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Scoping review protocol on the impact of antimicrobial resistance on cancer management and outcomes

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ABSTRACT

Introduction Antimicrobial resistance (AMR) is a growing global public health concern and is becoming a significant challenge in the management of patients with cancer. Due to the immunosuppressive nature of cancer treatment, infection is a common complication and the necessary high usage of antibiotics increases the risk of AMR. Failure to adequately prevent and treat infection in patients with cancer as a result of AMR can increase the morbidity and mortality of the disease. The objective of this scoping review is to understand the relationship between AMR and cancer in order to develop effective antimicrobial stewardship in this patient population and minimise the detrimental effects of AMR on cancer outcomes.

Methods and analysis This scoping review will follow the Arksey and O'Malley methodology framework. An exploratory review of the literature on antibiotic resistance in cancer care will help to define the research questions (stage 1). A broad range of electronic databases (MEDLINE ALL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Embase) and search terms will be used to retrieve relevant articles published between 2000 and 2021 (stage 2). Studies will be systematically selected based on the eligibility criteria by two independent reviewers (stage 3). The titles and abstracts will be appraised to determine whether articles meet the eligibility criteria. This will be followed by screening of the full texts and only relevant publications will be retrieved. Data will then be extracted, collated and charted (stage 4); and the summary of aggregated results will be presented (stage 5).

Ethics and dissemination As this scoping review will collect and synthesise data from publicly available sources, no ethics review is required. When data collection and summarisation is completed, results will be disseminated through peer-reviewed publication and the key findings of the review will be presented at relevant conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present protocol is for a scoping review for original studies, as an optimal way of dealing with the limited evidence available on antimicrobial resistance in cancer care.
⇒ Relevant published articles were retrieved from major biomedical databases from major biomedical databases (MEDLINE ALL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Embase) by conducting a comprehensive search and screening the reference lists of the included studies.
⇒ Only original articles published in English in scientific journals between 2000 and 2021 were considered eligible for inclusion.

INTRODUCTION

Antimicrobial resistance (AMR) is a growing public health challenge globally and is estimated to cause 750 000 deaths annually.[1] AMR is also responsible for significant strain on health systems due to increased hospital admissions, extended stays, more intensive care unit admissions and the need for additional isolation beds. AMR is estimated to add US$20 billion annually to direct healthcare costs in the USA, and €1.1 billion in the European Union, as well as losses in productivity.[2 3] Research into the effect of AMR on the management and outcomes of other diseases is also growing. Within oncology, evidence suggests that AMR is adversely affecting the effective delivery of cancer treatments and increasing adverse outcomes.[4]

Bacterial infections are a common complication in patients with cancer due to both disease-related and treatment-related immunosuppression.[5] They are responsible for the hospitalisation of 20% of the patients with cancer on treatment and a further 8.5% of the cancer deaths due to severe sepsis.[1 6] Antibiotic resistance in patients with cancer increases the likelihood of such severe infection. AMR occurs when pathogens (such as bacteria, fungi, viruses and parasites) develop the ability to adapt and survive, even when they are exposed to antimicrobial medicines designed to kill or limit their growth. As a result, medicines become ineffective and infections persist in the body, increasing the risk of dissemination and mortality.[7]

In patients with haematological cancer, vulnerability to infection occurs due to

disease-related impairment in bone marrow production of neutrophils, defects in adaptive B-cell-mediated immunity and/or lack of splenic function.[8] In patients with solid tumours, severe disease-related neutropenia is uncommon, but other factors increase the risk of invasive infection such as damage to natural anatomic barriers (eg, skin and mucosal surfaces) and cancer-related surgeries.[9] Beyond disease-related immunosuppression, cancer treatments such as chemotherapy, radiation, surgical procedures and haematopoietic transplantation may also contribute to neutropenia, aggravating the susceptibility to bacterial infections. The use of medical devices, such as central lines and peripheral lines, provides a route for bacteria to enter the body. A recent study conducted in Germany in patients with haematological and solid tumours showed that the incidence rate of central line-associated blood stream infections was 10.6 per 1000 central vascular catheters days, equating to a prevalence of 18.2%.[10] Common sites of infection include the skin, the bloodstream, respiratory system, urinary tract, the hepatobiliary and intestinal tracts. Most infections in these patients are caused by the individual resident microflora. However, after hospitalisation, nosocomial infection can occur, and institutional pathogens must be considered as the causal agents in case of empirical antibiotic therapy.[9]

