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Neurotoxicity associated with cancer chemotherapy: the first study in the Palestinian healthcare system

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Abstract

Background Chemotherapy-induced neurotoxicity is a significant concern in cancer treatment as it adversely affects treatment outcomes. However, research on this subject within the Palestinian healthcare system is limited. This study aimed to evaluate the prevalence, clinical manifestations, and associated factors of neurotoxicity in cancer patients receiving chemotherapy in Palestine.

Methods This retrospective cohort study included 196 cancer patients who underwent chemotherapy at multiple hospitals across Palestine. Data on patient demographics, cancer characteristics, chemotherapy regimens, and neurotoxicity symptoms were extracted from electronic medical records. Neurotoxicity was evaluated using a comprehensive 65-item functional neurotoxicity scale.

Results A total of 196 cancer patients were included in the study. The median age was 56.9 years, with the majority being female (113 out of 196; 57.7%) and diagnosed with solid cancers (140 out of 196; 71.4%). The most common agents utilized were fluorouracil/5-FU (108 patients; 55.1%) and oxaliplatin (96 patients; 49.0%). Neurotoxicity symptoms were highly prevalent, with 119 patients (60.7%) experiencing moderate neurotoxicity and 47 patients (24.0%) experiencing severe neurotoxicity. The severity of neurotoxicity was significantly associated with female sex (p-value = 0.032) and a diagnosis of solid cancer (p-value = 0.015), while patients exhibiting neurotoxicity were also significantly older (p-value = 0.045) and received a larger number of chemotherapy cycles (p-value = 0.037).

Conclusion This study highlights the significant prevalence of chemotherapy-induced neurotoxicity among cancer patients in Palestine and underscores the need for personalized treatment approaches and proactive symptom management strategies. Multidisciplinary collaboration among healthcare providers, researchers, and policymakers is essential to develop comprehensive guidelines and interventions aimed at optimizing patient outcomes. Furthermore, additional research is warranted to explore the long-term impact of neurotoxicity and to evaluate the effectiveness of supportive care interventions in this population.

Keywords Neurotoxicity, Chemotherapy, Cancer, Patient care, Palestine

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Background

Cancer has emerged as a major global public health challenge and remains the second leading cause of death worldwide [1]. In Palestine, cancer imposes a significant health burden, with recent statistics from the West Bank and Gaza Strip reporting 5,030 new cases and 3,011 deaths in 2022 [2–4]. This disparity between global data and local evidence underscores a critical need for research that directly addresses the unique challenges faced in Palestinian healthcare.

Multiple treatment modalities, including surgery, chemotherapy, and radiotherapy, are commonly employed in cancer management [5–7]. The choice of therapy is influenced by factors such as cancer type, disease stage, and patient health status, all of which can affect treatment outcomes and the incidence of adverse effects. Among these, chemotherapy-induced neurotoxicity has garnered substantial international attention due to its potentially debilitating and long-lasting effects on patients' daily functioning and quality of life [8–10].

Global studies estimate that approximately 30–40% of patients receiving chemotherapeutic agents develop peripheral neuropathy, while up to 75% may experience measurable cognitive impairments [11–13]. Chemotherapy-induced peripheral neuropathy is one of the most frequently documented neurological complications of cancer treatment, leading to increased morbidity and, in some cases, mortality [9, 11, 14–16]. Despite these well-documented effects internationally, the incidence and characteristics of neurotoxicity in Palestinian patients remain unclear.

The manifestation of nervous system toxicity is influenced by several variables, including treatment dose, route of administration, drug interactions, and individual patient susceptibility [17–19]. For example, a recent retrospective cohort study using a disproportionality analysis of VigiBase—the WHO's global safety database—reported over 48,000 neurological adverse events linked to chemotherapeutic agents. In addition, specific complications such as posterior reversible encephalopathy syndrome and cerebral venous sinus thrombosis have been described in smaller cohorts [20, 21]. These findings highlight the global relevance of chemotherapy-induced neurotoxicity and underscore the need for localized studies.

Given the widespread use of chemotherapy and its potential to induce serious neurological complications, a critical research gap exists in the Palestinian context. To date, no comprehensive studies have explored the prevalence, clinical manifestations, and determinants of chemotherapy-induced neurotoxicity among Palestinian cancer patients. Therefore, this study aimed to evaluate the impact of cancer pharmacotherapy on the nervous system within this population. Specifically, the objectives were to: (1) assess the occurrence of neurotoxic side effects; (2) describe their clinical manifestations; and (3) identify factors associated with the development of chemotherapy-induced neurotoxicity.

Methods

Study design and settings

This was a cohort study. Data regarding cancer type, time since diagnosis, treatment regimens, duration of treatment, and past medical and surgical histories were extracted from the patients' medical records. In addition, patients completed a questionnaire.

In this study, patients undergoing chemotherapy in the Palestinian healthcare system were included, while those from the Gaza Strip and East Jerusalem were excluded. This exclusion was mandated by the unstable political situation in these areas and by considerable logistical and administrative obstacles. Access to patients in these regions was limited by the need for specific travel permissions, which were difficult to secure.

