Original Article

Incidence and Cost of Chemotherapy-Induced Adverse Drug Reactions Among Cancer Patients in a Charitable Hospital

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Abstract

Introduction: Chemotherapy-induced adverse drug reactions (ADRs) are one of the major consequences of cancer therapy that affects patients' quality of life, outcomes of the treatment, morbidity, and mortality and increases the economic burden. The study's objective was to evaluate the incidence, causality, severity, and preventability and to calculate the direct medical cost of chemotherapy-induced ADRs among cancer patients. **Materials and Methods:** A prospective observational study was conducted for 8 months in patients above 18 years and receiving chemotherapy. ADRs were evaluated for their causality, severity, and preventability using different ADR assessment scales, and the economic burden for different ADRs was based on their direct medical costs. **Results:** A total number of 230 patients were enrolled in the study, out of which 84 patients developed 148 ADRs. Patients who received chemotherapy showed a higher incidence of ADRs in 45–55 years of age group (30.95%), females (69.04%), solid tumors (92.85%), stage III (55.95%), and double regimen (61.90%). Paclitaxel and carboplatin were reported to cause most ADRs, such as anemia (14.18%) and leucopenia (6.75%). ADRs were assessed using scales. As per the WHO-UMC scale, 59.4% ADRs were possible, followed by probable (39.2%). The majority of the ADRs were mild (52%) in severity. About 41.9% reactions were probably preventable, and 3.4% were definitely preventable. **Conclusion:** The overall incidence of ADRs was 36.52%. The direct medical cost incurred for the management of ADRs was 457.23 USD.

Keywords: *Causality, costs, incidence, preventability, severity*

Introduction

Cancer is the abnormal proliferation of cells, the second leading cause of death after heart diseases.[1] Chemotherapy is a type of treatment that includes single or combination drugs that interfere with the ability of cancer cells to divide and proliferate.[2] Chemotherapy-induced adverse drug reactions (ADRs) are one of the major consequences of cancer therapy that affects patients' quality of life, outcomes of the treatment, morbidity, mortality, and economic burden.[1]

The severity of the ADRs is determined by the drug use pattern, disease severity, and other co-morbidities. The prevention of chemotherapy-induced ADRs is required to improve drug efficacy and patients' Quality of Life (QoL).[3] Chemotherapy-induced ADRs are unwanted drug effects that substantially impact the patients, including additional cost requirements for investigations, additional drug therapy, prolonged hospitalization, admission, and emergency hospital visits. They can also lead to disability or required intervention to prevent the damage.[4] The study's objective was to evaluate the incidence, causality, severity, and preventability and to calculate the direct medical cost of chemotherapy-induced ADRs among cancer patients.

Materials and Methods

Study design and setting

A prospective observational study was conducted for 8 months (September 2017–April 2018). This study was conducted on cancer patients receiving chemotherapy in the Oncology Department, Deralakatte, Mangaluru. This study was approved by the Institutional Ethics Committee (REF: NGSMIPS/IEC/06/2017–18), NGSMIPS, Mangaluru.

Study criteria

The inclusion criteria comprised patients above 18 years of age, either gender, all cancerous patients receiving chemotherapy, and patients on six chemotherapy cycles. Pregnant,

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lactating women, and patients not willing to participate in the study were excluded.

Data collection

The information was obtained from the patient's clinical records, including demographics (age, gender, social habits, stage of cancer, tumor type, and chemotherapy regimens) and complaints on admission, and routine laboratory investigations were collected. Demographics of the patients were studied to find out the patterns of ADR. Identification of ADRs was made based on the regular follow-up of the patients by analyzing the subjective findings.

Analysis of chemotherapy-induced ADRs

In order to assess the likelihood that a drug has caused the reaction, the causality assessment was done using Naranjo and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale.[5,6] Depending on the severity, ADRs were classified into mild, moderate, and severe reactions using the criteria developed by Hartwig *et al*.[7] for severity assessment. ADRs were categorized into definitely preventable, probably preventable, and not preventable using the modified Schumock and Thornton scale.[8]

Cost analysis of ADRs

The direct medical costs involved in the management of ADRs were collected from the Hospital Medical Billing System (HMBS). Items included in the cost incurred for the management of ADRs were additional or prolonged hospitalization, additional treatment, clinical investigational charges, additional procedures, and other costs incurred, such as other healthcare professional and nursing charges due to ADRs. The cost data were presented in USD (1USD = 65 INR).

Statistical analysis

The analysis was done using descriptive statistics. χ^2 test/ Fisher's exact test was applied to test the association between categorical variables, with *P*-value less than 0.05 considered statistically significant. Statistical software (SPSS version 20.0) was used to analyze the data.

