Evidence of clinical benefit of WHO essential anticancer medicines for children, 2011–2021

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Summary

Background Access to essential cancer medicines is a key determinant of childhood cancer survival. WHO published the Model List of Essential Medicine for Children (EMLc) and updated it every two years since 2007 to promote better access to medicines for children. This study aimed to assess whether the inclusion of essential anticancer medicines for respective indications for children was based on evidence of significant clinical benefit between 2011 and 2021.

Methods We identified all anticancer medicine indications added to the WHO EMLc Section 8 since 2011 and extracted evidence of benefit documented in the corresponding technical reports. Evidence in children was defined as evidence that included participants under 12, and graded into five levels, according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence. We analyzed whether each anticancer medicine indication was listed with documented OS benefit or improvements in surrogate measures based on the highest level of documented evidence in children.

Findings A total of 115 anticancer medicine indications were added to the EMLc from 2011 to 2021, of which 101 (87.8%) had some clinical evidence in children and 4 (3.5%) were added without any clinical evidence. Among the 101 medicine indications, none were added with level-1 evidence in children, and 43 (42.6%), 11 (10.9%), 41 (40.6%), and 6 (5.9%) were listed with level-2, level-3, level-4, and level-5 evidence in children, respectively. Only eight (7.9%) medicine indications were reported to have OS benefit, another 12 (11.9%) were reported to have improvements on surrogate measures, and 81 (80.2%) were listed in the EMLc without documented improvements in either OS or surrogate measures.

Interpretation Most anticancer medicine indications of the WHO EMLc were added based on limited evidence of statistically significant clinical benefit in children. Our results suggest that WHO should refine requirements for clinical benefit criteria and permissible forms, quality, and reporting of evidence of essential anticancer medicines for children, specify whether anticancer medicine indications have required evidence of clinical benefit in children, and provide further details in its technical reports that summarise the available evidence.

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Introduction

Cancer is a major cause of non-communicable disease-related cause of death among children worldwide. The estimated annual global childhood cancer incidence is about 400,000 cases, nearly 90% of which occur in low-and middle-income countries (LMICs).[1–3] While the development of modern multidisciplinary care contributes to cure rates of more than 80% among children with cancer in high-income countries, less than 30% of children with cancer in many LMICs are cured due to

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Research in context

Evidence before this study
Pharmaceutical therapy plays a critical role in treating childhood cancers, hence, access to essential cancer medicines is a key determinant of childhood cancer survival. We searched PubMed from database inception through October 10, 2022, without language restrictions for full papers, using the search terms "essential medicine", and "child", "children" or "paediatric", and "cancer", "neoplasm", "tumour", or "oncology". One author (LB) screened relevant abstracts and full-text articles to retrieve background information on the topic. We also screened the World Health Organization (WHO) technical documents for the 3rd to 8th versions of the WHO Model List of Essential Medicines for Children (EMLc). As a tool to guide countries and regional authorities in selecting their national essential medicines, the WHO EMLc should list medicines with high-quality evidence of clinical benefit. However, the general absence of evidence on medicine efficacy in children might make it difficult for WHO to implement its principle. Relevant research is lacking. Although several papers have discussed criteria for and processes of the WHO EMLc selection of anticancer medicines, most research focused on evaluating access to and affordability of essential anticancer medicines recommended by the WHO EMLc. One survey compared oncologists' perceptions of priority anticancer medicines in their settings with WHO essential anticancer medicines. Two studies analyzed the approval status and evidence of anticancer medicines recommended in the 5th version and 7th version of WHO EMLc, respectively. None has systematically investigated the evidence of clinical benefit of anticancer medicines for respective indications added to the WHO EMLc over the past 10 years.

Added value of this study
This study assessed whether medicine indications added to the WHO EMLc between 2011 and 2021 have statistically significant evidence of clinical benefit based on WHO documents. We extracted evidence of clinical benefit and relevant information on study design (sample age, study type, trial group, control group) and results for each anticancer medicine indication by reviewing all references cited in the WHO EMLc corresponding technical reports. Our results showed that 101 of the 115 anticancer medicine indications included in the WHO EMLc between 2011 and 2021 had some clinical evidence in children below 12 years of age. However, none was listed based on a systematic review of randomized trials and only 42.6% were listed based on RCTs. Only eight were reported to have OS benefit and another 12 were reported to have benefit according to improvements in surrogate measures. A total of 81 anticancer medicine indications were listed in the EMLc without documented improvements on either OS or surrogate measures.

