OPTIMISING CANCER SUPPORTIVE CARE IN QATAR

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"Doctor of Philosophy"

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DECLARATION

Cancer is a complex disease, which renders cancer patients in need of significant pharmaceutical supportive care, to reduce the complications of the disease and cancer drug therapy. Therefore, optimising cancer supportive care may enhance patients' outcomes, improve quality of life (QoL), reduce hospital length-of-stay (LOS) for complications or adverse events, and decrease healthcare cost.

Lately, the oncology clinical pharmacists are playing a quite important role in cancer care. Over the last two decades, the field of oncology clinical pharmacy has grown due to improved knowledge, and experience. The roles of pharmacists have shifted from being a "*drug-oriented*" to a more "*patient-oriented*" service, much as the transformation in oncology management from a "*disease-focused*" to a "*patient-focused*" approach.

I have been working as an Advanced Oncology Clinical Pharmacist at the National Centre for Cancer Care & Research (NCCCR) in Qatar since 2007, and as an Adjunct Faculty in the College of Pharmacy at Qatar University since 2011. I have been leading the clinical pharmacy services at NCCCR since 2014, with strong commitment to enhancing cancer patients' clinical outcomes. I've worked on several research projects over the past ten years and have provided answers to a variety of research topics that have helped us optimise practice and improve clinical outcomes. A significant portion of my work focused on the optimal use of antimicrobial agents and enhancing palliative care and drug/disease related symptoms management to enhance therapeutic effectiveness while reducing side effects and enhancing patients' quality of life (QoL).

I designed, led, and completed a variety of research projects that were inspired by the gap in clinical practise, while building a substantial body of research along the way. Numerous research papers that I produced have been published in highly ranked peer-reviewed journals and are eligible for inclusion in my thesis. With the help of my supervisor, I have carefully selected six significant cancer supportive care research studies that I have conducted and published to be included in this PhD thesis.

I declare that none of the content in this thesis has been used in any previous academic award submissions.

I also declare that all content in this thesis were my original work, and any citations to or use of information from other sources have been properly acknowledged.

Shereen Elazzazy

ACKNOWLEDGEMENTS

I want to express my gratitude to my kids and my parents for their love, encouragement, and faith in my ability to advance my career and to overcome any obstacles in my path.

My research journey started with great support and guidance of Dr. Manal Zaidan (my previous Pharmacy Director), who really believed in my capabilities and competencies. The appreciation is extended to Dr. Anas Hamad (the current NCCCR Pharmacy Director) - he is an eminent researcher. Without his support, I would not be able to extend my research efforts to the level I have reached.

A big thank you is extended to all co-authors who shared all the research efforts with me, and the clinical pharmacy team in NCCCR - the competent solders in the cancer battle. Furthermore, I'd like to acknowledge the great professional, technical, regulatory, and financial support of Hamad Medical Corporation (HMC) Medical Research Centre (MRC) and HMC Institutional Review Board (IRB)

Last but not least, I want to express my gratitude to Dr. Shereen El Nabhani (my PhD supervisor). She has been a very close mentor to me while I was a PhD student at Kingston University, and she provided me with a lot of help when I was writing this thesis.

AUTHOR STATEMENT REGARDING AUTHORSHIP

This considerable collection of work consists of a total of 6 research studies that discuss cancer supportive care. Together with my supervisor, I have chosen to concentrate on 6 research papers on the role of oncology pharmacists in optimising cancer supportive care, the management of cancer patients' complications, and antimicrobial use in cancer settings in Qatar in order to write a coherent PhD thesis. These studies are listed below as key publications KP1- KP6. I was the lead PI (primary investigator)/ co-PI on 4 papers, and significant contributing co-author on 2 papers.

In accordance with the requirements, I hereby estimate my % of contribution to each of the 6 KPs that are included in this thesis.

Key Publications (KPs)

- **KP1:** Taghrid Abu Hassan, Sumaya Al Yafei, Radwa M Hussein, Sahar Nasser, Ahmed Basha, Hafedh Ghazouani and **Shereen Elazzazy***. The Role of the Pharmacist in Decreasing Discharge Medication Discrepancies for Cancer Patients in Qatar: A Prospective Cohort Study. ACTA Scientific Cancer Biology 3.3 (2019): 02-09.

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  As the lead-PI and the corresponding author of this study, I formulated the study design, led the proposal writing and grant request, followed-up ethics and approvals with HMC MRC and IRB, designed the data collection tools, validated the collected data, revised the analysed data and results, facilitated team discussions, wrote the manuscript, submitted the article for publication, and addressed the reviewer comments. My contribution in this study is estimated as 70%.

- **KP2:** Nabil H. Omar, **Shereen Elazzazy***, Abdulqadir J Nashwan Yassin Eltorki, Oraib Abdallah, Hebatalla Afifi, Nancy Kassem, Mohamed Yassin, Anas Hamad. Perceptions and Expectations of Health Care Providers towards Clinical Pharmacy Services at the Tertiary Cancer Centre in Qatar. JOPP, J Oncol Pharm Practice 0(0) 1–11, 72. September 2019. doi.org/10.1177/1078155219882076

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In this study I was the co- Principle Investigator (co-PI) and the corresponding author. I led the study initiation, conceptualised the idea, designed the study, selected the team members, wrote the proposal and grant request, and followed-up ethics and approvals with the MRC and the IRB. Furthermore, I led in designing and validating the surveys, designing data collection tools, validating the collected data, analysing the data, team discussions, writing the manuscript, submitting the article for publication, and addressing reviewer comments. My contribution in this study was estimated as 65%.

- **KP3:** Sahar M Nasser, Arwa Sahal, Anas Hamad, **Shereen Elazzazy***, "Effect of denosumab versus zoledronic acid on calcium levels in cancer patients with bone metastasis: A retrospective cohort study", Journal of Oncology Pharmacy Practice, 2019. doi.org/10.1177/1078155218820927

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In this study as well, I was the Lead PI and the corresponding author. I led the study, starting from the initiation, idea conceptualization and study design, selecting the team members, writing proposal and grant request, to following-up ethics and approvals with the HMC MRC and the IRB. Simultaneously, I led the designing of data collection tools, validation of the collected data, data analysis, writing the manuscript, submitting the article for publication, and addressing reviewer comments. My contribution in this study was estimated as 70%.

- **KP4:** Nabil Omar, Kareem El-Fass, Abdelrahman I Abushouk, Noha Elbaghdady, Ahmed Barakat, Ahmed Noreldin, Dina Johar, Mohamed Yassin, Anas Hamad, **Shereen Elazzazy**, Said Dermime. "Diagnosis and Management of Haematological Adverse Events Induced by Immune Checkpoint Inhibitors: A Systematic Review". Front. Immunol. Oct. 2020. 11:1354. doi:10.3389/fimmu.2020.01354

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In this systematic review study, I had a significant contribution. I was profoundly involved in the protocol development, literature collection, literature review and interpretation of data, studies eligibility team discussions, critical revision of the manuscript for important intellectual content, manuscript submission, and addressing reviewer comments. I estimate my contribution in this study as 40-50%.

- **KP5:** Ahmed S, Hammuda A, **Elazzazy S**, Black E. "Point prevalence survey of antibiotic utilisation in oncology patients". J Infect Dev Ctries, 2013; 7(12):990-993. doi:10.3855/jidc.3126

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  In this article review study, I was the Co-PI. I was leading all HMC/ MRC approvals, budget, and logistics, in addition to discussions with the clinical teams in NCCCR. Additionally, I was intensely involved in the idea formulation, study design, writing proposals and grant requests, ethics and approvals, designing data collection tools, validation of the collected data, funding organisation, manuscript writing, and publication and manuscript submission and addressing reviewer comments. I estimate my contribution in this study as 55%

- **KP6:** Ziad G. Nasr, Alya Babiker, Marwa Elbasheer, Aisha Osman, **Shereen Elazzazy** and Kyle John Wilby, "Implications of an antimicrobial stewardship intervention in a tertiary care teaching hospital in Qatar". East Mediterr Health J. World Health Organisation (WHO) 2018. doi.org/10.26719/emhj.18.026

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  I had a significant contribution in this article, as the lead investigator in HMC leading all the approvals and logistics, in addition to communications with the clinical teams in NCCCR. Furthermore, I was

heavily involved in writing the proposals and grant requests, structuring the Quality Improvement (QI) phase, staff education, data collection, validation of the data, and manuscript review and publication. My contribution in this study was estimated as 40%

LIST OF TABLES

LIST OF ABBREVIATIONS

ACCP: American College of Chest Physicians

ADEs: Adverse Drug Events

AMR: Antimicrobial Resistance

AMS: Antimicrobial Stewardship

ASCO: American Society of Clinical Oncology

ASHP: American Society of Hospital Pharmacists

BMI: Body Mass Index

BOPA: British Oncology Pharmacy Association

BSAC: British Society for Antimicrobial Chemotherapy

BSIs: Bloodstream Infections

BTAs: Bone-Targeting Agents

CDC: Disease Control and Prevention

CrCl: Creatinine Clearance

CTLA-4: cytotoxic-T-lymphocyte antigen 4

DE: Denosumab

DRPs: Drug Related Problems

DVT: Deep Venous Thrombosis

ECDC: European Centre for Disease Prevention and Control

EGOPP: Egyptian Guide for Oncology Pharmacy Practice

EHRs: Electronic Health Records

EMRO: East Mediterranean Regional Office

ESA: Erythropoiesis-Stimulating Agent

ESAC: European Surveillance of Antibiotic Consumption

ESPAUR: English Surveillance Programme for Antimicrobial Utilisation and Resistance

ESMO: European Society for Medical Oncology

FDA: Food and Drug Administration

FIP: International Pharmaceutical Federation

FTE: Full-time equivalent

g: gram

GCC: Gulf Cooperation Council

HAI: Healthcare Associated Infections

HCPs: Healthcare professionals

HMC: Hamad Medical Corporation

HRQOL: Health-related quality of life

ICIs: Immune Checkpoint Inhibitors

ICU: Intensive Care Units

IPE: Interprofessional Education

IQR: Interquartile Range

irAEs: Immune-Related Adverse Events

IRB: Institutional Review Board

IVIG: Intravenous Immunoglobulin

JCI: Joint Commission International

KP: Key Publication

KPIs: Key Performance Indicators

KRS: Khorana Risk Score

LOS: Length of Stay

MASCC: Multinational Association of Supportive Care in Cancer

MDT: Multidisciplinary Team

MENA: Middle East and North Africa

mg: milligrams

MIC: Minimum Inhibitory Concentration

MM: Multiple Myeloma

MMR: Mixed Methods Research

MRC: Medical Research Centre

NCCCR: National Centre for Cancer Care & Research

NCCN: National Comprehensive Cancer Network

NICE: National Institute for Health and Care Excellence

NMPs: Non-Medical Prescribers

P&T: Pharmacy and Therapeutics

PCS: Prospective Cohort Study

PD-1: Programmed Cell Death Protein 1

PD-L1: Programmed Cell Death-Ligand 1

PDSA: Plan-Do-Study-Act

PE: Pulmonary Embolism

PHCC: Primary Health Care Corporation

PI: Principle Investigator

PPS: Point Prevalence Survey

QI: Quality Improvement

QNCR: Qatar National Cancer Registry

QPS: Quality and Patients' Safety

RCS: Retrospective Cohort Study

RCTs: Randomised controlled trials

RWD: Real-World Data

RWE: Real-World Evidence

SACT: Systemic Anti-Cancer Therapies

SWOC: Strengths, Weaknesses, Opportunities and Challenges

UAE: United Arab Emirates

UKHSA: The UK Health Security Agency

VTE: Venous Thromboembolism

WHO: World Health Organisation

ZA: Zoledronic acid

%T > MIC: The proportion of time that plasma concentrations are above minimum inhibitory concentration

ABSTRACT

According to the 2022 World Health Organisation (WHO) statement, cancer was the world's leading cause of death in 2020, accounting for up to 10 million deaths, close to one in every six. Whereas, the 2020 UK Cancer Research report showed that in England and Wales, more than 375,000 cases are diagnosed with cancer every year during the period of 2016 - 2018, with 167,147 cases of fatalities over 2017-2019 (Cancer Research UK, 2020). A cancer diagnosis and its following treatment can have an overwhelming effect on a patient's QoL, as well as on the life of their family (NICE, 2019). Regardless of their individual circumstances, cancer type, stage, or anti-cancer medication, all cancer patients have a fundamental right to supportive care (NICE, 2019). Hence, it is crucial to optimise cancer supportive care, in order to improve patients' clinical outcomes, compliance with therapy, QoL, and cost effectiveness of cancer care, as well as to ensure that cancer patients get the most out of their anticancer treatments.

Real-world studies enable oncology healthcare professionals to comprehend regional variances in clinical practise and the reported real-world outcomes. RCTs frequently exclude participants with co-morbid conditions, advanced age, and low performance status. This leaves a gap in the body of knowledge regarding the effectiveness and safety of cancer therapy for this cohort of patients. Therefore, it is necessary to have a deeper knowledge of Real-World Evidence (RWE) to better understand therapy outcomes in real practice (Banerjee and Prasad, 2020).

The Multidisciplinary Team (MDT) approach has been proven to improve patients' clinical outcomes. The oncology pharmacist is a core member of cancer MDTs in Qatar. Over the last 15 years, oncology clinical pharmacists have been showing a significant independent role in cancer supportive care in Qatar, which significantly reflects on clinical, economic, and psycho-social outcomes of cancer patients.

This thesis contributes to cancer supportive care real-world research, and different approaches towards improvement of therapeutic outcomes. It includes six studies, with a considerable representation of different real-world research methodologies, including a retrospective cohort study, a prospective cohort study, a healthcare survey, a Point Prevalence Survey (PPS), a systematic review, and a mixed method study.

The aim of the KP1 study was to assess the impact of the oncology pharmacists' interventions during the discharge reconciliation process in the outpatient pharmacy. This study included a total of 4293 orders of medications for 591 patients/prescriptions. The results revealed a sum of 278 (47%) prescriptions required

pharmacists' interventions. Plus, 32% (190/591) of the prescriptions had medication discrepancies, and 21% (122/591) had medication errors, as detected by the pharmacists. In KP2, the purpose was to assess how different healthcare providers (HCPs) perceived the oncology clinical pharmacy service in NCCCR. The results showed that different oncology HCPs in Qatar perceived a growing need for the clinical pharmacy profession in the following proportions: 96% for pharmacists, 90% for doctors, and 64% for nurses, with statistical significance (p=0.002). The majority of respondents noted that the clinical pharmacy service has the greatest influence with detecting medication errors (85%), patients' education (82%), and participation in clinical rounds (82%).

Focusing on cancer drugs related complications, KP3 aimed to assess the safety of Bone-Targeting Agents (BTAs) in bone metastasis. This study included 271 patients who received 1141 doses of BTAs (denosumab and zoledronic acid). The results showed – with statistical significance – that in Qatar's population hypocalcaemia was more frequent in denosumab patients than zoledronic acid patients. Whereas, about 60% of hypocalcaemia patients on both drugs did not receive calcium or vitamin D supplements. KP4 was a systematic review, aimed to identify the most popular techniques for diagnosing and managing the haematological Immune Related Adverse Events (irAEs) with the use of Immune Checkpoint Inhibitors (ICIs) by analysing the published data from case reports and case series. This study included 49 articles in total, with 118 cases reported haematological irAEs with ICIs. It concluded that, the most frequent irAEs were thrombocytopenia, haemolytic anaemias, and aplastic anaemias. Furthermore, steroids were used in 68% (80/118) of the reported events for the management of haematological irAEs, with a failure rate of 20% (16/80).

KP5 and KP6 are two studies focused on Antimicrobial Stewardship (AMS). KP5 was a PPS conducted to identify the prevalence of antimicrobial use for oncology patients in Qatar. It showed that by including 58 inpatients, the overall prevalence of antibiotic use was 43% (25/58). However, the compliance with the regional prescribing restriction requirements fell short of expectations, as only 58% (19/33) of prescriptions were issued by privileged prescribers. While in KP6, the study's aim was to assess the level of AMS knowledge, outcomes, and barriers among Qatar's cancer management team. This study included a total of 219 prescriptions during the course of the 6 PPSs. The results showed that the compliance continued to be low as 60% (similar to KP5). Yet, educational interventions resulted in significant improvement, with an overall compliance rate of 96%.

In conclusion, this thesis will address the published real-world studies conducted using a variety of

methodologies on cancer supportive care in Qatar, and shed light on recommendations and strategies for improving the outcomes of this type of care, as well as how they relate to clinical practise.

