressed simultaneously to ensure that patients can have timely access to the medicines they need.

WHO Model List of Essential Medicines

The WHO Model List of Essential Medicines (EML) is not intended to be a comprehensive list of all effective medicines and is developed around the idea that “some medicines are more important than others”. [1] Essential medicines are those that meet the priority health care needs of the population and should be available in functioning health systems at all times at a price the individual and community can afford. [2] Widespread availability of essential medicines in the public sector is central to promoting equity of access. The Model List should guide the development of national and institutional essential medicines lists, be the basis of public sector procurement programs and inform schemes that reimburse medicine costs. Beyond country-level impact, the Model List is the basis of the medicine supply systems of major international organizations such as UNICEF and other not-for-profit supply agencies.

The first Model List in 1977 identified 208 medicines that together could provide safe, effective treatment for the majority of communicable and non-communicable diseases (NCDs). In 2015, the challenges of communicable diseases remain, however the prevention and management of NCDs including cancers are a major focus of international efforts, supported by an UN political declaration and a WHO NCD Global Action Plan. [3,4] Access to essential NCD medicines and health technologies are critical to progress.

This article will discuss some of the factors taken into account by the Expert Committee in developing the WHO Model List of Essential Medicines for Children (EMLc). We examine the approach used and its relevance for considering further additions of medicines for pediatric cancers and for the review of the adult cancer section of the Model List.

Essential Medicines for Cancer in Children

In 2009 the Expert Committee on the Selection and Use of Essential Medicines considered the relevance of including cytotoxics on the WHO EMLc. One view expressed was that the relevance of the WHO EMLc may be limited in countries with

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Abbreviations: ASCO, American Society of Clinical Oncology; ALL, Acute lymphoblastic leukemia; EML, Model List of Essential Medicines; EMLc, Model List of Essential Medicines for Children; EMLc, Model List of Essential Medicines for Children; G-CSF, Granulocyte colony-stimulating factor; LMICs, Low and middle-income countries; NEML, National Essential Medicine List; NICE, National Institute for Health and Care Excellence; PFS, Progression-free survival; UHC, Universal health coverage; WHO, World Health Organization; WHO-CHOICE, CHOosing Interventions that are Cost-Effective

¹Essential Medicines and Health Products Department, World Health Organization, Geneva, Switzerland; ²Departments of Pediatrics, Pathology and Medicine, McMaster University and McMaster Children’s Hospital, Hamilton, Ontario, Canada

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*Correspondence to: Nicola Magrini, Essential Medicines and Health Products Department, World Health Organization, 20, avenue Appia, 1211 Geneva 27, Switzerland. E-mail: magrini@who.int

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the capacity to purchase and safely administer cytotoxic agents and the capacity to develop protocols to guide their use.[5] However, an alternative argument was that the WHO Model List does guide the development of national EMLs, signalling the importance of the medicines and the need for governments to consider them as a priority for purchasing. The latter argument is particularly relevant in low and middle-income countries (LMICs), given that at least 80% of children with cancer live in these countries and access to curative treatments with long-term event-free survival and other highly effective therapy is often limited or non-existent.[6]

At the 2011 meeting, the Expert Committee endorsed the inclusion of medicines for the treatment of acute lymphoblastic leukemia (ALL), Wilms tumor and Burkitt lymphoma in the EMLc. (Table I) However, a request to include imatinib was refused, based on the rarity of chronic myelogenous leukemia in children, the limited evidence at that time of efficacy and safety in Philadelphia chromosome-positive ALL, and the high cost of the drug.[7] The inclusion of medicines for the three cancers in children does not imply these are the only tumor types for which there are effective treatments. The scope of cancers considered was determined by the application submitted to the Expert Committee. A more comprehensive review of tumour types in children was undertaken in preparation for the 2015 Expert Committee deliberations. This review used a disease-based rather than an agent-based approach recognizing that combination chemotherapy is required for effective treatment of many malignancies.[8] A consultative process involving pediatric and adult oncologists from around the world with subsequent extensive peer review of briefings and medicine regimens resulted in proposals for the addition of five medicines to the EMLc, i.e., cisplatin, carboplatin, ifosfamide, dacarbazine, and etoposide.[9] While these relate to applications to address treatments for rhabdomyosarcoma, retinoblastoma, osteosarcoma, Ewing sarcoma and Hodgkin lymphoma, (Table I) these medicines can also be used to manage other cancers in children.