Implications of all the available evidence
Our study demonstrated that most anticancer medicine indications listed in the WHO EMLc were added based on limited evidence of statistically significant clinical benefit in children, which is inconsistent with the WHO principle that essential anticancer medicines must be supported by substantial clinical evidence of comparative efficacy with due attention given to the overall quality of evidence. In view of difficulties in obtaining paediatric data on medicines generally, our results suggest that WHO should refine requirements for clinical benefit criteria and permissible forms, quality, and reporting of evidence of essential anticancer medicines for children, specify whether anticancer medicine indications have required evidence of clinical benefit in children, and provide further details in its technical reports that summarise the available evidence.

poor access to and affordability of quality care, including effective anticancer medicines.[4,5] As pharmaceutical therapy plays a critical role in childhood cancer treatment, access to essential anticancer medicines is a key determinant of childhood cancer survival.[6,7]

To promote better access to medicines for children, the World Health Organization (WHO) published the first version of the Model List of Essential Medicine for Children (EMLc) in 2007, which has then been updated every two years. In the 2007 WHO EMLc, all anticancer medicines listed in the 15th Model List of Essential Medicines (EML) for adults were included, except tamoxifen, without review of evidence of efficacy and safety in children.[8] In 2009, the WHO Expert Committee on the Selection and Use of Essential Medicines recommended that carboplatin replace cisplatin on the 2nd EMLc.[9] In 2011, the Committee endorsed the recommendation that essential anticancer medicines for children should focus on common treatable tumours in childhood. Thus, only anticancer medicines for the following three conditions were recommended to be included in the 3rd WHO EMLc: acute lymphoblastic leukaemia (ALL), Wilms tumour (WT), and Burkitt lymphoma (BL).[10] Since 2015, the WHO EMLc has added anticancer medicines for more indications, with considerations of paediatric cancer incidences and clinical evidence of comparative efficacy and safety.[11]

Earlier studies have found that anticancer medicines are frequently approved by regulatory agencies without quality evidence of adequate clinical benefit, especially for childhood cancers.[12–14] In a regulatory review of paediatric clinical trials for cancers by the United States Food and Drug Administration during 2001–2019, 51.9% of trials in solid tumour indications and 16.7% of trials in hematologic malignancies had a control arm, and 47.5% of trials were adequately powered to evaluate primary efficacy endpoints.[15]

The WHO EMLc, as a guide for countries and regional authorities to select their national essential medicines,[8,16] should list medicines with high-quality evidence of clinical benefit.[11,17] However, no studies have systematically investigated the evidence of clinical benefit of anticancer medicines added to the WHO EMLc over the years. We aimed to assess whether the inclusion of essential anticancer medicines for respective indications (i.e., medicine indications) for children between 2011 and 2021 was based on evidence of significant clinical benefit.

Methods

Data source

As the WHO EMLc retained the EML's all essential anticancer medicines except tamoxifen in 2007, and did not review evidence of efficacy and safety in children until 2011, this study was based on the 3rd to 8th versions of WHO EMLc published from 2011 to 2021 and the corresponding technical reports (*The selection and use of essential medicines*) summarising the meetings of the WHO Expert Committee.[10,11,18,19] We identified all anticancer medicine indications added to the WHO EMLc Section 8 (*Immunomodulators and Antineoplastics*) since 2011, including cytotoxic medicines, targeted therapies, and hormones and antihormones. Supportive agents, filgrastim, allopurinol, mesna, rasburicase, and calcium folinate, were excluded.

Two researchers extracted any reported evidence of clinical benefit and relevant information on study design (sample age, study type, trial group, and control group) and results for each anticancer medicine indication by reviewing all references cited in the technical reports independently. They then cross-checked data extracted for accuracy and one of the two rechecked data before final analyses. Data used in this study is publicly available and thus human subjects research review was not required according to Peking University Institutional Review Board.

Procedures

Evidence in children was defined as evidence generated from samples including patients under 12, considering the WHO EMLc primarily serves children under 12 years of age.[8] We graded evidence into five levels, according to the *Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence*[20]: (1) level 1, systematic review of multiple randomized trials or n-of-1 trials; (2) level 2, randomized trial or observational study with large magnitude of effect (statistically significant difference between results of treatment and control groups); (3) level 3, non-randomized controlled cohort/follow-up study, and systematic review without randomized trials or n-of-1 trials; (4) level 4, case-series, case–control studies, or historically controlled studies, including single-arm studies; (5) level 5, narrative literature review and expert comments.

