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ORIGINAL ARTICLE

Access to essential anticancer medicines for children and adolescents in Europe

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Background: Essential anticancer medicines are an indispensable component of multidisciplinary treatment of paediatric malignancies. A European Society for Medical Oncology (ESMO) study reported inequalities in the availability of anticancer medicines for adult solid tumours and provided a model for the present survey. The aim of this survey was to assess the accessibility of essential medicines used in paediatric cancer patients aged 0 to 18 years across Europe from 2016 to 2018.

Methods: A list of medicines was drawn with input from the European Society for Paediatric Oncology (SIOP Europe) Clinical Research Council referring to the World Health Organization Model List of Essential Medicines for Children (WHO EMLc) 2017. A survey was sent to nominated national clinician and pharmacist rapporteurs and parent associations in up to 37 countries; answers were obtained from 34 countries.

Results: The full survey list contained 68 medicines, including 24 on the WHO EMLc 2017. Health professionals reported that 35% of all medicines were prescribed off-label in at least one country and that 44% were always available in >90% of countries. Only 63% of the EMLc 2017 medicines were reported as always available. The main determinant of unavailability was shortages, reported for 72% of medicines in at least one country. Out-of-pocket costs were reported in eight countries. Twenty-seven percent of orally administered medicines were never available in child-friendly formulations. Parents detailed individual efforts and challenges of facilitating ingestion of oral medicines as prescribed. Inequalities in access to pain control during procedures were reported by parents across Europe.

Conclusions: Children and adolescents with cancer in Europe experience lack of access to essential medicines. Urgent actions are needed to address shortages, financial accessibility, availability of safe age-appropriate oral formulations, and pain management across Europe.

Key words: paediatric oncology, anticancer medication, public policy, medication shortage, out-of-pocket

INTRODUCTION

Essential cytotoxic medicines are a principal component of evidence-based best practice in paediatric cancer care, generating an 80% disease-free survival at 5 years in malignancies affecting children and adolescents <18 years of age.[1-3] Most medicines used for childhood cancers are off-patent, available as generics, inexpensive, and prescribed off-label in the paediatric population.[4] Over the last 50 years, their safety and efficacy in children and adolescents have been established through prospective cross-border academic trials, although the relevant paediatric information has not been systematically incorporated into the Summary of Product Characteristics (SmPCs).

Important discrepancies in 5-year disease-free survival of children and adolescents with cancer have been reported across Europe. It is unknown to what degree inequities in access to, and availability of, medications contribute to these discrepancies. Access to cytotoxic medicines by children and adolescents has been identified as a substantial

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concern in low- and middle-income countries.[5] Furthermore, shortages have been increasing, affecting countries across income levels. In 2016, the European Society for Medical Oncology (ESMO) conducted a survey on the availability, out-of-pocket costs, and accessibility of anticancer medicines in Europe, which demonstrated major issues regarding access to anticancer medicines which were most pronounced in countries with lower levels of economic development.[6] The medicines for the treatment of haematological malignancies, which represent one-third of paediatric cancers, were out of scope of the ESMO study.

One objective of the EU Joint Action on Rare Cancers (JARC), 724161, EU Health Programme, was to assess the accessibility of essential therapies for children and adolescents with cancer in Europe and to provide recommendations to the European Union (EU) and national governments based on the generated evidence.[7] This project explored the barriers and bottlenecks in access to essential medicines used for the treatment and care of children and adolescents with cancer in all EU Member States (MSs) and other countries in the European Society for Paediatric Oncology (SIOP Europe, or SIOPE) region (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.12.015). Access was defined based on the notion of 'obtaining the needed medicine'[8] and encompassed availability, described as being able to obtain the prescribed medicine as needed in a timely manner, and affordability in terms of out-of-pocket cost for the patient. Shortages were defined according to the World Health Organization (WHO) definition.[9]

METHODS

The survey was coordinated by a Core Working Group (CWG) of representatives from SIOPE, Childhood Cancer International — Europe (CCI-Europe, the European federation of parent and survivor associations), the European Society of Oncology Pharmacy (ESOP), and ESMO. The questions and methodology were based on those previously developed by ESMO.[6,10]

