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The real-world use of drugs for the management of cancer in pediatric population: a scoping review protocol.

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Abstract

Objective: The objective of the forthcoming scoping review is to investigate and describe the actual management of pediatric cancer patients who access various clinical settings.

Introduction: The overall cancer management with the aid of drugs is a multifaceted process to treat the diagnosed patients, which is usually along with another treatment modalities. This process also involves controlling the emerged harmful symptoms attributed to cancer or cancer treatment using drugs in an effort to enhance patients' experience during treatment course and improve their quality of life, besides avoiding the long-lasting detrimental clinical impact.

Inclusion criteria: All observational studies that focus on the use of drugs in cancer patients aged <18 years will be included in this scoping review in any clinical sittings without restrictions on geography. Randomised controlled trials (RCTs), case reports, conference abstracts systematic reviews, reviews, opinions (including expert opinions), commentaries and clinical trials are not eligible for inclusion.

Methods: A search of PubMed (Medline), Embase, Scopus will be carried out. To uncover unpublished articles; MedRxIV, Open Grey, Google Scholar, ProQuest Dissertations and Theses and British Library Theses online service (EthOS) will be considered. All English-language observational studies from January 2013 to present will be eligible for inclusion. Relevant English-translated literature will be also searched. Screening of abstract/title and full text of included articles will be done by the primary reviewer after reaching the agreement with a second reviewer on ten percent of collected articles. Authors will present the extracted data in tabular and diagrammed forms, if necessary, accompanied with narrative summary that aligns with scoping review's aims. In case of any disagreement, the resolution will be passed through discussion or with a third reviewer.

Introduction

Notwithstanding the outbreak of unfamiliar diseases in the last ten years, local authorities, international health institutions, and pharmaceutical companies still prioritize threats of cancer and cancer-related health complications. Moreover, each year allocated budget is established for the sake of cancer management and funding cancer-oriented research. Based on WHO data, about 400000 children and adolescents aged between 0-19 are newly diagnosed with cancer per annum (1). The incidence of pediatric cancer is on increase which is attributed to some extent to the improvement in registration and diagnosis. From 2015 to 2017, the incidence of pediatric cancer in UK increased by 15%, similar trend was reported between 1993-1995(2). Leukemia, Central nervous system (CNS) tumors and lymphoma are common among this age group(1).

Compared to the adult population, the pediatric population has limited somatic mutations. However, data has revealed that the likelihood of alterations in the predisposed genes in this vulnerable population is more predominant and occurs through different mechanisms such as gene fusion. These genetic alterations contribute to the development of cancer(3). Unfortunately, the exact causes of cancer in the pediatric population are still questionable. But the considerable contribution of high exposure to ionizing radiation and certain viruses (herpesviruses, …) are reported. Maternal exposure to other environmental contributors such as alcohol during gestation might play a crucial role in the development of cancer(4-6).

Vulnerability in pediatrics is the main concern in the medical community, it has different forms related to undetected medical conditions, decision-making, and other considerations(7). Thus, it is mandatory to focus on the clinical requirement of this group especially pediatrics with diseases like cancer. The diversity of histological determinants of pediatric oncology has been documented in the literature which is apparently challenging in the research field (8). Apart from that, the small population of pediatrics hinders research and investigation regardless of research method type (9).

Besides surgery and radiation-based approaches, the integration of systemic chemotherapy in the treatment plan for cancer is well known. This integration takes place either as an adjuvant or neoadjuvant treatment alongside other treatment approaches, each form of treatment has specific short-term and long-term goals. Through different mechanisms, alkylating agents, mitotic spindle inhibitors, anthracyclines, and topoisomerase inhibitors are examples of chemotherapeutic drug classes that target specific cancer cell moieties to disrupt cellular biological processes(10). For instance, Grümme et al. highlighted the use of two options of chemotherapeutic regimens in the management of retinoblastoma including alkylating agents, topoisomerase inhibitors, and mitotic inhibitors(11).

Tackling drug resistance, reducing drug-related toxicity and other benefits have encouraged the health community to highlight in immunotherapy to manage cancer. Some immunotherapeutic agents are approved to be used in pediatrics with cancer but the limitations are still addressed in the pediatric area despite all benefits and their use among adult patients(12) . The use of rabbit anti-thymocyte globulin, rituximab, and bortezomib in pediatric patients who underwent allogeneic HSCT was mentioned by Shekhovtsova et al. (13).