Overall survival (OS) was regarded as the gold-standard primary end point for anticancer medicines.[21] We analyzed the highest level of documented evidence in children of each anticancer medicine indication to categorize them into three groups: (1) documented OS benefit, if the study results demonstrated that the anticancer medicine indication had evidence of statistically significant OS benefit compared with a control group; (2) lack of OS benefit, if the medicine did not prolong survival for patients in a given indication in the trial (i.e., results on OS benefit were not statistically significant); and (3) unknown OS benefit, if comparative OS results were not reported. For the anticancer medicine indications listed with documented lack of OS benefit or unknown OS benefit, we further categorized them into three types: (1) documented improvements in surrogate measures, if the study found statistically significant changes in a surrogate measure (such as progression-free survival, disease-free survival, or event-free survival for indications for solid tumours and hematological malignancies, as well as overall response rate for indications for hematological malignancies); (2) no improvement in surrogate measures; and (3) unknown improvement in surrogate measures.

Outcomes

The main outcomes were whether essential anticancer medicine indications in WHO EMLc were listed based on clinical evidence in children under 12 and whether medicine indications were listed based on improvements in either OS or surrogate measures in the sources cited in the WHO EMLc technical reports.

Statistical analysis

We conducted descriptive analyses for anticancer medicine indications added to the 3rd to 8th WHO EMLc in terms of clinical evidence in children under 12 and the levels of evidence based on the technical reports. Furthermore, we analyzed whether the anticancer medicine indications were added based on documented OS benefit according to the highest level of documented evidence in children of each anticancer medicine indication. We then identified whether the medicine indications without documented OS benefit were added based on shown improvements in surrogate measures. All analyses were conducted using the software Microsoft Excel 2019.

Ethics statement

The study was exempted from IRB review as the publicly available data did not contain any confidential patient information.

Role of the funding source

Results

Summary of added anticancer medicine indications, 2011–2021

A total of 115 anticancer medicine indications for children were added to the WHO EMLc from 2011 to 2021, comprising 97 cytotoxic medicine indications, eight targeted therapy indications, and ten hormone and antihormone indications (Fig. 1). There was no addition of new anticancer medicine indications for children in 2013 and 2017 versions of the WHO EMLc.

Evidence of clinical benefit in children documented in the technical reports

According to the WHO EMLc technical reports, 101 (87.8%) of the 115 anticancer medicine indications were added based on some clinical evidence in children, while 10 (8.7%) were added based on evidence in adolescents or adults (i.e., individuals aged 12 years and above) only, and 4 (3.5%) were added without any clinical evidence. Fig. 1 shows that the proportion of anticancer medicine indications with clinical evidence in children differed over the years as well as across

medicine types. The proportion of anticancer medicine indications added with clinical evidence in children was 94.1% (n = 20/21) in 2011–2013. In subsequent years, the proportion fluctuated: 76.9% (n = 30/39) in 2015–2017, 100.0% (n = 31/31) in 2019, and 83.3% (n = 20/24) in 2021. In terms of medicine types, 80.0% (n = 8/10) of hormone and antihormone indications were added based on clinical evidence in children, while the proportion was higher in cytotoxic medicine indications (87.6%) and targeted therapy indications (100.0%).

Among the 101 anticancer medicine indications added with clinical evidence in children, none had level-1 evidence in children. For 43 (42.6%) anticancer medicine indications, the highest level of documented evidence in children was level 2; 11 (10.9%), 41 (40.6%), and six (5.9%) medicine indications had level-3, level-4, and level-5 evidence, respectively. As shown in Fig. 2, eight (7.9%) anticancer medicine indications had significant OS benefit according to level-2 evidence in children. Nearly a sixth of medicine indications (18, 17.8%) were reported to have no significant OS benefit as compared with the control, of which three had improvements in a surrogate measure and 15 showed no improvement on surrogate measures mainly based on level-2 evidence (Supplement Table S1). Among the 75 anticancer medicine indications with unknown OS benefit, 63 were also listed with unknown improvement in surrogate measures, three had no improvement on surrogate measures, and nine had improvement in a