The list of medicines was established based on the WHO's Model List of Essential Medicines for Children 2017 (WHO EMLc)[11] and the expertise of the SIOPE Clinical Research Council members representing all disease-oriented European Clinical Trial Groups and national paediatric haematology and oncology societies. Four medicines on the WHO EMLc were excluded due to their nature as supportive agents: allopurinol, calcium folinate, filgrastim, and mesna. The final list validated by the CWG contained 68 medicines (full survey list), of which 24 were WHO EMLc 2017 medicines (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.12.015).

Two questionnaires (Supplementary Appendices S1 and S2, available at https://doi.org/10.1016/j.annonc.2020.12.015) addressed health professionals (physicians and pharmacists) and parents, respectively. The questionnaires were designed in an online format using SurveyMonkey software, pretested, and approved by the CWG. Whereas the list of medicines used in the survey to health professionals did not include supportive agents, the questionnaire to parents asked about this aspect in an overarching manner.

The questionnaire for health professionals was built around the agreed list of anticancer medicines. There were six overarching topics, most requiring a separate response for each medicine: use in children and adolescents, regulatory approval for use in children and adolescents (authorisation), availability, barriers to prescribing, costs for the patient, and child-friendly formulation availability.

The questionnaire for parents contained five overarching topics: shortages, out-of-pocket payments, the need to adjust oral formulations for children, the availability of agents to control side-effects, and the availability of painkillers and anaesthesia/sedation during procedures. The time frame of reference was the preceding 24 months.

The geographical scope of the survey included 37 countries: all EU MSs, additional countries covered by SIOPE, and Montenegro outside of the SIOPE membership. Two rapporteurs per country were sought from among health professionals: one paediatric oncologist and one oncology pharmacist; these were nominated by the national members of SIOPE and ESOP, respectively. SIOPE rapporteurs from 36 countries and ESOP rapporteurs from 24 countries were identified. Data from parents were sought from all CCI-Europe-affiliated organisations in the aforesaid region. Parents from 32 countries were thus invited to participate, with the number of target respondents asked to take part varying from 1 to 7 per country. The survey was released in April-May 2018 and closed in November 2018.

Results from the questionnaire to health professionals were collated for all 68 medicines as well as separately for the 24 WHO EMLc 2017 medicines. For countries where the physician and the pharmacist initially provided divergent answers, the two rapporteurs were asked to supply a common validated response. If there was absence of agreement between rapporteurs, the final answer was encoded as 'Don't know' to avoid bias in favour of a particular response. Where further information was required, a teleconference with the respondent(s) was held. Parent organisations were responding based on their experience at the hospital rather than at the national level, and answers from the same country could differ. In such cases, data from parents were analysed individually without aggregation by country.

RESULTS

Responses from health professionals were obtained from 30 countries: 25 EU MSs and 5 non-EU countries: Israel, Norway, Serbia, Switzerland, and Turkey. Responses from both physician and pharmacist were obtained from eight countries (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.12.015). Answers from parents were obtained from 31 organisations in 20 countries, including 16 EU MSs and 4 non-EU countries: Bosnia and Herzegovina, Montenegro, Serbia, and Switzerland. There was a median of one and up to four parent answers received per country.