Traditionally, essential medicines have been defined as those meeting the priority health care needs of the population.[2] Childhood cancers challenge this definition as they are rare rather than priority diseases based on estimates of incidence and prevalence; however, high cure rates make a compelling case for anti-neoplastic drugs being essential medicines for children. The Expert Committee has acknowledged previously that assessing public health relevance is broader than simple estimates of disease incidence and prevalence; other factors considered include the burden of the disease using estimates such as disability-adjusted life-years, addressing region-specific needs, (e.g., for the treatment of some tropical diseases), situations where there is a potentially large impact or high effectiveness of a medicine when the target condition is relatively uncommon, and the possible political impact of identifying a medicine as essential for the purpose of advocacy. [10]

The Committee has shown a willingness to take a disease-based approach, focusing on specific cancers rather than individual cytotoxic drugs, and has suggested some priority for listing curative treatments and those offering longer periods of remission over those delivering marginal gains in life expectancy. The experience of 2011 also indicates that the magnitude of the clinical benefit is the major criterion for selection and that cost implications are a relevant subsequent consideration.

A disease-based approach to cancer treatments presents a number of challenges, in particular in drawing boundaries around

TABLE I. Proposed List of Cancers in Children With Nominated Essential Medicines for EMLc 2015

Disease*	Medicine
Acute lymphoblastic leukemia	Asparaginase Cyclophosphamide Cytarabine Daunorubicin Dexamethasone Doxorubicin Etoposide Hydrocortisone Mercaptopurine Methotrexate Methylprednisolone Prednisolone Thioguanine Vincristine
Wilms tumour	Dactinomycin Doxorubicin Vincristine
Burkitt lymphoma	Cyclophosphamide Cytarabine Doxorubicin Etoposide Prednisolone Vincristine
Adjuvant medicines	Allopurinol Mesna
Ewing Sarcoma	Cyclophosphamide Doxorubicin Etoposide Ifosfamide ^a Vincristine
Hodgkin lymphoma	Cyclophosphamide Dacarbazine Doxorubicin Etoposide Prednisolone Vincristine
Osteosarcoma	Doxorubicin Carboplatin Cisplatin Ifosfamide ^a Methotrexate
Retinoblastoma	Carboplatin Etoposide Vincristine
Rhabdomyosarcoma	Cyclophosphamide Dactinomycin Ifosfamide ^a Vincristine

*Diseases and medicines in italics proposed for addition in 2015.

^aRequires accompanying mesna.

what should be included in a WHO Model List. The most effective treatments will be those used in first or second-line regimens; it is unclear whether the Expert Committee will consider the smaller, often marginal, clinical benefits of third and subsequent lines of therapy or regimens for metastatic disease sufficient to justify inclusion as essential medicines. These may be considered in subsequent rounds of revisions to the Model List. The listing of medicines on the EML also needs to take account of essential surgical and radiotherapeutic interventions that are the cornerstones

of the management of some cancers, thus strengthening the linkages between standard treatment guidelines and selection lists.