Results

A total number of 230 patients were enrolled in the study; 84 patients developed 148 ADRs. All the patients underwent six cycles of chemotherapy without any dropouts. The overall incidence of ADRs was 36.52%. During the study, the higher incidences of ADRs were observed in the age group of 45–55 years (30.95%), and the mean age of the patients with ADRs was 53.32±12.99 and without ADRs was 49.17±15.76 years. Female patients had a higher incidence (69.04%) of ADRs when compared with the males. There was no significant association between gender and ADRs. Higher incidence of ADRs was developed in solid tumors (92.85%) than in hematological tumors (7.14%). Out of the 84 patients, the higher incidence of ADRs was observed in stage III (55.95%), followed by stage IV (23.80%). The majority of the patients had prolonged their hospitalization from 1 to 3 days (4.76%) due to ADRs. There was a significant association ($P = 0.004$) between ADRs and hospital stay. The higher incidences of ADRs were observed in doublet regimens (61.90%), followed by triplet regimens (23.80%). The demographics details of patients are depicted in Table 1.

The most commonly observed ADRs were anemia 54 (36.48%), followed by leucopenia 27 (18.24%). The doublet regimen responsible for these ADRs was paclitaxel and carboplatin. The most commonly affected organ system was the hematological system (61.5%), followed by the gastrointestinal (12.8%) system. The chemotherapy regimen, cycles, organ system, and their ADRs are summarized in Table 2. According to the WHO probability scale, most of the ADRs were possible (59.4%), followed by probable (39.2%). As per the Naranjo scale, most of the ADRs were possible (53.4%), followed by probable (45.9%). Most of the ADRs were predictable (97.3%), and 2.7% of the ADRs were not predictable. The assessments of ADRs using different scales are depicted in Table 3.

Out of the 148 ADRs, only 64 ADRs (43.24%) incurred the cost for the management. The utmost cost was incurred for the hematological system (226.70 USD), followed by the gastrointestinal system (95.66 USD). The utmost cost was observed in patients presented with leucopenia (135.16 USD), followed by vomiting (83.85 USD). The economic burden was the highest for the moderate type of reactions who had hospitalization due to ADRs (346.06 USD). The cost analysis of different ADRs is summarized in Table 4.

Discussion

In the present study, the overall incidence of ADRs was 36.52%, which was consistent with the study conducted by Khandelwal *et al.*,[3] which reported that ADR in patients receiving chemotherapy was 37.70%. So the present study resembles the previous study in that the overall incidence was 37%.

Out of the 84 ADR patients, higher incidences of ADRs were reported in the age group between 45 and 55 years. The studies conducted by Behera *et al*.[9] and Rao *et al*.[10] show that the incidences of ADRs were higher in 41–60 years than the other age groups. This study corresponds with the previous studies in which 40–55 years had a greater number of ADRs.

In the present study, greater incidences of ADRs were observed in females (69.04%) than in males (30.95%). The preceding studies reported that higher incidences of ADRs were in females when compared with males. The present study is in coincidence with the previous studies.[3,9,11]

Majority of the patients presented with solid tumors (93.91%) when compared with hematological tumors (6.08%), which resembles the study conducted by Lyman *et al*.,[12] in which solid tumors (88.15%) were the most commonly observed than hematological tumors (11.84%).