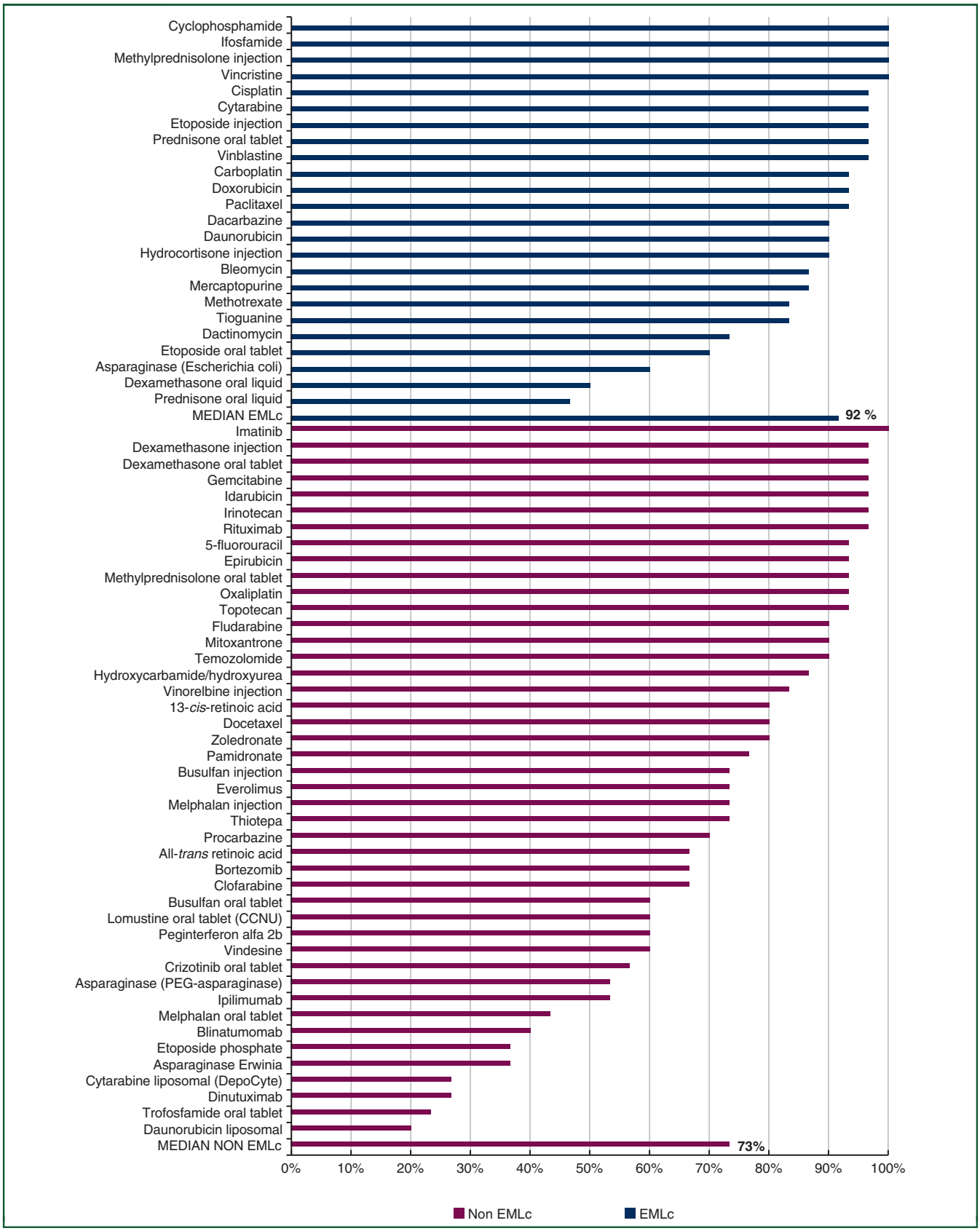

Figure 1. Percentage of countries in which each of the 68 medicines were always available over the last 24 months.
EMLc, Model List of Essential Medicines for Children.