For ALL, Wilms tumor and Burkitt lymphoma in children, the Expert Committee opted only for the inclusion of medicines for steps 1 and 2 of the treatment protocols where step 1 designated a common regimen for all patients and step 2 introduced additional drugs for high risk patients. This stepladder approach of essential medicine requirements was presented in the 2011 review of agents for the treatment of common tumors in children.[11] The Expert Committee declined to include medicines for steps 3–5 (step 3: dose intensification regimens and alternatives for steps 1 and 2; step 4: drugs requiring intensive monitoring and supportive treatment to ensure safe use; step 5: full range of treatment options, including hematopoietic stem cell transplant where appropriate). Future applications to the Committee will address treatment beyond steps 1 and 2. It is possible that the Committee may again choose to identify core essential medicines that address steps 1 and 2 or may identify effective treatments further along the therapeutic algorithm that might be considered essential in countries with the resources and capacity to deliver higher levels of cancer care. Thus the list would be more than a basic list of cancer medicines and adaptable to the needs of countries with different levels of cancer service provision.

Magnitude of Clinical Benefit and Prioritising for Gain

Cure and improvements in overall survival are the most important clinical outcomes. In 1996 the American Society of Clinical Oncology (ASCO) expressed the view that “*in general, there is no minimum benefit above which treatments are justified; rather, benefits should be balanced against toxicity and cost.*”[12] Recent criticisms of the growing costs of cancer care and the subsequent burden on health care systems have focused attention on the magnitude of the clinical benefit that is offered by some new expensive therapies. Some commentators have suggested the need to raise the bar of efficacy for regulatory approval of medicines in oncology, and that trials should not be declared positive unless they show pre-specified clinically important differences in survival. [13,14]

The ASCO Cancer Research Committee has convened four disease-specific working groups to define clinically meaningful goals for trials in pancreas, breast, lung, and colon cancer.[15] All four groups selected overall survival as the primary clinical endpoint, stipulating a hazard ratio (HR) ≤ 0.8 corresponding to improvement in median overall survival of 2.5–6 months, depending on the setting, as the minimum incremental improvement over standard therapy that defines a clinically meaningful outcome. The European Society for Medical Oncology (ESMO) is working to develop validated and reproducible tools to formally assess the clinical benefits of cancer treatments.[16] The tools prioritise outcomes (living longer versus living better with improvements in quality of life) and try to distinguish highly beneficial treatments from those with modest, limited or marginal benefits. Curative and non-curative interventions are assessed separately, and threshold values for hazard ratios, absolute gains for overall survival, disease-free survival and progression-free survival (PFS) are being developed and field tested.

Attempts to specify clinically relevant improvements are not new. In 2009 the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom addressed additional criteria for the appraisal of end of life treatments, proposing that in

patients with a short life expectancy, normally less than 24 months, there should be “sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.”[17] Writing on the possible links between clinical benefit and drug pricing, Kantarjian and colleagues suggest that extremely effective drugs could be those that prolong survival by more than 6 months or by more than one-third of life expectancy (e.g., 12 months becomes ≥ 16 months), or drugs that improve long-term survival or PFS by more than an absolute 10%. The authors contrast these benefits with medicines offering minimal efficacy (“statistically significant” survival benefits of ≤ 2 months or that produce an increase in survival of less than a relative 15%).[18] Fojo and colleagues note the importance of standardized measures of clinically meaningful improvement as a part of a community conversation regarding the sustainability of the current trajectory of expenditure on cancer care in the United States.[19]

It is unclear if the WHO Expert Committee will propose or define, in absolute terms, a clinically relevant benefit for cancer treatment as a means of deciding which anti-neoplastic drugs to include as essential medicines in the Model List. However, considering medicines along a scale of benefits may assist countries to choose and prioritise cytotoxic agents for national EMLs and seems consistent with the previous listings in the EMLc. Particularly challenging for decision-makers are the interventions that are highly effective in small subsets of cancer patients with specific genetic mutations or translocations, and where there is no or limited treatment response in most patients.[20] Decisions will depend on country-level capacity to accurately test and identify those patients who are likely to benefit from treatment.