The study was conducted at four major hospitals—An-Najah National University Hospital, Al-Watani Hospital, Al Isteshari Hospital, and Bit Jala Hospital—which represent the principal centers for cancer care in Palestine. Although cancer care in Palestine is largely fragmented and there is no specialized cancer treatment hospital [2], these facilities house major oncology departments and serve as the primary sites where patients with cancer are treated, and where chemotherapy and neurology services are provided. The study was carried out between November 2023 and February 2024.

Population

The study population comprised patients undergoing chemotherapy in Palestinian hospitals and cancer care centers. Patients were included if they were confirmed cancer cases receiving chemotherapy, were 18 years of age or older, and had a clearly documented history of chemotherapy as part of their treatment, regardless of the year of diagnosis. Because the study aimed to assess chemotherapy-induced neurotoxicity, patients receiving chemotherapy cycles for any type of cancer were included. Patients were included if they received treatment protocols that involved chemotherapeutic agents either alone or in combination with other agents.

Patients lacking complete documentation of chemotherapy treatment or neurotoxicity symptoms were excluded from this study. It is important to note that patients who received other treatments—such as immunotherapy or radiation therapy in combination with chemotherapy—were not excluded. This decision was based on the widespread use of combination therapies in oncology practice. Moreover, including these patients

provides insights into neurotoxicity in real-world oncology settings.

Sample size

According to recent estimates, the 5-year prevalence of cancer cases in the occupied Palestinian territories in the West Bank and Gaza Strip was 12,955, and the number of deaths was 3,011 [4]. It is important to note that cancer care is largely fragmented in the Palestinian healthcare system. While the majority of cancer cases are often diagnosed in Palestinian hospitals, a considerable proportion of these patients are referred or travel to receive treatment outside the country. Assuming that half of the prevalent cases were from the West Bank and using a survival rate of 70%, the sample size was calculated using a 95% confidence interval and a margin of error of 5%. For this study, 354 patients were needed.

Sampling method and data collection

In this study, data were collected from multiple sources, including patient interviews and reviews of medical records and visit notes. Neurotoxicity-related symptoms, as reported by patients and documented in their records and/or visit notes, were recorded verbatim, including all instances of low body temperature along with other symptoms.

Interviews were conducted to assess the severity of the neurotoxicity-related symptoms. A validated 65-item functional neurotoxicity scale, which evaluated neurological functions such as sensory, motor, autonomic, and cognitive performance, was used during these interviews. Final-year medical students (RW, AA, and AQ), who were trained in patient interviews throughout medical school under the guidance of their mentors, conducted the interviews and collected the data. Patients rated each symptom on a five-point Likert scale (0–4), where 0 indicated the absence of symptoms and 4 indicated extremely severe symptoms. To assess overall neurotoxicity, a cumulative score was computed for each patient by summing the individual item scores. Patients were classified into categories of no/mild neurotoxicity (total score < 30), moderate neurotoxicity (31–80), or severe neurotoxicity (> 80) based on predetermined criteria and expert evaluation. These cutoff levels were established using previously published protocols and expert agreement to ensure clinical significance, thereby allowing a systematic examination of neurotoxicity prevalence and its determinants.

The questionnaire and data collection form were initially developed in English. Because no previously validated Arabic version of the 65-item functional neurotoxicity scale was available, the scale underwent a rigorous process of cultural adaptation and validation for use with Arabic-speaking populations. The translation process involved forward translation by two independent translators from English to Arabic. Any discrepancies in the translations between the two independent translators were resolved through discussion and consensus. A back-translation was then conducted by a third independent translator to ensure the accuracy and conceptual equivalence of the Arabic version with the original English scale. The back-translation was carefully compared to the original, and any remaining inconsistencies were addressed through discussion and consensus. To further ensure cultural relevance and clarity, the translated scale was reviewed by physicians and researchers who were fluent in both languages. The scale items were reviewed for their appropriateness, clarity, and potential cultural sensitivities. Based on the feedback of the reviewers, some items were subjected to minor adjustments in wording to improve comprehensibility and cultural equivalence. The adapted scale was then pilot-tested with a sample of 10 Arabic-speaking adults. Participants were asked about their understanding of the items and response options, and any difficulties they reported were addressed. The Arabic version of the scale was pilot tested with 15 patients. The internal consistency of the Arabic version of the 65-item functional neurotoxicity scale was high, as indicated by a Cronbach's alpha of 0.89. Test-retest reliability, assessed with a Pearson's correlation coefficient, was also strong (Pearson's $r = 0.92$), suggesting good stability of the scale scores over time. Construct validity was supported by the congruence between the symptoms reported by the patients on the scale and the symptoms documented in their medical records and visit notes. Specifically, the presence and severity of functional neurotoxicity symptoms reported by patients on the scale were consistent with the clinical observations and diagnoses recorded by their healthcare providers.

In addition, demographic variables—such as cancer type, the presence of metastases, past medical history, and treatment details (including medications/chemotherapeutic agents, doses, duration, and dosing frequency)—were collected from the medical records and visit notes. The face and content validity of the data collection form was confirmed through a review by a panel of experts comprising oncologists, neurologists, and pharmacologists. After reaching consensus among the panelists, the final version of the form was developed. The questionnaire is provided in the supplementary materials as Supplementary Table S1.