With the growing challenges of AMR, broader antibiotics are being used for prophylactic, empiric and therapeutic approaches to manage infections. These can fundamentally alter the microbiome, which in turn may alter responses to therapy for patients with cancer. Two landmark studies in mice provided the first evidence that the microbiome may directly impact the effectiveness of immune checkpoint blockade (ICB).[11 12] Retrospective data has also demonstrated that in patients receiving ICB, overall survival and progression-free survival are longer in patients who are not exposed to antibiotics, and antibiotic use in the 42 days before starting ICB appears to be most detrimental to outcome.[13 14] Preclinical models have demonstrated that manipulation of the gut microbiome through faecal transplantation may reverse clinical resistance to ICB.[15 16] The gut bacteria may modulate the response to ICB through production of the metabolite inosine, and further research is ongoing to clarify these mechanisms.[17]

Improving understanding of the impact of AMR on cancer care outcomes is an important step toward mitigating the potential detrimental effects of AMR on cancer outcomes and promoting antimicrobial stewardship in the oncology community. It will help to identify factors that increase AMR and factors that increase the impact of AMR on outcomes and determine the importance of AMR toward cancer outcomes. This review aims to assess the state of the literature on AMR and cancer, to understand the bidirectional impact of AMR and cancer management, and to identify any published interventions and ongoing initiatives to address the challenge of AMR and cancer.

METHODS AND ANALYSIS

Protocol design

The scoping review represents an appropriate methodology for reviewing the literature on AMR and cancer to generate an overview of research undertaken in this area, to determine the range of studies that are available, to understand their key findings and to identify evidence gaps. This scoping review on AMR in cancer care will be conducted using the framework recommended by Arksey and O'Malley,[18] with the review process organised into five stages: Stage 1: Identifying the research question; Stage 2: Identifying relevant studies; Stage 3: Study selection; Stage 4: Charting the data; Stage 5: Collating, summarising and reporting the results.

Stage 1: identifying the research question

The primary question for this review is: What is known in the literature about AMR in patients with cancer? An exploratory review of the literature on AMR in cancer care helped to further refine the scope of the protocol.

On the basis of the initial exploratory research, the following research subquestions were identified:

1. How does AMR affect cancer treatment and outcomes?
2. How does cancer treatment affect AMR?
3. What are the gaps in research related to cancer care and AMR?

Stage 2: identifying relevant studies

This stage of the scoping review process aims to identify the criteria that will be used to select the studies for inclusion in the review. A preliminary search was conducted in Ovid MEDLINE ALL (MEDLINE and Epub Ahead of Print and In-Process & Other Non-Indexed Citations). The search was limited to human studies and articles published in English between January 2000 and May 2021. A combination of controlled vocabulary terms and text words was used in the subject block structure. The full search strategy is provided in online supplemental table 1.

The PICO tool was used to map the research question and identify relevant search terms. This tool guides the inclusion of relevant evidence in the database focusing on the research scope and avoiding unnecessary searching.[19] The search strategy comprises three main components: patients with cancer (population); and association between antimicrobial/antibiotic resistance (intervention) and mortality, morbidity, prognosis or treatment (outcome). The search strategy was split into two subgroups: haematological and solid tumours, since these subgroups have their own characteristics. The first subject block will include either haematological cancer terms OR solid tumour terms; the second subject block will contain antimicrobial/antibiotic resistance terms; the third block will comprise bacterial infection terms; and the last block will consist of terms for the outcomes of interest, such as prognosis mortality, morbidity, risk.

Based on the initial scoping process, research in progress, conference proceedings/abstracts, dissertations/

Table 1 Data extraction framework

Main category	Description
1. Authors	
2. Title	
3. Journal	
4.Year of publication	
5. Study design	
Study aims	
6. Sample size (if applicable)	
7. Demographic data	Specify the countries and regions covered by the study, country income levels, age groups.
8.Year(s) of data collection (if applicable)	
9. Description of the study population	Specify if the intervention targets individuals within subpopulation groups. If applicable: 1. Describe setting of the study population: inpatient versus outpatient.
10. Reported outcomes	Describe the intervention outcomes reported in the study. If applicable: 1. Prevalence of AMR. 2. Risk factors associated with AMR. 3. Impact of AMR on (i). i. Overall survival. ii. Cancer-related outcomes. iii. Length of in-hospital stay.
11. Description of activities to address AMR and cancer	
12. Discussion of gaps, unmet needs and future directions	

AMR, antimicrobial resistance.

theses or books/book chapters will be excluded. We also will limit the search to English language publications between 2000 and 2021, as AMR has changed significantly over the last two decades, and earlier publications are likely to have limited relevance to the current clinical environment. Although AMR encompasses resistance to antibacterial, antiviral, antifungal and antiparasitic drugs, this review will restrict to antibiotic resistance due to the large volume of literature on each of these topics. Reference lists and bibliographies of relevant articles identified will be hand searched to identify additional publications of relevance.