Costs of Cancer Medicines From a Health Systems Perspective

Guidance from the WHO Executive Board in 2001 proposed that any new addition to the Model List would take due regard of the public health significance, efficacy, safety, adverse events, comparative efficacy and cost-effectiveness of the medicine, noting that neither absolute treatment cost nor patent status should be a reason to reject a proposed addition to the Model List.[21] There are no universally agreed principles of economic analysis that apply to decision-making at the global level. Incremental or marginal cost-effectiveness analyses are predicated on assumptions about existing levels of care and answer questions about how to spend the next available health dollar. This may inform decision-making at the country level where implicit or explicit thresholds for cost-effectiveness exist. However, it is less certain that such economic analyses are relevant to inform decision-making in LMICs where there are severe budget constraints, and the opportunity costs of spending in one area of health at the expense of another (or another area of public sector infrastructure) are more obvious. Simpler and more straightforward presentations of the budget implications of treatments at the country level may be more appropriate.

Alternative approaches such as those of WHO-CHOICE (CHOosing Interventions that are Cost-Effective) aim to provide policy makers with evidence for deciding on interventions and programs that maximize health for the available resources.[22] The generalized cost-effectiveness analysis makes no assumptions about comparator treatments, but takes account of setting-specific factors such as the burden of disease, health system practice, and

economic conditions. These types of analyses might be applied in LMICs to determine which interventions for cancer in children provide the maximum health gains for the available resources and can be included in national cancer programs.

The challenges of cancer treatment costs extend beyond the direct costs of medicines and relate to overall health system capacity. In sub-Saharan Africa, the 2012 per capita government expenditure on health (US\$) was as low as \$10.4 in Uganda, \$17.0 in Benin and Kenya, and \$47.4 in Ghana compared to \$308.8 in South Africa, \$3009.4 in the UK and \$5538.4 in Switzerland.[23] These financial constraints in LMICs contribute to a limited supply of medicines and small numbers of specialised treatment centres compounded by delayed diagnoses requiring treatment for more advanced disease (or disease presenting too late for treatment), poor management of drug administration and related toxicity complicated by comorbidities especially malnutrition. [20,24] Five-year survival rates have been found to be directly proportional to a number of demographic, economic, and health indicators; most substantially annual government healthcare expenditure per capita. [25]

High rates of treatment-related morbidity and mortality associated with intensive chemotherapy and radiation therapy require management in appropriate clinical care environments and by access to often expensive antimicrobials to manage febrile neutropenia. National medicine budgets in LMICs will be challenged to provide access to these agents. Granulocyte colony stimulating factor (G-CSF) may have a role in reducing the incidence of febrile neutropenia and morbidity of cancer chemotherapy, and is mandatory for some pediatric cancer protocols.[26] However it can be an expensive agent and is not yet included in the WHO Model List of Essential Medicines. Even in high-income settings, the appropriate role of G-CSF is being debated as part of measures in oncology aimed at improving care while reducing costs.[27]

An integral part of cancer treatment is access to medicines for symptom relief and palliative care. A section addressing some palliative care needs was added to the EMLc in 2013 following a submission from the International Association for Hospice and Palliative Care. While listing as an essential medicine cannot guarantee availability, the EML should identify priority medicines for procurement in the public sector. In the case of morphine and related opioid medicines, national legislative requirements limit access to medicines for pain relief.

Issues of Feasibility and Implementation in Providing Cancer Services

Developing national cancer programs is much more than identifying and procuring essential cancer medicines. In proposing a global list, the Expert Committee must take account of the wide variability in capacity and constraints to the delivery of high quality cancer services at the country level. There are problems with the availability of equipment for radiotherapy in many LMICs, limiting radiotherapy as a treatment option that is central to the management of some cancers.[28] WHO is working to develop a list of priority medical devices for cancer management, to include the continuum of screening, diagnosis, treatment and palliative care, targeting LMICs as part of a project funded by OFID (The OPEC Fund for International Development). The resultant document and ultimate in-country implementation exercises aim to support countries as

they develop or improve national selection of devices for cancer care adapted to their health care settings.

