RESEARCH REPORTS

Chemotherapy-Induced Opportunistic Infection Among Cancer Patients Treated in the Oncology Unit of the Main Tertiary Hospital in the Maldives

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ABSTRACT *This study aimed to determine the significant relationship between cytotoxic chemotherapy and opportunistic infections (OIs) in cancer patients. This cross-sectional study used census sampling to include 101 patients receiving chemotherapy at Indira Gandhi Memorial Hospital, Maldives, from 1 January 2022 to 30 November 2023. Data were analyzed using SPSS version 29, with Pearson's chi-squared test used to assess associations between OIs and clinical variables. No significant association was found with demographics or comorbidities. However, OIs were significantly associated with neutropenia, advanced cancer stage, combined chemotherapy increased number of cycles, prolonged treatment duration, and use of invasive devices. Neutropenia occurred in 42.57% (n=43) of patients, and 15.84% (n=16) developed OIs during the nadir period. Bacterial infections were most common, with Klebsiella pneumoniae being the predominant pathogen. Theses findings highlight the importance of monitoring immunosuppression, treatment intensity, and procedural risks to reduced OIs in patients undergoing chemotherapy.*

Keywords: Cancer, Chemotherapy, Opportunistic Infections, Neutropenia

Introduction

In the Maldives, cancer was classified as the third leading cause of non-communicable diseases (NCD)-related deaths in 2020 (Ministry of Health, Maldives, 2021). Despite advances in cancer treatment, non-cancer-related mortalities, such as infectious diseases, are on the rise (Yang et al., 2021). Approximately 60% of cancer-related deaths result from infections (Zheng et al., 2021). Several factors influence cancer patients' outcomes, including pre-existing immune deficiencies, comorbidities, past infections, malnutrition, stress, and the side effects of cancer treatments (such as chemotherapy, immunosuppressive drugs, and invasive procedures), rendering them susceptible to life-threatening infections (Zheng et al., 2021).

While chemotherapy has been known to improve cancer morbidity, chemotherapeutic drugs are also potential myelosuppressants, often leading to neutropenia. These adverse effects create conditions for opportunistic infections to complicate the clinical course of hospitalised cancer patients (Delgado & Guddati, 2021).

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To address the knowledge gap, this study retrospectively examines the frequency of OIs in cancer patients undergoing chemotherapy at IGMH from 1 January 2022 to 30 November 2023. For this study, OIs are defined as infections caused by bacteria, fungi, viruses, or parasites that typically do not cause disease but become pathogenic when the body's defence system is impaired (Centre for Disease Control and Prevention [CDC], n.d.). This study investigates infectious disease patterns among high-risk populations receiving chemotherapy.

This article explores the link between patient demographics, risk factors, cancer and chemotherapy details, and neutropenia with opportunistic infections. Insights from our cross-sectional study aim to identify associations between chemotherapy-induced neutropenia and opportunistic infections.

Literature review

Cancer patients undergoing chemotherapy and radiotherapy are highly susceptible to infections due to cytopenia, compromised immune systems, disruption of anatomic barriers, and exposure to nosocomial (hospital-acquired) pathogens as a result of both the disease and its treatments (Taur & Pamer, 2016). Opportunistic infections can significantly affect the clinical course of cancer patients (Da Silva & Casella, 2022).

Cytotoxic chemotherapy, a cornerstone in cancer treatment damages hematopoietic cells, often causing neutropenia and increasing the risk of opportunistic infections (Taur & Pamer, 2016). Neutropenia delays inflammatory responses, predisposing post-chemotherapy patients to bacterial, viral, and fungal infections. According to Da Silva & Casella (2022), the development of opportunistic infections is the most common cause of morbidity and mortality associated with chemotherapy. However, other literature, such as Fan et al. (2021), highlights chemotherapy-induced hepatotoxicity and cardiotoxicity as additional common causes of death in cancer patients (Da Silva & Casella, 2022; Fan et al., 2022).

A study published in 2019 revealed variations in the neutropenia patterns based on different chemotherapy regimens and their durations, highlighting their impact on infectious complications (Kawasaki et al., 2019). Okanuka et al. (2021) demonstrated that specific chemotherapy regimens, particularly those involving cytotoxic agents (e.g., cyclophosphamide, vinorelbine) and monoclonal antibodies (e.g., bevacizumab, trastuzumab) in combination with cytotoxic agents, significantly increase the likelihood of opportunistic infections due to their strong association with conditions such as neutropenia and granulocytopenia.

In addition to particular chemotherapy agents and treatment duration, neutropenia can be influenced by the concurrent administration of immunotherapy or radiotherapy (Vaillant, 2022). A 2014 study by Nissen et al. found significantly higher infectious complications in haematological cancer patients receiving a combination of rituximab (immunotherapeutic agent) and chemotherapy compared to rituximab monotherapy ($p < 0.001$) (Nissen et al., 2014). Conversely, a 2020 study by Liu et al. (2020) indicated an increased risk of opportunistic infections with immunotherapy alone (Liu et al., 2020). A study on oral cancer patients before and after radiotherapy by Anjali et al. (2020), highlighted that head and neck radiotherapy disrupts oral microbiota, making patients more susceptible

to drug-resistant opportunistic infections (Anjali et al., 2020). Terrones-Campos et al. (2022) conducted a study on patients with solid tumours, revealing that the severity of neutropenia was higher in those receiving both chemotherapy and radiotherapy, with infections occurring more frequently in this subset of patients (Terrones-Campos et al., 2022).