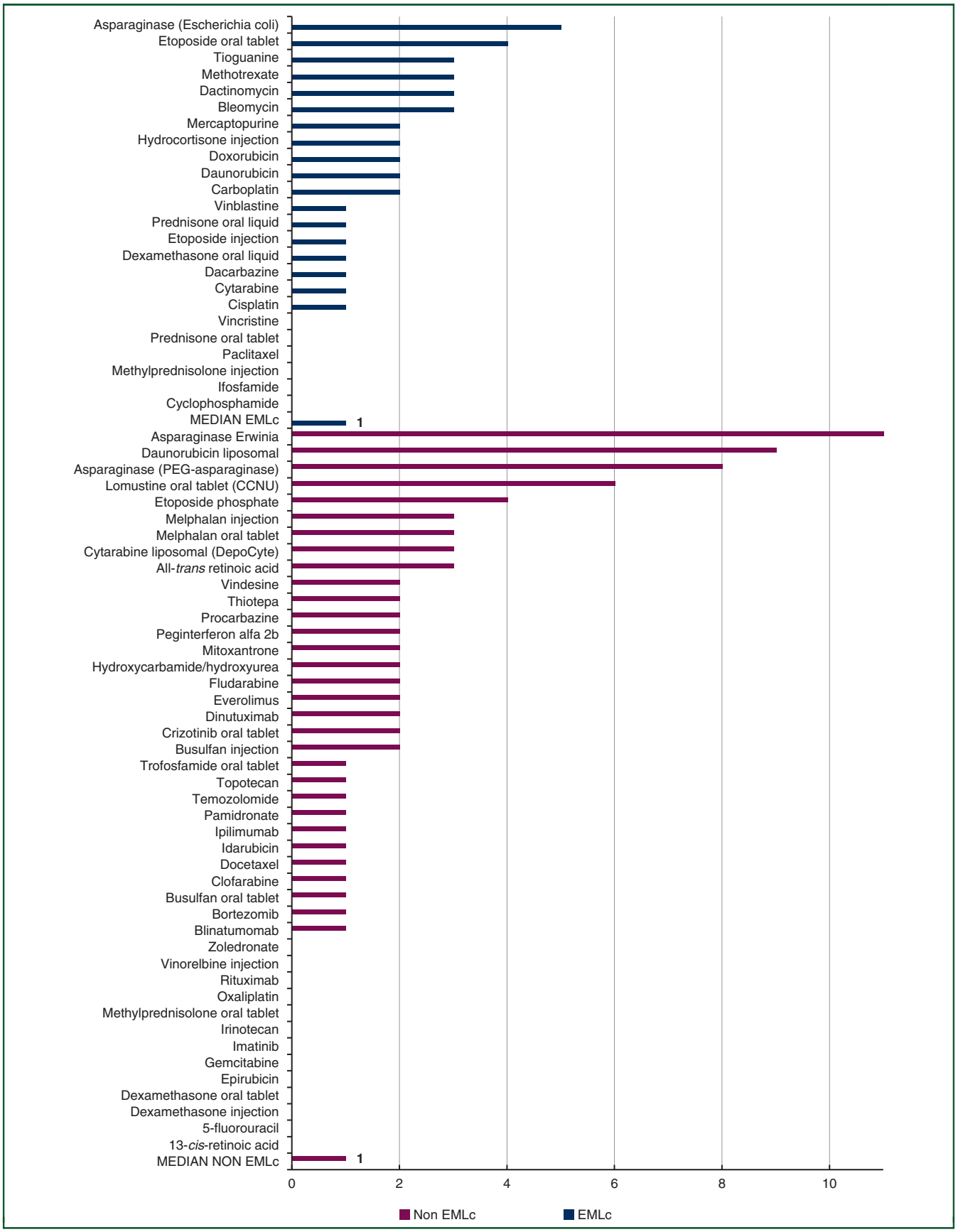

Figure 2. Number of countries reporting medicine shortages over the last 24 months for each of the 68 medicines.
EMLc, Model List of Essential Medicines for Children.

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Use and authorisation

Between 53% and 100% of the 68 medicines on the full survey list (median 89%) and between 75% and 100% (median 96%) of the 24 EMLc medicines were reported as used (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.12.015). Professionals reported that a median of 51% of the full list of medicines was 'authorised' for use in children by relevant authorities, ranging from 22% in Finland to 91% in Italy. Of the 24 EMLc medicines, a higher median of 69% were reported as authorised across all countries, ranging from 17% to 100%.