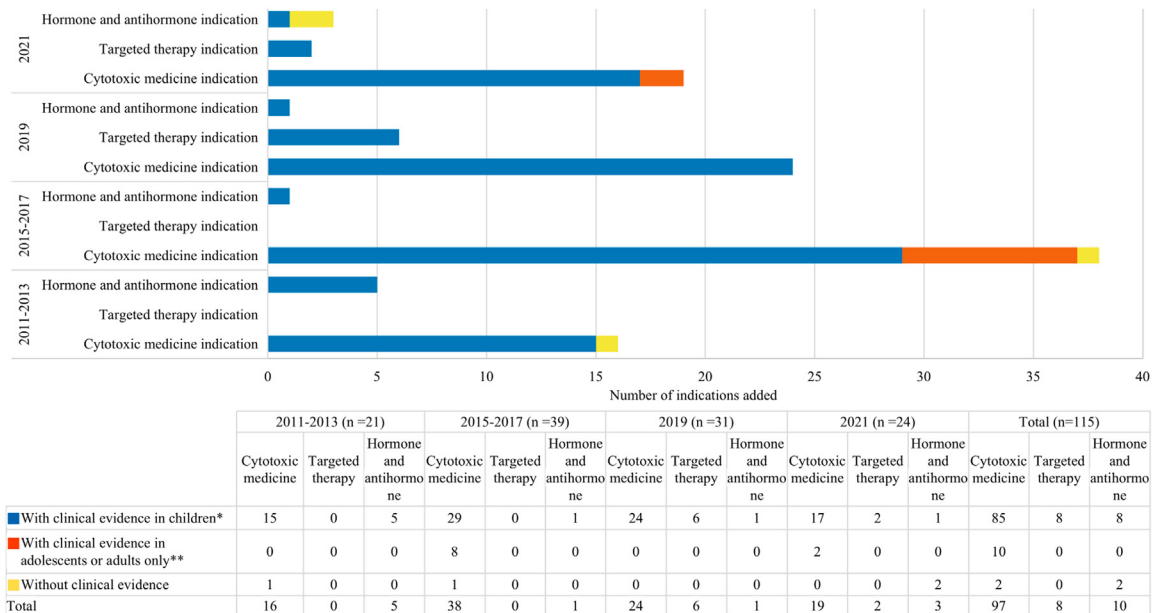|	2011-2013 (n=21)			2015-2017 (n=39)			2019 (n=31)			2021 (n=24)			Total (n=115)		
	Cytotoxic medicine	Targeted therapy	Hormone and antihormone	Cytotoxic medicine	Targeted therapy	Hormone and antihormone	Cytotoxic medicine	Targeted therapy	Hormone and antihormone	Cytotoxic medicine	Targeted therapy	Hormone and antihormone	Cytotoxic medicine	Targeted therapy	Hormone and antihormone
With clinical evidence in children*	15	0	5	29	0	1	24	6	1	17	2	1	85	8	8
With clinical evidence in adolescents or adults only**	0	0	0	8	0	0	0	0	0	2	0	0	10	0	0
Without clinical evidence	1	0	0	1	0	0	0	0	0	0	0	2	2	0	2
Total	16	0	5	38	0	1	24	6	1	19	2	3	97	8	10