Neutrophils, the most abundant leukocytes, are vital for innate immunity (Alshamamari, 2019). Neutropenia defined by an ANC below $<2000 \times 10^6$, can result from certain chemotherapies, bone marrow cancers, metastatic cancer, and radiotherapy (Sapkota et al., 2020; Neutropenia, 2023). Neutropenia is graded as: grade 1 (1500-2000/mm3), grade 2 (1000-1499/mm3), grade 3 (500-999/mm3), and grade 4 (<500/mm3) (<500) (Sapkota et al., 2020) The timing of neutrophil decline is linked to chemotherapy administration, reaching its lowest point (nadir) between 7 and 14 days post-treatment, marking the highest infection risk. Neutrophil production typically resumes within 3 to 4 weeks (Neutropenia, 2023; Barbor, 2015).

Several studies on cancer patients have identified common bacterial agents (Escherichia coli, Pseudomonas aeruginosa, Klebsiella spp., Staphylococcus spp., and Streptococcus spp.), and highlighted viral associations, particularly with herpes simplex, varicella zoster, and respiratory viruses, among others (Badr et al., 2016; Islas-Muñoz et al., 2018; Lubwama et al., 2019; Marchetti et al., 2017). These studies noted that viral infections are often underreported due to the need for molecular diagnostic techniques (Badr et al., 2016; Islas-Muñoz et al., 2018; Lubwama et al., 2019; Marchetti et al., 2017). Additionally, Candida spp. and Aspergillus spp. were identified as the most common fungal pathogens in cancer patients (Singh et al., 2017).

Nissen et al. (2014) found no statistically significant association between age, comorbidities, and infectious complications in haematological cancer patients receiving chemotherapy and Rituximab ($p > 0.69$) (Nissen et al., 2014). However, Brahmer et al., (2011) reported a tendency for females to experience a higher incidence of grade 5 neutropenia or neutropenia-induced infections compared to males.

Beyond comorbidities, additional risk factors contribute to the likelihood of opportunistic infections. José and Brown (2012) found that undergoing surgery after chemotherapy initiation increases the risk of opportunistic infections in immunocompromised patients. Furthermore, invasive devices, such as tunnelled central venous catheters in adult cancer patients, have been linked to serious bloodstream infections, with neutropenia further increasing the risk of infection (Howell et al., 1995). Thai et al. (2012) reported that patients with advanced cancer are more susceptible to infections, which contributes to higher mortality rates (Thai et al., 2012). This finding aligns with Bertești eanu et al. (2020), who observed that patients with advanced-stage oral and pharyngeal cancer are more susceptible to HPV infections (Bertești eanu et al.'s, 2020).

Objectives and Hypothesis

Our general objective is to determine whether there is a significant relationship between cancer chemotherapy and opportunistic infections. The specific objectives

of this study are to identify the occurrence of OIs in cancer patients receiving chemotherapy at IGMH, investigate the association between OIs and various factors such as patient demographics (age at diagnosis, sex), cancer stage, and risk factors (comorbidities, surgical history post-initiation of chemotherapy, and use of invasive devices), and explore the impact of chemotherapy variables (type, regimen, duration) on the development of OIs. Additionally, the study aims to determine whether neutropenia is significantly associated with OIs in these patients.

The primary focus of this investigation is on the associations between chemotherapy-related factors, risk factors, and neutropenia, with each hypothesis undergoing thorough testing to provide valuable insights into the complex relationships among these variables within the context of cancer treatment.

Materials and Methods

Records of cancer patients who were treated with chemotherapy at IGMH during the period 1 January 2022 to 30 November 2023 were reviewed and evaluated in this cross-sectional study using secondary data from IGMH. The study utilised a census sampling methodology. The inclusion criteria for this study included cancer patients registered at IGMH in the stated study duration, and patients receiving or received at least one cycle of chemotherapy in IGMH during this period. The exclusion criteria included patients who received chemotherapy outside of IGMH. A total of 101 patients met the inclusion criteria for our study.

Data collection commenced after obtaining written permission from IGMH, NHRC, NHA, and the MNU Research Ethics Committee. Secondary data from HINAI, accessed through IGMH medical records, was entered into an access-restricted Google Sheet with reversible anonymisation so that only researchers could re-link the data with the corresponding numerical value. Patient details, including medical history, treatments, and lab results, were input manually. The data collection period spanned from 30 November 2023 to 10 December 2023.

The researchers input HINAI data into a Google Sheet, cross-checked it twice for consistency, and then exported the numerical data to SPSS version 29.0 for analysis.