Calculated based on the number of medicines reported as used but not authorised by respondents, the median percentage of medications administered off-label was 35% of the full survey list and 25% of the EMLc. In 10 countries, namely, Austria, Belgium, Croatia, Cyprus, Czech Republic, Germany, Italy, Portugal, Israel, and Turkey, none of the EMLc medicines used in these countries were reported as prescribed off-label.

Availability including shortages

Thirty of the 68 medicines on the full survey list (44%) and 15 of the 24 WHO EMLc medicines (63%) were reported as always available in at least 90% of the countries (Figure 1). Furthermore, five essential medicines routinely used for the treatment of the most frequent paediatric malignancy,

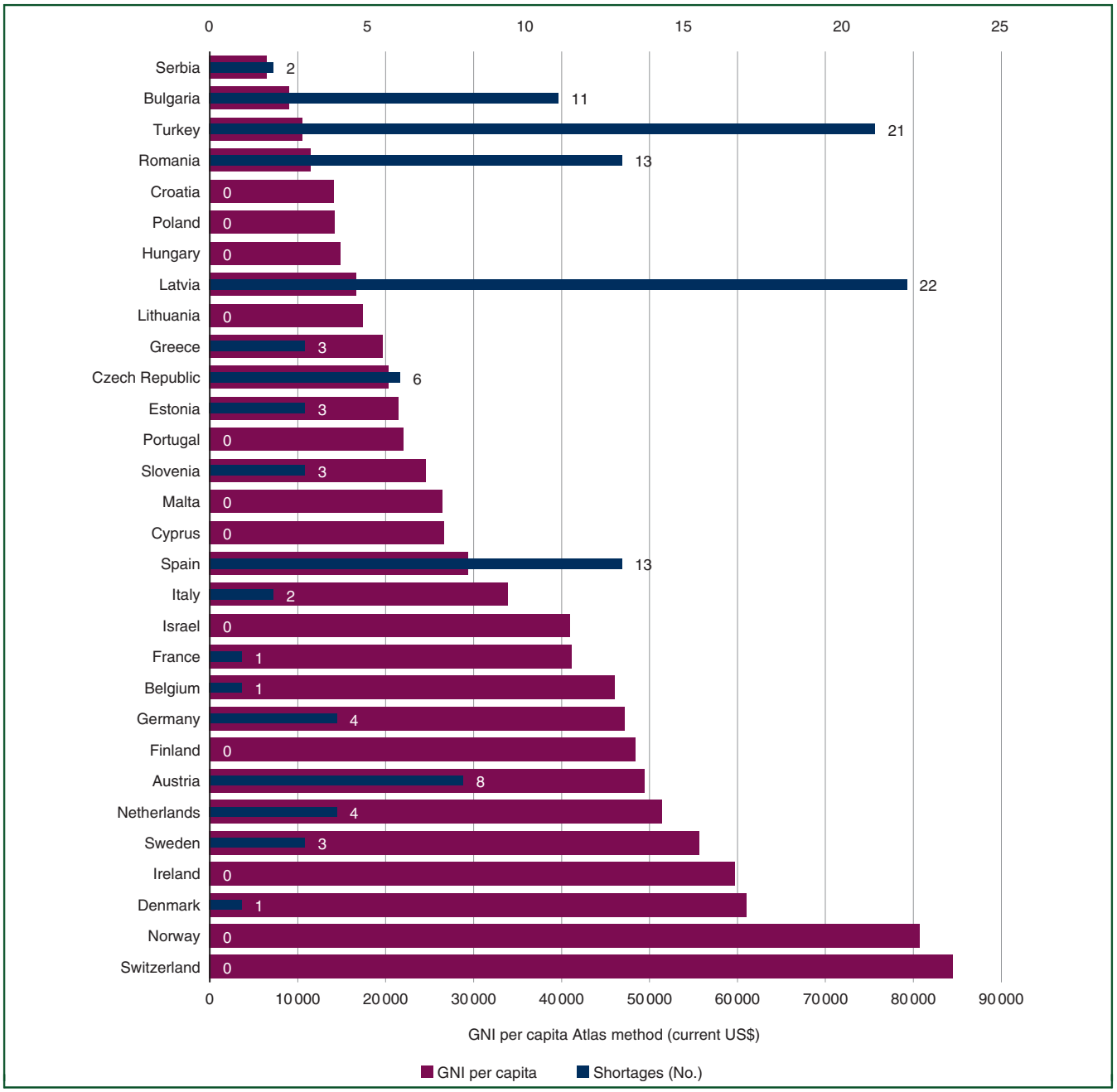

Figure 3. Relationship between number of reported shortages and gross national income (GNI) per capita.