1. INTRODUCTION

1.1. Importance of Optimising Cancer Supportive Care

Cancer is a complex disease with multiple complications. Supportive care in cancer aims to prevent and manage disease and treatment related complications, to control symptoms, improve QoL, prolong overall survival, and maintain cost effectiveness (Popescu et al., 2021a). National supportive care societies in different countries such as France (Association Francophone des Soins Oncologiques de Support), Italy (Network Italiano Cure di Supporto in Oncologia), Russia (Russian Society of Supportive Care in Oncology), India (Indian Association of Supportive Care in Cancer), and Japan (Japanese Association of Supportive Care in Cancer) promote cancer supportive care and enhancement programmes (Popescu et al., 2021b). Moreover, different guidelines including the Multinational Association of Supportive Care in Cancer (MASCC), the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO) highlight the significant need for supportive care in cancer management throughout the whole journey, from diagnosis through treatment to post-treatment care (MASCC, 2021). ASCO guidelines was the first in 2012 to state the importance of early cancer supportive care (Osman et al., 2018). This was later endorsed by the ESMO guidelines (Popescu et al., 2014). As per the MASCC definition "*cancer supportive care includes management of physical and psychological symptoms and side effects to improve the quality of rehabilitation, secondary cancer prevention, survivorship, and end-of-life care*". Additionally, it was highlighted by the MASCC that some of the strategies were proposed to optimise cancer care such as focusing on mitigation of cancer symptoms and complications, preventing/reducing treatment related toxicities, and improving communication between patients and HCPs to boost patients' knowledge about disease and prognosis. In addition, MASCC emphasised the recommendations to focus on supportive care to ease therapy related complications to promote the benefit from active therapy, moderation of the emotional burden on patients and their families, and providing psychosocial support for cancer survivors (MASCC, 2021).

Cancer care cost is high and is predicted to further increase in the future due to the increase in population, aging, and improved survival rates, along with changes in treatment patterns and costs of care after cancer diagnosis. In addition, despite the advancement of cancer management, a substantial portion of cancer patients continue to experience morbidity and symptoms that need further care, which adds to therapy cost. The global financial burden of cancer care has increased as a result of the rise in cancer incidences,

emergency care hospitalisations, early intensive care unit admissions, and expenses of complications' management (Berman et al., 2020). Therefore, cancer supportive care and preventing/managing morbidity associated with Systemic Anti-Cancer Therapy (SACT) is a serious public health and financial burden. Published evidence has shown that timely access to cancer supportive care can increase survival rates and quality of life while also reducing health costs (Basch et al., 2017; Cooksley et al., 2018; Monnery et al., 2018).

1.2. Multidisciplinary/Interdisciplinary Approach to Cancer Care Optimisation

Since 1995, multidisciplinary teams (MDTs) have been advocated as an essential component of the best cancer care, and acknowledged as best practice by governments, academic societies, and cancer organisations around the world. The use of MDTs in cancer care is a natural progression that takes into account the advancements made by various professions and disciplines, as well as the use of several treatment modalities and patient support programmes. Cancer screening, service planning, and clinical care for cancer patients and survivors are all influenced by the application of the multidisciplinary/ interdisciplinary approach with a wide range of professions involvement. Global data showed that applying MDTs approach to practices is projected to increase long-term survival to 70%. It has additionally reflected on the total survival that is expected to increase to 60% by 2035 (Selby et al., 2019), while, it was presented in the literature that the 5-year overall age-standardised relative survival rates for the time periods 2007–2011, 2012–2016, and 2017–2021 were, respectively, 38.3%, 40.6%, and 42.9% (Li et al., 2022). .

A clinical trial performed in Ohio, US, observing 610 cancer patients, showed that an interdisciplinary approach to cancer care significantly improved patient outcomes. The aim of this trial was to assess the impact of standard care for patients with Stage III or IV lung, gastrointestinal, or gynaecologic cancer prior to and post the implementation of an interdisciplinary Supportive Care Team (SCT) in routine patient care. As a result, the introduction of the interdisciplinary approach led to a significant impact on the Health-related quality of life (HRQOL) (Daly et al., 2013).

Currently, the Oncology Clinical Pharmacist is a core member in advanced practice and healthcare systems, and Cancer MDTs, with responsibilities to offer evidence-based recommendations for a safe and acceptable use of medications. Many articles acknowledge the significant role of the oncology pharmacists in patients'

supportive care as a member in the SCT and MDTs, reflecting this role in improving clinical outcomes (Boşnak et al., 2019; Holle et al., 2020). AMBORA trial is a randomised trial that was developed to assess the impact of pharmacological and pharmaceutical care by the oncology pharmacists on medication safety and oncology patient-reported outcomes during treatment with new oral SACT. The study results showed that when compared to the control group, the intervention group's antitumor drug-related issues were notably reduced (3.85 v 5.81 [mean], P= 0.001). Additionally, the intervention group's risk of death, serious side effects, medication discontinuation, unplanned hospitalisations, and other outcomes were statistically significant in their favour with an HR of 0.48 (95% CI, 0.32 to 0.71, P= 0.001 (Dürr et al., 2021). Therefore, oncology pharmacy service development and incorporation into the multidisciplinary team of oncology improves the holistic patient-centred approach and maximises the safety and efficacy of SACT. One benefit of incorporating the role of the oncology pharmacist into the multidisciplinary patient-centred practise of cancer management is a reduction in potentially fatal medication incidents and cancer drug administration errors. Another benefit is working with oncologists to select the best cancer drug regimens for patients. This in addition to the benefit of preventing potential occupational risk to the healthcare professionals (HCPs) who handle cancer drugs, whilst providing patients with the best therapeutic options. (Dürr et al., 2021; Hin and Hong, 2019).

1.2.1 Interdisciplinary Approach to Cancer Care Optimisation in Qatar

Per Qatar National Cancer Registry (QNCR) 2018, a total of 2137 cases were diagnosed in 2018, with a crude incidence rate of 77.42 per 100,000, and 207 mortality cases. Remarkably, the first national cancer control programme in the GCC was introduced in 2011 by Qatar. Cancer treatment in Qatar was revolutionised by the National Cancer Strategy “A Path to Excellence” (2011-2016) and its companion document, “the Qatar National Cancer Research Strategy” (2012) (Qoronfleh, 2020). Cancer mortality rates have now become comparable to those in nations with long-standing national cancer strategies (Allemani et al., 2018). Since the National Cancer Strategy was introduced in Qatar in 2011, significant progress has been made. Cancer services that are formally implemented as per the international standards are producing results on equivalence with those of nations with a longer history of comprehensive cancer care. Before the development of Qatar’s current evidence-based guidelines and robust healthcare standards, Qatari cancer patients used to seek cancer care abroad in western cancer centres. However, the populace now has more faith in cancer services provided in Qatar, as seen by the constant rise in demand for those services, particularly among Qataris (Qoronfleh, 2020).

Interdisciplinary and multidisciplinary approaches are prominent in healthcare management in Qatar. This is reflected by the Cancer National Advisory Workgroups that were formulated and managed by Qatar's Ministry of Public Health (MoPH) as a national clinical advisory council for each cancer type. Those advisory groups are made up of interdisciplinary representation of HCPs from different major health sectors in Qatar including, HMC, the Primary Health Care Corporation (PHCC), and private centres. They serve as knowledgeable resource organisations for the State of Qatar and the MoPH regarding the requirements of particular cancer populations. In addition, for each type of cancer, fourteen specialised medical multidisciplinary teams (MDTs) have been formally established. In 2015, new positions have been created, including those of MDT and Patient Pathway Coordinators, as well as the addition of Clinical Pharmacists with international postgraduate training (Doctor of Pharmacy or Master's degree) and Cancer Clinical Nurse Specialists with locally delivered Master's in Cancer Nursing degrees (Qoronfleh, 2020). Hence, as a member of the breast, lung and palliative care national clinical advisory councils and MDTs, I have contributed to this national strategy.

In addition to their role on the national advisory councils, the Oncology Clinical Pharmacists are heavily involved in the interdisciplinary cancer clinical care in Qatar (NCF, 2022). They contribute to the safe and effective use of SACT in different settings, from planning and selection, prescribing, forecasting, and patient education to monitoring. They offer the oncologists expert guidance in selecting the right SACT for a particular malignancy and constructing a personalised SACT based on the patients' fitness and suitability for SACT. Furthermore, they are heavily involved in the development of standardised SACT protocols to avoid the risk of seriously adverse events due to prescribing errors. In addition, oncology pharmacists guarantee the clinical integrity of SACT for full anti-neoplastic effective use and safe administration of these medications by nursing staff. Most importantly, they play an essential role in providing direct patient care services like medication counselling for patients and their caregivers to better understand their SACT, and drug monitoring and therapeutic management (e.g., making sure patients receive enough pre-medications for administration of SACT). Moreover, they are heavily involved in oncology clinical guidelines and policy writing, updating, and monitoring. As I'm the oncology clinical pharmacy services leader, I have a strategic opportunity to share clinical, research and academic ideas with leaders on corporate and national levels and share findings and recommendations to reach the optimum patients' goals as per the international best-practice.

1.3. Importance of Real-World Evidence in Optimising Cancer Supportive Care

Randomised controlled trials (RCTs) are considered the "gold standard" for evaluating the efficacy and safety of novel treatments to the standard of care (Sibbald and Roland, 1998). Well-designed RCTs will grant an equal distribution of factors to reduce the impact of confounding bias on key outcomes between treatment groups. RCTs use methods including allocation concealment, blinded assessment, and intention-to-treat analysis to further minimise bias and warrant that variations in outcomes across treatment groups can be attributed to the study interventions (Collins et al., 2020). Accordingly, RCTs' key strength is their superior internal validity, which allows the assessment of the effectiveness of therapies. However, due to the discrepancy between the patient population and care delivery in real-world settings, RCTs have low external validity, limiting its generalisability (Tang et al., 2023).

According to Tang et al. (2023), only 3% of cancer patients are recruited in RCTs, clinical trial participants do not accurately reflect the whole patient population. Despite the fact that older patients are more frequently diagnosed with cancer, older patients (65 years of age and older) are more frequently underrepresented in RCTs. The underrepresentation of patients with complicated health concerns, socioeconomic deprivation, and members of racial and ethnic minorities is another issue. RCTs may not be able to collect enough information on the efficacy and tolerability of the tested therapies in patients with co-morbidities and a low performance status as a result of this (Murthy et al., 2004). Additionally, due to the sample size and follow-up period, RCTs are limited in their capacity. As a result, RCTs are limited in their ability to provide results that represent patients who are underrepresented and results with unusual and persistent adverse effects, particularly those with late onset that could happen after the RCT is over (Tang et al., 2023).

Currently, there is an increased interest in Real-World Evidence (RWE), as it covers those gaps of the RCTs. Real-World Data (RWD) have the advantage of being collected from patients during ordinary medical care. Studies that use this data therefore include a wider cross-section of the patient population than RCTs, perhaps leading to more generalizable findings with higher external validity. Real-world investigations can be carried out more quickly and cheaply than traditional RCTs, when the necessary infrastructure and data are available. In comparison to RCTs, studies employing RWD often have larger sample numbers and longer periods of follow-up, facilitating the identification of late and unusual side effects. RWE can therefore

provide insights into broader, more diverse patient groups in everyday practise, which contrasts with and adds to the information derived from the research of rigidly specified, homogeneous individuals in RCTs. Hence, RWE is as crucial as the RCTs.

Therefore, in 2018, the United States (US) Food and Drug Administration (FDA) initiated the framework of the RWE Programme. As per FDA definition, RWD refers to *"patients' data that is collected through a variety of sources such as electronic health records (EHRs), medical claims and billing data, data from product and disease registries, and patient-generated data (includes in-home-use settings and mobile devices)*". While RWE is defined as "*the clinical evidence obtained from the analysis of RWD that provides information about usage, risks, and benefits of a medical product derived from sources other than traditional randomised clinical trials*" (Schurman, 2019).

RWE is increasingly being used to optimise cancer supportive care, as it provides a wealth of information on how treatments and interventions work in real-world settings. It can be used to assess the effectiveness of cancer supportive care interventions and treatments in real-world settings. For example, RWE can be used to compare the effectiveness of different interventions, such as chemotherapy and radiation therapy in different settings. Moreover, it can also be used to identify areas where supportive care interventions may be lacking, or to identify unmet needs in cancer survivorship (Nabhan et al., 2019). RWE can also be used to evaluate the safety and effectiveness of cancer supportive care interventions. For example, RWE can be used to evaluate the risk of adverse events associated with a particular intervention. Additionally, RWE can be used to assess the cost-effectiveness of a particular therapy alternative, as well as to assess the quality of cancer supportive care services. Finally, RWE can actively identify gaps in cancer supportive care, which may reflect on policy decisions updates and identifying areas where additional resources may be needed (Banerjee and Prasad, 2020; Tang et al., 2023).

Lately, we see that RWE has drawn a lot of attention in helping the US FDA's registration of new treatments and label extensions. A recently published systematic review on FDA.gov oncology approvals from 2015 to 2020 were examined. This study discovered that successful oncology product approvals complemented efficacy data from single-arm trials with results from external control real-world investigations. Plus, it was found that 11/133 initial and 2/573 supplementary oncology approvals included RWE from 2017 till 2020. All real-world studies were retrospective in design, with chart reviews as the most frequent data source and overall response rates, such as in the pivotal trial, as the most frequent main outcome (Arondekar et al., 2022).

Real-World studies form the foundation of the majority of my research. My research aim- in general and in this thesis in particular- is to analyse real-world data on cancer supportive care, as well as to assess the effectiveness of therapies and any gaps in current approaches to cancer management, in addition to evaluating the critical role of each healthcare discipline in supporting patients' care and ensuring a successful treatment course, focusing on the oncology pharmacists.

Hence, taking into consideration the above mentioned aim, this PhD thesis is divided into three chapters (1) the role of oncology pharmacists in optimising cancer supportive care in Qatar; (2) the management of cancer patients' complications; (3) antimicrobial use in cancer supportive care in Qatar. In each chapter, I discuss and reflect on two KPs. For each KP, a brief is given on the literature review, the purpose for the study, a concise summary of the results, in addition to, the reflection of my work on literature and its impact on clinical practise.

2. CHAPTER 1 - The Role of Oncology Pharmacists in Optimising Cancer Supportive Care in Qatar

2.1. Article Review and Rational of The Study

Over decades, the oncology clinical pharmacists' role expanded, from the clinical and safety checks during dispensing cancer-related medications in inpatient and outpatient pharmacy settings, to the collaborative decision making on the treatment plans with the clinical team and direct patients' care at bed side and ambulatory care clinics (Holle et al., 2020). Different studies showed the importance and the impact of the clinical pharmacists' interventions that significantly improved patient-reported outcomes, for example Liekweg *et al*'s study that focused on breast and ovarian cancers in 2012 (Liekweg et al., 2012). Whereas, the integration of the clinical pharmacist role in ambulatory setting have been investigated in many trials since 1982 to date. Furthermore, participation of pharmacists in outpatient pharmacy services for cancer patients improved symptom, satisfaction, and wellbeing scores (Dürr et al., 2021; Maleki et al., 2019). A good example of that is the oral SACT programme managed by pharmacists, which improved tyrosine kinase inhibitor adherence rates in chronic myeloid leukaemia patients by approximately 23% (Lam and Cheung, 2016).

From the perspective of outcomes, the impact of a pharmacist-led interdisciplinary patient care activities led to improvements in symptom scores for pain, nausea, and constipation (Valgus et al., 2010). Evidently, we can track different models worldwide of positive clinical and economic outcomes that resulted in the extension of the oncology pharmacist clinical role. Starting with the clinical outcome, in China, a pharmacist-managed oncology outpatient clinic showed the effectiveness of pharmacist interventions in resolving drug related problems (DRPs) and improving adverse reactions (Zhao et al., 2021). They were able to record 316 DRPs, identifying adverse drug reactions (ADRs), drug interactions, untreated indication, and non-adherence. In this study, 261 (82.6%) DRPs were resolved, and 345 (90.3%) interventions were accepted by patients or physicians. Likewise, in Singapore, pharmacists' interventions in pharmacist led oncology clinics were identified as clinically 'significant' or 'very significant' and showed potential positive influence on patient outcomes (Chew et al., 2015). Additionally, in the US, pharmacist-managed oral SACT clinic played a proactive role to identify preventable medication errors, manage adverse drug reactions, monitor medication therapy, and improve patients' adherence. Hence, from those models, we can recognise the significant impact of oncology pharmacists on the direct and indirect patients' outcomes, including significant statistical and clinical

prevention of adverse events and patient satisfaction (Dürr et al., 2021). Therefore, in the United Kingdom (UK), the British Oncology Pharmacy Association (BOPA) encourages pharmacists and nurses to continue their work as non-medical prescribers (NMPs) and enhance their roles within the cancer services team. This can be seen through BOPA's 2018 statement, there are multiple potential models, with a concentration on Oncology/Haematology Out-Patient Clinic Models, for pharmacists to work as NMPs (BOPA, 2018).

The oncology pharmacists' interventions impact is not only limited to the clinical outcomes, but it also has direct economic and financial impacts. In Japan, pharmacist collaboration to oncologist outpatient clinics provided economic benefit, where the pharmacists' interventions achieved more than 100,000 US dollars savings in 1 year (Kamata et al., 2017). Another review article from the US highlighted the cost effectiveness reflected by applying pharmacists' managed therapy approach for patients' post stem cell transplant (Merten et al., 2013).