Despite its promising impact, using targeted drugs or molecularly targeted in the pediatric field is still restricted. Like immunotherapy, researchers and clinicians have to investigate and carry out more research before expanding its use for the treatment of cancer(12).

The overall management of cancer involves the control of symptoms associated with the disease itself or emerging from administrated treatment approach, this kind of care is referred to as supportive care. Supportive care encompasses the application of non-oncological drugs that are substantially indicated for the management of negative physical and psychological impacts on patients' health(14).

Unfortunately, cancer patients generally are susceptible to bacterial, viral, fungal, and infections across their bodies which lead to detrimental complications provided that clinical control is not established to prevent and treat such infections. Thus, controlling all possible types of infections is a priority in pediatric cancer care. Some common conditions potentiate the occurrence of infection during this situation such as neutropenia. Literature has focused on this condition over the last few years(15-17). Through observational studies, Timsit et al., Hafez et al., Döring et al. and Siddaiahgari et al. revealed some of the used drugs in the treatment or prophylaxis of the infections(15, 16, 18, 19).

Some drugs target the gastrointestinal system to reduce some related symptoms, constipation, for example, or prevent some side effects (such as mucositis) attributable to administrating treatment . Also, neurological and pulmonary complications should be taken into consideration during the treatment and management of cancer in pediatrics(20).

Pediatric cancer patients who receive chemotherapy are prone to some unavoidable complications and oncological emergencies such as tumor lysis syndrome which can be lethal under certain conditions. Drugs are the first line of options to treat and prevent this syndrome(21).

Nausea and vomiting are documented among pediatric cancer patients, these symptoms are discom-forting and can be life-threatening in certain uncontrollable situations. With differing etiology (chemo-therapy, tumor triggered,) (22, 23).Willier et al. demonstrated some prophylaxis drugs in their observational studies(22).

To present, regardless of the identified and unidentified triggers, management of pain in pediatric cancer patients, is still challenging but analgesics besides other drug classes are workable options to lessen cancer-related pain and enhance the overall experience taking into consideration the variability of the pain experience (24) . Beng et al. identified two types of analgesics in the inpatient management of cancer(20) .

Hematological concerns and clotting problems also arise under certain circumstances which necessitate a prompt clinical response. Thrombocytopenia can be attributable to certain chemotherapy regimens that could precipitate bleeding. Although the incidence of thrombosis in this age group is generally low, thrombosis is a medical burden in the management of cancer in pediatric patients, it could be triggered by the treatment itself, specific cancer type, or a combination of many factors(25). In the Netherlands, Klaassen et al. found a noticeable incidence and recurrence of venous thrombosis in a single center. Such conditions warrant the administration of a full anticoagulant regimen in addition to thromboembolism-prophylactic drugs which might be encouraged in the former setting(26).

The actual picture of drug utilization in the area of pediatric cancer is somewhat vague across the world. No previous systematic reviews or scoping reviews described the real-world pharmacological management of cancer and its relevant symptoms in children. Hence, conducting the scoping review will be the most appropriate method to shed light on this area. The scoping review aims to disclose available literature concerning the real-world treatment

of cancer and relevant symptoms using drugs to provide a broad overview of the value of drugs for the pediatric population who are diagnosed with cancer. Enhancing the overall management of cancer in this vulnerable age group would likely be associated with improving patients' quality of life, reducing suffering during treatment, and eventually additional survival in the long term.

Review question

What drugs have been used for the treatment or management of the pediatric population who are diagnosed with cancer in clinical institutions or facilities?

Keywords

Childhood; Drug utilization; Oncology; Scoping review; Treatment

Eligibility criteria

Participants

The forthcoming review plans to involve studies that consider children and adolescent patients under the age of 18 with diagnosed cancer who accessed treatment in any authorized clinical settings. No exclusions will be applied based on cancer type. Studies solely focused on pediatric or adolescent with other chronic, acute diseases or disorders and that have symptoms resembling that of cancer will be excluded.

