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Original Article

An Account of Acute Adverse Drug Reactions Occurring in a Day-Care Chemotherapy Unit of a Tertiary Care Cancer Hospital—A Prospective Observational Study

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Abstract

Introduction Acute adverse drug reactions (ADRs) in day-care chemotherapy are not uncommon and are easily manageable on most occasions. However, sometimes they may lead to untoward events. It is paramount to document and analyze such events in contemporary medical oncology practice for the best utilization and planning of available personnel and resources.

Objective Our objective was to analyze the acute ADRs occurring in day-care cancer chemotherapy settings.

Materials and Methods ADRs reported in a day-care cancer chemotherapy setting, during the administration of chemotherapy, were prospectively observed and analyzed from 01 June 2020 to 31 December 2020. ADRs were classified into anaphylactic, allergic, and gastrointestinal (GI) (nausea/vomiting/heart burns/chest tightness). All ADRs were graded according to the Common Terminology Criteria for Adverse Events Version 5.0. Suspected drugs, time to reaction, and corrective measures were analyzed.

Results During the study period, a total of 10,120 sessions of day-care chemotherapy were administered. ADRs were noticed in 118 cases (1.18%). Among the reported ADRs, the mean and median age of the patients in this study was 52 years (21–88). Women outnumbered men ($n = 81$, 68.64% vs $n = 37$, 31.36%). Anaphylactic reactions (50.92%) were the most common followed by allergic (25.15%) and GI reactions (23.93%). No grade IV reaction was observed. Oxaliplatin-induced allergic reactions ($n = 28$, 23.73%) were noted most frequently. In majority of sessions ($n = 93$, 78.81%), the same chemotherapy regimen was readministered and completed uneventfully after the administration of antihypersensitivity medications.

Conclusion Serious ADRs are rare in current day-care chemotherapy administration. Most acute ADRs were of mild grade and successfully managed with antihypersensitivity medication.

Keywords
- ADRs
- chemotherapy sessions
- type of reactions
- severity

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Introduction

Adverse reactions to chemotherapy drugs occurring at various time intervals are well described.[1] Many current systemic treatment protocols include biological agents like monoclonal antibodies, immune checkpoint inhibitors in addition to the standard cytotoxic chemotherapy drugs either alone or in combinations. Despite administering the standard premedication, in reality acute adverse drug reactions (ADRs) do occur in the day-care chemotherapy setting. We report the incidence of all the allergic reactions in the day-care chemotherapy units of Basavatarakam Indo-American Cancer Hospital and Research Institute (BIACH-RI), Hyderabad, India

Our aim was to analyze the acute ADRs occurring in day-care cancer chemotherapy units in terms of causality and management.

Material and Methods

This was a prospective observational study carried out in the department of medical oncology at the day-care setting and a tertiary care teaching cancer hospital. All patients receiving chemotherapy in the day-care setting in the institute between 1st June 2020 and 31st December 2020 were included in the study in which 10,120 day-care chemotherapy sessions, that is, 3,360 patients were included. Each session of day-care chemotherapy was counted as one; hence, one patient could have received more than one session of chemotherapy. In each session of chemotherapy, patients were given the standard of care premedication, chemotherapy, and/or monoclonal antibody/immune checkpoint inhibitor as per the treatment protocol. All acute drug reactions were recorded and documented according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[1] Reactions were classified into allergic, anaphylactic and gastrointestinal (GI) reactions.

A patient was identified to have an allergic reaction if he/she developed a disorder characterized by an adverse local or general response from exposure to a drug.[1]

Anaphylaxis is defined as a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response, clinically, identified as breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness.[1]

GI reactions were identified as any one of the symptoms including dysphagia, nausea and vomiting, heartburn, and regurgitations. Each of the adverse reactions was classified into five grades as per CTCAE version 5.0.[1]

The outcome measures of the study consisted of:

- Primary outcome measures: frequency of ADR in day-care chemotherapy setting.
- Secondary outcome measures: type of ADR and its grading, suspected drug, and outcomes of ADRs.

All patients aged 18 years and above undergoing day-care chemotherapy in the study period were included in the study irrespective of the number of cycles. Each day-care chemotherapy administration was called one "session." The total number of chemotherapy sessions during the study period formed the denominator for analysis.