In our institute – the National Centre for Cancer Care & Research (NCCCR) – the main and the only cancer centre in Qatar, the crucial role of the oncology pharmacists was identified, then the clinical pharmacy service was applied since 2009. Therefore, it was essential to measure the impact of the oncology pharmacists' interventions on patient care as represented in Key Publication 1 (KP1), and to assess the HCPs' perception towards the oncology clinical pharmacy service, which is reflected in Key Publication 2 (KP2).

2.2. The Role of the Oncology Pharmacist in Decreasing Medication Discrepancies

Oncology patients usually have complex medication profiles. Therefore, hospital discharge is a sensitive step in oncology patients' care, during which there is a high chance of medication discrepancies, including but not limited to therapeutic duplications, omissions, unnecessary medications, and confusion. This said, discharge reconciliation is a critical step to prevent DRPs. During the process of discharge reconciliation, the most appropriate and accurate list of medications the patient should be taking after discharge should be created. It should consider certain factors, such as newly prescribed, discontinued, adjusted, and continued home medications, as well as those put "on hold" during admission. (Wong et al., 2008).

The goal of the pharmacist at discharge is to review the medications the patient was taking prior to admission and those initiated at the hospital in order to conclude the medications the patient should be

taking post-discharge, aiming to ensure that all changes are intentional, whilst resolving any discrepancies. As per the American Society of Hospital Pharmacists (ASHP), the application of this concept resulted in the decline in the percentage of patients discharged with medication errors from 76% to 47%, and with the average number of medication errors decreasing from 2.5 to 1.8 errors per patient (Pedersen et al., 2017).

Thus, as in many other institutes, the oncology pharmacists pertain a critical role in medication reconciliation, as it starts upon admission with the clinical pharmacist and ends upon discharge with the outpatient pharmacist. As a result, our oncology outpatient pharmacists play a vital role in preventing and adjusting discharge medications discrepancies (Aje et al., 2021).

In this study, the aim was to evaluate the impact of the interventions of the oncology pharmacists in the outpatient pharmacy during discharge reconciliation, and its reflection on reducing medication errors and discrepancies. Meanwhile, it also detected the most common medication-related problems amongst our population.

This work was published in the ACTA Scientific Cancer Biology Journal and here it's referred to as Key Publication 1 (KP1).

2.2.1. Methodology

This study was a prospective observational cohort study. All adult cancer (oncology and haematology) patients that were discharged from any inpatient unit (ward 1, ward 2 and palliative care unit) in NCCCR were included. However, the ambulatory care patients who were discharged from the Short Stay unit or the SACT infusion (Day Care) unit were excluded. The duration of the study was 10 months (from April 2014 to January 2015).

To benchmark our findings, the definition of prescribing medication errors of ASHP Guidelines 1993 was used, stating that, it is the incorrect drug selection (based on indications, contraindications, known allergies, existing drug therapy, and other factors), dosage form, dose, route, concentration, rate of administration, or usage directions of a prescribed drug that a doctor has prescribed or privileged to prescribe.

To note, the definitions of medication discrepancies (intentional and unintentional) according to (Lehnbom et al., 2014), are: 1) Medication discrepancy: "*A difference between the medication recorded as prescribed for a patient and the current medication reported by a patient*". 2) Intentional medication

discrepancy: **"***A doctor decides to change a patient's medication regimen, hence what was recorded as prescribed and what medication is being taken by a patient are different*". Whereas, 3) Unintentional medication discrepancy: "*Any unexplained difference between what was recorded as prescribed and what medication is being taken by a patient*" (Lehnbom et al., 2014).

To identify any discrepancies or errors, the pharmacists were revising all the discharge order details (including calculation errors, writing trade or brand name, weight based dosing, extra doses, wrong medication, wrong route, wrong dose, wrong interval, wrong rate, incomplete orders, unclear orders and any other unacceptable order details) and reconciling the discharge prescriptions with the medication history of the patient before and during the admission (including medication name, dose, frequency, and route of administration). The outpatient oncology pharmacists' interventions were identified, communicated with the prescriber, and documented in the data collection sheet identifying the acceptance/ rejection of the recommendations. Consequently, all interventions were classified as either medication discrepancies or medication errors.

The study's list of discrepancies included but were not limited to the following: prescribing without authorization, inaccurate home dose of medication, the need for an additional medication, untreated conditions, duplication therapy, alternative therapies, medication use without a prescription, inappropriate duration, and the need for an appropriate laboratory test.

Since Qatar welcomes multinational HCPs, it was expected that a subjective approach may impact data accuracy due to the variable backgrounds and approaches. Therefore, to overcome this limitation, a standardised form was developed to be completed by the pharmacist to include the details of the identified intervention, where an extensive review was conducted before including any data for analysis.

2.2.2. Key Results

A total of 591 patients/prescriptions of 4293 medication orders were included in our study. A sum of 278 (47%) prescription required the pharmacists' interventions. The pharmacists were able to identify 32% (190/591) of prescriptions with medication discrepancies, and 21% (122/591) prescriptions with medication errors.

Effectively, the outpatient oncology pharmacist played a significant role in identifying medication errors and preventing patients' harm as follows: incomplete orders (69/1000 orders), wrong dose (37/1000 orders) and orders of extra doses (22/1000 orders), as illustrated in table 1.

Table 1 - Types and frequency of medication errors (N= 122)

Medications Errors Prevented by Pharmacist	Number (%)	Rates Per 1000 Orders
Incomplete Order	42 (34%)	69
Wrong Dose	22 (18%)	37
Extra Doses Given	13 (11%)	22
Wrong Interval/Rate	13 (11%)	22
Wrong Medication	8 (7%)	12
Trade Name	4 (3%)	6
Calculation Errors	2 (2%)	3
Unclear Order	2 (2%)	3
Weight Based Dosing	2 (2%)	3
Wrong Route	0 (0%)	0
Others	14 (12%)	23

Table 2 - Types and Frequency of DRPS (N = 190)

Types of DRPs	Number (%)
Prescribing Without Privilege	56 (29%)
Additional Drug Required	45 (24%)
Alternative Therapy	33 (17%)
Inappropriate Duration	14 (7%)
Duplication Therapy	9 (5%)
Untreated Condition	8 (4%)
Medication Use Without Indication	3 (2%)
Inaccurate Home Dosing	3 (2%)
Dose Missed	3 (2%)
Appropriate Lab Recommended	2 (1%)
Others	14 (7%)

As presented in table 2, the most common DRPs were prescriptions without privilege 29%, additional drug requirement 24%, and the need of alternative therapy 17%.

2.2.3. Limitations

During the course of the study, it was configured that the form used to document the interventions did not capture the amount of time required to resolve each problem, limiting the ability to evaluate the effect on the pharmacists' workload and the patients' waiting time. Hence, the average time per intervention was extrapolated from the literature to be minimum of 8 minutes approximately, including calling the physician and the actual correction of the prescription (Onatade et al., 2017).

2.2.4. Reflection and Impact

An Observational Cohort Study (OCS) can either be a Prospective Cohort Study (PCS) or a Retrospective Cohort Study (RCS). KP1 is an example of PCS that presents RWE. When correctly conducted, the PCS has the strongest level of evidence when compared to other observational study designs (Setia, 2016). KP1 study had very limited bias potential, as all patients during the study period were included with no selection bias. Also, the intervention of the pharmacist was a one-time event, at the time of the visit with no subject loss bias.

This study is one of the unique studies that focused on the impact of oncology pharmacists' interventions in Qatar and in the GCC. The results of this study showed significant impact on patients' care and safety outcomes. This led to a change of practice to be as follows: 1) the study methodology was introduced to practice, where currently, Oncology Pharmacists in Qatar are revising all the discharge orders to identify prescriptions with medication discrepancies and medication errors. 2) The identified clinical interventions are to be documented in patients' files using a "Pharmacists' Clinical Interventions" form (that was used in the study), including the acceptance by prescriber, the level of the impact, the action, the need for follow-up, etc. The report of the identified, solved, and documented clinical interventions is now one of the pharmacy Key Performance Indicators (KPIs). Moreover, it is used as a tool to evaluate the pharmacists' performance as an element of the annual appraisal, evaluating the contribution of the pharmacists to the patients' care, cost saving, and workload. 3) To give the pharmacists the time to focus on the clinical aspect of the medications review, two approaches were applied: a) Automation and Medication Dispensing Solutions were introduced to practice and b) the role of the pharmacy technicians was expanded to cover more dispensing tasks to free the pharmacists for more clinical tasks. An economic impact and cost benefit study was recently published, showing that, in the NCCCR environment, the clinical pharmacist intervention is a cost-beneficial practise. This is due to how it prevents Adverse Drug Events (ADEs) and has significant financial advantages compared to the

intervention's cost. During a 3-month follow-up period, the oncology pharmacists conducted and documented a total of 1,352 interventions. The overall benefit was 53,834,206 US dollars, which included cost avoidance of 53,492,040 US dollars and cost savings of 342,166 US dollars, primarily as a result of the medication dose reduction and advice to take additional medications. After conducting sensitivity analyses to validate the accuracy of the findings, the benefit-to-cost ratio was 174:1(Abushanab et al., 2022).

The KP1 study was cited on an international level, supporting the need for the clinical pharmacists' intervention in the oncology settings (Moghli et al., 2021) and (Vanessa Oliveira, 2021), which is an Integrated Multi-professional Residence and Professional Area of Health Residence Completion Work, presented to the Federal University of Rio Grande Do Sul Porto Alegre Clinic Hospital.

2.3. Perception and Expectations of Health Care Providers Towards Oncology Clinical Pharmacy in Optimising Cancer Supportive Care

Currently, the oncology clinical pharmacists are integral members of the interdisciplinary clinical team. Based on their education and training, their clinical knowledge, literature evaluation skills, and understanding of the complexity of cancer care, they are qualified to be a source of evidence-based care to the patient with cancer, and provide education for both patients and HCPs about SACT and supportive care medications. This significant role is showed to improve patients' clinical outcome. They also have an effective input in the development of policies, standards, clinical protocols, pathways, and guidelines (Holle et al., 2020).

In Qatar, Oncology Clinical Pharmacists have a national role in, not only managing cancer care, but also putting the clinical care standards, and national guidelines and policies that govern cancer care. Oncology Clinical Pharmacists are essential members in different clinical care teams, disease MDTs of different cancer types, different committees and workgroups, and tumour boards. They are heavily involved in the development of corporate and hospital policies, standards, clinical protocols, pathways, and guidelines with collaborative and leading roles (NCF, 2022).

A previous study was conducted in Qatar in 2011, where it investigated the physicians' perception and expectations from their experiences with the pharmacists at HMC, the main and largest governmental healthcare corporation in the country. HMC includes 13 secondary and tertiary care hospitals, NCCCR being one of them. This study included 205 completed questionnaires with a response rate of 41%. The main perception of physicians towards the clinical pharmacy service were to educate patients about appropriate and safe use of drugs (89%), and to attend the health-care team drug related inquiries and consultations during bedside rounds (57%). Those results were met with a satisfactory level of comfort and meeting expectations (61% and 65%, respectively). However, physicians reported a poor experience with pharmacists giving them clinical recommendations (either drug specific or patient specific). To the best of our knowledge, this was the first and potentially the only study to be conducted on the practice of clinical pharmacy including oncology/haematology clinical pharmacy in Qatar. However, it did not just focus on the oncology/haematology specialty. Therefore, little was known about the oncology clinical pharmacy service and the perception of other HCPs towards it, especially physicians and nurses (Zaidan et al., 2011).

In this study (KP2), the aim was to assess the perception and expectations of HCPs towards the

oncology/haematology clinical pharmacy service at NCCCR in Qatar. To our best knowledge, this is the first study in the Gulf region to focus on this area.

This work was published in the Journal of Oncology Pharmacy Practice, and it is referred to as Key Publication 2 (KP2).

2.3.1. Methodology

This study was a cross-sectional survey, conducted from January 2018 to May 2018. A validated survey was developed. To reach the validation of this survey, it was adapted from previously published qualitative interviews/studies with HCPs in the Arab region and China, after obtaining their permission of use. Consecutively, the survey was piloted with a sample of 10 HCPs from different specialties to evaluate the comprehensiveness, readability, and clarity of all questionnaire items. The survey was directed to HCPs in NCCCR, including physicians, operational (non-clinical) pharmacists, dietitians, and nurses. Based on the responses, minor modifications were considered, and the final survey was developed in both the paper and online versions.

To avoid any potential bias, the survey was sent to HCPs to be filled independently, as a self-administered electronic/paper survey. It was focused on the clinical pharmacy services in NCCCR, evaluating the perception and expectations of HCPs towards the service, perceived barriers to clinical pharmacists' role, and suggested area for improvement.

Hence, it included four domains:

Domain 1: to measure the perception of HCPs towards the clinical pharmacy services.
Domain 2: to measure the expectations of HCPs from the clinical pharmacy services at NCCCR.
Domain 3: to obtain the perceived barriers that can hinder the clinical pharmacists' role.
Domain 4: to concentrate on areas of improvement regarding clinical pharmacy services at NCCCR.

The survey was sent to 375 HCPs, including all sub-specialties in NCCCR: oncology/haematology/palliative care physicians, inpatient/outpatient/IV preparation/chemotherapy preparation pharmacists, inpatient/outpatient nurses, and dietitians.

2.3.2. Key results

The response rate to the survey was 30%; A total of 112/375 HCPs responded. The majority were

nurses, 52/112 (46%), followed by physicians 30/112 (27%).

2.3.2.1. Perception

HCPs showed positive perception towards the clinical pharmacy services at NCCCR as shown in Table 3.

Different HCPs showed interest in clinical pharmacy profession in Qatar, as follows 95.7% for pharmacists, 90% for physicians and 64.2% for nurses, with statistical significance (p=0.002).

Table 3 - Perceptions of health care providers at NCCCR towards clinical pharmacy services (N=112)

Statements	n (%)					
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Median (IQR)
▪ A clinical pharmacist is more helpful when they are located in the ward/clinic as opposed to having to call them	1 (0.9)	2 (1.8)	13 (11.6)	43 (38.4)	53 (47.3)	4 (1)
▪ It is helpful when a clinical pharmacist checks orders before they are carried out	0	0	9 (8)	43 (38.4)	60 (53.6)	5 (1)
▪ A clinical pharmacist can improve the quality of patient care in a hospital setting	0	0	8 (7.1)	45 (40.2)	59 (52.7)	5 (1)
▪ A clinical pharmacist is a valuable patient educator	0	1 (0.9)	5 (4.5)	45 (40.2)	61 (54.5)	5 (1)
▪ A clinical pharmacist is an integral part of the medical team	0	0	3 (2.7)	50 (44.6)	59 (52.7)	5 (1)
▪ A clinical pharmacist can perform medication counseling efficiently	0	0	9 (8)	43 (38.4)	60 (53.6)	5 (1)
▪ A clinical pharmacist in a clinical ward team is a requirement for hospital accreditation	0	0	14 (12.5)	54 (48.2)	44 (39.3)	4 (1)
▪ A clinical pharmacist is able to minimise medication errors	0	2 (1.8)	13 (11.6)	49 (43.8)	48 (42.9)	4 (1)
▪ There is increasing interest in clinical pharmacy as a profession in Qatar	0	0	23 (20.5)	46 (41.1)	43 (38.4)	4 (1)

▪ A clinical pharmacist has the required skills to deal with cancer patients	0	0	23 (20.5)	46 (41.1)	43 (38.4)	4 (1)
▪ A clinical pharmacist is knowledgeable in chemotherapy dosing and dosage adjustments	0	0	11 (9.8)	62 (55.4)	39 (34.8)	4 (1)
▪ A clinical pharmacist is capable of counseling patients about use of chemotherapeutic agents	0	0	8 (7.1)	53 (47.3)	51 (45.5)	4 (1)

NCCCR = National Centre for Cancer Care and Research; IQR = interquartile range. Missing data = 1.

2.3.2.2. Expectations

HCPs expectations regarding clinical pharmacy services at NCCCR considering the top expectations are summarised as follows: 1) Provide recommendations on choosing the most appropriate medications (82%); 2) Communicate details on pharmaceutical availability and shortages (82%); 3) Support in the prescribing of cost-effective medications by regularly disseminating pharmacoeconomic data (75%); 4) Engage in active research (74%).

The thought-provoking component was the other expectations that were proposed by the respondents, encouraging the need to extend the privilege of the Oncology Clinical Pharmacists in pertaining their privileged to co-sign orders, adjusting chemotherapy prescriptions (under supervision of physicians), and review of discharge medications to ensure completeness and accuracy.

2.3.2.3. Perceived Barriers

Adding to the high perception and expectations from the clinical pharmacy service, HCPs recognised some barriers that can impede the impact of the clinical pharmacy service on patients' care (as shown in Table 4.

HCPs believed that the specific responsibilities of clinical pharmacists are not clearly defined. However, HCPs appreciated the impact of clinical pharmacists' involvement in tasks that may interrupt the continuity of patient care. Nevertheless, most HCPs acknowledged the high level of trust in the clinical pharmacist's abilities and their availability.

Moreover, respondents suggested further barriers impacting the clinical pharmacists' role such as:

shortage of staff, work over-load, duty rotations, and language barrier (with non-Arabic and non-English speaking patients).

