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ISOPP is a global society of oncology pharmacy practitioners with a diverse membership representing every continent (excluding Antarctica!)
Our mission is to advance oncology pharmacy care and improve the quality of life of patients with cancer throughout the world. We achieve this by providing education, professional development activities, and the development of global Standards of Practice for oncology pharmacy. Through our Advocacy Task Force, we work together with national and global partners (e.g. UICC) to build oncology pharmacy capacity in under-resourced areas of the world and to advocate for equitable access to oncology and supportive care medicines. As such, we are pleased to be invited to comment on this years proposed additions to the WHO Essential Medicines List for cancer and look forward to working with WHO and the global oncology community.

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ISOPP Commentary on cost/ affordability of agents proposed for addition to the WHO EML Cancer list 2021

This commentary applies to the following agents for proposed addition to the WHO EML Cancer list: ***Anti PD1 Inhibitors, Anakinra, BRAF/MEK Inhibitors, Cyclin Dependent Kinase CDK4,6 Inhibitors, Osimertinib, Pertuzumab, Ibrutinib, Fulvestrant, Daratumumab, Tislelizumab, Zanubrutinib, Rasburicase***

The inclusion of essential cancer medicines in national medicines lists has been quite uneven around the world. High-income countries (HICs) have been able to ensure greater accessibility to essential cancer medicines compared to Low-and-Middle-income countries (LMICs)[1]. Many LMICs are increasingly referencing and utilizing the WHO EML as a guide for the development of national medicine lists. Kenya uses the WHO essential list as a model and a template for development and review of the national essential medicines list. Thailand also uses WHO EML as a guide. In Brazil however, while there is a national EML, antineoplastic agents are not part of the list. Since 2010, the Brazilian EML has become a list of "financeable" medicines[2].
In Malaysia, medicines included in the WHO EML are not necessarily listed on the Malaysian Essential drug list, but all are generally marketed and available in innovator or generic form.

Cancer treatment is expensive, and the high prices of cancer medicines are significantly impacting access to these agents in LMICs[3]. A recent systematic review showed that in LMICs, there are wide variations in cancer drug prices and availability amongst brands and across different countries. The inaffordability of these agents by patients with low-income levels, has resulted in treatment abandonment sometimes in the setting of curable disease[4]. Access to cancer medicines is a particular problem for children in LMICs; a tragedy given that many pediatric cancers have high cure rates[5-7]. Drug shortages and increasing drug costs are impacting children and adolescents with cancer in HICs as well, especially when pediatric formulations/vial sizes are unavailable[8].

Across the LMICs, disparities exist in care between the public and the private healthcare settings as well as between larger teaching and/or referral healthcare settings and smaller facilities.
In Thailand for example, the University hospitals have more oncology drugs available than local hospitals.

Aguiar et al[9] point out that the increasing costs of newly approved/marketed antineoplastic medicines, (as high as $150 000/patient per year) represent a major barrier to patients' access to treatments globally. In Brazil, for example, patients' access to innovative treatments depends greatly on whether the individual has private health insurance. In the public health sector, patients' access to cost-effective innovative treatments varies according to the financial capacity of the facility, leading to inequalities within the same healthcare system[9].

The reimbursement models for new agents in some countries do not support full courses of treatment for some cancers or may hinder standardization and rational use of anticancer medicines nationally. Oncology drug funding in Brazil falls into this category with reimbursement of medicines being linked to specific diagnoses and 'line of treatment'[10]. As such each service can use the medicines it deems most appropriate for the patient, provided they are registered in Brazil. This model fosters disparity in the therapeutic approaches of cancer care facilities, resulting in inequity in access to anticancer medicine and disparate outcomes for similar cancers. Clinical Protocols and Therapeutic Guidelines for all types of cancers are not available[10]. Therefore, there is no standardization of treatment, making it impossible to assess the quality of care provided by different cancer care facilities. In Kenya, the National Hospital Insurance Fund (NHIF) reimburses a standard rate of approximately USD 250 (KES 25000) per cycle of first line treatment to a maximum of six cycles and approximately USD 1500 (KES 150000) per cycle of second line and complex treatment to a maximum of four cycles per financial year. In other countries e.g. Zimbabwe, there is no public funder of health care and the majority of the population does not have health coverage. Therefore, patients who are not privately insured fund their own treatment. In these populations, cost-minimisation tends to take precedence over cost-effectiveness during selection of recommended treatments.