Statistical analysis

IBM SPSS was used for data management and analysis. Frequencies and percentages were computed. The chi-square test or Fisher's exact test was employed to compare categorical variables, while continuous variables were compared using the Mann–Whitney U test

or Kruskal–Wallis test. A p-value of < 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in compliance with international ethical principles in scientific research, including those stated in the Declaration of Helsinki. It was approved by the Institutional Review Board of An-Najah National University (Ref. no. Med. Oct. 2023/69). Permissions were obtained from the administrations of the participating hospitals and centers, enabling access to patients. Written informed consent was obtained from all patients prior to their participation. The confidentiality of data and the privacy of patients were strictly maintained.

Results

Characteristics of the patients

During the study period, 354 patients were approached. Of these, 41 did not provide written informed consent, 24 began but did not complete the 65-item questionnaire, 46 lacked complete documentation of chemotherapy treatment, and 47 did not exhibit neurotoxicity symptoms. Ultimately, 196 patients provided informed consent, had complete medical records, and completed the questionnaire. A STROBE flow diagram is provided as Supplementary Figure S1. The median age of the patients was 56.9 [48.0, 63.0] years. Among the patients, 113 (57.7%) were female, 175 (89.3%) were married, 113 (57.7%) were overweight or obese, 103 (52.6%) were unemployed, and 61 (31.1%) were smokers (Table 1). Of the patients, 140 (71.4%) had solid cancers, and 56 (28.6%) had hematological cancers. Colon, breast, and lung cancers were the most frequent among solid tumors, while lymphomas were the most common hematological malignancy. Additionally, 83 (42.3%) patients had metastases. Furthermore, 69 (35.2%) patients had a past medical history, and 39 (19.9%) had previously undergone surgery (Table 1). The median duration of chemotherapy was 5.0 [2.0, 10.3] months, and the median number of chemotherapy cycles administered was 4.0 [2.0, 6.0]. Male patients were more likely to be employed and were more frequently smokers, whereas female patients were more likely to have diabetes

Table 1 Characteristics of the sample

Variable	Both sexes (*n* = 196, 100%)	Male (*n* = 83, 42.3%)	Female (*n* = 113, 57.7%)	
	Median [Q1, Q3]	Median [Q1, Q3]	Median [Q1, Q3]	*p*-value
Age (years)	56.0 [48.0, 56.0]	57.0 [49.0, 63.0]	53.0 [43.5, 63.0]	0.244
Body mass index (kg/m2)	26.0 [22.8, 29.6]	24.9 [22.8, 28.4]	26.3 [22.8, 29.8]	0.424
Chemotherapy cycles (n)	4.0 [2.0, 6.0]	4.0 [2.0, 5.0]	5.0 [2.5, 7.0]	0.256
Duration of treatment (months)	5.0 [2.0, 10.3]	5.0 [2.0, 9.0]	4.0 [2.0, 10.5]	0.877
Duration of cancer (months)	7.0 [3.3, 13.2]	6.2 [3.1, 12.0]	7.0 [3.7, 14.7]	0.767
	n (%)	**n (%)**	**n (%)**	
Marital status, married	175 (89.3)	75 (38.3)	100 (51.0)	0.676
Body mass index category, obese	46 (23.5)	18 (9.2)	28 (14.3)	0.217
Employment status, unemployed	103 (52.6)	4 (2.0)	99 (50.5)	**< 0.001**
Smoking status, yes	61 (31.1)	44 (22.4)	17 (8.7)	**< 0.001**
Cancer type				
Solid cancers	**140 (71.4)**	**49 (25.0)**	**91 (46.4)**	**< 0.001**
Gastrointestinal cancer	61 (31.0)	27 (13.8)	34 (17.2)	
Breast cancer	30 (15.3)	0 (0.0)	30 (15.3)	
Gynecological cancer	19 (9.6)	0 (0.0)	19 (9.6)	
Lung cancer	16 (8.2)	11 (5.6)	5 (2.6)	
Other	14 (7.1)	11 (13.3)	3 (2.7)	
Hematological cancers	**56 (28.6)**	**34 (17.3)**	**22 (11.2)**	
Current treatment modality				
Chemotherapy alone	66 (33.7)	27 (13.8)	39 (19.9)	0.772
Chemotherapy combined with other modalities, including immunotherapy and radiation therapy	130 (66.3)	56 (28.6)	74 (37.8)	
Metastases, yes	83 (42.3)	39 (19.9)	44 (22.4)	0.260
Having any other comorbidity, yes	69 (35.2)	27 (13.8)	42 (21.4)	0.502
Having diabetes mellitus, yes	19 (9.7)	3 (1.5)	16 (8.2)	**0.014**
Past surgical history, yes	39 (19.9)	14 (7.1)	25 (12.8)	0.362

Q1: lower quartile, Q3: upper quartile, statistically significant p-values are boldface

mellitus. Details of the characteristics of the patients are shown in Supplementary Table S1.

The chemotherapeutic and other agents received by the patients

In this study, patients received treatment protocols that combined chemotherapeutic agents alone or with other therapies, including targeted therapy and corticosteroids (Table 2). Detailed information on the combined chemotherapeutic and additional agents used in patient treatment is provided in Supplementary Table S3.