Table 4 - Perceived barriers that can limit a clinical pharmacist's role (N=112)

Statements	n (%)					
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Median (IQR)
The specific responsibilities of a clinical pharmacist are not clearly defined.	2 (1.9)	18 (16.7)	30 (7.8)	41 (38)	17 (15.7)	4 (1)
Physicians and other healthcare members are unaware of the benefits of having a clinical pharmacist on their team	7 (6.5)	40 (37)	23 (21.3)	29 (26.9)	9 (8.3)	3 (2)
Healthcare members are unable to judge the knowledge and level of skills of the clinical pharmacist	3 (2.8)	33 (30.6)	31 (28.7)	33 (30.6)	8 (7.1)	3 (2)
Healthcare members have a low level of trust in the clinical pharmacist's abilities	13 (12)	53 (49.1)	19 (17.6)	17 (15.7)	6 (5.6)	2 (1)
The clinical pharmacist does not have the proper communication skills needed for interaction with other healthcare providers	10 (9.3)	36 (33.3)	30 (27.8)	24 (22.2)	8 (7.4)	3 (2)
Healthcare professionals have no prior experience of working with a clinical pharmacist	10 (9.3)	37 (34.3)	27 (25)	26 (24.1)	8 (7.4)	3 (2)
Involvement of clinical pharmacists in other tasks interrupt the continuity of patient care	8 (7.4)	31 (28.7)	24 (22.2)	31 (28.7)	14 (13)	3 (2)
Clinical pharmacists are not accessible when needed	10 (9.3)	43 (39.8)	26 (24.1)	20 (18.5)	9 (8.3)	3 (2)

Legend = missing data = 4, IQR = interquartile ranges

2.3.2.4. Areas of improvement

Most of the responders highlighted that the maximum impact of the clinical pharmacy service lean towards the reviewing of medication errors (84.8%), attending clinical bedside rounds (82.1%), and

patients and family's education (82.1%).

However, what was really significant was their recommendations to improve the clinical pharmacist's role to optimise patients' care such as: the availability of full time clinical pharmacist in SACT infusion (Day-Care) unit, initiating oncology pharmacist-led clinics, reviewing of newly diagnosed patients' SACT protocols and providing education during clinic visits and prior the admission to Day-Care unit, increasing number of staff, and to focus more on providing discharge patients' education. Notably, responders accentuated that the clinical pharmacists deserve more privileges and further support.

2.3.3. Impact and Reflection on clinical practice

Surveys are one of the most used study types in healthcare epidemiology research. Surveys can be very helpful for understanding the beliefs and behaviours of large groups of people since they are often easier to conduct and less expensive than many other study types. Survey research has advantages in terms of cost efficiency, generalisability, dependability, and adaptability. Yet, survey research has limitations such as inflexibility and a lack of potential depth. (Safdar et al., 2016).

Healthcare surveys can be run by mail, phone, online, or face-to-face. Each type has its advantages and disadvantages. KP2 is an example of paper-based independently filled healthcare surveys. It was filled by the participants and sent to the study authors anonymously. The main advantage of this type of surveys is avoiding the potential bias/ pitfall due to distinctive participation (Lallukka et al., 2020; Safdar et al., 2016). Whereas, the major disadvantage is the low response rate. Therefore, the response rate in KP2 was 30%. However, results were significant and reflective.

This study had significant impact on Oncology Clinical Pharmacy Practice on a national and regional level. Nationally, most of the responders' recommendations were taken forward to extend the oncology clinical pharmacy practice in Qatar. Consequently, 20% of full-time equivalent (FTE) expansion was considered by recruiting 2 clinical pharmacists. Plus, the extension of the availability of full-time clinical pharmacists in SACT infusion (Day-Care) unit, covering both oncology and haematology patients, reviewing patients' SACT protocols prior the admission to Day-Care unit, attending drug information questions by patients, caregivers, physicians, and nurses, and providing SACT education to newly diagnosed patients. Additionally, escalating the role of the clinical pharmacist in discharge medication reconciliation and patients' education.

One of these study recommendations was to extend the role of the Oncology Clinical Pharmacists in the ambulatory setting. This was taken forward, in which it was a great step for me to command the

development of the Oncology Clinical Pharmacist-Led Clinic in Qatar. To my knowledge, it is the first Oncology Clinical Pharmacist-Led Clinic in the MENA region; the 1st clinic initiated was breast cancer, a successful story that was highlighted in the Federation International Pharmaceutical (FIP)**,** Hospital Pharmacy**,** Eastern Mediterranean Feature - Newsletter 90 ("Launching an Oncology Clinical Pharmacist-Led Clinic in Qatar," 2020). This has, consequently, extended the service to cover bone marrow transplant, multiple myeloma (MM), and gastrointestinal cancer, and recently all solid tumour cases. Currently, I'm leading a new research study entitled "Impact of collaborative pharmacist-managed multiple myeloma clinic at Qatar's National Centre for Cancer Care and Research" ID # MRC-01-22-767.

Empowering the Oncology Clinical Pharmacists with more privileges was another suggested area of improvement that came out from the KP2 study. This was reflected on the development of the Oncology/ Haematology Clinical Pharmacy Privilege Collaborative Practice Agreement with physicians, upon the initiation of the MM clinic to support the clinical pharmacist prescribing privileges, including dose adjustment, renewal of medication (specified medications only), and order appropriate labs as necessary.

On a regional level, recently this thriving initiative of the first Oncology Clinical Pharmacist-Led Clinic in the region was presented in the GCC Pharmacy Congress of October 2022 in Dubai, United Arab Emirates (UAE), which imitated multiple communications from pharmacy leaders in Oman, Saudi Arabia and the UAE that aim to have the same model applied in other GCC countries in the near future.

Furthermore, this study was cited in 9 peer reviewed publications, and reflected as a model of "Studies Documenting the Value of the Oncology Clinical Pharmacist" (with full illustration of the results) in the Egyptian Guide for Oncology Pharmacy Practice (EGOPP) 2022. EGOPP was developed by the General Administration for Drug Utilisation and Pharmacy Practice of the Egyptian Drug Authority Central Administration of Pharmaceutical Care. The EGOPP is a working document highlighting the areas of improvement in oncology pharmacy practice and aiming for guidance to unify, improve, and standardise the oncology pharmacy contribution to patient care in Egypt by developing a structured and systematic approach to oncology pharmacy practice (Younis G, 2022). This approach is well-established in different areas of the world. The North American model is represented in the Haematology/Oncology Pharmacy Association (HOPA) documents (HOPA, 2019) and the British model in BOPA document 2018 (BOPA, 2018). Those documents are good examples of well-established models, including different areas of pharmacy practice (inpatient, ambulatory care, infusion centres, etc.) that elaborates on the value of the oncology clinical practice as per western guidelines.

3. CHAPTER 2 - Management of Cancer Patients' Complications in Qatar

3.3. Article Review and Rational of The Studies

Cancer complications are common. They can be disease-related like bone metastasis, treatment-related like haematological toxicities related to the use of SACTs, or a mix of both like the development of Venous Thromboembolism (VTE). The incidence and severity of cancer complications increase as the disease progresses. Cancer complications significantly impact morbidity and mortality. Therefore, the management of cancer related complications is a key value that can improve patients' clinical outcomes and QoL (Nelson et al., 2000).

3.2. The Impact of Denosumab vs Zoledronic Acid on Calcium Levels in Cancer Patients with Bone Metastasis

Bone metastasis is one of the most common disease related complications in cancer, with an incidence that can reach up to 75% (Nelson et al., 2000). It is more common in multiple myeloma (MM), breast and prostate cancers. With bone metastasis, patients experience sequential skeletal complications, such as hypercalcemia, bone pain, fractures, and spinal cord compression. Consequently, those complications negatively impact patient's QoL. (Coleman, 2000)

Radiotherapy and systemic Bone-Targeting Agents (BTAs) are the main non-surgical options of bone metastasis management. BTAs play a substantial role in controlling symptoms and complications of bone metastasis (Coleman, 2000). The most effective and used BTAs with bone metastasis are bisphosphonates (e.g. zoledronic acid) and monoclonal antibody (e.g. denosumab). Zoledronic acid (ZA) is an intravenous bisphosphonate, it has a direct apoptotic effect on osteoclasts and acts as a potent inhibitor of bone resorption and skeletal calcium release (J. Roelofs et al., 2010). While Denosumab (DE) is a fully human monoclonal antibody. It has high affinity to RANKL (a human receptor activator of nuclear factor kappa-B ligand), preventing bone destruction and reducing complications of bone metastases (Hofbauer et al., 2001). Based on their mechanism of action, hypocalcaemia is a common adverse event of both BTAs. Studies showed that hypocalcaemia incidence is higher with DE than ZA due to the high potency of RAKNL inhibitors at reducing bone turnover, thus decreases the level of calcium in circulation (Mansinho et al., 2016; Snedecor et al., 2013).

In our institute, both ZA and DE are extensively used. Hypocalcaemia has been observed with both agents. International guidelines do not favour one BTA over the other, unless a patient has a contraindication to one of the two agents by which the other BTA will be recommended. For example, ZA is contraindicated in the following conditions: acute renal impairment CrCl <35 mL/minute, pregnancy, breast-feeding, and bisphosphonates allergy ("Zoledronic Acid Monograph," 2022). Therefore, DE may be considered in renal impairment ("Denosumab Monograph," 2022).

The aim of this study was to assess the efficacy and safety of ZA and DE based on the calcium level. The primary objective was to evaluate the incidence of hypercalcemia (Ca level >2.55 mmol/l) and hypocalcaemia (Ca level <2.1) while receiving ZA and DE. The secondary objectives were to identify factors that contribute with hyper and hypocalcaemia with ZA and DE amongst our population, evaluate the grade of hypocalcaemia, and the effect of the supplementation (calcium/vitamin D) on calcium levels.

This study was published in the Journal of Oncology Pharmacy Practice, and it's referred to as Key Publication 3 (KP3).

3.2.1. Methodology

This was a nationwide retrospective real-world cohort study. The study period was 12 months (from August 2015 to July 2016). All adult cancer patients diagnosed with bone metastasis secondary to a solid tumour or MM, receiving either ZA or DE were observed. All patients' electronic records, laboratory and medication records review including age, gender, diagnosis, corrected calcium level, creatinine clearance, and calcium/vitamin D supplementation were considered. However, exclusion criteria included patients who received BTA for any other indications (e.g. osteoporosis or hypercalcemia of malignancy).

3.2.2. Key results

A total of 271 patients receiving ZA (n= 152) and DE (n= 119) for bone metastasis were included in KP3 study. This group of patients had a total of 1141 administration visits (ZE =776, DE=365). Both treatment groups baseline characteristics were similar.

Corrected calcium levels of each visit were evaluated. Hypocalcaemia was more frequent with DE compared to ZA with statistical significance (5.4% vs. 3.1% respectively, OR=0.52, 95% CI [0.28 – 0.95]; p= 0.034). However, the incidence of hypercalcemia was still higher in the DE group vs. ZA group

(8.5% and 3.1% respectively, OR= 0.33, 95% CI [0.19– 0.58]; $p<0.0001$). Hypocalcaemia incidence was more common in breast cancer (27.3%), followed by ovarian cancer (25%) and MM (22.7%).

Most of the detected hypocalcaemia events were grade 1 (ZA= 3% and DE= 4.9%) with no fatal events reported. It has also been observed that approximately 60% of patients with hypocalcaemia did not receive calcium/vitamin D supplementation. Additionally, around 43% (66/152) of patients on ZA received supplementation vs. 34% (40/119) on DE (p = 0.10). Expectedly, a higher incidence of hypocalcaemia was observed among patients who did not receive supplements (ZA = 67% and DE = 65%) with OR=1.08, 95% CI [0.31 – 3.8], p = 0.9).

3.2.3. Impact and Reflection on Clinical Practice

KP3 in this thesis is an example of RCSs. To avoid selection bias as one of the most common bias in RCSs, all solid tumour and MM patients that received BTAs during the study period were included. Furthermore, to eliminate the impact of the confounding factors that might cause hypocalcaemia, all factors like renal failure, vitamin D deficiency, or pre-existing hypoparathyroidism were screened and studied.

This study had a local impact on the clinical practice in Qatar, as well as global evidence. At the time when this study was initiated, the RWE and head-to-head comparison between ZA and DE were not considerably imparting, which gave this study an advantage adding to the existing evidence. Thus, it was cited in 16 articles in different languages ("Google Scholar, Citation, Effect of Denosumab Versus Zoledronic Acid on Calcium Levels in Cancer Patients with Bone Metastasis. A Retrospective Cohort Study," n.d.)

On a local practice level, I was able to share the findings of this study with the oncology Pharmacy and Therapeutics (P&T) and the Clinical Pathway and Guideline (CPG) committees and put a protocol of the BTAs use for cancer patients in Qatar. This protocol included prescribing, dispensing, and administering DE. The aim was to improve compliance to the use of DE as per FDA/EMA approved indications, mandate the follow-up on the calcium level before prescribing, dispensing and administering DE, and impower the pharmacists and nurses to contribute to clinical decision making. The role of pharmacists and nurses was potentiated to monitor calcium level before dispensing/administering DE. In case of hypocalcaemia, they should communicate with the physician to hold BTAs (to be resumed upon calcium correction), supplement calcium, and follow-up. This empowered role of the HCPs has valuable input on the patients' care and reflected on clinical outcome on decreasing the incidence of hypocalcaemia

amongst our patients.

3.3. Haematological Immune Related Adverse Events (irAEs) Induced by Immune Checkpoint Inhibitors (ICIs)

Cancer therapy has been revolutionised by the use of immune system modulation rather than direct treatment of the cancer cells. This change was specifically sparked by ICIs, which regulate interactions between T lymphocytes and antigen-presenting cells as well as tumour cells (Hodi et al., 2010). The first approved ICI for cancer therapy was an anti-cytotoxic-T-lymphocyte antigen 4 (CTLA-4), then anti-programmed cell death 1 (PD-1) and anti-programmed cell death-ligand 1 (PD-L1). The first indication for the use of ICIs in cancer management was for metastatic melanoma (Kramer et al., 2021). Published data highlighted the ICIs toxicities, known as immune-related adverse events (irAEs). Nevertheless, they have a different mechanism and management approach if we compare them with the traditional injectable SACTs (Kroll et al., 2022).

All organ systems can be impacted by a wide spectrum of irAEs. The highest reported irAEs occurrences are dermatologic, gastrointestinal/hepatic, endocrine, and pulmonary systems. On the other hand, cardiovascular, neurological, and haematological irAEs are less common and have higher mortality rates.

Haematologic toxicities, as rare irAEs, have an estimated incidence of 0.04–3.6%, but they are becoming more prevalent with the usage of ICIs. The mortality rates for haematological irAEs are significant (14%) and are difficult to cure (Kramer et al., 2021).

ICIs started to be introduced to practice in Qatar in 2015. The first ICI introduced to NCCCR formulary was pembrolizumab. Up to this current moment, 4 ICIs are formulary in Qatar (pembrolizumab, nivolumab, atezolizumab and avelumab). However, other ICIs are treated as a non-formulary item if they are not included in the HMC formulary, where they are provided to patients as part of the non-formulary programme on a patient-specific basis (Hamad et al., 2023). Based on the experience of ICIs usage and the documentation of irAEs via the ADRs reporting system in Qatar, I was able to identify different types and incidence of irAEs amongst the population in Qatar as I was conducting a real-world study on the documented ICIs-related ADRs. In this RWD review, I revised all the documented ICIs-related ADRs during the period of 42 months (from January 2015 to June 2018) to identify 89 documented irAEs of 20 types. Unexpectedly, haematological irAEs were the 7th most common irAEs in Qatar, with an incidence of 8% (7/89), which is significantly higher than the published data. Furthermore, the management of those 7 cases was not consistent due to the uncertainty of the diagnosis and the relevance of the presentation to the use of the ICIs. I presented this RWD at the GCC Immune Oncology summit in 2018

(Elazzazy, 2018). The discussion that followed my presentation highlighted the absence of attention to haematological irAEs of ICIs use in cancer, and the need for synthesising published evidence on the management of this rare but critical irAE. In addition, there was no clear consensus in guidelines on how to grade and manage haematological toxicity from ICIs. The aim of this new piece of work was to conduct a systematic review that would analyse the available published data from case reports and case series; hence, identify the most used methods of diagnosis and management of such rare and unrecognised irAEs.

This study was published in the Frontiers in Immunology, and it is referred to as Key Publication 4 (KP4).

3.3.1. Methodology

KP4 is a systematic review. To attain relevant publications, we looked for any applicable case reports or series in the bibliographies of pertinent studies up until January 2019, using Medline, OVID, and Web of Science. Additionally, we used Web of Conferences and Open Grey to search conference proceedings and grey literature. Studies that were enrolled were clustered according to the drugs used and haematological irAEs reported. Patient characteristics, haematological irAEs, and management methods were all extracted. Naranjo scale was utilised to perform causality assessment, and the Pierson-5 evaluation scheme was used for quality assessment. Inclusion criteria were case reports/series of solid tumours: reporting haematological irAEs; using ICIs as monotherapy or combinations either during clinical practice or as part of a clinical trial; English language; and adults or paediatrics. Exclusion criteria were non-solid tumours; irAEs other than haematological irAEs; haematological irAEs related to the use of medications other than ICIs; and the use of ICIs out of the FDA/ EMA approval at the date of data extraction.