Table 1: Demographic details of patients with and without ADRs

Category		Patie nts with ADRs, *n* = 84 (%)	Patients without ADRs, *n* = 146 (%)	*P*-value	Total number of patients, *n* = 230 (%)
Age group	<25	1 (1.19)	7 (4.79)	0.162	8 (3.47)
	25–35	5 (5.95)	21 (14.38)		26 (11.30)
	35–45	19 (22.61)	27 (18.49)		46 (20)
	45–55	26 (30.95)	35 (23.97)		61 (26.52)
	55–65	20 (23.80)	40 (27.39)		60 (26.08)
	>65	13 (15.47)	16 (10.95)		29 (12.60)
Gender	Male	26 (30.95)	56 (38.35)	0.317	82 (35.65)
	Female	58 (69.04)	90 (61.64)		148 (64.34)
Social habits	Smoker	4 (4.76)	24 (16.43)	—	28 (12.17)
	Alcoholic	3 (3.57)	24 (16.43)		27 (11.73)
	Substance abuse	1 (1.19)	4 (2.73)		5 (2.17)
	Both alcoholic and smoker	2 (2.38)	10 (6.84)		12 (5.21)
	Alcoholic, smoker, and substance abuse	1 (1.19)	2 (1.36)		3 (1.30)
	No social habits	73 (86.90)	82 (56.16)		155 (67.39)
Tumor type	Solid	78 (92.85)	138 (94.52)	—	216 (93.91)
	Hematological	6 (7.14)	8 (5.47)		14 (6.08)
Stages of cancer	Stage I	1 (1.19)	2 (1.36)	—	3 (1.30)
	Stage II	16 (19.04)	21 (14.38)		37 (16.08)
	Stage III	47 (55.95)	82 (56.16)		129 (56.08)
	Stage IV	20 (23.80)	41 (28.08)		61 (26.52)
Length of hospital stay	1–3	4 (4.76)	146 (100)	0.004	150 (65.21)
	3–5	3 (3.57)	—		3 (1.30)
	5–7	3 (3.57)	—		3 (1.30)
	>7	3 (3.57)	—		3(1.30)
	No length of stay	71 (84.52)	—		71(30.86)
Chemotherapy regimens	Single regimen	10 (11.90)	28 (19.17)	—	38 (16.52)
	Doublet regimen	52 (61.90)	75 (51.36)		127 (55.21)
	Triplet regimen	20 (23.80)	38 (26.02)		58 (25.21)
	Quadruple regimen	2 (2.38)	5 (3.42)		7 (3.04)

Table 2: Chemotherapy regimen and their ADRs

Chemotherapy regimens		ADRs	Frequency, *n* = 148 (%)
Single regimen	Docetaxel	Anemia	5 (3.37)
		Alopecia	1 (0.67)
		Constipation	1 (0.67)
	Azacitidine	Injection site erythema	1 (0.67)
		Thrombocytopenia	1 (0.67)
	Carboplatin	Anemia	1 (0.67)
		Myalgia	1 (0.67)
	Trabectedin	Anemia	1 (0.67)
Doublet regimen	Docetaxel + Oxaliplatin	Anemia	1 (0.67)
		Vomiting	1 (0.67)
		Diarrhea	1 (0.67)
	Doxorubicin + Cyclophosphamide	Anemia	4 (2.70)
		Leukopenia	3 (2.02)
		Alopecia	5 (3.37)
		Rash	1 (0.67)
		Constipation	1 (0.67)
		Cough	1 (0.67)
		Abdominal pain	1 (0.67)
	Paclitaxel + Carboplatin	Peripheral neuropathy	3 (2.02)

Table 2: Continued

Chemotherapy regimens		ADRs	Frequency, *n* = 148 (%)
		Anemia	21 (14.18)
		Diarrhea	1 (0.67)
		Leukopenia	10 (6.75)
		Vomiting	1 (0.67)
		Alopecia	4 (2.70)
		Thrombocytopenia	2 (1.35)
		Abnormal blood urea	2 (1.35)
		Myalgia	1 (0.67)
		Elevated AlkPO4ase	1 (0.67)
		Seizure	1 (0.67)
	Docetaxel + Carboplatin	Vomiting	1 (0.67)
		Neutropenia	1 (0.67)
	Paclitaxel + Capecitabine	Vomiting	2 (1.35)
		Nausea	1 (0.67)
	Pemetrexed + Carboplatin	Anemia	2 (1.35)
		Fatigue	1 (0.67)
		Neutropenia	1 (0.67)
	Oxaliplatin + Capecitabine	Anemia	4 (2.70)
		Leukopenia	2 (1.35)
		Vomiting	1 (0.67)
		Peripheral neuropathy	1 (0.67)
		Thrombocytopenia	2 (1.35)
		Nausea	1 (0.67)
	Etoposide + Cisplatin	Anemia	1 (0.67)
	Gemcitabine + Oxaliplatin	Increased serum creatinine	1 (0.67)
	Ifosfamide + Etoposide	Anemia	1 (0.67)
	Irinotecan + Flurouracil	Anemia	1 (0.67)
	Gemcitabine + Carboplatin	Febrile neutropenia	1 (0.67)
	Dooxorubicin + Carboplatin	Neutropenia	1 (0.67)
Triplet regimen	Irinotecan + Oxaliplatin + Capecitabine	Insomina	1 (0.67)
		Anorexia	1 (0.67)
		Anemia	1 (0.67)
		Diarrhea	1 (0.67)
		Leukopenia	1 (0.67)
		Vomiting	1 (0.67)
	Vincristine + Doxorubicin + Cyclophosphamide	Anemia	1 (0.67)
		Pain	1 (0.67)
		Fatigue	1 (0.67)
		Fever	1 (0.67)
	Epirubicin + Oxaliplatin + Capecitabine	Anemia	1 (0.67)
		Leukopenia	3 (2.02)
		Vomiting	2 (1.35)
		Alopecia	1 (0.67)
		Rash	1 (0.67)
		Cough	1 (0.67)
		Elevated AlkPO4ase	1 (0.67)
		Abnormal AST and ALT	1 (0.67)
	Doxorubicin + Vinblastine + Dacarbazine	Leukopenia	3 (2.02)
		Stomatitis	1 (0.67)
	Irinotecan + Oxaliplatin + Flurouracil	Leukopenia	1 (0.67)
		Elevated AlkPO4ase	1 (0.67)
	Docetaxel + Flurouracil + Cisplatin	Leukopenia	1 (0.67)
		Anemia	2 (1.35)
	Rituximab + Doxorubicin + Cyclophophamide	Anemia	1 (0.67)
		Leukopenia	1 (0.67)