acute lymphoblastic leukaemia (ALL), were reported as always available in only ≤60% of the responding countries. The relevant medicines are the three asparaginase agents (*E. coli*, PEG-, and *Erwinia*) and two corticosteroids (oral liquid dexamethasone and prednisone/prednisolone).

Shortages were reported by health professionals in at least one country for 49 of the 68 medicines on the full survey list (72%) and for 18 of the 24 WHO EMLc medicines (75%) (Figure 2). The three asparaginases used in the treatment of ALL had shortages reported in among the largest number of countries: *E. coli* in 5 countries, PEG- in 8 countries, and *Erwinia* in 11 countries. Overall, the number of reported shortages tended to be greater in countries with lower gross national income (GNI) per capita (Figure 3). The five countries with the largest number of medicines in shortage (>10) were Bulgaria, Latvia, Romania, Spain, and Turkey.

Financial burden

Health professionals in eight countries reported patient out-of-pocket costs; these concerned 2% to 18% of the medicines reported as used in each country (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2020.12.015). Out-of-pocket costs for 9% to 25% of the EMLc medicines used were reported in five countries: Bulgaria, Estonia, Finland, Romania, and Spain. In five countries (Bulgaria, Latvia, Poland, Romania, and Turkey) the full costs for all medicines were out-of-pocket. In Finland and Spain, out-of-pocket costs ranged from 50% to full cost, while only a small prescription fee applied in Estonia.

Among parents, 32% of the respondents reported paying for all or part of their child's hospital treatment. These parents were from seven countries: Belgium, Bosnia and Herzegovina, Bulgaria, Estonia, Romania, Serbia, and Switzerland. Parents reported requesting support from non-governmental organisations as the most frequent action to address financial accessibility issues.

Age-appropriate formulations

Of the 28 orally administered medicines on the survey list, 27% were never available in child-friendly doses and formulations in at least one country.

Consequently, 21 parents (68% of respondents) reported having to adjust the dose and formulation of the child's medicine, including by crushing or cutting pills (9 responses, 43%), breaking pills in half (5 responses, or 24%), or dissolving pills and subsequently mixing them with food or flavoured liquids (2 responses, or 9.5%). One parent reported using a nasogastric tube to administer the diluted medicine.

Parents highlighted the potential risks and the high stress associated with manually adjusting the medicine's format. Concerns included the difficulty of ensuring that the dosage was as prescribed and the possible risk of self-harm by manipulating cytotoxic agents.

Control of side-effects and pain

Parents who reported that medicines to control side-effects were available 'always' or 'usually' ranged from 94% for nausea and vomiting medicines, to only 47% for anxiety treatments (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2020.12.015). The percentage of parents who reported that pain control medicines for specific procedures were always available was 48% for lumbar puncture to 61% for tumour biopsy (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2020.12.015). The sole reporting parent from Montenegro and one of the parents from Serbia indicated that pain control during lumbar puncture and bone marrow aspirates was never available.