Table 2 Chemotherapeutic and other agents combined and used to treat the patients

Agent	*n* (%)
Alkylating agents	
Cyclophosphamide	48 (24.5)
Other	6 (3.0)
Antimetabolites	
Fluorouracil/5-FU	108 (55.1)
Capecitabine/Xeloda	25 (12.8)
Other	10 (5.0)
Platinum-based agents	
Cisplatin	27 (13.8)
Oxaliplatin	96 (49.0)
Carboplatin	14 (7.1)
Microtubule inhibitors	
Vincristine/Oncovin	29 (14.8)
Paclitaxel/Taxol	10 (5.1)
Other	9 (4.6)
Topoisomerase inhibitors	
Doxorubicin/Adriamycin	58 (29.6)
Etoposide	39 (19.9)
Irinotecan	29 (14.8)
Topotecan	13 (6.6)
Idarubicin	1 (0.5)
Targeted therapy	
Rituximab	23 (11.7)
Bevacizumab	12 (6.1)
Trastuzumab	9 (4.6)
Cetuximab	8 (4.1)
Other	9 (4.5)
Proteasome inhibitors	(0.0)
Bortezomib/Velcade	4 (2.0)
Corticosteroids	
Prednisone	25 (12.8)
Dexamethasone	4 (2.0)
Miscellaneous	
Folinic acid/leucovorin	135 (68.9)
Bleomycin	39 (19.9)
Gemcitabine	10 (5.1)
Zoledronic acid	9 (4.6)
Other	32 (16.0)

Prevalence of neurotoxicity as measured by the functional neurotoxicity scale

Patients were asked to rate the severity of their neurotoxicity symptoms using the 65-item functional neurotoxicity scale. Their ratings are presented in Table 3.

The median score on the 65-item functional neurotoxicity scale was 68.0 [48.0, 89.0]. Among the patients, 119 (60.7%) exhibited moderate neurotoxicity and 47 (24.0%) exhibited severe neurotoxicity, as presented in Table 4.

Association between the variables of the patients and neurotoxicity

The severity of neurotoxicity was significantly associated with female sex (p-value = 0.032) and a diagnosis of solid cancer (p-value = 0.015). Additionally, patients who experienced neurotoxicity were significantly older (p-value = 0.045) and received a larger number of chemotherapy cycles (p-value = 0.037). These associations are shown in Table 5.

Table 6 summarizes the key neurotoxic effects associated with the primary chemotherapeutic agents based on the 65-item functional neurotoxicity scale. Specifically, oxaliplatin was mainly linked to peripheral sensory alterations (numbness/weakness in the arms and legs, cold extremities, and sensitivity to touch), cisplatin to similar peripheral effects plus auditory disturbances (ringing in the ears), cyclophosphamide to cognitive impairments (trouble processing new information and short-term memory loss), and paclitaxel/Taxol to combined motor and sensory deficits (numbness/weakness, sensitivity, wrist/ankle drop, and muscle twitching). This concise summary, as detailed in Table 6, might provide clinicians with a practical reference for targeted monitoring and management of neurotoxicity in patients receiving these treatments.

Discussion

Chemotherapy-induced neurotoxicity and neuropathies are common and constitute a significant challenge for both cancer patients and their care providers [8, 10, 20, 21]. These adverse effects can negatively impact therapy continuity and patient outcomes [22]. In this study, we investigated the occurrence, clinical manifestations, and associated factors of neurotoxicity among patients undergoing chemotherapy within the Palestinian healthcare system. To our knowledge, this is the first study in Palestine to comprehensively assess the various forms of neurotoxicity and neuropathy in this patient population. Our findings reveal that neurotoxicity and neuropathies are prevalent among cancer patients undergoing chemotherapy in the Palestinian healthcare system. These results are valuable to oncologists, neurologists, and other healthcare providers involved in cancer care in Palestine, and may inform the development of strategies to