Table 2: Continued

Chemotherapy regimens		ADRs	Frequency, *n* = 148 (%)
	Docetaxel + Epirubicin + Cyclophosphamide	Anemia	1 (0.67)
	Bevacizumab + Docetaxel + Oxaliplatin	Anemia	1 (0.67)
	Docetaxel + Doxorubicin + Cyclophosphamide	Alopecia	1 (0.67)
	Rituximab + Vincristine + Cyclophosphamide	Anemia	2 (1.35)
		Leukopenia	1 (0.67)
	Cetuximab + Paclitaxel + Carboplatin	Abnormal blood urea	1 (0.67)
	Methotrexate + Fluorouracil + Cyclophosphamide	Fever	1 (0.67)
Quadruple regimen	Rituximab + Doxorubicin + Vincristine + Cyclophosphamide	Anemia	2 (1.35)
		Leukopenia	1 (0.67)
		Lymphopenia	1 (0.67)
Cycles	Cycle I	26 (17.6)	
	Cycles II	36 (24.32)	
	Cycles III	20 (13.51)	
	Cycles IV	28 (18.91)	
	Cycles V	31 (20.94)	
	Cycles VI	7 (4.72)	
Organ system	Hematological system	91 (61.5)	
	CNS and PNS	8 (5.4)	
	Gastrointestinal system	19 (12.8)	
	Hepatic	4 (2.7)	
	Musculoskeletal system	3 (2.0)	
	Renal system	4 (2.7)	
	Respiratory system	2 (1.4)	
	Skin and appendages	15 (10.1)	
	Others	2 (1.4)	

AST = aspartate transaminase, ALT = alanine transaminase

Table 3: Causality, severity, preventability, and predictability of ADRs

Category		Frequency, *n*=148 (%)
WHO scale	Certain	1 (0.6)
	Probable	58 (39.2)
	Possible	88 (59.4)
	Unclassified	1 (0.9)
Naranjo's scale	Probable	68 (45.9)
	Possible	79 (53.4)
	Unlikely	1 (0.7)
Hartwig's severity scale	Level 1	25 (16.9)
	Level 2	47 (31.8)
	Level 3	47 (31.8)
	Level 4a	5 (3.4)
	Level 4b	23 (15.5)
	Level 5	1 (0.7)
Preventability scale	Definitely preventable	5 (3.4)
	Probably preventable	62 (41.9)
	Not preventable	81 (54.7)
Predictability scale	Predictable	144 (97.3)
	Not predictable	4 (2.7)
Management of ADRs	Drug withdrawn	4 (2.7)
	Dose altered	2 (1.4)
	No change	142 (95.9)
Treatment of ADRs	Specific	68 (45.9)
	Symptomatic	1 (0.7)
	Nil	79 (53.4)

Table 3: Continued

Category		Frequency, *n*=148 (%)
Outcome of ADRs		
	Recovery	61 (41.2)
	Continuing	86 (58.1)
	Unknown	1 (0.7)
	Other	—
Dechallenge	Definite improvement	3 (2.02)
	No improvement	1 (0.67)
	No dechallenge	144 (97.29)
Rechallenge	Recurrence of symptoms	1 (0.67)
	No rechallenge	147 (99.38)