In practice, even if an essential cancer medicine is included on a national medicines list, cost might preclude its use, it might be prescribed or used inappropriately, poor system infrastructure might prevent it being accessed by those who could benefit, or drug quality may be suspect. There is also need for harmonization of drug selection with registration. Some of the medicines listed as essential medicines or complementary are also not readily available in the LMICs. Kenya listed Pembrolizumab 100mg/4ml in the KEML as a fee for service product. However, the medicine remains unregistered by the pharmacy and poisons board of Kenya and availability is on special import permit. Nivolumab is also currently not registered. Medicines which undergo the special import route undergo less stringent regulation, and the risk of importation of substandard/ counterfeit medicines increases. This is particularly a challenge with biologics which do not have established biosimilar status e.g. daratumumab, pembrolizumab, nivolumab and other monoclonal antibodies. There may be a need for centralised review e.g. WHO pre-qualification and publication of a list of pre-qualified products.

Other examples include Rasburicase (vs Allopurinol) listing as standard prophylactic therapy for all patients across the LMICs which would be challenging to implement because there is lack of published data linking it to better reduction of clinical TLS, Acute Kidney Injury (AKI) & mortality https://pubmed.ncbi.nlm.nih.gov/28272834/. On the other

hand, listing it as standard treatment for established TLS sounds more justifiable especially for resource restricted countries/regions where renal replacement therapy is not readily available & patients usually present to the hospital late. In such scenario, the goal would be to get the uric acid level down as soon as possible.

Rasburicase is not on the Malaysian Essential Drug List and is not marketed in Malaysia (not registered with the Drug Control Authority of Malaysia). Special permits must be acquired from the Ministry of Health and its use is limited to the treatment of established TLS.
Generic Rasburicase (1.5mg) can be acquired at around 400+ Ringgit Malaysia which is much cheaper than the innovator.

Kenya listed Rasburicase 7.5mg/vial on the Kenya Essential Medicine List 2019. However, the medicine is not currently registered/retained by the pharmacy and poisons board and remains unavailable in the public hospitals.

Of the medicines recommended for inclusion on the WHO EML, the following are currently registered with the Kenya Pharmacy and Posions Board mostly as the innovator: Enzalutamide, Everolimus and Palbociclib (CDK 4, 6 Inhibitor). Many of the medicines included in WHO EML 2019 and consequently on KEML 2019 remain unavailable and are not currently registered for use in the country. In Brazil all cancer medicines recommended for inclusion on the WHO EML are currently registered.

Potential strategies to address the access problems should be discussed and implemented. Suggestions include: universal health coverage for essential cancer medicines, more equitable models for pricing cancer medicines, reducing development costs, optimizing regulation, and improving reliability in the global supply chain[11]. Access and affordability of biomarker testing required to identify patients who are most likely to benefit from some of these cancer medicines are a barrier for LMICs[11]. It is also noteworthy that the optimum use of cancer medicines depends on the effective delivery of multiple health care services and the proper training of [allied] health care workers.

Other strategies to improve access, can involve: managing costs through regional cooperation; coordinated procurement mechanisms; comprehensive pricing policies; differential pricing; licensing agreements; expanding the mandate of the International Agency for Research on Cancer (IARC) so that it can facilitate the affordable procurement of oncology drugs by LMICs; discuss the interaction of intellectual property rights with the international trade regime and how trade agreements can and do impact cancer treatment access and affordability; and stimulate the production of generic and biosimilar medicines.[12-18]

The cost/affordability of the drugs we have identified, coupled with the health care system infrastructure/resources required to deliver them make these agents highly unlikely to be ‘adoptable’ to National EML lists/formularies in LMICs. This is largely informed by the poor/non-uptake of costly agents currently on the list by health authorities in LMICs. We ask the Expert Committee to consider these cost implications in making their final decision on adding these agents to the WHO EML for cancer.

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