DISCUSSION

Access to essential anticancer medicines should be available for all children and adolescents with cancer.[12] In a recent global survey, 42.9% of respondents from low- and middle-income economies reported suboptimal access to essential medicines for paediatric malignancies.[13] To redress this issue, the International Society of Paediatric Oncology (SIOP) and CCI produced recommendations to improve global access.[3]

In Europe, equal access to the best paediatric cancer care and expertise is a major goal of the scientific, clinical, and patient community and incorporated in the European Standards of Care for Children with Cancer and the SIOPE Strategic Plan.[14,15] It is being operationalised through the European Reference Network on Paediatric Cancer (ERN PaedCan).[16]

Conducted as part of the EU JARC project, this study was the first to survey paediatric oncology and haematology clinicians, oncology pharmacists, and parents in Europe regarding access to medicines used in childhood cancer treatment and care. The study encompassed all medicines identified by European experts as essential, which resulted in a higher number of agents compared with the WHO EMLc 2017, and it included seven non-EU countries. The findings will assist SIOPE and partner organisations to formulate evidence-based recommendations to decision-makers at the national and European levels to improve access to essential therapies for all children and adolescents with cancer in the region.

Defining essential medicines for childhood cancer is an evolving process and discrepancies exist between different authorities. In June 2019, the 7th revised WHO EMLc was released containing 14 additional anticancer medicines.[17] Ten of these were already included in the present survey. The WHO EMLc 2019 also includes the realgar-indigo naturalis formulation used in China for the treatment of acute promyelocytic leukaemia, but this medicine is not authorised in Europe. In May 2019, Unguru et al.[18] published a list of essential chemotherapy and supportive care agents for children in the United States that contains 47 anticancer medicines. All but five of these [aldesleukin (interleukin 2), arsenic trioxide, mechlorethamine, prednisolone

Table 1. Economist Intelligence Unit-European Society for Medical Oncology (EIU-ESMO) recommendations to address shortages of inexpensive essential medicines (Vyas et al.[26])

- Introduce legislation for early notification requirements for medicines shortages.
- Establish European strategic plans for medicines shortages.
- Introduce incentives for production infrastructure improvements, including financial incentives to address the economic causes of manufacturing issues; incentives for suppliers to remain in these markets should also be considered.
- All countries to develop catalogues or databases of shortages based on a common minimum set of data requirements, including a common European Union definition of medicines shortages.
- Develop national essential medicines lists based on the World Health Organization's Essential Medicines List.
- Establish procurement models designed to prevent medicines shortages, including tender-cycle harmonisation.

oral/suspension, tretinoin] were included in the JARC list. Among them, aldesleukin (interleukin 2) is used in the United States, but not in Europe, in combination with dinutuximab for the treatment of neuroblastoma.

Disclaimers

This study was a perception survey of qualified field reporters as data were not corroborated relative to policy documents of the relevant authorities. Thus, a degree of reporting error cannot be excluded. Likewise, answers may not be fully representative of the situation in respondents' countries. The number of countries where all three respondent groups (clinicians, pharmacists, and parents) provided input was limited, and findings may not be generalisable to all European countries. Despite these acknowledged shortcomings, the results provide an insightful snapshot at the time of the survey of the situation experienced daily by health professionals and parents across Europe.

Implications

Licensing. Based on information from health professionals, off-label use in children and adolescents was estimated for one-third of all medicines and for one-fourth of the WHO EMLc medicines on the survey list. Off-label use *per se* is not a major concern in paediatric cancers, particularly in relation to the WHO EMLc 2017 medicines. Indeed, the international paediatric haematology and oncology community has established the efficacy, toxicity, dosage, and pharmacokinetics of these agents through academic prospective clinical trials that validated standard treatments to achieve an overall 80% disease-free survival rate at 5 years. Accordingly, the goal of ensuring that the essential anticancer medicines are always available and affordable across Europe for all children and adolescents who need them takes precedence over requesting an SmPC update.

Shortages. A major finding from health professionals is that only 44% of all medicines and 63% of the WHO EMLc 2017 medicines on the survey list were always available over the 2-year reference period in $\geq$90% of the countries. Shortages were the main reason for unavailability and tended to affect countries with lower GNI per capita. The questionnaire did not ask for details on shortage frequency and duration; it was therefore not possible to fully evaluate the extent of the resulting access issues. Shortages were most frequently reported for asparaginases and corticosteroids. These medicines are used daily in the treatment of ALL, which has a high cure rate and is the most commonly occurring paediatric malignancy, with 5000 newly diagnosed patients per year in Europe.[19] Shortages of essential medicines for treating ALL can thus have critical implications for children's and adolescents' lives, which exemplifies the severity of the issue.[20]