Table 4: Cost analysis of different ADRs

Category			No. of ADRs with cost (*n* = 64)	Total cost (INR)	Total cost (USD)
Organ system	Hematological system		36	14,735.87	226.70
	CNS and PNS		6	5,476.15	84.24
	Gastrointestinal system		12	6,218.53	95.66
	Musculoskeletal system		3	1,788.8	27.52
	Respiratory system		2	136.5	2.1
	Skin and appendages		3	1,121.2	17.24
	Others		2	243.1	3.74
ADRs	Diarrhea		1	213.82	3.28
	Leukopenia		12	8,785.85	135.16
	Vomiting		8	5,450.78	83.85
	Rash		2	1,003.8	15.44
	Constipation		2	462	7.10
	Peripheral neuropathy		3	523.65	8.05
	Anemia		19	917.5	14.11
	Thrombocytopenia		2	711.62	10.94
	Injection site erythema		1	117.40	1.80
	Neutropenia		2	2,903.9	44.67
	Fatigue		2	243.1	3.74
	Fever		2	4,892.5	75.26
	Perineal pain		1	1,520	23.38
	Pain on legs		1	100.8	1.55
	Myalgia		1	168	2.58
	Cough		2	136.5	2.1
	Abdominal pain		1	91.93	1.41
	Seizure		1	60	0.92
	Febrile neutropenia		1	1,417	21.8
Severity	Moderate	Level 3	40	3,069.74	47.22
		Level 4(a)	5	4,096.37	63.02
		Level 4(b)	18	22,494.04	346.06
	Severe	Level 5	1	60	0.92

CNS = central nervous system, PNS = peripheral nervous system

Out of the 230 patients, most of the patients received doublet regimen in which the frequently prescribed doublet regimens that had caused the majority of the ADRs were paclitaxel and carboplatin (31.7%), followed by doxorubicin and cyclophosphamide (10.77%); these findings correspond to the study conducted by Khandelwal *et al*.,[3] in which higher incidence of ADRs was observed in patients who received paclitaxel and carboplatin (11.8%), followed by doxorubicin and cyclophosphamide (9.62%). The most commonly affected organ system by chemotherapy was the hematological system (61.5%), followed by the gastrointestinal system (12.8%) and skin and appendages (10.1%), which is in correspondence with the studies conducted by Khandelwal *et al*.[3] and Behera *et al*.,[9] in which the hematological system (39.86% and 24.22%) was mostly affected by different ADRs followed by skin and appendages (23.88% and 16.57%), respectively. The present study is consistent with the

previous study in which the hematological system is commonly affected but varied in other organ systems.

In the study, frequently occurring ADRs were anemia (36.5%), followed by leucopenia (18.2%), alopecia (8.1%), and anorexia (6.1%), whereas in the studies conducted by Behera *et al.*[9] and Shrestha *et al.*,[11] it was reported that anemia had occurred in the majority of the patients, followed by neutropenia, neuropathy, muscular weakness, and thrombocytopenia. The current study findings correspond to the previous study in which the most occurring ADR was anemia, and other ADRs did not have resemblance with the earlier studies.[9]

According to the WHO-UMC scale and Naranjo scale for assessing causality, most of the ADRs were possible (59.4% and 53.4%), followed by probable (39.2% and 45.9%). The studies conducted by Swathi *et al.*[10] and Rao *et al.*[13] reported that the WHO probability scale and Naranjo scale were used during the causality assessment, and most of the ADRs were possible followed by probable.

Severity assessment by the Hartwig scale exhibited that most of the ADRs were mild, followed by moderate. There were no deaths due to ADRs that resembled the studies conducted by Wahlang *et al.*[14] and Chopra *et al.*,[15] who reported that most of the ADRs were mild followed by moderate and severe without any deaths being observed.

The hematological system had the highest total cost (226.70 USD) followed by the gastrointestinal system (95.66 USD), and the highest total cost was observed in patients who presented with leukopenia (135.16 USD) followed by vomiting (83.85 USD). A study conducted by Rajakannan *et al.*[16] reported that the hepatic system (7520.09 USD) had the highest total cost, followed by skin and appendages (5176.26 USD). Hepatocellular damage (7520 USD) had the highest cost incurred, followed by nephropathy (2436 USD). The present study was conducted in the oncology department, whereas the previous study was conducted in general medicine.

In the present study, the utmost cost incurred for the ADRs was in a moderate level of severity (Level 4b = 346.06 USD). Rajakannan *et al.*[16] reported that a moderate level of severity (Level 4a = 12629.63 USD) of ADRs had incurred the utmost cost. This resembles the previous study, in which the cost incurred at a moderate level was higher than that of the present study.

Limitations

The study's main limitations include that the duration is less, single centric, and the only direct cost was calculated.

Conclusion

The overall incidence of ADRs was found to be 36.52%. Paclitaxel and carboplatin were reported to cause most ADRs, such as anemia (14.18%) followed by leucopenia (6.75%). The direct medical cost incurred for the management of ADRs was 457.233 USD. Regular detection, monitoring, evaluating, and preventing ADRs can minimize the economic burden of treating the ADRs.

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Conflicts of interest

There are no conflicts of interest.

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