Pearson's Chi-square tests of independence were conducted between opportunistic infections and the variables (comorbidities, surgical history after starting chemotherapy, invasive devices, and neutropenia). Fisher-Freeman-Halton Exact tests assessed the relationship between opportunistic infections and the variables (age at diagnosis, sex, cancer stage, chemotherapeutic regimen, and duration).

Results

Descriptive Results

Following the inclusion and exclusion criteria, a total of 101 cancer patients who received chemotherapy at IGMH from 1 January 2022, to 30 November 2023 were included in the study. The age of the selected patients ranged from age 5 to 80 (mean age: 53), with the majority falling within the 35-65 age category (Table 1.1). Of the available population, 72.27% (n = 73) were female. Breast cancer was the most commonly occurring cancer, at 46.53% (n = 47), followed closely

by haematological cancers at 12.87% (n = 13) and lung cancer 11.88% (n = 12). The predominant stage of cancer present throughout was noted to be stage 4, at 38.61% (n = 39).

Providing insight into patients' risk factors, 53.47% (n = 54) of patients had a comorbidity, while 31.68% (n = 32) had a history of surgery post-initiation of chemotherapy, and 37.62% (n = 38) had invasive devices in situ after starting chemotherapy. Further details of comorbidities are provided in Supplementary Table 3.1.

On average, chemotherapy lasted over four months, with the majority (56.44%, n = 57) spanning between three to six months. A total of 74.26% (n = 75) patients received combined chemotherapy during their treatment, while 21.78% (n = 22) received monotherapy, and the remaining 3.96% (n = 4) received multiple lines of therapy. The most frequently administered combined chemotherapy regimen was found to be mitotic inhibitors with alkylating agents at 36.71% (n = 29), whilst mitotic inhibitors were the prevalent drug type for monotherapy at 42.31% (n = 11) (Table 1.1). Overall, 89.11% (n = 90) of patients were prescribed G-CSF and 38.61% (n = 39) received immunotherapy alongside their chemotherapy regimen.

Among the available 47 nadir periods, 36.17% (n = 17) showed neutropenia. A significant finding was that 42.57% (n = 43) of cancer patients had recorded neutropenia during the course of treatment. Further details of average ANC values prior to and post-cycle, during nadir for consecutive cycles, are shown in Supplementary Table 3.1. Furthermore, trends in ANC values over chemotherapy duration are shown in Figure 1.3, which illustrates a declining trend of these values throughout chemotherapy.

Table 1.1. Demographic Characteristics, risk factors, details of chemotherapy, admissions and neutropenia of cancer patients that received chemotherapy in IGMH from 2022 to 2023

Demographic variables		**Frequency (N)**	**Percentage (%)**
Age	Under 35	6	5.94
	35-65	76	75.25
	Over 65	19	18.81
Sex	Male	28	28.00
	Female	73	72.00
Type of cancer	Breast	47	46.53
	Hematological	13	12.87
	Lung	12	11.88
	Reproductive	11	10.89
	Other[1]	18	17.82
Stage of cancer	1	8	7.92
	2	25	24.75
	3	29	28.71
	4	39	38.61

Risk factors			
Comorbidities	Yes	54	53.47
	No	47	46.53
Surgical history post chemotherapy	Yes	32	31.68
	No	69	68.32
≥1 invasive device post chemotherapy	Yes	38	37.62
	No	63	62.38
Details of chemotherapy			
Treatment followed	Chemotherapy only	74	73.27
	Concurrent chemoradiotherapy	27	26.73
	Combined	75	74.26
Type of chemotherapy regimen	Monotherapy	22	21.78
	Combined + Monotherapy	4	3.96
Duration of chemotherapy (months)	< 3	28	27.72
	3 – 6	57	56.44
	6 – 9	14	13.86
	9 – 12	1	0.99
	> 12	1	0.99
Chemotherapy cycles	< 5	52	51.50
	5 to 10	41	40.60
	> 10	8	7.90
Drug regimen followed (combined therapy)	Mitotic inhibitor + Alkylating agent	29	36.71
	Anti-tumor antibiotic + Mitotic inhibitor + Alkylating agent	23	29.11
	Antimetabolite + Alkylating agent	11	13.92
	Others[2]	16	20.25
Drug regimen followed (monotherapy)	Mitotic inhibitor	11	42.31
	Alkylating agent	3	11.54
	Antimetabolite	5	19.23
	Others[3]	7	26.92
Immunotherapy	Yes	95	94.06
	No	6	5.94
Details of neutropenia			
Admissions that match nadir period (n=36)	Yes	20	55.56
	No	16	44.44

Neutropenia during chemotherapy duration	Yes	43	42.57
	No	58	57.43
≥ 1 episode of neutropenia	Yes	23	53.49
	No	20	46.51
Neutropenia grading in chemotherapy duration (n = 101)	Grade 0	66	65.35
	Grade 1	11	10.89
	Grade 2	8	7.92
	Grade 3	7	6.93
	Grade 4	9	8.91
Neutropenia during nadir (n=47)	Yes	17	36.17
	No	30	63.83