Table 3 Answers of the patients on the 65-item functional neurotoxicity scale

#	Item	0	1	2	3	4
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
1	Anxiety	69 (35.2)	28 (14.3)	38 (19.4)	35 (17.9)	26 (13.3)
2	Mood swings	55 (28.1)	20 (10.2)	47 (24.0)	46 (23.5)	28 (14.3)
3	Enraged behavior or anger	66 (33.7)	21 (10.7)	25 (12.8)	41 (20.9)	43 (21.9)
4	Excessive shyness, (not typical to your personality)	148 (75.5)	21 (10.7)	15 (7.7)	5 (2.6)	7 (3.6)
5	Irritability (not typical to your personality)	79 (40.3)	25 (12.8)	36 (18.4)	24 (12.2)	32 (16.3)
6	Low body temperature (below 36.3 ℃)	181 (92.3)	5 (2.6)	6 (3.1)	4 (2.0)	0 (0.0)
7	Insomnia (can't get to sleep or return to sleep)	60 (30.6)	18 (9.2)	43 (21.9)	33 (16.8)	42 (21.4)
8	Dizziness	90 (45.9)	34 (17.3)	33 (16.8)	25 (12.8)	14 (7.1)
9	Sound in ears (ringing or hearing your heart beat)	115 (58.7)	25 (12.8)	21 (10.7)	20 (10.2)	15 (7.7)
10	Psychological symptoms, even thoughts of suicide	124 (63.3)	30 (15.3)	27 (13.8)	13 (6.6)	2 (1.0)
11	Sensitivity to sound	81 (41.3)	22 (11.2)	28 (14.3)	45 (23.0)	20 (10.2)
12	Indecisiveness	137 (69.9)	25 (12.8)	22 (11.2)	8 (4.1)	4 (2.0)
13	Feeling of being overwhelmed or fearful	89 (45.4)	29 (14.8)	40 (20.4)	29 (14.8)	9 (4.6)
14	Metallic taste in your mouth	60 (30.6)	18 (9.2)	38 (19.4)	36 (18.4)	44 (22.4)
15	Bad breath	128 (65.3)	32 (16.3)	15 (7.7)	13 (6.6)	8 (4.1)
16	Bleeding gums	158 (80.6)	20 (10.2)	9 (4.6)	2 (1.0)	7 (3.6)
17	Sensitive teeth	102 (52.0)	22 (11.2)	24 (12.2)	21 (10.7)	27 (13.8)
18	Canker sores or other sores in the mouth	111 (56.6)	26 (13.3)	22 (11.2)	8 (4.1)	29 (14.8)
19	Floaters, shadows or swimmers when you read or look into the sky	130 (66.3)	35 (17.9)	16 (8.2)	13 (6.6)	2 (1.0)
20	Dyslexia or loss of place while reading, even as a child	152 (77.6)	23 (11.7)	13 (6.6)	8 (4.1)	0 (0.0)
21	Swelling eyelids	133 (67.9)	22 (11.2)	18 (9.2)	18 (9.2)	5 (2.6)
22	Peeling on the top layer of skin (hands, feet)	122 (62.2)	16 (8.2)	20 (10.2)	25 (12.8)	13 (6.6)
23	Dry skin	86 (43.9)	23 (11.7)	28 (14.3)	38 (19.4)	21 (10.7)
24	Heart pain (angina) and you are under 45 years old	143 (73.0)	17 (8.7)	22 (11.2)	12 (6.1)	2 (1.0)
25	Depression	90 (45.9)	42 (21.4)	23 (11.7)	25 (12.8)	16 (8.2)
26	Gout (arthritic pain, especially in big toes)	130 (66.3)	15 (7.7)	18 (9.2)	15 (7.7)	18 (9.2)
27	Pain in shoulders or upper back	75 (38.3)	17 (8.7)	41 (20.9)	33 (16.8)	30 (15.3)
28	Twitching eyelids	144 (73.5)	28 (14.3)	14 (7.1)	7 (3.6)	3 (1.5)
29	Anemia	81 (41.3)	51 (26.0)	36 (18.4)	20 (10.2)	8 (4.1)
30	Wrist/ankle drop or weak extensor muscles	128 (65.3)	19 (9.7)	18 (9.2)	18 (9.2)	13 (6.6)
31	Hair falls out (not normal male pattern baldness)	49 (25.0)	33 (16.8)	26 (13.3)	22 (11.2)	66 (33.7)
32	Sensitivity to light	118 (60.2)	16 (8.2)	27 (13.8)	23 (11.7)	12 (6.1)
33	Fatigue after exercising (feeling worse)	33 (16.8)	25 (12.8)	43 (21.9)	48 (24.5)	47 (24.0)
34	Bad night vision or seeing halos around lights	152 (77.6)	17 (8.7)	18 (9.2)	7 (3.6)	2 (1.0)
35	Shortness of breath, with very little effort	98 (50.0)	37 (18.9)	35 (17.9)	20 (10.2)	6 (3.1)
36	Excessive thirst and/or frequent urination	88 (44.9)	32 (16.3)	34 (17.3)	25 (12.8)	17 (8.7)
37	Red eyes or tearing	104 (53.1)	28 (14.3)	19 (9.7)	27 (13.8)	18 (9.2)
38	Blurred vision at times	100 (51.0)	30 (15.3)	31 (15.8)	25 (12.8)	10 (5.1)
39	Morning stiffness	97 (49.5)	23 (11.7)	18 (9.2)	23 (11.7)	35 (17.9)
40	Sensitivity to smells (chemicals such as petrochemicals, perfumes, air fresheners)	91 (46.4)	25 (12.8)	21 (10.7)	25 (12.8)	34 (17.3)
41	Chronic fatigue or weakness	41 (20.9)	38 (19.4)	34 (17.3)	37 (18.9)	46 (23.5)
42	Non-restful sleep	73 (37.2)	23 (11.7)	25 (12.8)	40 (20.4)	35 (17.9)
43	Receive static shock more often & with more dramatic effect than normal	159 (81.1)	23 (11.7)	6 (3.1)	3 (1.5)	5 (2.6)
44	Trouble processing new information	144 (73.5)	35 (17.9)	11 (5.6)	5 (2.6)	1 (0.5)
45	Word reversal or trouble finding words	139 (70.9)	32 (16.3)	18 (9.2)	5 (2.6)	2 (1.0)
46	Sensitivity to touch	149 (76.0)	19 (9.7)	13 (6.6)	10 (5.1)	5 (2.6)
47	Short-term memory loss	130 (66.3)	25 (12.8)	27 (13.8)	10 (5.1)	4 (2.0)
48	Chronic sinus congestion	125 (63.8)	25 (12.8)	22 (11.2)	16 (8.2)	8 (4.1)
49	Dry non-productive cough	112 (57.1)	29 (14.8)	29 (14.8)	16 (8.2)	10 (5.1)
50	Muscle twitching	133 (67.9)	28 (14.3)	21 (10.7)	7 (3.6)	7 (3.6)
51	Excessive sweating, especially at night	117 (59.7)	17 (8.7)	27 (13.8)	23 (11.7)	12 (6.1)
52	Joint pain - not necessarily true arthritis - can move from joint to joint	74 (37.8)	18 (9.2)	31 (15.8)	32 (16.3)	41 (20.9)