The comprehensive search strategy will be executed in the following databases: MEDLINE ALL (MEDLINE and Epub Ahead of Print and In-Process & Other Non-Indexed Citations), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Embase, all from the OvidSP platform.

Stage 3: study selection

Following the third stage of the framework of Arksey and O'Malley's framework articles identified through the outlined search strategy will be obtained. All identified articles will be uploaded into Covidence, an online systematic review manager and screening tool. Duplicate articles will be removed automatically in Covidence.[20]

Two independent reviewers will conduct an appraisal of the titles and abstracts to judge whether articles meet the eligibility criteria.[21] Discrepancies between the reviewers will be reconciled by a third reviewer. Those articles that do not meet the eligibility criteria based on title review will be excluded. Studies that focus solely on the chemical properties of antibiotics or general use of antibiotics in patients with cancer with no antibiotic resistance data will also be excluded. Any articles for which an assessment of relevance cannot be made based on the title and abstract review will continue to full text where eligibility will be determined.

Full texts of all articles that meet the inclusion criteria will be retrieved and reviewed to determine which articles will be subject to data extraction and synthesis. The full-text review will also be conducted by two independent reviewers and a third reviewer will reconcile any differences in selection. Agreement between authors in the process of selecting articles will be evaluated by using Kappa statistics (inter-rater reliability).

Stage 4: charting the data

Based on the preliminary scoping phase, a data extraction framework including nine categories was developed. This framework will be used to assess all full-text articles meeting our inclusion criteria (table 1). The framework

will be pilot-tested by two independent reviewers on a sample of the included studies in order to ensure that the coding framework is consistently applied. Discrepancies will be resolved by consensus, or by arbitration of a third reviewer. If necessary, the categories will be modified, and the data extraction framework revised accordingly.

Stage 5: collating, summarising and reporting the results

Analysis of the collected data will provide information on the body of research that has been conducted on AMR in cancer care. We will identify areas where there is consensus in management of AMR in cancer, and where more research and guideline development are needed. Final results will be stratified into two groups: haematological and solid cancer, as they have unique properties and characteristics. The susceptibility to infections among these two groups differ due to the intensity of chemotherapy and its cytotoxic effects on the gastrointestinal tract cells. Thus, the degree to which antibiotic resistance is a major problem for these two groups of malignancies may differ, warranting a separate analysis of the scope of the problem. Results will be presented descriptively and quantitatively, as appropriate. The data summarisation, analysis and reporting process will follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. The PRISMA-ScR checklist contains 20 essential reporting items and 2 optional items.[22]

The results of this scoping review will directly inform ongoing advocacy efforts focused on AMR and cancer. The Union for International Cancer Control, a large non-governmental organisation in Geneva focused on global cancer control, launched an international task force on AMR and cancer in 2020 to raise awareness of the issue of AMR within the oncology community and to develop targeted approaches to reduce the impact of AMR on cancer outcomes. Understanding the scope of the evidence in this area is an essential step to develop evidence informed policy and programmes to address AMR. Following the critical step of raising awareness and increasing knowledge on the issue, a key focus area of the task force and the cancer community is to advocate for rational use of existing therapies and access to novel therapies and rapid infectious diseases diagnostics globally.

ETHICS AND DISSEMINATION

As this scoping review will collect and synthesise data from publicly available sources, no ethics review is required. The results of this scoping review will be used to summarise the current field of AMR and cancer, including both solid tumour and haematological malignancies. The data will be informative for various stakeholders including researchers, public health organisations, cancer organisations, hospitals and patients. When data collection and summarisation is completed, we aim to produce an article reporting the results of the scoping review that will be disseminated to stakeholders through open access publication in a relevant cancer journal. We will also aim to present and disseminate results at relevant conferences.

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