3.3.2. Key results

A total of 49 publications including 118 cases were found in the search results. Melanoma (58%) and lung cancer (26%) were the most common cancer types deliberated. Thrombocytopenia, haemolytic anaemias, and aplastic anaemias were the most often reported haematological irAEs with ICIs (such as nivolumab, ipilimumab, and pembrolizumab). Agranulocytosis and neutropenia were adverse reactions with lower reporting rates. Regarding the history of autoimmune or haematological diseases, no information was provided in 62% (73/118), whereas 15% (18/118) of cases reported prior autoimmune or haematological illness, and 23% (27/118) of cases had no prior autoimmune or haematological diseases.

Bone marrow biopsy was performed to confirm the haematological irAEs in 61% (71/118) of patients. The most serious haematological irAEs were reported as, grade 4 in 44% (52/118) of cases, and grade 5 in two cases. For haematological irAEs management, steroids were utilised in most of the reported cases, 68% (80/118), with a failure rate of 20% (16/80). Rituximab, IVIG, and combinations of the three choices at different doses were among the additional therapy alternatives. Additionally, blood component transfusions were some of the other methods that were employed.

The most significant drug-specific findings were for Ipilimumab haematological irAEs that were described in 16 cases in 14 papers, of which 94% (15/16) were melanoma. The most used irAEs management therapy were steroids (8 cases), followed by IVIG (7 cases). After therapy, 69% (11/16) of cases reached full recovery. With Nivolumab, 20 cases of haematological irAEs were documented in 17 case studies. The majority were lung cancer, 65% (13/20). The rate of full recovery after therapy was 55% (11/20) using IV corticosteroids. However, IVIG, platelets transfusion, IV romiplostim, and oral steroids were also used, with therapy failure of 40% (8/20). Consequently, a significant number of patients stopped taking nivolumab due to haematological irAEs. Moreover, the combination of Ipilimumab and Nivolumab caused haematological irAEs in 6 patients of metastatic melanoma (5 reports). After the use of rescue medications, the curative rate was 83% (5/6). Notably, Rituximab was a frequently used medication. Pembrolizumab was the cause in 13 cases of 12 studies. Markedly, Evan's syndrome was reported in one case. The curative response rate of the irAEs was 85% (11/13) after receiving steroids (IV or oral), and IVIG. However, Durvalumab usage was associated with a fatal allo- and immune-mediated thrombocytopenia in one lung cancer case. The patient received steroid therapy, polyvalent immunoglobulins, and platelet transfusions with little improvement. Finally, one patient with metastatic Merkel cell cancer experienced deadly immune thrombocytopenia (ITP) with Avelumab. The use of steroids and IVIG treatments were shown to be ineffective, and the patient died within a month after being diagnosed.

3.3.3. Reflection on clinical practice and future directions

A systematic review is a type of review that identifies, analyses, and summarises all relevant evidence using consistent methods. It provides an explicit response to a well-stated research topic and details the methods employed to reach the conclusion. The research methods used in a systematic review are intended to minimise bias, which distinguishes it from other types of reviews (Julian Higgins and James Thomas, 2022).

KP4 was my first systematic review study. This gave me the opportunity to learn how to run a systematic review, including protocol development, identifying study objectives and the criteria for choosing which research to include or omit, and how to locate research papers from Medline, OVID, Web of Science, Web of Conferences, and Open Grey. Additionally, I have also learned to ensure the validity and reliability of the systematic review, the need to discuss the findings with the study team and obtaining the results and conclusions after analysing the obtained data.

By conducting this extensive piece of work, employing a reliable technique of a systematic review (as my first systematic review), it was a very good opportunity to boost my research skills in this methodology.

This article is the first systematic review and one of a very limited number of articles that focused on the haematological irAEs of the novel agent ICIs up to the time of publication. It was shortlisted for the Qatar Virtual Immuno-Oncology Conference 2020 poster award, winning the second place. To date, KP4 has been cited 12 times.

The types of the haematological irAEs reported in the literature included similar features as presented with the reported cases in Qatar, including neutropenia, pancytopenia, leukopenia, thrombocytopenia, and different types of anaemia. Therefore, the findings of this review were reflected on the practice in NCCCR, especially when it comes to management. Hence, in NCCCR, steroids (IV or oral), rituximab and IVIG are now considered the standard options to manage haematological irAEs.

The main limitation of this study was reflecting case reports and case series, which usually have a small number of patients and inconsistent patient features and findings. Hence, future randomised controlled trials on haematological irAEs of ICIs should receive more focus to produce higher quality data in this area and guide future practice and study in this field.

Lately, ASCO guideline updates in 2021 illustrated the management of haematological irAEs of the ICIs based on grading (Schneider et al., 2021). KP4 findings and ASCO updates are under revision in NCCCR to develop Qatar's guidelines of management of irAEs in patients treated with ICIs.

To further evaluate the current practice on irAEs of ICIs in Qatar, I'm running a new research study, titled "Safety of immune checkpoint inhibitors for cancer treatment: Real-world retrospective data analysis in Qatar" ID # MRC-01-19-455.

4. CHAPTER 3 - Antimicrobial Use in Cancer Supportive Care in Qatar

4.1. Article Review and Rationale

Infection is the second leading cause of death amongst cancer patients. Meanwhile, infections pose to be one of the most common problems in cancer. Additionally, the risk of death from a deadly infection is 3 folds higher comparing to patients without cancer. Therefore, using antimicrobials for cancer patients is essential and common, especially for those immunocompromised (Nanayakkara et al., 2021). This said, using both prophylactic and treatment antimicrobials could be considered for neutropenic cancer patients that might be in need of a protracted course of therapy. In cancer settings, the prolonged and widespread use of broad-spectrum antimicrobials can negatively impact the infection-related morbidity and mortality, yet, it can lead to the development of Antimicrobial Resistance (Lustberg, 2012).

Antimicrobial Resistance (AMR) is defined by the UK National Institute for Health and Care Excellence (NICE) guidelines as "*the loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines*" (NICE, 2015). It is a pressing challenge to the success of cancer treatment. AMR is a recognised global problem by international organisations such as the WHO and the Disease Control and Prevention (CDC) (Nanayakkara et al., 2021). By 2050, drug-resistant illnesses are expected to be the cause of approximately 10 million additional deaths if the scientific community does not manage and replenish our antibiotic supply (de Kraker et al., 2016).

More importantly, high rates of AMR are negatively impacting cancer care. Failure of antimicrobials not only increases sepsis risk, but also increases sepsis-related mortality and sepsis-related healthcare cost in cancer settings (Williams et al., 2004). The misuse and overuse of antimicrobials are two important factors that magnitude the risk of AMR (Hollis and Ahmed, 2013). AMR is a critical threat that can hinder the progress of cancer care. Therefore, to protect cancer patients and decrease the future antibiotic-resistant infections, it is crucial to optimise the use of the currently available antimicrobials and to develop new antimicrobial options.

AMR is associated with unfavourable results in cancer patients. A published meta-analysis showed that, in post-chemotherapy infections, 26.8% of microorganisms were found to be resistant to the usual prophylactic antibiotics. The same study forecasted that, if antibiotic efficacy were reduced by 30%–70%, patients receiving chemotherapy for haematological malignancies would have 4,000–10,000

extra infections, and 500–1,000 additional fatalities each year in the United States (Teillant et al., 2015).

According to the UK government's O'Neill report, by 2050, AMR will lead to 10 million mortality cases annually, surpassing cancer as the leading cause of death (8.2 million each year) (O'Neill, 2016). In order to improve AMR monitoring, the UK Health Security Agency (UKHSA) publishes the national annual report on the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). It provides information on the use of antibiotics, and supports programmes and toolkits designed to improve antibiotic prescribing in the community and in hospitals. In England, there were 2.2% more serious antibiotic-resistant infections in 2021 than there were in 2020, according to the most current study from 2022. This translates to 148 serious infections caused by AMR every day in 2021, despite the fact that the prevalence of antibiotic-resistant diseases was lower than it was during the COVID-19 pandemic. Information and resources on the UK's goals to have antimicrobial resistance contained and controlled by 2040 are available as part of the government's efforts to address the AMR problem (GOV.UK, 2022). Additionally, a number of recent studies confirmed the link between AMR and unfavourable outcomes in patients with solid tumours as well as haematological malignancies (Cattaneo et al., 2018; Levene et al., 2018; Marín et al., 2014).

AMR's impact on antibiotic efficacy reflects on the prolongation of hospital admissions, which significantly increased healthcare costs. In the US, AMR is predicted to cost its economy $35 billion a year in lost productivity and nearly $20 billion in health care costs (Nelson et al., 2021). Moreover, the average cost of treatment for a case of febrile neutropenia following chemotherapy in 2020 ranged from $50,000 to $60,000 (Tori et al., 2020).

AMS is a fairly new approach in optimising antimicrobial use. As per the UK NICE guidelines, AMS is defined as "*an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness"* (NICE, 2015). Cancer care facilities managing patients with cancer and/or those undergoing haematopoietic stem cell transplantation (who are vulnerable to serious infections and require numerous courses of antimicrobial therapy over the course of treatment) should pay special attention to AMS. These patients may stand to gain the most from AMS as previous drug exposure is a significant risk factor leading to acquiring an infection that is resistant to antimicrobials. Different studies in hospital-wide intervention programmes have shown the influence of AMS on decreasing overall AMR and cutting antimicrobial costs (Patterson et al., 2016; Freifeld et al., 2011; Cook et al., 2006; Bantar et al., 2003).

As per the British Society for Antimicrobial Chemotherapy (BSAC), implementing AMS programmes

has been linked to a reduction in cancer patient mortality rates in general and patients with febrile neutropoenia in particular (BSAC, 2018).

4.2. Point Prevalence Survey (PPS) of Antimicrobial Utilisation Amongst Oncology Patients in Qatar

International PPSs have been used to describe the use of antimicrobial agents (Dellit et al., 2007). In 2012, literature describing AMS programmes in the Middle East was limited. An evaluation of existing antimicrobial usage was required in order to create an AMS programme that will satisfy the specific needs of the Qatari community. Hence, the idea of the first PPS was initiated in 2012. The purpose of this study was to describe the usage of antimicrobial agents in this population, and to identify the prevalence of antimicrobial utilisation for oncology in Qatar.

This study was published in the Journal of Infection in Developing Countries (JIDC) and is referred to here as Key Publication 5 (KP5).

4.2.1. Methodology

This study was designed as a PPS. All NCCCR wards were included (one ward per day), with validation conducted on the same day. All patients admitted to the oncology and haematology wards in Qatar were included, and their use of antimicrobials were screened. Patients' electronic and paper-based charts were used to gather information. Data was collected from NCCCR on 3 separate days over a period of 2-weeks from April 26 to May 3, 2012. An adapted version of the 2006 European Surveillance of Antimicrobial Consumptions (ESAC) PPS audit tool was used to audit each medical ward during the course of a single day (Ansari et al., 2009). All patient demographics, details on the used antimicrobial agents (including dose, route, frequency, and duration), reason for initiation (treatment/prophylaxis), and culture results (if available) were collected. Additionally, a review of adherence to regional prescribing standards, febrile neutropenia recommendations, and prescribing based on culture results were assessed.

4.2.2. Key results

During the study period, 58 inpatients in total were included, with 43% (25/58) overall prevalence of antimicrobial use. The 25 study participants were prescribed a total of 33 antimicrobial medications, where 94% (31/33) of antimicrobial orders were prescribed to treat an active infection, and 6% (2/33) were for prophylaxis.

Penicillin/Beta-lactamase inhibitor combinations accounted for 39% (13/33) of all antimicrobial agent uses, followed by carbapenems with 15% (5/32). The intravenous route was used to administer 73% (24/33) of the recommended antimicrobials.

In 82% (27/33) of the prescriptions, the reason for prescribing the antimicrobial was included. Febrile neutropenia 21% (7/33), bacteraemia 18% (6/33) and fever 15% (5/33) were the most commonly reported causes of antibiotic use. Only 24% (8/33) of all antimicrobial orders included information about the planned duration of the antimicrobial therapy.

The compliance to the regional prescribing restriction criteria was below expectations, as 58% (19/33) of prescriptions were written by approved prescribers. For 96% (24/25) of the patients, cultures before the initiation of empirical antibiotics therapy were done. Furthermore, 100% (6/6) of the empirically started antibiotic matched sensitivity culture results. Only 33% (2/6) of patients, followed the local febrile neutropenia protocol ("NCCCR Febrile Neutropenia Protocol (CPRO 10543)," 2009).

4.2.3. Impact and reflection on clinical practice

KP5 was an example of an institutional PPS. In this study, a 2006 ESAC PPS audit tool was used for validation. As per the European Centre for Disease Prevention and Control (ECDC), PPS studies are designed to gather uniform data from various sites over a certain period of time (European Centre for Disease Prevention and Control., 2019). At the same time, PPS is an established method for identifying specific needs within institutions. Antibiotic use inside and across institutions has been characterised using PPSs on a global scale. This kind of audit is helpful in identifying how prescribing practices developed over time and how they vary amongst institutions. PPSs are also helpful for identifying the quality improvement goals and assessing the success of an institution's antimicrobial stewardship initiatives (Aldeyab et al., 2011).

As far as I'm aware, this study is the first PPS in the Middle East, which is reflected by being cited in 13 articles up to today.

Worldwide, systemic antimicrobial drugs are reportedly utilised in 29% - 38% of cases (Aldeyab et al., 2011; Seaton et al., 2007; Zarb et al., 2011). KP4 study findings showed the increased rate of antimicrobials use (43%) in the cancer care settings in Qatar, although these results might be acceptable due to the nature of the immunocompromised cancer population. However, it highlighted the immediate need for AMS in the cancer care centre in Qatar in order to rationalise the antimicrobials use among the cancer patients, minimise the risk of AMR, and decrease the financial burden of antimicrobials use on

the healthcare system. Therefore, in 2014 the AMS programme was initiated in NCCCR as a pharmacy initiative interdisciplinary collaborative programme. I led the programme initiation in collaboration with the infectious disease chairman. NCCCR AMS team included oncology physicians, haematology physicians, infectious disease physicians, clinical pharmacists, infection control officers, nurses, microbiology laboratory physicians, and quality and safety officers. This programme is one of the Quality and Patients' Safety (QPS) programmes in NCCCR that was acknowledged by the Joint Commission International (JCI) surveyors, while qualifying NCCCR as a JCI accredited academic health centre.

4.3. The Impact of the Antimicrobial Stewardship Programme in the Cancer Centre in Qatar

The results of the PPS (KP5) brought to light the urgent need for AMS in the cancer care centre in Qatar. The implementation of AMS in cancer settings is expected to reflect on direct patient care, improve patient outcomes, decrease the utilisation of antimicrobials, decrease the incidence of AMR, and decrease the cost on the healthcare system (by decreasing the utilisation of antimicrobials, and shortening the admissions LOS).

KP5 – the first oncology focused PPS in Qatar – showed that only 58% of antimicrobial prescriptions for cancer patients adhered to local or national antimicrobial prescribing standards in Qatar ("HMC Antimicrobial Prescribing (CL 7197)," n.d.). As a result, AMS was developed in NCCCR, and the local regulations have been amended accordingly. However, up to 2016, neither the effectiveness of this service nor the influence of educational interventions on clinical practice have been systematically evaluated. This generated the idea of a new study to assess the level of knowledge, the outcomes, and the challenges of AMS among the cancer management team in Qatar, focusing on the implications of an AMS intervention in NCCCR.

This study was published in East Mediterranean Health Journal, published by the WHO Regional Office for the Eastern Mediterranean (WHO/EMRO), and is referred to as Key Publication 6 (KP6).

4.3.1. Methodology

This study is a mixed methods study consisting of PPSs, quantitative follow-up PPS, and semi-structured interviews, in addition to a quality improvement methodology. It included all NCCCR oncology, haematology, bone marrow transplant, and palliative care admitted patients. It was run over 4 phases. First, in order to analyse how well local prescription standards were followed when giving antimicrobials to cancer patients, six cross-sectional baseline PPSs of antimicrobials prescribing were performed. This audit was done on six different days, over an 11-day period between February 14 and February 24, 2016. Then, follow-up data were collected for patients who spent at least two days of admission and got at least two doses of antimicrobials during those days. The aim of the follow-up was to assess the appropriateness of antimicrobial use during hospital stays.

Second, to address the gaps identified in phase 1, an educational intervention was deployed. To make sure that a systematic quality improvement methodology was considered, a Plan-Do-Study-Act (PDSA) was used to track changes and measure outcomes. PDSA is a quality improvement methodology. It's

founded by the Institution for Health Improvement, with the objective of establishing a functional association between modifications to healthcare systems' operational procedures and variations in outcomes (Speroff and O'Connor, 2004). In this phase, an on-the-spot bedside educational intervention was conducted by the study team. It was performed during the multidisciplinary rounds in the wards targeting all stakeholders of the clinical teams (each team included a medical consultant, medical fellows, medical residents, a clinical pharmacist, and nurses) within four medical teams (infectious diseases, oncology, haematology/bone marrow transplantation, and palliative care). The aim was to explain the goal of the intervention, and to collect feedback for future improvement.