Table 3 (continued)

#	Item	0	1	2	3	4
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
53	Difficulty losing weight regardless of diet or exercise	71 (36.2)	23 (11.7)	31 (15.8)	36 (18.4)	35 (17.9)
54	Persistent fungal or viral infection, including athlete's foot, warts, jock itch	137 (69.9)	20 (10.2)	14 (7.1)	14 (7.1)	11 (5.6)
55	Candida	148 (75.5)	15 (7.7)	11 (5.6)	11 (5.6)	11 (5.6)
56	Frequent illness, prolonged illness or sick days	137 (69.9)	26 (13.3)	12 (6.1)	10 (5.1)	11 (5.6)
57	Numbness or weakness in arms and legs	65 (33.2)	18 (9.2)	38 (19.4)	34 (17.3)	41 (20.9)
58	Headaches	75 (38.3)	40 (20.4)	43 (21.9)	24 (12.2)	14 (7.1)
59	Trouble adding or dividing numbers in your head	145 (74.0)	31 (15.8)	14 (7.1)	6 (3.1)	0 (0.0)
60	Fluctuating constipation and diarrhea	53 (27.0)	26 (13.3)	28 (14.3)	40 (20.4)	49 (25.0)
61	Stomach pain for no apparent reason	83 (42.3)	27 (13.8)	33 (16.8)	28 (14.3)	25 (12.8)
62	Appetite swings	66 (33.7)	31 (15.8)	37 (18.9)	32 (16.3)	30 (15.3)
63	Frequent muscle aches, cramps, unusual sharp sudden pains	95 (48.5)	37 (18.9)	26 (13.3)	13 (6.6)	25 (12.8)
64	Rashes or rosacea	136 (69.4)	23 (11.7)	17 (8.7)	10 (5.1)	10 (5.1)
65	Cold extremities (hands and feet)	95 (48.5)	23 (11.7)	30 (15.3)	28 (14.3)	20 (10.2)

Table 4 Prevalence of neurotoxicity

Neurotoxicity	*n* (%)
No/mild	30 (15.3)
Moderate	119 (60.7)
Severe	47 (24.0)

mitigate the burden of neurotoxicity and neuropathies and ultimately improve patient outcomes.

The quantitative findings of our study revealed that 60.7% of patients experienced moderate neurotoxicity while 24.0% experienced severe neurotoxicity, amounting to an overall burden of approximately 85%. These rates lie at the upper end of the spectrum compared with international reports, where prevalence estimates of

Table 6 Summary of neurotoxic effects associated with key chemotherapeutic agents based on the 65-item functional neurotoxicity scale

Agent	Neurotoxicity
Oxaliplatin	Numbness or weakness in arms and legs, cold extremities (hands and feet), and sensitivity to touch
Cisplatin	Numbness or weakness in arms and legs, and sound in ears (ringing, consistent with ototoxicity)
Cyclophosphamide	Trouble processing new information, and short-term memory loss
Paclitaxel/Taxol	Numbness or weakness in arms and legs, sensitivity to touch, wrist/ankle drop or weak extensor muscles, and muscle twitching

Table 5 Association between the variables of the patients and neurotoxicity

Variable	Neurotoxicity			*p*-value
	No/mild	Moderate	Severe	
	n (%)	*n* (%)	*n* (%)	
Sex				
Male	17 (8.7)	53 (27.0)	13 (6.6)	**0.032**
Female	13 (6.6)	66 (33.7)	34 (17.3)	
Cancer type				
Solid	22 (11.2)	77 (39.3)	41 (20.9)	**0.015**
Hematological	8 (4.1)	42 (21.4)	6 (3.1)	
Having any other comorbidity				
No	23 (11.7)	76 (38.8)	28 (14.3)	0.292
Yes	7 (3.6)	43 (21.9)	19 (9.7)	
Having diabetes mellitus				
No	27 (13.8)	106 (54.1)	44 (22.4)	0.671
Yes	3 (1.5)	13 (6.6)	3 (1.5)	
	Median [Q1, Q3]	**Median [Q1, Q3]**	**Median [Q1, Q3]**	
Age (years)	53.0 [40.0, 66.0]	57.0 [49.5, 64.5]	52.0 [40.0, 59.0]	**0.045**
Treatment cycles (n)	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	5.0 [3.5, 8.0]	**0.037**
Duration of treatment (months)	4.0 [3.0, 9.0]	4.0 [2.0, 10.0]	6.0 [3.0, 11.0]	0.338
Duration of cancer (years)	6.2 [2.7, 11.2]	7.2 [4.0, 13.7]	6.2 [3.1, 11.9]	0.792