Fig. 1: Clinical evidence of anticancer medicine indication additions to WHO EMLc, 2011–2021. * Evidence in children: evidence generated from samples including patients under 12. ** Evidence in adolescents or adults: evidence generated from samples including patients aged 12 or above only.
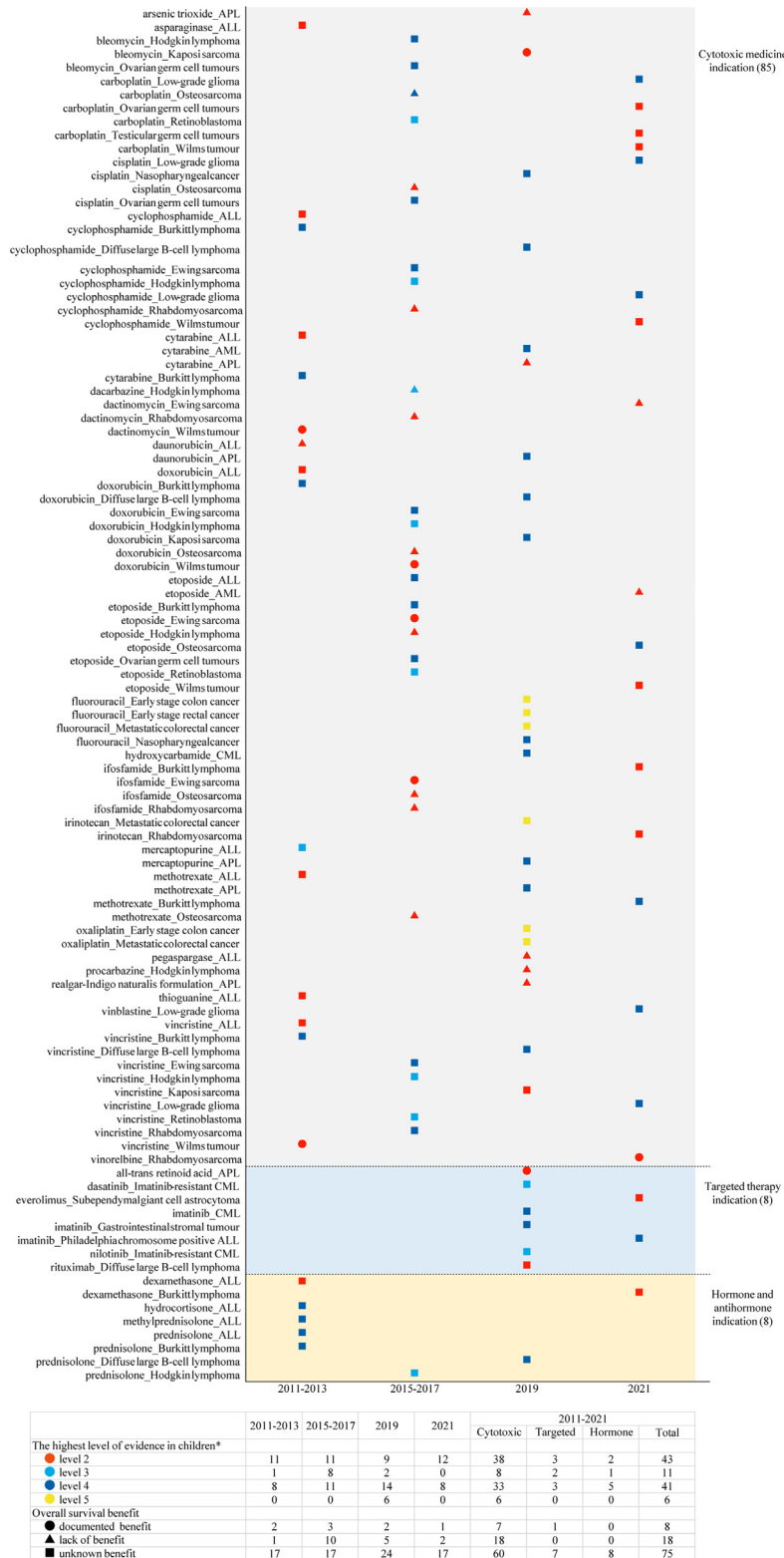
Fig. 2: Quality of clinical evidence of anticancer medicine indications in WHO EMLc, 2011–2021. ALL, Acute lymphoblastic leukaemia; AML, Acute myeloid leukaemia; CLL, Chronic lymphocytic leukaemia; CML, Chronic myeloid leukemia; OCEBM, Oxford Centre for Evidence-Based

surrogate measure. In summary, only 12 (12.9%) of the 93 anticancer medicine indications without documented OS benefit were listed with some improvement in surrogate measures, while the remaining medicine indications had no statistically significant effect on surrogate measures (18, 19.4%) or did not report comparative results on surrogate measures (63, 67.7%) (Supplement Fig. S1). Details are presented in Supplement Table S1.

Discussion

This study demonstrated that 101 of the 115 anticancer medicine indications included in the WHO EMLc between 2011 and 2021 were listed with clinical evidence from studies in children below 12 years of age. None of the listings cited a systematic review of randomized trials (level 1) and 42.6% of the 101 were based on RCTs (level 2). Among the 101 anticancer medicine indications listed with evidence in children, eight had documented OS benefit, another 12 had improvements in surrogate measures, and 81 were added to the EMLc without an effect on either OS or surrogate measures, according to their highest level of documented evidence in children.