These ADRs were collected as per BIACH-RI protocol; hence, the data collection form mainly consisted of (►**Fig. 1**):

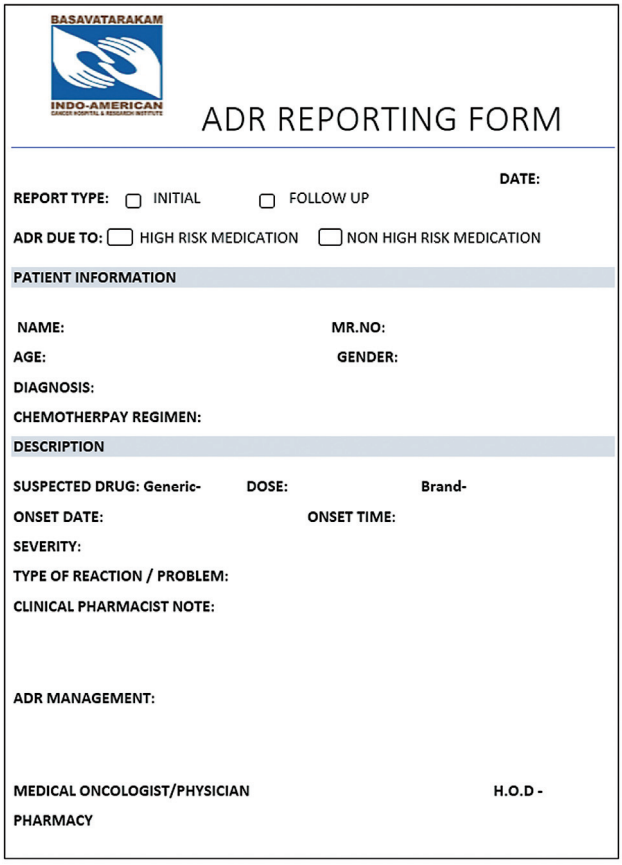
- Demographic details of patients: name, age, gender, and hospital register number.
- Diagnosis, chemotherapy regimen.
- Type of ADR and its severity.
- Suspected drug.
- Corrective action.

Exclusion criteria: Patients receiving blood or blood products in the day-care setting were excluded from the analysis.

Statistical analysis: Reactions were tabulated and analyzed using simple statistical methods using the Microsoft excel program (mean–median range).

Ethics

This was an observational study, and there was no study-specific intervention. Institutional ethics committee approval was obtained from the institutional ethics committee BIACH-RI, Hyderabad Dt 16 June 2020(IEC/2020/08). Informed consent waiver showed obtained and showed (►**Fig. 2**). Authors certified that the study was performed in accordance with the ethical standards as laid down in the


BASAVATARAKAM INDO-AMERICAN CANCER HOSPITAL & RESEARCH INSTITUTE

ADR REPORTING FORM

DATE:

REPORT TYPE: ☐ INITIAL ☐ FOLLOW UP

ADR DUE TO: ☐ HIGH RISK MEDICATION ☐ NON HIGH RISK MEDICATION

PATIENT INFORMATION

NAME: MR.NO:

AGE: GENDER:

DIAGNOSIS:

CHEMOTHERPAY REGIMEN:

DESCRIPTION

SUSPECTED DRUG: Generic- DOSE: Brand-

ONSET DATE: ONSET TIME:

SEVERITY:

TYPE OF REACTION / PROBLEM:

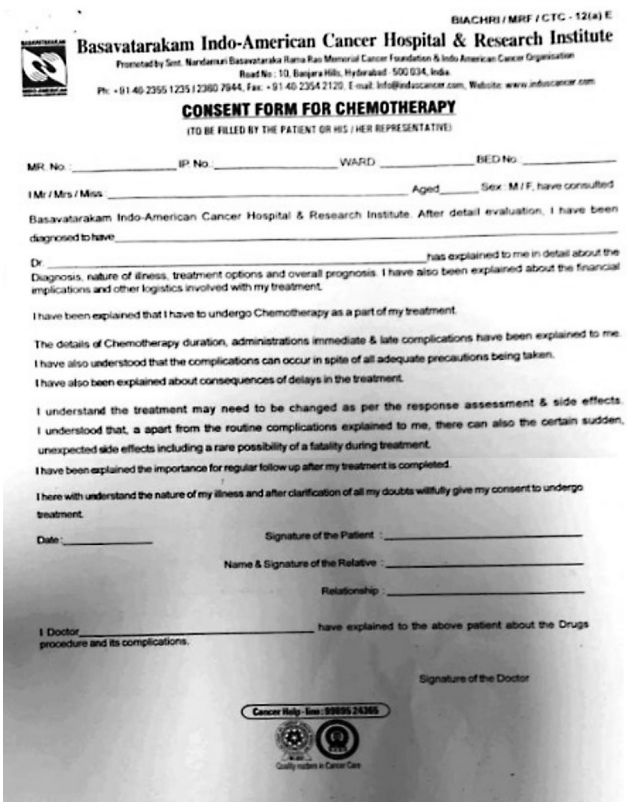
CLINICAL PHARMACIST NOTE:

ADR MANAGEMENT:

MEDICAL ONCOLOGIST/PHYSICIAN H.O.D -

PHARMACY

Fig. 1 Data collection form



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CONSENT FORM FOR CHEMOTHERAPY

(TO BE FILLED BY THE PATIENT OR HIS / HER REPRESENTATIVE)

MR. No. _____ IP. No. _____ WARD _____ BED No. _____

I Mr / Mrs / Miss _____ Aged _____ Sex : M / F, have consulted Basavatarakam Indo-American Cancer Hospital & Research Institute. After detail evaluation, I have been diagnosed to have _____

Dr. _____ has explained to me in detail about the Diagnosis, nature of illness, treatment options and overall prognosis. I have also been explained about the financial implications and other logistics involved with my treatment.

I have been explained that I have to undergo Chemotherapy as a part of my treatment.

The details of Chemotherapy duration, administrations immediate & late complications have been explained to me.
I have also understood that the complications can occur in spite of all adequate precautions being taken.
I have also been explained about consequences of delays in the treatment.

I understand the treatment may need to be changed as per the response assessment & side effects.
I understood that, a apart from the routine complications explained to me, there can also the certain sudden, unexpected side effects including a rare possibility of a fatality during treatment.
I have been explained the importance for regular follow up after my treatment is completed.

I here with understand the nature of my illness and after clarification of all my doubts willfully give my consent to undergo treatment.

Date : _____ Signature of the Patient : _____

Name & Signature of the Relative : _____

Relationship : _____

I Doctor _____ have explained to the above patient about the Drugs procedure and its complications.

Signature of the Doctor

Cancer Help-line : 99595 24365

Quality matters in Cancer Care

Fig. 2 Consent form.

1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Results

A total of 10,120 daycare chemotherapy sessions, that is, 3,360 patients were included in the study.

Baseline characteristics are given in ►**Table 1**.

A total number of 118 allergic reactions were noticed in the study period, which accounted for 1.18% of all the chemotherapy sessions administered in day-care setting. Among those who developed allergic reactions, women outnumbered men ($n = 81$, 68.64% vs. $n = 37$, 31.36%). Reactions were most observed in patients taking chemotherapy for breast cancer ($n = 24$, 20.34%) followed by upper GI cancer ($n = 23$, 19.49%), colorectal cancer ($n = 19$, 16.10%), and then lymphoma ($n = 18$, 15.25%).

Anaphylactic reactions were most commonly observed followed by allergic and GI reactions. Grade I anaphylactic reactions were observed in 12 (07.36%) cases, grade II in 48 (29.45%), and grade III in 23 (14.11%). Grades I, II, and III allergic reactions accounted for 4 (02.45%), 23 (14.11%), and 14 (08.59%) cases, respectively. GI reactions were of grade I in 2 (01.23%), grade II in 21 (12.88%), and grade III in 16 (09.82%). No grade IV reaction was observed. These are shown in ►**Tables 2** and **3**.

Drugs observed to cause reactions are shown in ►**Table 4**. Oxaliplatin ($n = 28$, 23.73%) was the drug most observed to be associated with a reaction followed by paclitaxel ($n = 21$, 17.80%), carboplatin and others ($n = 14$, 11.86%).

Most of the reactions occurred within 30 minutes of starting the intravenous chemotherapy ($n = 61$, 51.6%). Lesser number of reactions occurred between 30 minutes and 2 hours ($n = 29$, 24.58%) and toward the end of the infusion ($n = 28$, 23.73%) as shown in ►**Table 5**.