Q1: lower quartile, Q3: upper quartile, statistically significant p-values are boldface

chemotherapy-induced neurotoxicity have ranged from as low as 14% to over 70%, depending on the specific chemotherapeutic agents used, treatment duration, and patient-related factors [10, 17, 19, 20, 23]. For instance, a multinational study by Molassiotis et al. (2019) documented that patients receiving oxaliplatin- or taxane-based regimens experienced neurotoxicity rates as high as 71.4% [24]. In contrast, a pooled analysis across 28 countries reported that approximately 41% of cancer patients with chemotherapy-induced peripheral neuropathy demonstrated chronic painful symptoms persisting beyond six months [25]. It is noteworthy that our implementation of a comprehensive 65-item functional neurotoxicity scale—which assessed a wide range of neurological impairments beyond just pain—may partly account for the higher prevalence observed in our cohort. Moreover, studies performed in more advanced healthcare systems have frequently reported lower prevalence rates (often below 60%), possibly reflecting differences in optimized chemotherapy protocols, enhanced supportive care, and more proactive early intervention strategies [10, 17, 19, 20, 23–25]. Collectively, these quantitative differences suggest that regional disparities in treatment practices, patient monitoring, and supportive care measures substantially influence the burden of neurotoxicity, thereby underscoring the need for standardized assessment and tailored management strategies in the Palestinian healthcare setting.

Our findings revealed that female patients experienced significantly higher neurotoxicity compared to their male counterparts. This sex-based disparity may be attributed to several interrelated biological factors. For instance, differences in body composition— with females generally having a higher percentage of body fat—can affect the distribution of lipophilic chemotherapeutic agents, leading to increased accumulation in neural tissues [26–28]. This altered pharmacokinetic profile may result in prolonged exposure of nervous tissue to cytotoxic agents, thereby increasing the risk of neurotoxic effects [29]. Moreover, hormonal influences play a pivotal role. Estrogen, in particular, has been shown to modulate neuronal excitability and pain perception by affecting the expression and activity of ion channels, which are integral to nociceptive signaling [24, 30]. Estrogen-related pathways may also amplify inflammatory responses in peripheral nerves, potentially exacerbating the neurotoxic impact of chemotherapy. Additionally, genetic variations in drug-metabolizing enzymes—especially isoforms of the cytochrome P450 family—often differ between sexes and may result in slower clearance rates of chemotherapeutic drugs in females [31–33]. This slower clearance may lead to sustained drug concentrations, thereby increasing the likelihood of neurotoxicity. Collectively, these mechanisms provide a plausible explanation for the increased susceptibility of female patients to chemotherapy-induced neurotoxicity. Future research should focus on unraveling these complex biological interactions further, with the aim of developing tailored interventions to mitigate neurotoxicity among female cancer patients. In contrast to these clear sex differences, our analysis did not reveal a significant correlation between diabetes and neurotoxicity severity. Although prior studies have suggested that diabetes predisposes patients to peripheral neuropathy—likely due to underlying metabolic vulnerabilities [34, 35], our results may reflect effective glycemic control in our cohort, differences in the assessment tools used, or a divergence in the pathogenic mechanisms of diabetic neuropathy versus chemotherapy-induced neurotoxicity. Together, these findings underscore the importance of considering individual factors, such as sex and metabolic status, when tailoring chemotherapy regimens and monitoring for neurotoxic adverse effects.

In this study, cancer patients reported a wide range of neurotoxicity and neuropathy manifestations, including anxiety, mood swings, and cognitive deficits. Previous studies have documented that patients undergoing chemotherapy frequently experience significant peripheral neuropathies, such as numbness, tingling, and pain in the hands and feet, among other neurotoxic symptoms [8–13, 15–20, 21, 23, 25]. Taken together, these findings indicate that oncologists, neurologists, and other healthcare providers should adopt proactive assessment and management strategies to screen for, evaluate, and treat neurotoxicity and neuropathy as integral components of the care plan for cancer patients undergoing chemotherapy in Palestine. It is widely recognized that minimizing these adverse effects can improve both the overall well-being of patients and their treatment outcomes. In our study, older age, female sex, cancer type, and a higher number of chemotherapy cycles were associated with more severe neurotoxicity and neuropathy. Identifying these factors can help tailor treatment options to individual patients based on their demographic, disease, and health profiles [36–39]. Moreover, the current collaboration between oncologists and neurologists in Palestine is limited, representing a critical gap in care. Therefore, a multidisciplinary approach—leveraging the expertise of oncologists, neurologists, clinical pharmacists, and other healthcare providers—is essential for developing comprehensive care guidelines and treatment protocols to minimize the occurrence of neurotoxicity.

Numerous chemotherapeutic agents used in this study are recognized for their potential to induce neurotoxicity, exhibiting varying degrees of severity and distinct underlying causes. Platinum-based agents, particularly oxaliplatin and cisplatin, are highly neurotoxic and frequently result in chemotherapy-induced peripheral neuropathy, which is characterized by

tingling, numbness, and pain in the extremities [40, 41]. These effects stem from direct damage to sensory neurons and disruptions in DNA transcription. Furthermore, taxanes such as paclitaxel and docetaxel induce neuropathy by interfering with microtubule dynamics, thereby impairing neuronal function [42, 43]. Similarly, vinca alkaloids, such as vincristine, can cause progressive neuropathy, resulting in significant sensory and motor impairments [44]. Additionally, bortezomib, a proteasome inhibitor used in the treatment of multiple myeloma, has been linked to peripheral neuropathy, possibly due to its effects on protein degradation pathways [45, 46]. It has been hypothesized that the neurotoxic potential of these drugs is influenced by their lipophilicity, which determines their ability to cross the blood-brain barrier and induce central neurotoxic effects, including cognitive impairment [23]. Given the substantial burden of neurotoxicity observed in this study, further investigation into agent-specific neurotoxic patterns may help optimize chemotherapy regimens and improve patient outcomes.