The small numbers of trained oncologists in many LMICs further limits the types of cancer services that can be provided. Some experts have suggested that systems of care that do not require on-site oncologists are the only way to ensure treatment for many of the world's cancer patients.[29] Intensity-graduated treatments adjusted to the local capacity are proposed as one approach to selecting essential medicines, with more complex and demanding treatment regimens provided as experience and incremental resources permit.[30,31] In the Dominican Republic from 2005–2007 the two year survival rate for ALL in childhood was 40% and the toxic death rate 32%; but by reducing the intensity of the regimen to better match local “circumstances”, the survival rate increased to 70% and the toxic death rate dropped to 8%.[32]

The burden of pediatric cancer care regimens is illustrated by high rates of treatment abandonment in LMICs. [33,34] A review of 162 children diagnosed with cancer between 2008 and 2010 in Zambia found that only 13 (8%) completed a treatment regimen. [29] Most patients died during treatment (46%) or abandoned therapy (46%). Improved access to health insurance, support for transport costs, parental education, psychosocial support and communication with health care providers are important elements in reducing abandonment rates. In addition there may be socio-cultural issues with a sense of fatalism surrounding a cancer diagnosis, mistrust of the health care system, competing socio-economic demands and fear of specific components of treatment, such as chemotherapy, radical surgery and radiation that limit uptake of cancer treatment services.[35]

As survival rates for cancers in childhood have increased, so has the evidence of morbidity and earlier mortality of cancer survivors who develop chronic conditions or experience severe or life-threatening complications during adulthood.[36] In well-resourced settings the risks of these late effects can be managed, in part, by lifelong screening, surveillance, and the use of preventive therapies when needed. Regular follow-up and monitoring of cancer survivors will be much more challenging in LMICs.

The Role of the WHO Model List and Universal Health Coverage

WHO defines universal health coverage (UHC) as ensuring that all people can use the promotion, prevention, curative, rehabilitation, and palliative health services they need, that they are of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship.[37] In practice, UHC is most likely to be implemented as a gradual expansion of access to care beginning from an often narrow set of essential health services in LMICs. The scope of the services offered will be country and context-specific, and reflect the financial and human resources available to provide health care services. The *Seguro Popular* program in Mexico is an example of a national commitment to providing comprehensive health services, including access to care for children with ALL and other malignancies, implemented over a decade with financial protection for citizens who were previously excluded from insurance.[38] While such programs can increase coverage rates, achieving equitable pediatric cancer care is difficult. Evidence from Mexico demonstrates that while access to care has improved, regional differences in survival rates persist.[39]

At the country level, progress in UHC requires difficult resource allocation decisions and prioritisation among interventions, including those beyond the health sector. Effective tools are needed to support this decision-making to ensure the most efficient use of limited resources. Amongst these, the WHO Model List plays an important role in identifying essential medicines to support a country's health priorities. This assumes that decisions at the global level for the Model List influence medicine choices at the country level and for national EMLs. While there are few direct data available to support this contention, there was widespread Member State support for a resolution on improving access to essential medicines at the 2014 World Health Assembly. The Resolution (WHA67.22) requested that WHO "support Member States in sharing best practices in the selection of essential medicines and in developing processes for the selection of medicines for national essential medicines lists." [40]

CONCLUSIONS

High cure rates (exceeding 80% overall) or large magnitude of clinical benefit are strong arguments for continuing to review and update medicines for the treatment of cancers in children to the WHO Model List of Essential Medicines. Many of the agents recommended in the standard treatment protocols for cancers in children show such benefit and are relatively inexpensive, with established track records of known and acceptable safety. Notwithstanding the challenges of limited health budgets, it is important to take a disease-by-disease approach to decision-making, and to support countries to adopt or adapt global recommendations for their national EMLs. The inclusion of the most effective medicine regimens in the WHO Model List will contribute to giving cancer management the priority it deserves as part of the UN agenda to address non-communicable diseases and enhance access to essential medicines by children with cancer world-wide.

A disease-based approach coupled with the assessment of the magnitude of the clinical benefit provides an appropriate approach for considering further additions of medicines for pediatric cancers and for the review of the adult cancer section of the WHO Model List.

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