Concept

The review will include all observation-based studies that highlighted the utilization of drugs with different dosage forms in the treatment of cancer or as a part of the management approach for symptoms developed during the treatment course or cancer prognosis. Multidisciplinary literature will be considered given that it spotlights on use of drugs in the overall management of cancer for pediatric patients. Any observational study that focused on other treatment approaches (e.g. radiotherapy) without using drugs are excluded. Studies highlighting psychologically supportive care of pediatric cancer patients without considering drug utilization are also excluded. Inclusion will not involve observational articles focusing on the treatment outcomes with no details on the followed treatment approach.

Context

No limitation will be imposed in terms of geography and culture for the sake of a broad overview of real-world management of cancer in this vulnerable group age.

Types of Sources

To get an overview of the real-world pharmacological management in pediatric cancer area, all observational studies (cohort studies, cross-sectional studies...), and observational epidemiology studies will be considered. Authors will exclude randomised controlled trials (RCTS), case reports, conference abstracts, systematic reviews, reviews, opinions (including expert opinions), commentaries, and clinical trials. The designed scoping review will consider English-language literature from the year 2013 to present with the purpose of capturing

reasonable number of existing related research results. Literature that translated to English will be included provided that it follows the inclusion criteria. Sources of grey literature and reference lists of included articles will be searched.

Methods

The developed research strategy will be conducted in accordance with Joanna Briggs Institute (JBI) recommendations and PRISMA Extension for Scoping Reviews PRISMA-ScR protocol to retrieve targeted literature(27).

Search strategy

The scoping review seeks retrieving all potential published and unpublished literature. Using selected keywords and search terms, an initial basic search will be performed in Medline (PubMed) followed by analysis of titles and abstracts to capture all possible relevant text words highlighted in title and abstract in relation to research subject. A full search strategy of Medline is listed in Appendix 1. After identifying all possible keywords from initial search, full research strategy will be carried out in all selected electronic databases considering tailoring of keywords and text terms on the basis of the used information source. Following the iterative nature of this approach, additional keywords might be discovered and added to the established search strategy. Reference lists of included articles will be also examined for sake of further unpublished articles.

The included electronic bibliography databases are PubMed (Medline), Embase, Scopus.The selection of databases is generally chosen based on their relevance to medical treatment.

Grey literature will be searched to ensure the collection of unidentified literature. This will involve certain sources in particular; MedRxIV, Open Grey, Google Scholar, ProQuest Dissertations, and Theses and British Library Theses online service (EthOS). Google and will be searched as well.

Study/Source of Evidence selection

After conducting search, all identified articles will be exported into Covidence (https://www.covidence.org/). Ten percent of titles and abstracts of collected articles will be screened by an independent reviewer separately at the first stage and compared with the screening results of primary reviewer; if they agreed, primary reviewer will screen the rest of collected articles. The screening process will be done based on the information indicated by the title and abstract, titles and abstracts that don't meet inclusion criteria will be excluded. Articles that meet the inclusion criteria will be retrieved in full for more examination of the full text. Examination of full text will be done into two stages; at the first stage primary reviewer and a second reviewer examine ten percentage of full-text included articles if agreement is reached, primary reviewer will examine the rest of included articles. For articles with no abstract, assessment will proceed to a thorough full-text examination to assess the eligibility for inclusion criteria. Full-text articles that do not meet inclusion criteria will be excluded; the titles of former articles will be documented in a table with the exclusion reasons. Afterward, data extraction will include all articles which meet the inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Scoping Reviews (PRISMA-

ScR) will present the results of the search. In case of any disagreement, the resolution will be passed through discussion or with a third reviewer.

Data Extraction

The descriptive information will be collected from included articles, the appendix 2 illustrates the used data extraction tool. The extracted data will provide information on study characteristics, studied population, and outcomes related to the conducted scoping review. Data will be extracted by the primary reviewer after comparing the extraction results of ten percent of included articles done by a second reviewer. In case of any disagreement, the resolution will be passed through discussion or with a third reviewer. The modifications may be occurred during conducting of scoping review to encounter unanticipated necessary information. These modifications will be reported in the full scoping review report. If required, authors of articles that met the inclusion criteria will be contacted for further necessary details or inquiries.