Considering the critical role of pharmaceutical therapy in childhood cancer treatment, WHO has been optimizing processes for the selection of essential anticancer medicines to prioritize medicines with demonstrated efficacy and safety for paediatric cancer treatment.[6,11] In the first step, WHO reviewed and included basic and core chemotherapy medicines for the three selected common treatable tumours in childhood in 2011–2013 EMLc, most of which had been extensively used in treatment of childhood cancer for decades and hence whose early clinical data might be hard to access to, and some were even supported by no studies.[22,23] Research involving these classical medicines in the last few decades have been being conducted mainly to find safer and more effective treatment combinations rather than estimate the effectiveness of a certain medicine, attaching importance to potential improvements on measures such as incidence of relapse and event-free survival.[24] In the next step, WHO began to select essential anticancer medicines for more indications by evaluating applications for the WHO EMLc from individuals, societies, and companies,[11] and more than 80% of the anticancer medicine indications added

to the WHO EMLc had some clinical evidence in children in 2015–2021. According to a recent survey, the majority of anticancer medicines deemed essential by paediatric oncologists have been included in the current WHO EMLc.[7] Nevertheless, despite the emphasis on clinical evidence in children, the WHO EMLc has had limited ability to list anticancer medicine indications with traditionally defined high-quality clinical evidence, reflecting the limited availability of clinical trials in children.[14,15] From 2015 to 2021, 14 of the anticancer medicine indications added in the EMLc had no improvement on either OS or surrogate measures according to their highest level of documented evidence in children cited in the WHO EMLc technical reports. Imatinib for chronic myeloid leukemia (CML) and dasatinib and nilotinib for imatinib-resistant CML, which applied for EMLc inclusion more than once between 2015 and 2019, were previously rejected for providing evidence only in adolescents or adults but were later recommended for inclusion based on single-arm trials with unknown OS benefit in children in their latest application in 2019. The long-term comparative clinical benefit in children of most modern targeted therapies with high costs remains uncertain, which are thus rarely regarded as high-priority medicines by paediatric oncologists.[7] Further deliberation is necessary when selecting targeted therapies in WHO and national essential medicine lists.

Our findings indicate that inclusion of anticancer medicine indications in the WHO EMLc deviates from the principle that essential anticancer medicines must be supported by substantial clinical evidence of comparative efficacy with due attention given to the overall quality of evidence.[11] The absence and limited quality of evidence on medicine efficacy in children is common for anticancer medicines, attributable to the rarity of many of these malignancies and to difficulties in conducting paediatric trials, including but not limited to ethical, physiological, and economic challenges.[25,26] Although a series of legislative initiatives have been implemented in Europe and the USA to promote study of medicines in children, the low incidence and prevalence of childhood cancer, coupled with the complexity of paediatric study design, recruitment, and adequate patient consent, present challenges to the generation of comparative effectiveness evidence in the paediatric context.[25,27] As an important guide supporting countries in selecting national essential medicines and developing

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Medicine. * Evidence in children was defined as evidence generated from samples including patients under 12. Five levels of evidence were determined according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence: (1) level 1, systematic review of multiple randomized trials or n-of-1 trials; (2) level 2, randomized trial or observational study with large magnitude of effect (statistically significant differences between results of treatment and control groups); (3) level 3, non-randomized controlled cohort/follow-up study, and systematic review without randomized trials or n-of-1 trials; (4) level 4, case-series, case–control studies, or historically controlled studies, including single-arm studies; and (5) level 5, narrative literature review and expert comments.

medical recommendations for children, especially for resource-constrained settings, the current WHO EMLc may signal to national policymakers that essential medicines included in the list have demonstrated clinical efficacy and safety, without clarifying the differences in the nature and quality of clinical evidence justifying inclusion of these medicines for specific indications.[16,17] For example, when developing the list of essential anticancer medicines for children in Europe, the European Society for Paediatric Oncology (SIOPE) assessed evidence for medicines included in standard group in international or national treatment protocols from published literature, considered medicines supported by available evidence showing clinical benefit to be essential, and attached the extracted information on study design (e.g. study type and age category of study populations) and main findings of those supporting studies, but directly considered medicines included on the 2017 WHO EMLc essential without further literature research and assessment because "they had already been assessed by the WHO EMLc experts".[28] In addition, Dr. Unguru and his colleagues proposed a pediatric oncology-specific EML for the USA, which used the 2017 WHO EMLc as a starting point, as medicines included in the WHO EMLc "have been rigorously tested and proven safe and effective".[29]