[1]*Others include: Head and neck cancer (6), Gastrointestinal cancer (6), Endocrine cancer (3), Malignant neoplasm of connective and soft tissue (2), bladder cancer (1)*
[2]*Includes; Antimetabolite + Mitotic inhibitor (4), Anti-tumor antibiotic + Alkylating agent (3), Anti-tumor antibiotic + Mitotic inhibitor + Alkylating agent + Topoisomerase inhibitor (2), Alkylating agent + Topoisomerase inhibitor (2), Anti-tumor antibiotic + Mitotic inhibitor + Alkylating agent + Antimetabolite (1), Mitotic inhibitor + Alkylating agent + Topoisomerase inhibitor (1), Antimetabolite + Mitotic inhibitor + Alkylating agent (1), Antimetabolite + Mitotic inhibitor + Anti-tumor antibiotic (1), Anti-tumor antibiotic + Alkylating agent + Topoisomerase inhibitor (1)*
[3]*Bortezomib, Eribulin, Ado-trastuzumab emtansine*

A notable finding of the study is the incidence of opportunistic infections in 15.84% (n = 16) of the patient population. A total of 77 culture tests were conducted, with 27.27% (n = 21) yielding positive results. It is important to note that one patient may have multiple positive culture results involving different organisms. Thirty different organisms were identified, with bacterial infections being the most prevalent at 68.57% (n = 24), followed by fungal and viral infections at 14.29% (n = 5) and 8.57% (n = 3), respectively. Genitourinary system infections were the most common, occurring in 36.36% (n = 8) cases, followed closely by respiratory system infections at 31.82% (n = 7). Overall, the most frequently identified organism causing opportunistic infections was Klebsiella pneumoniae, accounting for 21.21% (n = 7) of cases (Table 1.2). Supplementary table 3.1 depicts the sites of detection of the infectious organisms.

Table 1.2. Opportunistic infections

Variables		**Frequency (N)**	**Percentage (%)**
Cultures done	Yes	31	30.69
	No	70	69.31
Positive culture results (N=77)[1]	Yes	21	27.27
	No	56	72.73
Opportunistic infection (n = 101)	Yes	16	15.84
	No	85	84.16

Type of infection	Bacterial	24	68.57
	Fungal[2]	5	14.29
	Viral	3	8.57
	Mixed growth	3	8.57
Type of organism and infection			
Bacterial	Klebsiella pneumoniae	7	21.21
	Pseudomonas aeruginosa	5	15.15
	E. coli	3	9.09
	Staphylococcus aureus	3	9.09
	Moraxella catarrhalis	1	3.03
	Acinetobacter baumannii	1	3.03
	Coagulase negative staphylococcus	1	3.03
	Burkholderia cepacia	1	3.03
	Morganella morganii	1	3.03
	Enterobacter cloacae	1	3.03
Virus	Human Metapneumovirus	1	3.03
	Herpes Zoster[3]	1	3.03
	Human Rhinovirus	1	3.03
Fungal	Candida albicans	2	6.06
	Candida tropicalis	1	3.03
Mixed growth		3	9.09
System affected	Genitourinary	8	36.36
	Respiratory	7	31.82
	Gastrointestinal	4	18.18
	Skin	2	9.09
	Hematological	1	4.55

[1]Number of overall cultures done for 101 patients is 77, 2Includes 2 clinically diagnosed fungal infections,

[3]Clinical diagnosis was considered

Figure 1.3. Trends of mean absolute neutrophil count (ANC) across chemotherapy duration for cancer patients receiving chemotherapy at IGMH

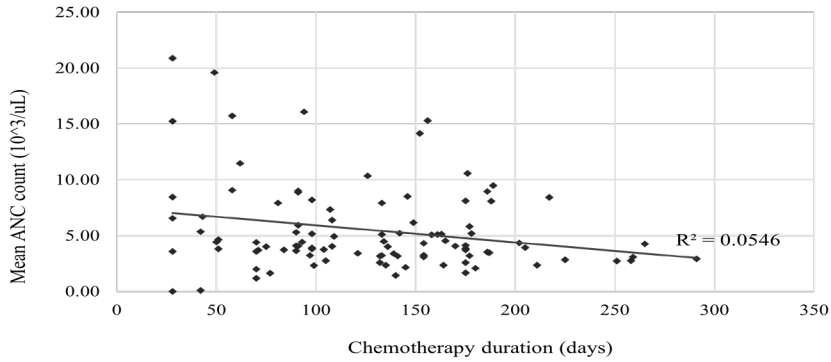

Figure 1.4. Trends of mean absolute neutrophil count (ANC) values before and after chemotherapy cycles during nadir period