Third, to evaluate the impact of the intervention, follow-up PPSs with the same methodology as in phase1 were conducted. Finally, a qualitative study involving a semi-structured interview was carried out. In this phase, interviews were performed to identify perceived barriers for AMS implementation, strategies to overcome them, and overall perception of the effectiveness of the educational intervention.

4.3.2. Key results

Key results are as listed below (based on each phase):

Phase 1:

Six-point prevalence studies

A total of 219 prescriptions were analysed over the 6 PPSs, with a range of 33-39 prescriptions in each PPS. The majority of the results were relatively consistent with KP5 results, with little improvement. For instance, 85% of prescriptions included the reason for use. The two most reported medical conditions for which antimicrobials were prescribed were the febrile neutropenia (21%) and bacteraemia (15%). Whereas carbapenems were the most utilised class of antibacterial drugs (21%), followed by cephalosporins (18%) and beta-lactam/beta-lactamase inhibitor (14%). Furthermore, most antibiotics were given via the intravenous route (58%). In addition, 60% complied with the local guidelines and regulations. However, in 37% of the cases, the justification for choosing not to adhere to the clinical practise recommendations was not documented.

Phase 2:

Educational intervention

After analysing the findings of phase 1 of our study, a number of recommendations and targets for

improvement in antimicrobial usage and prescribing behaviours were identified. The main emphasis was on accurate record-keeping in electronic health records. Making such information available will, also, aid in making sure that antibiotics are used appropriately, changed as necessary, and stopped on time.

The education intervention and PDSA significantly focused on the role of the clinical pharmacists involved, and its direct impact on the safe application of AMS.

Phase 3:

Follow-up PPSs

The follow-up data showed that a total of 46 prescriptions were monitored, with an overall compliance rate of 96% (44/46), as a result of the educational intervention. There were just two instances where an antibiotic was discontinued or switched to another antibiotic without a rationale or clear justification. In fact, antimicrobials were properly deescalated or stopped once cultures were revealed, or once the patients' clinical condition have improved. Whereas antibiotics were appropriately escalated from empiric coverage to broad-spectrum antibiotic in cases of clinical deterioration.

Phase 4:

Semi-structured interviews

As discussed in KP2, the clinical pharmacist at NCCCR acts as a core member of the multidisciplinary teams for oncology, haematology, palliative care, and infectious diseases. In phase 4, a total of three pharmacists who observed the educational intervention were interviewed. As a result of those interviews, the pharmacists linked the effective antimicrobial prescribing with a number of factors, such as: the cooperation and communication across the multidisciplinary teams; adherence to policies and guidelines; the electronic system errors; and clinical pharmacists' interventions.

The clinical pharmacists suggested some strategies to overcome barriers and improve AMS compliance, such as: improving communication amongst HCPs; developing a hospital AMS policy that must be followed; adhering to previously authorised local antimicrobial guidelines; and having backup antimicrobial alternatives in case of drug shortages. In addition, they highlighted the need for awareness-raising campaigns and educational sessions in the regular hospital meetings to share the updates on the use of antimicrobial agents and the benefits of consulting the AMS team.

4.3.3. Reflection on clinical practice and future directions

Lately, research methodologies have evolved, becoming more complex in their planning, and flexible in how they use several methodologies. Hence, Mixed Methods Research (MMR) became increasingly accepted and widespread. MMR makes it possible to investigate a study subject from various perspectives. For example, investigators can combine the detailed, subjective perceptions of complex reality gained from qualitative enquiry, with the standardised, transferable facts produced by quantitative study (Tashakkori and Teddlie, 2021).

An example of MMR is this study, KP6. In this thesis MMR was used including PPSs and healthcare interview, and quality improvement methodologies. Using the MMR study design, gave me the opportunity to use both qualitative and quantitative methodologies at the same study and learn how to mix both paradigms. Along with, reaching the best expected outcome while applying different methodologies, using the PPS audit to identify areas of improvement in NCCCR AMS practice to conduct interactive educational sessions. Then, reflect on the outcomes of those sessions, by both follow-up PPS to numerically assess the improvement, in addition to semi-structured interviews to identify the strategies recommended by HCPs to overcome the challenges. Although semi-structured interviews are frequently a successful method for gathering open-ended data, they also have some limitations, including the fact that not every interviewee makes a good participant. However, the participant pharmacists in KP6 were effectively engaged and enthusiastic to share their knowledge and recommendations.

This study was published by the WHO/EMRO in 3 languages (English, French and Arabic). It was cited 20 times so far in a variety of publications (in English, Spanish and French), including systematic reviews, original research articles, and a SWOC analysis (Strengths, Weaknesses, Opportunities and Challenges analysis).

KP6 study results reflected the minimal improvement in the prescribing pattern of the antimicrobials in NCCCR after the implementation of AMS. However, it also highlighted the areas of improvement that require further efforts to optimise the use of antimicrobials amongst cancer patients in Qatar. Based on the study recommendations, education campaigns on AMS, and antimicrobials policies and guidelines were initiated to all HCPs in NCCCR, and monthly for rotating medical and pharmacy residents as part of their initial orientation. However, the improvement should be tested to help clinicians to better understand the current practice and identify gaps and challenges, and to optimise the delivered patients' care. Therefore, I'm now co-leading a new study, titled "Pharmacy Based Analysis of Antibiotics' Use Among Cancer Patients with Suspected Infections/Sepsis, ID# MRC-01-22-810". The aim of this study

is to conduct a comprehensive pharmacy-based analysis of antibiotics' use among cancer patients with suspected infection/sepsis, including the appropriateness of antibiotics' use in those patients admitted to NCCCR. This new study is an observational non-interventional study. One part of the study is an RCS over a period of 6 years (2017- 2022). The second part is a PCS, monitoring the same parameters in patients with similar inclusion criteria during a period of three years (2023 –2025). This will empower the clinical teams in NCCCR to assess AMS and the efforts done over a course of 6 years, and the upcoming improvement in the coming 3 years.

Conclusion

Real world studies are an effective approach to evaluate practice outcomes in cancer care. My real-world research efforts enabled me to clearly articulate the important contributions played by the oncology pharmacists in cancer supportive care as a member of the MDTs in Qatar. In addition, it allowed highlighting opportunities for clinical practice improvement and ways to use cancer supportive therapy to improve clinical outcomes.

This thesis highlights six key publications of my real-world research studies that draw impactful conclusions on cancer supportive care. To start with, the significant value and influence of oncology pharmacists' role is highlighted. This role significantly enhances patients' clinical outcomes (KP1 and KP2). As recommended by HCPs, expanding the role of the Oncology Clinical Pharmacists in different directions can reflect on improving clinical and economical outcomes. For example, extending the role of the clinical pharmacists in drugs dosing and monitoring, and the introduction of the oncology pharmacist-led clinics (KP2). Presently, NCCCR is putting those research recommendations into effect, running the first Oncology Pharmacists-led clinics in the MENA region. Currently, I'm leading a new research study to evaluate the impact of the new services on patients' care.

Cancer supportive care is necessary to manage disease and therapy related complications. In Qatar, different BTAs can have different impact on calcium levels; denosumab has a significantly higher rate of hypocalcaemia if compared with zoledronic acid (KP3). To prevent hypocalcaemia related to the use of the BTAs, calcium supplementation and vitamin D, and close monitoring are recommended (KP3). These study observations led to the creation of a protocol for BTAs' use in cancer settings in Qatar, which covered the prescribing, dispensing, and administration of denosumab. This strategy enhanced the roles of pharmacists and nurses, who are currently making significant contributions to patient care, which resulted in a reduction in the incidence of hypocalcaemia among our patients.

Early detection and managing irAEs of ICIs is an impactful area of cancer supportive care. Therefore, careful monitoring is strongly advised. Steroids (IV or oral), rituximab, and IVIG are currently the most widely used treatments for haematological irAEs (KP4). Based on the findings of KP4, NCCCR clinical guidelines and practises have been modified. My upcoming goal is to conduct a new study to assess the incidence and management of haematological irAEs of ICIs, following the introduction of the updated guideline in Qatar.

Another domain of supportive care for cancer patients is the use of antimicrobials, either as a prophylaxis

or as a therapeutic option for this population of immunocompromised patients. AMS team formation, active HCP collaboration, and ongoing HCP education can result in considerable improvement in HCP adherence to AMS standards, which has a beneficial impact on outcomes (KP5 and KP6). Based on KP5 and KP6, AMS policies and procedures were updated, and KP6-based educational and enforcement initiatives were created. Currently, reduced antimicrobial use and shorter LOS are KPIs in NCCCR.

It has been a significant learning opportunity for me to investigate cancer RWD from various angles and with various research methodologies. This has helped me develop my research skills. Moreover, my systematic review demonstrated that I am capable of carrying out high quality literature research. This allowed me to advance research capacity and direct research in my department, as well as to mentor my peers, pharmacy interns, and advanced pharmacy students.

Over my research journey, I collaborated successfully with academic researchers from Qatari universities and other academic institutions in the region, as well as clinical practise researchers - nationally and regionally- including physicians, pharmacists, and nurses. This enhanced my capacity for teamwork, critical thinking, and viewing research and practice related strengths and limitations from different perspectives. In addition, it gave me the chance to use what I learned through academic studies in the real-world practice and vice versa. Therefore, my studies' findings and recommendations, impacted hospital, national, and regional practise by providing urgent answers that arose in clinical practice.

In presenting my research findings at national, regional, and international conferences, I obtained valuable experience and awards. Furthermore, by writing up my research findings, submitting them to highly-ranked peer-reviewed journals, and responding to inquiries that come up throughout the peer-review process, I gained good experience in these areas that qualified me to have an editorial role in highly-ranked peer reviewed journals. Finally, as a next step, I hope to expand my cancer research portfolio and advance my academic career.

REFERENCES

Abushanab, D., Gulied, A., Hamad, A., Rouf, P.V.A., Hail, M.A., Kassem, W.E., Hajj, M.E., Al-Badriyeh, D., 2022. Economic Impact and Cost Benefit of the Inpatient Clinical Pharmacist Interventions in Cancer Care Units (preprint). In Review. https://doi.org/10.21203/rs.3.rs-1180212/v1

Aje, A.A., Showande, S.J., Fakeye, T.O., 2021. Medication reconciliation knowledge among hospital pharmacists in Nigeria: A non-randomised controlled trial. Pharm. Educ. 21, 528–537. https://doi.org/10.46542/pe.2021.211.528537

Aldeyab, M.A., Kearney, M.P., McElnay, J.C., Magee, F.A., Conlon, G., Gill, D., Davey, P., Muller, A., Goossens, H., Scott, M.G., on behalf of the ESAC Hospital Care Subproject Group, 2011. A point prevalence survey of antibiotic prescriptions: benchmarking and patterns of use: A point prevalence survey of antibiotic prescriptions: benchmarking and patterns of use. Br. J. Clin. Pharmacol. 71, 293–296. https://doi.org/10.1111/j.1365-2125.2010.03840.x

Allemani, C., Matsuda, T., Di Carlo, V., Harewood, R., Matz, M., Nikšić, M., Bonaventure, A., Valkov, M., Johnson, C.J., Estève, J., Ogunbiyi, O.J., Azevedo e Silva, G., Chen, W.-Q., Eser, S., Engholm, G., Stiller, C.A., Monnereau, A., Woods, R.R., Visser, O., Lim, G.H., Aitken, J., Weir, H.K., Coleman, M.P., Bouzbid, S., Hamdi-Chérif, M., Zaidi, Z., Meguenni, K., Regagba, D., Bayo, S., Cheick Bougadari, T., Manraj, S.S., Bendahhou, K., Fabowale, A., Bradshaw, D., Somdyala, N.I.M., Kumcher, I., Moreno, F., Calabrano, G.H., Espinola, S.B., Carballo Quintero, B., Fita, R., Diumenjo, M.C., Laspada, W.D., Ibañez, S.G., Lima, C.A., De Souza, P.C.F., Del Pino, K., Laporte, C., Curado, M.P., de Oliveira, J.C., Veneziano, C.L.A., Veneziano, D.B., Latorre, M.R.D.O., Tanaka, L.F., Rebelo, M.S., Santos, M.O., Galaz, J.C., Aparicio Aravena, M., Sanhueza Monsalve, J., Herrmann, D.A., Vargas, S., Herrera, V.M., Uribe, C.J., Bravo, L.E., Garcia, L.S., Arias-Ortiz, N.E., Morantes, D., Jurado, D.M., Yépez Chamorro, M.C., Delgado, S., Ramirez, M., Galán Alvarez, Y.H., Torres, P., Martínez-Reyes, F., Jaramillo, L., Quinto, R., Castillo, J., Mendoza, M., Cueva, P., Yépez, J.G., Bhakkan, B., Deloumeaux, J., Joachim, C., Macni, J., Carrillo, R., Shalkow Klincovstein, J., Rivera Gomez, R., Poquioma, E., Tortolero-Luna, G., Zavala, D., Alonso, R., Barrios, E., Eckstrand, A., Nikiforuk, C., Noonan, G., Turner, D., Kumar, E., Zhang, B., McCrate, F.R., Ryan, S., MacIntyre, M., Saint-Jacques, N., Nishri, D.E., McClure, C.A., Vriends, K.A., Kozie, S., Stuart-Panko, H., Freeman, T., George, J.T., Brockhouse, J.T., O'Brien, D.K., Holt, A., Almon, L., Kwong, S., Morris, C., Rycroft, R., Mueller, L., Phillips, C.E., Brown, H., Cromartie, B., Schwartz, A.G., Vigneau, F., Levin, G.M., Wohler, B., Bayakly, R., Ward, K.C., Gomez, S.L., McKinley, M., Cress, R., Green, M.D., Miyagi, K., Ruppert, L.P., Lynch, C.F., Huang, B., Tucker, T.C., Deapen, D., Liu, L., Hsieh, M.C., Wu, X.C., Schwenn, M., Gershman, S.T., Knowlton, R.C., Alverson, G., Copeland, G.E., Bushhouse, S., Rogers, D.B., Jackson-Thompson, J., Lemons, D., Zimmerman, H.J., Hood, M., Roberts-Johnson, J., Rees, J.R., Riddle, B., Pawlish, K.S., Stroup, A., Key, C., Wiggins, C., Kahn, A.R., Schymura, M.J., Radhakrishnan, S., Rao, C., Giljahn, L.K., Slocumb, R.M., Espinoza, R.E., Khan, F., Aird, K.G., Beran, T., Rubertone, J.J., Slack, S.J., Garcia, L., Rousseau, D.L., Janes, T.A., Schwartz, S.M., Bolick, S.W., Hurley, D.M., Whiteside, M.A., Miller-Gianturco, P., Williams, M.A., Herget, K., Sweeney, C., Johnson, A.T., Keitheri Cheteri, M.B., Migliore Santiago, P., Blankenship, S.E., Farley, S., Borchers, R., Malicki, R., Espinoza, J.R., Grandpre, J., Wilson, R., Edwards, B.K., Mariotto, A., Lei, Y., Wang, N., Chen, J.S., Zhou, Y., He, Y.T., Song, G.H., Gu, X.P., Mei, D., Mu, H.J., Ge, H.M., Wu, T.H., Li, Y.Y., Zhao, D.L., Jin, F., Zhang, J.H., Zhu, F.D., Junhua, Q., Yang, Y.L., Jiang, C.X., Biao, W., Wang, J., Li, Q.L., Yi, H., Zhou, X., Dong, J., Li, W., Fu, F.X., Liu, S.Z., Chen, J.G., Zhu, J., Li, Y.H., Lu, Y.Q., Fan, M., Huang, S.Q., Guo, G.P., Zhaolai, H., Wei, K., Zeng, H., Demetriou, A.V., Mang, W.K., Ngan, K.C., Kataki, A.C., Krishnatreya, M., Jayalekshmi, P.A., Sebastian, P., Nandakumar, A., Malekzadeh, R., Roshandel, G., Keinan-Boker, L., Silverman, B.G., Ito, H., Nakagawa, H., Sato, M., Tobori, F., Nakata, I., Teramoto, N., Hattori, M., Kaizaki, Y., Moki, F., Sugiyama, H., Utada, M., Nishimura, M., Yoshida, K., Kurosawa, K., Nemoto, Y., Narimatsu, H., Sakaguchi, M., Kanemura, S., Naito, M., Narisawa, R., Miyashiro, I., Nakata, K., Sato, S., Yoshii, M., Oki, I., Fukushima, N., Shibata, A., Iwasa, K., Ono, C., Nimri, O., Jung, K.W., Won, Y.J., Alawadhi, E., Elbasmi, A., Ab Manan, A., Adam, F., Sanjaajmats, E.,