We suggest that WHO further standardize processes of selecting essential medicines and document the extent to which selected medicines meet stated criteria. The magnitude of clinical benefits is supposed to be the major criterion of the selection of WHO essential medicines, and clear and specific criteria might assist countries to prioritise medicines for their national lists.[30,31] The WHO Expert Committee suggested that anticancer medicine indications proposed to be included in the EML in 2019 should demonstrate a minimum of OS benefit of four to six months while no specific clinical benefit magnitude was stated for the WHO EMLc.[18] We recommend that the Expert Committee should identify clinical benefit criteria tailored to essential anticancer medicines for children by cancer types, refine requirements for permissible forms, quality, and reporting of evidence (e.g. evidence from RCTs, paediatric treatment protocols, historical cohorts, or otherwise), and then reassess evidence of clinical benefit of anticancer medicine indications included in or applying for inclusion in the WHO EMLc. Considering the specific characteristics of childhood cancers, criteria of benefit could include not only comparative improvements in survival or overall response rate, but also high cure rates achieved through use of established treatment paradigms.[31] The WHO EMLc should also document the level of evidence in children and the extent of documented clinical benefits to facilitate interpretation and decision making by users of the WHO EMLc in resource limited settings. Medicine indications listed could be categorised as essential or promising based on whether

having robust supporting evidence of clinical benefit in children or not, in keeping with the approach employed in SIOPE list development.[28,32] We also recommend that the WHO EMLc document should elaborate on recommendations for inclusion of medicine indications with insufficient clinical evidence, for example, if the medicine indication has been included in any international or national standard treatment protocols, and it would be better if the WHO state clearly whether different levels of evidence are acceptable in children, especially with rare diseases. We believe that clear evidentiary guidelines for inclusion of anticancer medicine indications on the WHO EMLc, which provide explicit guidance on permissible forms, quality, and reporting of evidence required for continued updating of the list for children, would further benefit future listing of novel medicines.

This study has several limitations. Firstly, as about half of the clinical studies cited in WHO EMLc documents did not include a control group, we could not apply alternative evidence rating schemes such as GRADE. The level of evidence is mainly based on study types without assessing risk of bias or other limitations of studies,[20] possibly not truly reflecting the quality of evidence and leading to an overestimation of the clinical benefit of medicine indications. However, our approach is consistent with earlier studies evaluating the strength of the available evidence in paediatric indications.[33–36] Secondly, as adolescents (aged 12–18) could use dosage forms of products designed for adults and thus the WHO EMLc prioritizes essential medicines for children under 12 years,[8] we defined evidence in children as evidence that included sample patients under 12 years. We regarded evidence whose sample age was not indicated as evidence in adolescents or adults only, which might have led to an underestimation of the clinical benefit in children. Thirdly, we identified the highest level of documented evidence of each anticancer medicine indication and assessed whether it was listed in the WHO EMLc with documented OS benefit or improvements in surrogate measures. We did not assess studies of lower-level evidence that might have shown some benefits of the medicine indication. This may have introduced some biases. Fourthly, this study was based on evidence cited in the WHO EMLc technical reports that might not cover all the clinical evidence of the anticancer medicine indications, therefore, our findings might not reflect the totality of the existing evidence on efficacy of essential anticancer medicine indications for children. We picked two essential anticancer medicine indications at random as example (doxorubicin for Kaposi sarcoma, and carboplatin for osteosarcoma), and searched PubMed for their clinical evidence from database inception to the time of their addition in WHO EMLc (23 July 2019 and 24 April 2015, respectively). We found that the outcome based on searching results of doxorubicin for Kaposi sarcoma was consistent with that of our study which was based on

WHO technical reports. However, the highest level of documented evidence in children of carboplatin for osteosarcoma based on our searching results differed from that of our study (level 4), as the WHO technical report failed to include one retrospective controlled analysis published in 2014, which was regarded as level-3 evidence.[37] Further research would be needed to systematically review clinical evidence to quantify the gap between evidence cited in WHO technical reports and evidence in general.

In conclusion, most anticancer medicine indications of the WHO EMLc were added based on limited evidence of clinical benefit in children. In view of difficulties in obtaining paediatric data on medicines generally, it would be helpful if WHO refined requirements for clinical benefit criteria and permissible forms, quality, and reporting of evidence of essential anticancer medicines for children, marked on the list whether anticancer medicine indications have required evidence of clinical benefit in children, and provided a more comprehensive technical assessment of the evidence to facilitate country-level decision making based on the evidence assessed by the WHO EMLc expert committee.

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