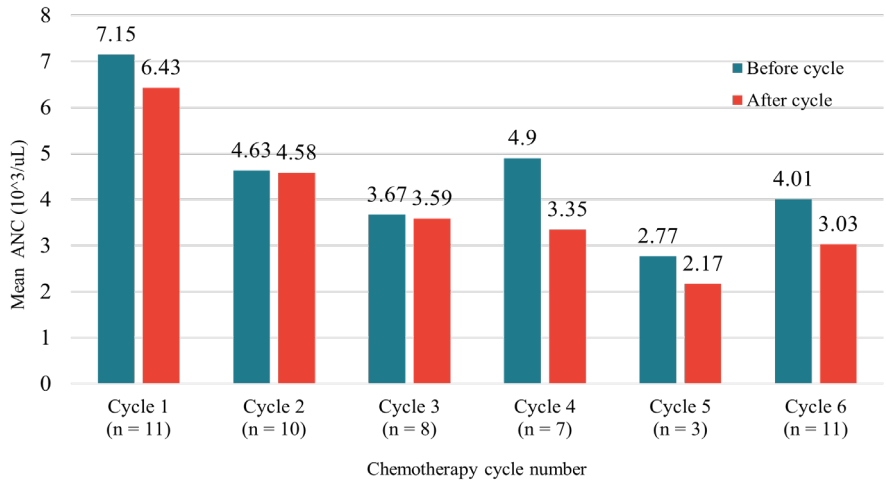

Table 2.1. Pearson Chi-square analysis in relation to opportunistic infections, neutropenia and neutropenia grading

Age at diagnosis and opportunistic infections							
Variable		Total	Opportunistic infection				p-value
			No		Yes		
			(n)	(%)	(n)	(%)	
Age at diagnosis (years)	< 35	6	5	83.33	1	16.67	0.103*
	35 to 65	76	67	88.16	9	11.84	
	> 65	19	13	68.42	6	31.58	
Total		101	85	84.16	16	15.84	
Sex and opportunistic infections							
Sex	M	28	22	78.57	6	21.43	0.369*
	F	73	63	86.30	10	13.70	
Total		101	85	84.16	16	19.01	
Stage of cancer and opportunistic infections							

Stage of cancer	1	8	8	100.00	0	0.00	0.009*
	2	25	25	100.00	0	0.00	
	3	29	24	82.76	5	17.24	
	4	39	28	71.79	11	28.21	
Total		101	85	84.16	16	15.84	
Comorbidities and opportunistic infections							
Comorbidities	No	47	42	89.36	5	10.64	0.275
	Yes	54	43	79.63	11	20.37	
Total		101	85	84.16	16	15.84	
Surgical history post-initiation of chemotherapy opportunistic infections							
Surgical history post-initiation of chemotherapy	No	69	58	84.06	11	15.94	1.000
	Yes	32	27	84.38	5	15.63	
Total		101	85	84.16	16	15.84	
Invasive devices and opportunistic infections							
Invasive devices	No	63	57	90.48	6	9.52	0.046
	Yes	38	28	73.68	10	26.32	
Total		101	85	84.16	16	15.84	
Treatment followed and opportunistic infections							
Treatment followed	Chemo-therapy	74	58	78.38	16	21.62	0.005*
	CCRT	27	27	100.00	0	0.00	
Total		101	85		16		
Line of Chemotherapy and opportunistic infections							
Line of Chemotherapy	Combined	75	67	89.33	8	10.67	0.022*
	Monotherapy	22	14	63.64	8	36.36	
	Multiple line therapy	4	4	100.00	0	0.00	
Total		101	85		16		

Combined drug regimen and opportunistic infections							
Combined drug regimen	Mitotic inhibitor + Alkylating agent	29	25	86.21	4	13.79	0.664*
	Anti-tumor antibiotic + Mitotic inhibitor + Alkylating agent	24	23	95.83	1	4.17	
	Anti-metabolite + Alkylating agent	12	11	91.67	1	8.33	
	Other	14	12	85.71	2	14.29	
Total		79	71		8		
Monotherapy drug regimen and opportunistic infections							
Monotherapy drug regimen	Mitotic inhibitor	10	7	70.00	3	30.00	0.862*
	Anti-metabolite	5	3	60.00	2	40.00	
	Alkylating agent	3	2	66.67	1	33.33	
	Other	7	6	85.71	1	14.29	
Total		25	18		7		
Chemotherapy duration and opportunistic infections							
Duration of chemotherapy (months)	< 3	28	22	78.57	6	21.43	0.042*
	3 to 6	57	52	91.23	5	8.77	
	6 to 9	14	10	71.43	4	28.57	
	9 to 12	1	1	100.00	0	0.00	
	12 to 15	1	0	0.00	1	100.00	
Total		101	85	84.16	16	15.84	
Chemotherapy cycles and opportunistic infections							