Tudev, U., Ochir, C., Al Khater, A.M., El Mistiri, M.M., Teo, Y.Y., Chiang, C.J., Lee, W.C., Buasom, R., Sangrajrang, S., Kamsa-ard, S., Wiangnon, S., Daoprasert, K., Pongnikorn, D., Leklob, A., Sangkitipaiboon, S., Geater, S.L., Sriplung, H., Ceylan, O., Kög, I., Dirican, O., Köse, T., Gurbuz, T., Karaşahin, F.E., Turhan, D., Aktaş, U., Halat, Y., Yakut, C.I., Altinisik, M., Cavusoglu, Y., Türkköylü, A., Üçüncü, N., Hackl, M., Zborovskaya, A.A., Aleinikova, O.V., Henau, K., Van Eycken, L., Valerianova, Z., Yordanova, M.R., Šekerija, M., Dušek, L., Zvolský, M., Storm, H., Innos, K., Mägi, M., Malila, N., Seppä, K., Jégu, J., Velten, M., Cornet, E., Troussard, X., Bouvier, A.M., Guizard, A.V., Bouvier, V., Launoy, G., Arveux, P., Maynadié, M., Mounier, M., Woronoff, A.S., Daoulas, M., Robaszkiewicz, M., Clavel, J., Goujon, S., Lacour, B., Baldi, I., Pouchieu, C., Amadeo, B., Coureau, G., Orazio, S., Preux, P.M., Rharbaoui, F., Marrer, E., Trétarre, B., Colonna, M., Delafosse, P., Ligier, K., Plouvier, S., Cowppli-Bony, A., Molinié, F., Bara, S., Ganry, O., Lapôtre-Ledoux, B., Grosclaude, P., Bossard, N., Uhry, Z., Bray, F., Piñeros, M., Stabenow, R., Wilsdorf-Köhler, H., Eberle, A., Luttmann, S., Löhden, I., Nennecke, A.L., Kieschke, J., Sirri, E., Emrich, K., Zeissig, S.R., Holleczek, B., Eisemann, N., Katalinic, A., Asquez, R.A., Kumar, V., Petridou, E., Ólafsdóttir, E.J., Tryggvadóttir, L., Clough-Gorr, K., Walsh, P.M., Sundseth, H., Mazzoleni, G., Vittadello, F., Coviello, E., Cuccaro, F., Galasso, R., Sampietro, G., Giacomin, A., Magoni, M., Ardizzone, A., D'Argenzio, A., Castaing, M., Grosso, G., Lavecchia, A.M., Sutera Sardo, A., Gola, G., Gatti, L., Ricci, P., Ferretti, S., Serraino, D., Zucchetto, A., Celesia, M.V., Filiberti, R.A., Pannozzo, F., Melcarne, A., Quarta, F., Russo, A.G., Carrozzi, G., Cirilli, C., Cavalieri d'Oro, L., Rognoni, M., Fusco, M., Vitale, M.F., Usala, M., Cusimano, R., Mazzucco, W., Michiara, M., Sgargi, P., Boschetti, L., Borciani, E., Seghini, P., Maule, M.M., Merletti, F., Tumino, R., Mancuso, P., Vicentini, M., Cassetti, T., Sassatelli, R., Falcini, F., Giorgetti, S., Caiazzo, A.L., Cavallo, R., Cesaraccio, R., Pirino, D.R., Contrino, M.L., Tisano, F., Fanetti, A.C., Maspero, S., Carone, S., Mincuzzi, A., Candela, G., Scuderi, T., Gentilini, M.A., Piffer, S., Rosso, S., Barchielli, A., Caldarella, A., Bianconi, F., Stracci, F., Contiero, P., Tagliabue, G., Rugge, M., Zorzi, M., Beggiato, S., Brustolin, A., Berrino, F., Gatta, G., Sant, M., Buzzoni, C., Mangone, L., Capocaccia, R., De Angelis, R., Zanetti, R., Maurina, A., Pildava, S., Lipunova, N., Vincerževskienė, I., Agius, D., Calleja, N., Siesling, S., Larønningen, S., Møller, B., Dyzmann-Sroka, A., Trojanowski, M., Góźdź, S., Mężyk, R., Mierzwa, T., Molong, L., Rachtan, J., Szewczyk, S., Błaszczyk, J., Kępska, K., Kościańska, B., Tarocińska, K., Zwierko, M., Drosik, K., Maksimowicz, K.M., Purwin-Porowska, E., Reca, E., Wójcik-Tomaszewska, J., Tukiendorf, A., Grądalska-Lampart, M., Radziszewska, A.U., Gos, A., Talerczyk, M., Wyborska, M., Didkowska, J.A., Wojciechowska, U., Bielska-Lasota, M., Forjaz de Lacerda, G., Rego, R.A., Bastos, J., Silva, M.A., Antunes, L., Laranja Pontes, J., Mayer-da-Silva, A., Miranda, A., Blaga, L.M., Coza, D., Gusenkova, L., Lazarevich, O., Prudnikova, O., Vjushkov, D.M., Egorova, A.G., Orlov, A.E., Kudyakov, L.A., Pikalova, L.V., Adamcik, J., Safaei Diba, C., Primic-Žakelj, M., Zadnik, V., Larrañaga, N., Lopez de Munain, A., Herrera, A.A., Redondas, R., Marcos-Gragera, R., Vilardell Gil, M.L., Molina, E., Sánchez Perez, M.J., Franch Sureda, P., Ramos Montserrat, M., Chirlaque, M.D., Navarro, C., Ardanaz, E.E., Guevara, M.M., Fernández-Delgado, R., Peris-Bonet, R., Carulla, M., Galceran, J., Alberich, C., Vicente-Raneda, M., Khan, S., Pettersson, D., Dickman, P., Avelina, I., Staehelin, K., Camey, B., Bouchardy, C., Schaffar, R., Frick, H., Herrmann, C., Bulliard, J.L., Maspoli-Conconi, M., Kuehni, C.E., Redmond, S.M., Bordoni, A., Ortelli, L., Chiolero, A., Konzelmann, I., Matthes, K.L., Rohrmann, S., Broggio, J., Rashbass, J., Fitzpatrick, D., Gavin, A., Clark, D.I., Deas, A.J., Huws, D.W., White, C., Montel, L., Rachet, B., Turculet, A.D., Stephens, R., Chalker, E., Phung, H., Walton, R., You, H., Guthridge, S., Johnson, F., Gordon, P., D'Onise, K., Priest, K., Stokes, B.C., Venn, A., Farrugia, H., Thursfield, V., Dowling, J., Currow, D., Hendrix, J., Lewis, C., 2018. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet 391, 1023–1075. https://doi.org/10.1016/S0140-6736(17)33326-3

Ansari, F., Erntell, M., Goossens, H., Davey, P., 2009. The European Surveillance of Antimicrobial Consumption (ESAC) Point‐Prevalence Survey of Antibacterial Use in 20 European Hospitals in 2006. Clin. Infect. Dis. 49, 1496–1504. https://doi.org/10.1086/644617

Arondekar, B., Duh, M.S., Bhak, R.H., DerSarkissian, M., Huynh, L., Wang, K., Wojciehowski, J., Wu, M., Wornson, B., Niyazov, A., Demetri, G.D., 2022. Real-World Evidence in Support of Oncology Product

Registration: A Systematic Review of New Drug Application and Biologics License Application Approvals from 2015–2020. Clin. Cancer Res. 28, 27–35. https://doi.org/10.1158/1078-0432.CCR-21-2639

Banerjee, R., Prasad, V., 2020. Are Observational, Real-World Studies Suitable to Make Cancer Treatment Recommendations? JAMA Netw. Open 3, e2012119. https://doi.org/10.1001/jamanetworkopen.2020.12119

Bantar, C., Sartori, B., Vesco, E., Heft, C., Saul, M., Salamone, F., Oliva, M.E., 2003. A Hospitalwide Intervention Program to Optimize the Quality of Antibiotic Use: Impact on Prescribing Practice, Antibiotic Consumption, Cost Savings, and Bacterial Resistance. Clin. Infect. Dis. 37, 180–186. https://doi.org/10.1086/375818

Basch, E., Deal, A.M., Dueck, A.C., Scher, H.I., Kris, M.G., Hudis, C., Schrag, D., 2017. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA 318, 197–198. https://doi.org/10.1001/jama.2017.7156

Berman, R., Davies, A., Cooksley, T., Gralla, R., Carter, L., Darlington, E., Scotté, F., Higham, C., 2020. Supportive Care: An Indispensable Component of Modern Oncology. Clin. Oncol. R. Coll. Radiol. G. B. 32, 781–788. https://doi.org/10.1016/j.clon.2020.07.020

BOPA, 2018. ONCOLOGY/HAEMATOLOGY PHARMACY NON-MEDICAL PRESCRIBING GUIDELINES (No. Version 4.1). Royal Pharmaceutical Society, British Oncology Pharmacy Association.

Boşnak, A.S., Birand, N., Diker, Ö., Abdi, A., Başgut, B., 2019. The role of the pharmacist in the multidisciplinary approach to the prevention and resolution of drug-related problems in cancer chemotherapy. J. Oncol. Pharm. Pract. Off. Publ. Int. Soc. Oncol. Pharm. Pract. 25, 1312–1320. https://doi.org/10.1177/1078155218786048

BSAC, 2018. ANTIMICROBIAL STEWARDSHIP: FROM PRINCIPLES TO PRACTICE. The British Society for Antimicrobial Chemotherapy [BSAC].

Cancer Research UK, 2020. Together we will beat cancer.

Cattaneo, C., Di Blasi, R., Skert, C., Candoni, A., Martino, B., Di Renzo, N., Delia, M., Ballanti, S., Marchesi, F., Mancini, V., Orciuolo, E., Cesaro, S., Prezioso, L., Fanci, R., Nadali, G., Chierichini, A., Facchini, L., Picardi, M., Malagola, M., Orlando, V., Trecarichi, E.M., Tumbarello, M., Aversa, F., Rossi, G., Pagano, L., 2018. Bloodstream infections in haematological cancer patients colonized by multidrug-resistant bacteria. Ann. Hematol. 97, 1717–1726. https://doi.org/10.1007/s00277-018-3341-6

Chew, C., Chiang, J., Yeoh, T., 2015. Impact of outpatient interventions made at an ambulatory cancer centre oncology pharmacy in Singapore. J. Oncol. Pharm. Pract. 21, 93–101. https://doi.org/10.1177/1078155213519836

Coleman, R.E., 2000. Management of bone metastases. The Oncologist 5, 463–470. https://doi.org/10.1634/theoncologist.5-6-463

Collins, R., Bowman, L., Landray, M., Peto, R., 2020. The Magic of Randomization versus the Myth of Real-World Evidence. N. Engl. J. Med. 382, 674–678. https://doi.org/10.1056/NEJMsb1901642

Cook, P.P., Catrou, P., Gooch, M., Holbert, D., 2006. Effect of reduction in ciprofloxacin use on prevalence of meticillin-resistant Staphylococcus aureus rates within individual units of a tertiary care hospital. J. Hosp. Infect. 64, 348–351. https://doi.org/10.1016/j.jhin.2006.06.033

Cooksley, T., Campbell, G., Al-Sayed, T., LaMola, L., Berman, R., 2018. A novel approach to improving ambulatory outpatient management of low risk febrile neutropenia: an Enhanced Supportive Care (ESC) clinic. Support. Care Cancer Off. J. Multinatl. Assoc. Support. Care Cancer 26, 2937–2940. https://doi.org/10.1007/s00520-018-4194-1

Daly, B.J., Douglas, S.L., Gunzler, D., Lipson, A.R., 2013. Clinical Trial of a Supportive Care Team for Patients With Advanced Cancer. J. Pain Symptom Manage. 46, 775–784. https://doi.org/10.1016/j.jpainsymman.2012.12.008

de Kraker, M.E.A., Stewardson, A.J., Harbarth, S., 2016. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? PLOS Med. 13, e1002184. https://doi.org/10.1371/journal.pmed.1002184

Dellit, T.H., Owens, R.C., McGowan, J.E., Gerding, D.N., Weinstein, R.A., Burke, J.P., Huskins, W.C., Paterson, D.L., Fishman, N.O., Carpenter, C.F., Brennan, P.J., Billeter, M., Hooton, T.M., 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Clin. Infect. Dis. 44, 159–177. https://doi.org/10.1086/510393

Denosumab Monograph, 2022.

Dürr, P., Schlichtig, K., Kelz, C., Deutsch, B., Maas, R., Eckart, M.J., Wilke, J., Wagner, H., Wolff, K., Preuß, C., Brückl, V., Meidenbauer, N., Staerk, C., Mayr, A., Fietkau, R., Goebell, P.J., Kunath, F., Beckmann, M.W., Mackensen, A., Neurath, M.F., Pavel, M., Dörje, F., Fromm, M.F., 2021. The Randomized AMBORA Trial: Impact of Pharmacological/Pharmaceutical Care on Medication Safety and Patient-Reported Outcomes During Treatment With New Oral Anticancer Agents. J. Clin. Oncol. 39, 1983–1994. https://doi.org/10.1200/JCO.20.03088

Elazzazy, S., 2018. Management of irAEs Tips and Tricks.

European Centre for Disease Prevention and Control., 2019. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals: ECDC PPS validation protocol version 3.1.2. Publications Office, LU.

Freifeld, A.G., Bow, E.J., Sepkowitz, K.A., Boeckh, M.J., Ito, J.I., Mullen, C.A., Raad, I.I., Rolston, K.V., Young, J.-A.H., Wingard, J.R., 2011. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clin. Infect. Dis. 52, e56–e93. https://doi.org/10.1093/cid/cir073

Google Scholar, Citation, Effect of Denosumab Versus Zoledronic Acid on Calcium Levels in Cancer Patients with Bone Metastasis. A Retrospective Cohort Study, n.d.

GOV.UK, 2022. Antimicrobial resistance (AMR).

Hamad, A., Elazzazy, S., Bujassoum, S., Rasul, K., Gaziev, J., Cherif, H., Al-Boloshi, Z., Hanssens, Y., Saleh, A., Rasheed, H.A., Al-Badriyeh, D., Babiker, A., Hmaidan, A.A., Al-Hail, M., 2023. Applying value-based strategies to accelerate access to novel cancer medications: guidance from the Oncology Health Economics Expert Panel in Qatar (Q-OHEP). BMC Health Serv. Res. 23, 15. https://doi.org/10.1186/s12913-022-08981-5

Hin, C.M., Hong, C.C., 2019. Oncology Pharmacist's Role and Impact on the Multidisciplinary Patient-Centre Practice of Oncology Clinic in Public Hospitals. Asia Pac. J. Health Manag. 14, 16. https://doi.org/10.24083/apjhm.v14i1.203

HMC Antimicrobial Prescribing (CL 7197), n.d.

Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., Gonzalez, R., Robert, C., Schadendorf, D., Hassel, J.C., Akerley, W., van den Eertwegh, A.J.M., Lutzky, J., Lorigan, P., Vaubel, J.M., Linette, G.P., Hogg, D., Ottensmeier, C.H., Lebbé, C., Peschel, C., Quirt, I., Clark, J.I., Wolchok, J.D., Weber, J.S., Tian, J., Yellin, M.J., Nichol, G.M., Hoos, A., Urba, W.J., 2010. Improved survival with ipilimumab in patients with metastatic melanoma. N. Engl. J. Med. 363, 711–723. https://doi.org/10.1056/NEJMoa1003466

Hofbauer, L.C., Neubauer, A., Heufelder, A.E., 2001. Receptor activator of nuclear factor-kappaB ligand and osteoprotegerin: potential implications for the pathogenesis and treatment of malignant bone diseases. Cancer 92, 460–470. https://doi.org/10.1002/1097-0142(20010801)92:3<460::aid-cncr1344>3.0.co;2-d

Holle, L.M., Segal, E.M., Jeffers, K.D., 2020. The Expanding Role of the Oncology Pharmacist. Pharmacy 8, 130. https://doi.org/10.3390/pharmacy8030130

Hollis, A., Ahmed, Z., 2013. Preserving Antibiotics, Rationally. N. Engl. J. Med. 369, 2474–2476. https://doi.org/10.1056/NEJMp1311479

HOPA, 2019. FURTHER DEFINING THE SCOPE OF HEMATOLOGY/ONCOLOGY PHARMACY PRACTICE.

J. Roelofs, A., Thompson, K., H. Ebetino, F., J. Rogers, M., P. Coxon, F., 2010. Bisphosphonates: Molecular Mechanisms of Action and Effects on Bone Cells, Monocytes and Macrophages. Curr. Pharm. Des. 16, 2950–2960. https://doi.org/10.2174/138161210793563635

Julian Higgins, James Thomas, 2022. Cochrane Handbook for Systematic Reviews of Interventions, Version 6.3, 2022.