The findings of this study have significant implications for clinical practice and policy-making in the Palestinian healthcare system. Healthcare providers should develop and implement comprehensive guidelines and protocols for the screening, evaluation, and management of neurotoxicity in cancer patients receiving chemotherapy. In addition, proactive monitoring and early intervention strategies should be implemented to reduce the occurrence of neurotoxicity. Moreover, healthcare providers must educate patients about the potential neurotoxic adverse effects of chemotherapy and develop educational interventions that empower patients throughout their treatment journey.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, although 354 cancer patients were initially evaluated for eligibility, only 196 were included in the final analysis after applying the inclusion and exclusion criteria. This reduction in sample size was due to factors such as refusal to participate, missing data, or other exclusions, which may limit the generalizability of our results. Second, due to political instability and significant logistical constraints, patients from Gaza and East Jerusalem were not included in the study; as a result, our findings predominantly reflect the experience of patients treated in hospitals located in the West Bank. This exclusion may limit the application of our results to the broader Palestinian cancer population, as patients in Gaza and East Jerusalem may have different socioeconomic backgrounds, face variations in healthcare access, and be subjected to alternative treatment regimens that could influence the prevalence and severity of chemotherapy-induced neurotoxicity [2]. We therefore urge caution when extrapolating our results to the entire region and recommend that future studies include these underrepresented populations to provide a more comprehensive picture of neurotoxicity across all Palestinian healthcare settings. Third, a portion of the data relied heavily on information documented in medical records, which may have been incomplete or inaccurately recorded, thereby affecting data quality, while reliance on self-reported neurotoxicity symptoms could have introduced recall and social desirability biases. Fourth, although our study highlights the role of specific chemotherapeutic agents in neurotoxicity, we did not explore dose-response relationships or potential mitigation strategies, leaving these important areas for future research. Fifth, the cross-sectional design of the study, without a long-term follow-up component, precludes assessment of how neurotoxicity symptoms may evolve over time. Future studies should adopt a prospective design with long-term follow-up to assess the trajectory of neurotoxicity. Such an approach would involve periodic assessments—ideally at intervals of 6 months to 1 year—beyond the immediate post-chemotherapy period, allowing researchers to track whether neurotoxicity symptoms persist, resolve, or even worsen in subsequent years. In addition to repeating the comprehensive 65-item functional neurotoxicity scale, future investigations could incorporate additional objective evaluations, such as neurophysiological tests or advanced imaging modalities, to better understand underlying structural or functional changes in the nervous system. These longitudinal assessments would also benefit from integrating patient-reported outcome measures to capture the impact of neurotoxicity on quality of life over time. Furthermore, identifying potential predictors for chronic neurotoxicity through long-term monitoring may enable earlier intervention and more personalized supportive care strategies. This approach would ultimately provide a more complete picture of chemotherapy-induced neurological impairment and its long-term ramifications, thereby informing clinical practice and health policy to mitigate neurotoxic risks among cancer patients. Sixth, potential sampling bias may have arisen because the hospitals included in the study were general hospitals with oncology units rather than dedicated primary oncology centers, which could influence the representativeness of our findings. Finally, although the 65-item functional neurotoxicity scale has been widely used, its validation in Arabic-speaking populations was not

explicitly addressed, and any necessary adaptations were not detailed, which may affect the interpretation of our results.

Conclusion

This study highlights the significant prevalence of chemotherapy-induced neurotoxicity among cancer patients in Palestine and underscores the need for personalized treatment approaches and proactive symptom management strategies. Collaboration among clinicians, researchers, and policymakers is essential for the development of comprehensive guidelines and interventions aimed at optimizing patient outcomes. Furthermore, additional research is warranted to explore the long-term impact of neurotoxicity and to evaluate the effectiveness of supportive care interventions in this population.

Supplementary Information

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Supplementary Material 1

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Author contributions
Sultan Mosleh, Razan Odeh, Ahmad Abuhassan, and Ramzi Shawahna were involved in the conception and design of the work, analysis and interpretation of data, and drafting and final approval of the manuscript. Roqaya Warrad, Aya Abushar, and Abdullah Qubbaj were involved in the data acquisition, analysis, drafting of the work and final approval of the version to be published. All authors approved the final manuscript.

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Data availability
All data analyzed in this study were included in the manuscript. The datasets used in the analysis or entered into statistical software can be obtained from the corresponding author upon making a reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in compliance with international ethical principles in scientific research, including those stated in the Declaration of Helsinki. It was approved by the Institutional Review Board of An-Najah National University (Ref. no. Med. Oct. 2023/69). Permissions were obtained from the administrations of the participating hospitals and centers, enabling access to patients. Written informed consent was obtained from all patients prior to their participation. The confidentiality of data and the privacy of patients were strictly maintained.

Consent to publish
Not applicable.

Competing interests
All authors report no competing interests.

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