Anticancer medicine shortages are a major concern worldwide and have been widely reported in recent years, including by the American Society of Health-System Pharmacists,[21] the European Association of Hospital Pharmacists,[22] and at the national level.[23] In 2018, the European Medicines Agency and Heads of Medicines Agencies held a workshop on the availability of authorised medicines where the consequences of oncology medicine shortages were reported by ESMO and several policy recommendations were made (Table 1).[24]

Financial toxicity. The survey showed that financial accessibility barriers predominantly involved countries with lower GNI per capita and, across all surveyed countries, were more common for newly approved expensive medicines. Out-of-pocket costs were reported in a total of 12 countries, and by both parents and health professionals in Bulgaria, Estonia, and Romania. Relating these data to statistics on government/social insurance coverage of pharmaceutical products,[25] no information was available for five countries, and findings converged for four countries with a coverage below 99%. The current perception findings for the other countries could not be consistently correlated with national government/social health coverage statistics. The study did not differentiate between private or public health insurance for out-of-pockets costs, and this aspect merits further research.

It is anticipated that affordability across Europe will become a major issue as new, innovative, and effective, but high-priced therapies for paediatric malignancies enter the market, for example, CAR (chimeric antigen receptor) T cells for relapsed ALL.

Lack of age-appropriate formulations. Health professionals reported that 27% of the oral essential medicines on the survey list were never available in an age-appropriate formulation for administration in young children. Parents

Table 2. European Society for Paediatric Oncology (SIOP Europe) recommendations to address unequal access to essential medicines in Europe

- Support European Society for Medical Oncology (ESMO) recommendations on shortages of oncology medicines.
- Define and validate a European List of Essential Medicines for childhood cancer and propose it as addition to the World Health Organization Model List of Essential Medicines for Children (WHO EMLc) in 2021.
- Set up, with European Society of Oncology Pharmacy (ESOP), recommendations for hospital pharmacists on the preparation of child-friendly formulations.
- Incentivise the development of age-appropriate formulations, including for generic anticancer medicines.
- Warrant relevant and adequate evaluation of new medicines for children and adolescents with cancer by health technology assessment bodies to ensure appropriate pricing and reimbursement strategies.
- 100% of children and adolescents undergoing procedures should receive pain control.
- Raise the awareness of policy makers, regulators, health professionals, and parents.

overwhelmingly confirmed this finding, reporting complex manual format adjustments and the distress experienced in the process. One example concerns temozolomide: this medicine is used for the treatment of tumours in children as young as <3 years of age but is only available in large-size capsules. Lack of child-friendly formulations of orally administered essential anticancer medicines is an issue that requires urgent solutions across Europe. Pharmacy departments in some countries are already preparing *ad hoc* liquid formulations for individual patients. At the European level, the ESOP Paediatric Working Group may provide a forum for cross-border sharing of initiatives on the preparation of age-appropriate formulations.

Supportive care provision. There were pronounced differences in the provision of pain control for painful procedures performed on children with cancer in European countries, as reported by parents. It is highly important to raise awareness of these inequalities and foster urgent change. Pain control during procedures should be explicitly recognised as standard care for children and adolescents with cancer and underpinned by rapid action to ensure access. While pain control agents are now available for numerous procedures involved in paediatric cancer diagnosis and treatment, it is of major concern that many children and adolescents in Europe do not have effective access to them.

CONCLUSION

The findings of the JARC survey demonstrate the need for coordinated European initiatives to ensure access to essential medicines for the treatment and care of children and adolescents with cancer. Focus areas are shortages, financial accessibility of newer agents, child-friendly formulations, and equal access to pain control. SIOPE supports the recommendations on essential medicine access produced by SIOP and CCI[3] as well as the Economist Intelligence Unit and ESMO recommendations n shortages in oncology[26,27] (Table 1). Recommendations that stem from the JARC survey are summarised in Table 2.

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DISCLOSURE

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