Assessing the quality of included articles will be done using an appropriate critical appraisal tool by the primary reviewer, CASP tool might be used in this assessment process.

Data Analysis and Presentation

Following data extraction, tabular and diagrammatic forms will be used to present extracted data in line with scoping review's objectives and research questions. These presentive forms will be implemented as necessary accompanied by a narrative summary for the purpose of answering scoping review questions and achieving the objectives. Using table(s), results will be categorized under main categories in light of incorporated findings to ensure that all relevant data is outlined.

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Conflicts of interest

The authors declare no conflict of interest.

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Appendices

Appendix I: Search strategy

Conducted on 16th February 2023

Number	Search terms	Retrieved articles
1	((((((((pediatrics [MeSH]) OR (pediatric* [tiab])) OR (paediatric* [tiab])) OR (child [MeSH])) OR (child* [tiab])) OR (adolescen* [tiab])) OR (infant*[tiab])) OR (newborn*[tiab])) OR (neonate* [tiab])	3341382
2	((((((((((((((((((((((((((((((Neoplasms [MeSH]) OR (neoplasm*[tiab])) OR (tumour*[tiab])) OR (tumor*[tiab])) OR (cancer*[tiab])) OR (carcinoma*[tiab])) OR (oncolog* [tiab])) OR (leukemia [MeSH])) OR (leukemia*[tiab])) OR (leukaemia*[tiab])) OR (lymphoma [MeSH])) OR (lymphoma [tiab])) OR (metastas*[tiab])) OR (malignanc* [tiab])) OR (sarcoma*[tiab])) OR (melanoma* [tiab])) OR (myeloma [tiab])) OR (Hodgkin [tiab])) OR (ependymoma [tiab])) OR (medulloblastoma* [tiab])) OR (non-hodgkin [tiab])) OR (neuroblastoma* [tiab])) OR (astrocytoma [tiab])) OR (craniopharyngioma [tiab])) OR (glioma* [tiab])) OR (meningioma* [tiab])) OR (ganglioglioma* [tiab])) OR (osteosarcoma* [tiab])) OR ("pleuropulmonary blastoma" [tiab])) OR (retinoblastoma [tiab])) OR (rhabdomyosarcoma [tiab])) OR (mesothelioma* [tiab])) OR (Pheochromocytoma* [tiab])) OR (paraganglioma* [tiab])	5061825
3	((((((((((((((drug prescriptions [MeSH]) OR (drug ADJ prescri* [tiab])) OR (pharmacotherap* [tiab])) OR (drug utilization [MeSH])) OR (drug ADJ utili* [tiab])) OR (drug ADJ usage [tiab])) OR (drug ADJ use [tiab])) OR (drug therapy [MeSH])) OR (drug ADJ therap* [tiab])) OR (defined daily ADJ dose* [tiab])) OR (prescribed daily ADJ dose* [tiab])) OR (drug ADJ dispens* [tiab])) OR (prescription ADJ pattern*[tiab])) OR (drug ADJ administration [tiab])) OR (pharmacoepidemiology [MeSH])) OR (pharmacoepidemiolog*[tiab])	1554198
4	(((((((case report*[ti]) OR (RCT [ti] OR randomised controlled study [ti])) OR (RCT [ti] OR randomized controlled study [ti])) OR (expert opinion*[ti])) OR (conference abstract*[ti])) OR (review*[ti])) OR (systematic review*[ti])) OR (clinical trial*[ti])	1023370
5	1 AND 2	384589
6	1 AND 2 AND 3	29998
7	6 NOT 4	28343
8	Limit 7 to date range of 2013- present, English language and Human species	7924

Appendix II: Data extraction instrument

	Article 1	Article 2
First Author, Year of publication, Country of origin, Language		
Title		
Aims		
Study design (cohort study, cross-sectional, …), sample size		
Targeted area (rural or urban), clinical settings (hospital, out-patient facility...)		
Demographics (Age, gender, Ethnicity)		
Cancer type, subtype, stage at diagnosis		
Used drug		
Indication		
Dose/ formulation (where available		
Prescriber (GP, hospital consultant, pharmacist, nurse...)		
Drug approval, Labelling status		
Reported limitations		
Additional notes		