Cycles of chemotherapy	< 5	52	43	82.69	9	17.31	0.011
	5 to 10	41	38	92.68	3	7.32	
	> 10	8	4	50.00	4	50.00	
Total		101	85		16		
Neutropenia and opportunistic infections							
Neutropenia	No	58	53	91.38	5	8.62	0.028
	Yes	43	32	74.42	11	25.58	
Total		101	85	84.16	16	15.84	
Neutropenia grading and opportunistic infections							
Neutropenia grading	0	58	53	91.38	5	8.62	0.015*
	1	11	10	90.91	1	9.09	
	2	13	9	69.23	4	30.77	
	3	8	7	87.50	1	12.50	
	4	11	6	54.55	5	45.45	
Total		101	85	84.16	16	15.84	
Immunotherapy and opportunistic infections							
Immuno-therapy	No	62	51	82.26	11	17.74	0.586
	Yes	39	34	87.18	5	12.82	
Total		101	85	84.16	16	15.84	
G-CSF and opportunistic infections							
G-CSF	No	11	10	90.91	1	9.09	1.000*
	Yes	90	75	83.33	15	16.67	
Total		101	85	84.16	16	15.84	
G-CSF and opportunistic infections							
G-CSF agent Total	Filgrastim	55	48	87.27	7	12.73	0.156*
	Pegfilgrastim	27	22	81.48	5	18.52	
	Filgrastim + Pegfilgrastim	8	5	62.50	3	37.50	
Total		90	75	83.33	15	16.67	

G-CSF and neutropenia

Variable		Total	Neutropenia				p-value
			No		Yes		
			(n)	(%)	(n)	(%)	
G-CSF	No	11	10	90.91	1	9.09	0.022*
	Yes	90	48	53.33	42	46.67	
Total		101	58	57.43	43	42.57	

Line of chemotherapy and neutropenia

Line of Chemotherapy	Combined	75	43	57.33	32	42.67	0.037*
	Monotherapy	22	15	68.18	7	31.82	
	Multiple line therapy	4	0	0.00	4	100.00	
Total		101	58	57.43	43	42.57	

Current chemotherapy and neutropenia grading

Variable		Total	Neutropenia grading								p-value
			1		2		3		4		
			n	%	n	%	n	%	n	%	
Current therapy	Chemo-therapy	74	3	4.05	11	14.86	7	9.46	10	13.51	0.007*
	CCRT	27	8	29.63	2	7.41	1	3.70	1	3.70	
Total		101	11	10.89	13	12.87	8	7.92	11	10.89	

Line of chemotherapy and neutropenia grading

Line of Chemo-therapy	Combined	75	10	13.33	7	9.33	7	9.33	8	10.67	0.042*
	Mono-therapy	22	0	0.00	4	18.18	1	4.55	2	9.09	
	Multiple line therapy	4	1	25.00	2	50.00	0	0.00	1	25.00	
Total		101	11	10.89	13	12.87	8	7.92	11	10.89	
Chemotherapy duration and neutropenia grading											
Duration of chemo-therapy (months)	< 3	28	1	3.57	3	10.71	0	0.00	8	28.57	0.010*
	3 to 6	56	6	10.71	7	12.50	7	12.50	2	3.57	
	6 to 9	15	3	20.00	2	13.33	1	6.67	1	6.67	
	9 to 12	1	1	100.00	0	0.00	0	0.00	0	0.00	
	12 to 15	1	0	0.00	1	100.00	0	0.00	0	0.00	
Total		101	11	10.89	13	12.87	8	7.92	11	10.89	

** = Fisher's Exact Test, CCRT = Concurrent chemoradiotherapy, Other[1] = gastrointestinal, head and neck, etc. Other[2] = Anti-tumor antibiotic + Alkylating agent, Anti-metabolite + Mitotic inhibitor, etc. Other[3] = Bortezomib, Ado-trastuzumab emtansine, etc.*

A Chi-square with the Fisher-Freeman-Halton Exact test was conducted to examine the relationship between opportunistic infections where a significant association, where a significant association was observed with the following variables: stage of cancer (p = 0.009), treatment received (p = 0.005), line of chemotherapy (p = 0.022), duration of chemotherapy (p = 0.042), and neutropenia grading (p = 0.015). Additionally, a significant association was found between neutropenia and the variables G-CSF (p = 0.022) and line of chemotherapy (p = 0.037). Furthermore, a significant association was observed between neutropenia grading and the variables: current therapy (p = 0.007), line of chemotherapy (p = 0.042), and chemotherapy duration (p = 0.010). However, no significant association was found between opportunistic infections and the variables age at diagnosis (p = 0.103), sex (p = 0.369), combined drug regimen (p = 0.664), monotherapy drug regimen (p = 0.862), G-CSF (p = 1.000), and G-CSF agents (p=0.156) (Table 2.1).

A Pearson Chi-square test of independence was conducted to examine the relationship between opportunistic infections, where a significant association was observed with the variables invasive devices (χ^2 = 5.013, df = 1, p = 0.046), cycles of chemotherapy (χ^2 = 9.320, df = 2, p = 0.011), and neutropenia (χ^2 = 5.328, df = 1, p = 0.028). However, no significant association was found between opportunistic infections and the variables comorbidities (χ^2 = 1.785, df = 1, p = 0.275), surgical history after starting chemotherapy (χ^2 = 0.002, df = 1, p = 1.000), or immunotherapy (χ^2 = 0.435, df = 1, p = 0.586).