Kamata, H., Suzuki, H., Sugama, Y., Demachi, K., Ikegawa, K., Igarashi, T., Suzuki, S., Tahara, M., Yamaguchi, M., 2017. Impact of clinical pharmacists collaborating with oncologists in outpatient cancer chemotherapy on cost of chemotherapy. Ann. Oncol. 28, ix74. https://doi.org/10.1093/annonc/mdx620

Kramer, R., Zaremba, A., Moreira, A., Ugurel, S., Johnson, D.B., Hassel, J.C., Salzmann, M., Gesierich, A., Weppler, A., Spain, L., Loquai, C., Dudda, M., Pföhler, C., Hepner, A., Long, G.V., Menzies, A.M., Carlino, M.S., Sachse, M.M., Lebbé, C., Baroudjian, B., Enokida, T., Tahara, M., Schlaak, M., Hayani, K., Bröckelmann, P.J., Meier, F., Reinhardt, L., Friedlander, P., Eigentler, T., Kähler, K.C., Berking, C., Zimmer, L., Heinzerling, L., 2021. Hematological immune related adverse events after treatment with immune checkpoint inhibitors. Eur. J. Cancer Oxf. Engl. 1990 147, 170–181. https://doi.org/10.1016/j.ejca.2021.01.013

Kroll, M.H., Rojas-Hernandez, C., Yee, C., 2022. Hematologic complications of immune checkpoint inhibitors. Blood 139, 3594–3604. https://doi.org/10.1182/blood.2020009016

Lallukka, T., Pietiläinen, O., Jäppinen, S., Laaksonen, M., Lahti, J., Rahkonen, O., 2020. Factors associated with health survey response among young employees: a register-based study using online, mailed and telephone interview data collection methods. BMC Public Health 20, 184. https://doi.org/10.1186/s12889-020-8241-8

Lam, M.S., Cheung, N., 2016. Impact of oncology pharmacist-managed oral anticancer therapy in patients with chronic myelogenous leukemia. J. Oncol. Pharm. Pract. Off. Publ. Int. Soc. Oncol. Pharm. Pract. 22, 741–748. https://doi.org/10.1177/1078155215608523

Launching an Oncology Clinical Pharmacist-Led Clinic in Qatar, 2020. . Int. Pharm. Fed. FIP Hosp. Pharm.

Lehnbom, E.C., Stewart, M.J., Manias, E., Westbrook, J.I., 2014. Impact of Medication Reconciliation and Review

on Clinical Outcomes. Ann. Pharmacother. 48, 1298–1312. https://doi.org/10.1177/1060028014543485

Levene, I., Castagnola, E., Haeusler, G.M., 2018. Antibiotic-resistant Gram-negative Blood Stream Infections in Children With Cancer: A Review of Epidemiology, Risk Factors, and Outcome. Pediatr. Infect. Dis. J. 37, 495–498. https://doi.org/10.1097/INF.0000000000001938

Li, Y., Feng, A., Zheng, S., Chen, C., Lyu, J., 2022. Recent Estimates and Predictions of 5-Year Survival in Patients with Gastric Cancer: A Model-Based Period Analysis. Cancer Control J. Moffitt Cancer Cent. 29, 10732748221099228. https://doi.org/10.1177/10732748221099227

Liekweg, A., Westfeld, M., Braun, M., Zivanovic, O., Schink, T., Kuhn, W., Jaehde, U., 2012. Pharmaceutical care for patients with breast and ovarian cancer. Support. Care Cancer 20, 2669–2677. https://doi.org/10.1007/s00520-012-1385-z

Lustberg, M.B., 2012. Management of neutropenia in cancer patients. Clin. Adv. Hematol. Oncol. HO 10, 825–826.

Maleki, S., Alexander, M., Fua, T., Liu, C., Rischin, D., Lingaratnam, S., 2019. A systematic review of the impact of outpatient clinical pharmacy services on medication-related outcomes in patients receiving anticancer therapies. J. Oncol. Pharm. Pract. Off. Publ. Int. Soc. Oncol. Pharm. Pract. 25, 130–139. https://doi.org/10.1177/1078155218783814

Mansinho, A., R Ferreira, A., Costa, L., 2016. Hypocalcemia in patients with metastatic bone disease treated with denosumab. Ann. Jt. 1, 16–16. https://doi.org/10.21037/aoj.2016.08.02

Marín, M., Gudiol, C., Garcia-Vidal, C., Ardanuy, C., Carratalà, J., 2014. Bloodstream Infections in Patients With Solid Tumors: Epidemiology, Antibiotic Therapy, and Outcomes in 528 Episodes in a Single Cancer Center. Medicine (Baltimore) 93, 143–149. https://doi.org/10.1097/MD.0000000000000026

MASCC, 2021. What is Supportive Care?, Supportive Care Makes Excellent Cancer Care Possible. Multinational Association of Supportive Care in Cancer, https://www.mascc.org/about-mascc.

Merten, J.A., Shapiro, J.F., Gulbis, A.M., Rao, K.V., Bubalo, J., Lanum, S., Engemann, A.M., Shayani, S., Williams, C., Leather, H., Walsh-Chocolaad, T., 2013. Utilization of Collaborative Practice Agreements between Physicians and Pharmacists as a Mechanism to Increase Capacity to Care for Hematopoietic Stem Cell Transplant Recipients. Biol. Blood Marrow Transplant. 19, 509–518. https://doi.org/10.1016/j.bbmt.2012.12.022

Moghli, M.A., Farha, R.A., Hammour, K.A., 2021. Medication discrepancies in hospitalized cancer patients: Do we need medication reconciliation? J. Oncol. Pharm. Pract. 27, 1139–1146. https://doi.org/10.1177/1078155220946388

Monnery, D., Benson, S., Griffiths, A., Cadwallader, C., Hampton-Matthews, J., Coackley, A., Cooper, M., Watson, A., 2018. Multi-professional-delivered enhanced supportive care improves quality of life for patients with incurable cancer. Int. J. Palliat. Nurs. 24, 510–514. https://doi.org/10.12968/ijpn.2018.24.10.510

Murthy, V.H., Krumholz, H.M., Gross, C.P., 2004. Participation in Cancer Clinical Trials: Race-, Sex-, and Age-Based Disparities. JAMA 291, 2720. https://doi.org/10.1001/jama.291.22.2720

Nabhan, C., Klink, A., Prasad, V., 2019. Real-world Evidence—What Does It Really Mean? JAMA Oncol. 5, 781. https://doi.org/10.1001/jamaoncol.2019.0450

Nanayakkara, A.K., Boucher, H.W., Fowler, V.G., Jezek, A., Outterson, K., Greenberg, D.E., 2021. Antibiotic

resistance in the patient with cancer: Escalating challenges and paths forward. CA. Cancer J. Clin. 71, 488–504. https://doi.org/10.3322/caac.21697

NCCCR Febrile Neutropenia Protocol (CPRO 10543), 2009.

NCF, 2022. ACHIEVING EXCELLENCE IN CANCER CARE: A Vision for 2022.

Nelson, K.A., Walsh, D., Abdullah, O., McDonnell, F., Homsi, J., Komurcu, S., LeGrand, S.B., Zhukovsky, D.S., 2000. Common complications of advanced cancer. Semin. Oncol. 27, 34–44.

Nelson, R.E., Hatfield, K.M., Wolford, H., Samore, M.H., Scott, R.D., Reddy, S.C., Olubajo, B., Paul, P., Jernigan, J.A., Baggs, J., 2021. National Estimates of Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Hospitalized Patients in the United States. Clin. Infect. Dis. 72, S17–S26. https://doi.org/10.1093/cid/ciaa1581

NICE, 2019. Improving supportive and palliative care for adults with cancer: the manual. National Institute for Clinical Excellence, London.

NICE, 2015. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use.

Onatade, R., Sawieres, S., Veck, A., Smith, L., Gore, S., Al-Azeib, S., 2017. The incidence and severity of errors in pharmacist-written discharge medication orders. Int. J. Clin. Pharm. 39, 722–728. https://doi.org/10.1007/s11096-017-0468-9

O'Neill, J., 2016. TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS.

Osman, H., Shrestha, S., Temin, S., Ali, Z.V., Corvera, R.A., Ddungu, H.D., De Lima, L., Del Pilar Estevez-Diz, M., Ferris, F.D., Gafer, N., Gupta, H.K., Horton, S., Jacob, G., Jia, R., Lu, F.L., Mosoiu, D., Puchalski, C., Seigel, C., Soyannwo, O., Cleary, J.F., 2018. Palliative Care in the Global Setting: ASCO Resource-Stratified Practice Guideline. J. Glob. Oncol. 4, 1–24. https://doi.org/10.1200/JGO.18.00026

Patterson, T.F., Thompson, G.R., Denning, D.W., Fishman, J.A., Hadley, S., Herbrecht, R., Kontoyiannis, D.P., Marr, K.A., Morrison, V.A., Nguyen, M.H., Segal, B.H., Steinbach, W.J., Stevens, D.A., Walsh, T.J., Wingard, J.R., Young, J.-A.H., Bennett, J.E., 2016. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin. Infect. Dis. 63, e1–e60. https://doi.org/10.1093/cid/ciw326

Pedersen, C.A., Schneider, P.J., Scheckelhoff, D.J., 2017. ASHP national survey of pharmacy practice in hospital settings: Prescribing and transcribing—2016. Am. J. Health. Syst. Pharm. 74, 1336–1352. https://doi.org/10.2146/ajhp170228

Popescu, R.A., Roila, F., Arends, J., Metro, G., Lustberg, M., 2021a. Supportive Care: Low Cost, High Value. Am. Soc. Clin. Oncol. Educ. Book Am. Soc. Clin. Oncol. Annu. Meet. 41, 1–11. https://doi.org/10.1200/EDBK_320041

Popescu, R.A., Roila, F., Arends, J., Metro, G., Lustberg, M., 2021b. Supportive Care: Low Cost, High Value. Am. Soc. Clin. Oncol. Educ. Book 240–250. https://doi.org/10.1200/EDBK_320041

Popescu, R.A., Schäfer, R., Califano, R., Eckert, R., Coleman, R., Douillard, J.-Y., Cervantes, A., Casali, P.G., Sessa, C., Van Cutsem, E., de Vries, E., Pavlidis, N., Fumasoli, K., Wörmann, B., Samonigg, H., Cascinu, S., Cruz Hernández, J.J., Howard, A.J., Ciardiello, F., Stahel, R.A., Piccart, M., 2014. The current and future role of the medical oncologist in the professional care for cancer patients: a position paper by the European Society for Medical Oncology (ESMO). Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 25, 9–15.

https://doi.org/10.1093/annonc/mdt522

Qoronfleh, M.W., 2020. Pathway to excellence in cancer care: learning from Qatar's experience. Precis. Med. Sci. 9, 51–61. https://doi.org/10.1002/prm2.12027

Safdar, N., Abbo, L.M., Knobloch, M.J., Seo, S.K., 2016. Research Methods in Healthcare Epidemiology: Survey and Qualitative Research. Infect. Control Hosp. Epidemiol. 37, 1272–1277. https://doi.org/10.1017/ice.2016.171

Schneider, B.J., Naidoo, J., Santomasso, B.D., Lacchetti, C., Adkins, S., Anadkat, M., Atkins, M.B., Brassil, K.J., Caterino, J.M., Chau, I., Davies, M.J., Ernstoff, M.S., Fecher, L., Ghosh, M., Jaiyesimi, I., Mammen, J.S., Naing, A., Nastoupil, L.J., Phillips, T., Porter, L.D., Reichner, C.A., Seigel, C., Song, J.-M., Spira, A., Suarez-Almazor, M., Swami, U., Thompson, J.A., Vikas, P., Wang, Y., Weber, J.S., Funchain, P., Bollin, K., 2021. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J. Clin. Oncol. 39, 4073–4126. https://doi.org/10.1200/JCO.21.01440

Schurman, B., 2019. The Framework for FDA's Real-World Evidence Program. Appl. Clin. Trials Appl. Clin. Trials 28.

Seaton, R.A., Nathwani, D., Burton, P., McLaughlin, C., MacKenzie, A.R., Dundas, S., Ziglam, H., Gourlay, Y., Beard, K., Douglas, E., 2007. Point prevalence survey of antibiotic use in Scottish hospitals utilising the Glasgow Antimicrobial Audit Tool (GAAT). Int. J. Antimicrob. Agents 29, 693–699. https://doi.org/10.1016/j.ijantimicag.2006.10.020

Selby, P., Popescu, R., Lawler, M., Butcher, H., Costa, A., 2019. The Value and Future Developments of Multidisciplinary Team Cancer Care. Am. Soc. Clin. Oncol. Educ. Book Am. Soc. Clin. Oncol. Annu. Meet. 39, 332–340. https://doi.org/10.1200/EDBK_236857

Setia, M.S., 2016. Methodology Series Module 1: Cohort Studies. Indian J. Dermatol. 61, 21–25. https://doi.org/10.4103/0019-5154.174011

Sibbald, B., Roland, M., 1998. Understanding controlled trials: Why are randomised controlled trials important? BMJ 316, 201–201. https://doi.org/10.1136/bmj.316.7126.201

Snedecor, S.J., Carter, J.A., Kaura, S., Botteman, M.F., 2013. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A cost-effectiveness analysis. J. Med. Econ. 16, 19–29. https://doi.org/10.3111/13696998.2012.719054

Speroff, T., O'Connor, G.T., 2004. Study Designs for PDSA Quality Improvement Research: Qual. Manag. Health Care 13, 17–32. https://doi.org/10.1097/00019514-200401000-00002

Tang, M., Pearson, S.-A., Simes, R.J., Chua, B.H., 2023. Harnessing Real-World Evidence to Advance Cancer Research. Curr. Oncol. 30, 1844–1859. https://doi.org/10.3390/curroncol30020143

Tashakkori, A., Teddlie, C., 2021. Sage handbook of mixed methods in social & behavioral research.

Teillant, A., Gandra, S., Barter, D., Morgan, D.J., Laxminarayan, R., 2015. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. Lancet Infect. Dis. 15, 1429–1437. https://doi.org/10.1016/S1473-3099(15)00270-4

Tori, K., Tansarli, G.S., Parente, D.M., Kalligeros, M., Ziakas, P.D., Mylonakis, E., 2020. The cost-effectiveness of empirical antibiotic treatments for high-risk febrile neutropenic patients: A decision analytic model. Medicine (Baltimore) 99, e20022. https://doi.org/10.1097/MD.0000000000020022

Valgus, J., Jarr, S., Schwartz, R., Rice, M., Bernard, S.A., 2010. Pharmacist-Led, Interdisciplinary Model for Delivery of Supportive Care in the Ambulatory Cancer Clinic Setting. J. Oncol. Pract. 6, e1–e4. https://doi.org/10.1200/JOP.2010.000033

Vanessa Oliveira, 2021. EVALUATION OF THE MEDICATION CONCILIATION PROCESS IN A PEDIATRIC ONCOLOGY UNIT IN A UNIVERSITY HOSPITAL IN FRONT OF ASSISTANCE ADAPTATIONS IN THE PANDEMIC SCENARIO.

Williams, M.D., Braun, L., Cooper, L.M., Johnston, J., Weiss, R.V., Qualy, R.L., Linde-Zwirble, W., 2004. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. Crit. Care 8, R291. https://doi.org/10.1186/cc2893

Wong, J.D., Bajcar, J.M., Wong, G.G., Alibhai, S.M., Huh, J.-H., Cesta, A., Pond, G.R., Fernandes, O.A., 2008. Medication Reconciliation at Hospital Discharge: Evaluating Discrepancies. Ann. Pharmacother. 42, 1373–1379. https://doi.org/10.1345/aph.1L190

Younis G, 2022. Egyptian Guide for Oncology Pharmacy Practice, in: Egyptian Guide for Oncology Pharmacy Practice. Egyptian Drug Authority, Central Administration of Pharmaceutical Care, General Administration for Drug Utilization and Pharmacy Practice.

Zaidan, M., Singh, Wazaify, Tahaineh, 2011. Physicians’ perceptions, expectations, and experience with pharmacists at Hamad Medical Corporation in Qatar. J. Multidiscip. Healthc. 85. https://doi.org/10.2147/JMDH.S14326

Zarb, P., Amadeo, B., Muller, A., Drapier, N., Vankerckhoven, V., Davey, P., Goossens, H., on behalf of the ESAC-3 hospital care subproject group, Metz-Gercek, S., Jansens, H., Markova, B., Kontemeniotou, C., Andrasevic, A., Vlcek, J., Frimodt-Moller, N., Mitt, P., Lyytikainen, O., Bertrand, X., de With, K., Antoniadou, A., Ternak, G., Cunney, R., Raz, R., Brusaferro, S., Dumpis, U., Butkyte, V., Marcel, B., Zarb, P., Haug, J.B., Pawlowksa, J., Teixeira, I., Ratchina, S., Cizman, M., Sora, M., Skoog, G., Zanetti, G., Filius, M., Sardan, Y.C., Cooke, J., Webb, H., Davey, P., Heginbothom, M., 2011. Identification of targets for quality improvement in antimicrobial prescribing: the web-based ESAC Point Prevalence Survey 2009. J. Antimicrob. Chemother. 66, 443–449. https://doi.org/10.1093/jac/dkq430

Zhao, X., Xu, R., Wang, Y., Zhu, W., Hu, H., Shen, Z., Guo, C., Zhang, J., 2021. Impacts of Pharmacists-Managed Oncology Outpatient Clinic on Resolving Drug-Related Problems in Ambulatory Neoplasm Patients: A Prospective Study in China. Inq. J. Health Care Organ. Provis. Financ. 58, 004695802110096. https://doi.org/10.1177/00469580211009662

Zoledronic Acid Monograph, 2022.