Discussion

The present study revealed that 42.57% (n = 43) of 101 patients experienced neutropenia during chemotherapy treatment, and 15.84% (n = 16) had OIs. Additionally, our study demonstrated that a declining trend in mean absolute neutrophil count (ANC) values as chemotherapy progresses (Figure 1.3). Similar findings were reported by Ramon-Lopez et al. (2009), who also observed a decrease in ANC levels throughout chemotherapy in breast cancer patients

Mean ANC values before and after chemotherapy cycles (during nadir) were also evaluated, showing that ANC values during the nadir post-cycle were lower than pre-cycle values (Figure 1.4). This aligns with the findings of Anazoeze et al., (2015), who reported a statistically significant drop in mean ANC value post-chemotherapy compared to pre-chemotherapy values. Several established studies, such as Taur and Pamer (2016), Hoggatt et al. (2015), and Da Silva & Casella (2022), highlight the association between neutropenia and opportunistic infections as a significant complication of chemotherapy. Our study of 101 patients revealed a similar significance between these variables ($p = 0.028$)

Okera et al. (2010) study, studying patients with solid tumours, reported that 50% of all neutropenia episodes occurred at or near the initiation of chemotherapy cycles 1 and 2 (Okera et al., 2010). Similarly, Rahman et al. (1997) found that the risk of neutropenia-induced infection was significantly higher during the initial courses of chemotherapy in metastatic breast carcinoma patients. Our findings align with these studies, demonstrating a noteworthy negative association between the neutropenia severity and chemotherapy duration. Severe neutropenia (grade 4) was observed in 72.73% (n = 8) of cases within the early months (< 3 months) of chemotherapy. This explains the inverse significance observed between chemotherapy duration ($p = 0.042$) and number of cycles ($p = 0.011$) with opportunistic infections (Table 2.1). Figure 3.2 in supplementary material highlights the distribution of neutropenia and opportunistic infection incidence throughout chemotherapy cycles, showing that opportunistic infections are more prevalent at the commencement of the chemotherapy cycles, aligning with the time frame highlighted by Okera et. al (Okera et al., 2010).

Yang and Kido (2011) stated that pegfilgrastim, a sustained-duration form of filgrastim, leads to a dose-dependent increase in neutrophils, with its elimination rate decreasing at higher doses. In our study, 54.46% (n = 55) and 26.73% (n = 27) of patients received filgrastim and pegfilgrastim, respectively. Our results align with Yang & Kid (2011), as pegfilgrastim contributed to 17.58% fewer neutropenia episodes than filgrastim. Additionally, our study found a significant inverse association between G-CSF use (89.11%, n = 90) and neutropenia ($p = 0.022$), with 58.33% (n = 48) of G-CSF patients not developing neutropenia. However, no significant association was observed between G-CSF and opportunistic infections ($p=1.000$), contradicting Bohlius et al. (2003), who reported a reduced relative risk of neutropenia and infection with G-CSF. Among G-CSF recipients (n = 90), 83.33% (n = 75) did not develop opportunistic infections. The lack of significance in the findings may be attributed to early diagnosis and treatment by clinicians to achieve favourable clinical outcomes.

Conversely, our research did not find a significant association between the

patients receiving immunotherapy 38.61% (n = 39) and opportunistic infections (p = 0.586) (Table 2.1). This contradicts Liu et al. (2020), who reported an increased risk of opportunistic infections with immunotherapy. A possible explanation is the high percentage of patients receiving G-CSF (n = 90), which stimulates neutrophil production, thereby reducing occurrence of chemotherapy-induced neutropenia and opportunistic infections (Bendall & Bradstock, 2014). Future research should explore the correlations between immunotherapy dosage, antibiotic use, and steroid therapy with neutropenia and opportunistic infections.

Our study identified the genitourinary (36.36%, n = 8) and respiratory (31.82%, n = 7) systems as the most affected by infection. This aligns with Nesher and Rolston (2014) and Mohammed et al. (2014), who reported that respiratory and urinary tract infections are predominant among opportunistic infections. Of 77 positive cultures, bacterial and fungal infections accounted for 68.57% (n = 24) and 14.29% (n = 5), respectively, consistent with Zembower (2014). Klebsiella pneumoniae was the most prevalent pathogen (21.21%, n = 7), in line with Santos et al. (2020), who reported its significance in cancer patients undergoing chemotherapy.

Bertești eanu et al. (2020) reported an association between advanced-stage oral and pharyngeal cancers and increased HPV infection, corroborating our observed significant association between cancer stage and opportunistic infections (p = 0.009) (Table 2.1) (Bertești eanu et al., 2020). Among the 16 OIs patients in our study, 68.80% (n = 11) were in stage 4 cancer.

Okunaka et al. (2021) analysed 48 chemotherapeutic drugs and found that certain regimens significantly increase the risk of OIs. Cluster analysis grouped these drugs into two categories: one strongly linked to conditions such as febrile neutropenia and neutropenic sepsis, which increase infection risk. Principal component analysis revealed that cytotoxic agents (e.g., alkylating agents, antineoplastic antibiotics, and platinating agents) were closely associated with infections following neutropenia. In contrast, protein kinase inhibitors and monoclonal antibodies showed distinct neutropenia-related side effects.

However, in our study we found no significant association between OIs and the specific drug regimens used in monotherapy (n = 25, p = 0.862) or combination therapy (n = 79, p = 0.664). A significant difference was observed between the outcomes of monotherapy and combination therapy (p = 0.022) (Table 2.1). A possible factor that may account for the divergence in results is that, among the 101 patients in our study, specific regimens were being utilised by only a small subset of individuals, with as few as one or two patients per drug regimen. This could have decreased the likelihood of identifying a significant association between drug regimen and opportunistic infection.

A notable association was also found between the line of chemotherapy (combined, monotherapy, or multiple-line therapy) and the severity of neutropenia (p = 0.042) (Table 2.1). Out of the 11 patients who had severe neutropenia (grade 4), 72.72% (n = 8) were receiving combination therapy. This finding is supported by the evidence presented by Lalami et al. (2006), which showed that patients taking combination therapies such as CAE (cyclophosphamide, doxorubicin, etoposide) experienced higher grades of neutropenia.

Treatment duration and concurrent radiotherapy can also impact outcomes. In a study by Anjali et al. (2020), oral cancer patients undergoing CCRT faced disrupted oral microbiota, heightening their vulnerability to drug-resistant opportunistic infections. This contrasts with our findings, which revealed a significant difference in opportunistic infections between the CCRT (26.73%, n = 27) and chemotherapy alone groups (73.27%, n = 74) (p=0.005). Of the 15.84% (n = 16) patients who had opportunistic infections, all of them exclusively underwent chemotherapy alone; none in the CCRT group had such infections. The observed discrepancy may stem from the limited number of patients undergoing CCRT in our study (26.73%, n = 27) (Table 2.1).

In examining the interplay between opportunistic infections, patient demographics, and treatment-related complications in cancer patients undergoing chemotherapy, our study delves into several key factors. There was no significant association between opportunistic infections and age at diagnosis (p = 0.103) or comorbidities (p = 0.275). This aligns with Nissen et al. (2014), who demonstrated a lack of statistically significant association between age, comorbidities, and infectious complications in haematological cancer patients receiving chemotherapy. Similarly, Rahman et al. (1997) found no association between age and chemotherapy-induced infections in patients with metastatic breast carcinoma receiving salvage chemotherapy. Additionally, our study did not observe a significant association between sex and opportunistic infections (p=0.369). Dessaleng et al. (2023) found no association between sex and the occurrence of neutropenia, from which it is plausible to infer that there would be no significance with opportunistic infections either.

Apart from comorbidities, additional risk factors such as surgery after initiation of chemotherapy and the use of invasive devices were also investigated. A significant association was not found between surgical history after initiation of chemotherapy and opportunistic infections (p = 1.000). Our findings do not align with those of José and Brown (2012), who found that surgery after chemotherapy initiation increases the risk of opportunistic infection in immunocompromised patients. A plausible reason for the discrepancy in our findings is the routine administration of postoperative prophylactic antibiotics, as noted by Callender (1999), who found that sulbactam-ampicillin reduces postoperative infection rates in head and neck cancer surgery patients. Another risk factor that was examined was the use of invasive devices, which showed that out of the 16 patients who had opportunistic infections, 62.50% (n = 10) had invasive devices. Upon closer examination of the relationship between opportunistic infection and the utilisation of invasive devices, a significant association was identified (p = 0.046) (Table 2.1). This finding aligns with Howell et al. (1995), who highlighted that invasive devices, such as central venous catheters, further elevate the risk of infection.

In IGMH, enhanced patient care is achieved through consistent follow-ups, administration of prophylactic antibiotics, G-CSFs administration, and immunotherapy when required. Chemotherapy administration is paused upon detection of neutropenia, resuming only after its correction. Future research could be improved by enhancing the standards of laboratory testing, cultures, and molecular testing to detect viral infections in the Maldives.

Conclusion

This study supports the significance of chemotherapy-induced neutropenia and opportunistic infections. It was found that severe neutropenia and opportunistic infections were more prevalent in early chemotherapy cycles and duration, suggesting enhanced monitoring during this period. Advanced-stage cancer, combination chemotherapy, and invasive devices further increased opportunistic infection risk. Notably, infections were more common in chemotherapy-only patients than those receiving CCRT. Future research should explore the impact of radiotherapy on neutropenia and opportunistic infections. Limitations of this study include a limited sample (from 2022 to 2023), potentially reducing broader applicability.

Additionally, the unavailability of diagnostic tools for a wider range of viral pathogens could impact research outcomes. Future studies should expand sample sizes and incorporate advanced diagnostics to enhance reliability.

Conflict of interest

The authors affirm that the study was carried out without any commercial or financial ties that could be perceived as a potential conflict of interest.

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