Chemotherapy infusion was stopped after the reaction was noticed, and appropriate medication was administered to counter the reaction in all cases. Reinfusion of the same drug was attempted and successfully completed when possible. Some patients required chemotherapy to be withheld for that cycle. In majority of sessions ($n = 93$, 78.81%), the same chemotherapy regimen was restarted and completed successfully after a short break and medications. Upon restarting the same chemotherapy after a break and corrective action, 14 patients (11.86%) had a recurrence of a similar reaction and chemotherapy was discontinued for that session. Eleven patients (9.32%) had grade III reaction, and chemotherapy was stopped for that session. The chemotherapy regimen was changed for 11 patients in subsequent cycles, and the remaining patients tolerated the therapy in subsequent cycles uneventfully.

Table 1 Baseline characteristics

Age (years)	Mean median age 52 y (21–88)	
Gender	Male number (%) Female number (%)	$N = 37$, 31.36% $N = 81$, 68%
Primary malignancy	Breast Upper GI Colorectal Lymphoma Ovary Endometrium Cervix Pancreas Tongue Lung Other	$N = 24$, 20.34% $N = 23$, 19.49% $N = 19$, 16.10% $N = 18$, 15.25% $N = 15$, 12.71% $N = 4$, 3.39% $N = 4$, 3.39% $N = 3$, 2.54% $N = 3$, 2.54% $N = 2$, 1.69% $N = 3$, 2.54%

Abbreviation: GI, gastrointestinal.

Table 2 Type of reactions and its severity

Sl. no:	Severity	Anaphylactic reactions (%)	Allergic reactions (%)	GI- reactions (%)	Total
1	Grade 1	12 (07.36%)	04 (02.45%)	2 (01.23%)	18 (11.04%)
2	Grade 2	48 (29.45%)	23 (14.11%)	21 (12.88%)	92 (56.44%)
3	Grade 3	23 (14.11%)	14 (08.59%)	16 (09.82%)	53 (32.52%)
	Total	83 (50.92%)	41 (25.15%)	39 (23.93%)	163 (100.00)

Abbreviation: GI, gastrointestinal.

Table 3 Signs and symptoms of ADR reaction

Sl. no	Type of reaction	Signs and symptoms	No. of sessions	Percentage
1	Anaphylactic reactions	Breathing difficulty	33	16.67
2		Dizziness	21	10.61
3		Hypotension	2	1.01
4		Cyanosis	8	4.04
5		Shivering with/without chills	26	13.13
6		Fever	4	2.02
7		Loss of consciousness	3	1.52
8	GI reactions	Chest tightness	3	1.52
9		Nausea and vomiting	14	7.07
10		Heart Burns	8	4.04
11		Epigastric pain/stomach pain	14	7.07
12		Loose stools	1	0.51
13	Allergic reactions	Rashes	35	17.68
14		Mucositis	0	0
15		Itching	20	10.10
16		Peeling of skin/burning sensation	6	3.03
		Total	198	100.00

Abbreviations: ADR, adverse drug reaction; GI, gastrointestinal.

Discussion

Adverse reactions to chemotherapy drugs have been well studied and described in the literature including acute, subacute, and chronic toxicities of different classes of chemotherapy drugs.[2] Standard premedication is administered for every chemotherapy protocol. In spite of taking adequate precautions, acute drug reactions like allergic, anaphylactic reactions pose a challenge in day-care units. ADRs are most often seen in multichemotherapy regimens than single-drug regimens. A similar observation was made by Hartwig et al who reported that allergic, anaphylactic reactions along with hematological reactions are most often seen in multiagent chemotherapy regimens.[2,3] In addition, nausea, vomiting, epigastric burning sensation, and regurgitations were commonly reported. We analyzed acute drug reactions occurring exclusively in the day-care setting. We grouped all the acute drug reactions into three groups: allergic reactions, anaphylactic reactions, and GI symptoms. To the best of our knowledge, this is the largest single-center study of exclusive day-care chemotherapy infusion-related systemic reactions.

The observed 118 reactions accounted for 1.18% of all the day-care chemotherapy infusions in the study period. The incidence is low but all the reactions occurred even after giving all the prescribed premedication. There seems to be a higher incidence among women; similar observations were made in earlier studies.[4–9] The reason for gender difference is not clearly understood. But it can be explained by the higher incidence of breast cancer seen in our study population, similar to other studies.[7,10,11] However, there have been several other reports with men experiencing more number of ADRs than women.[12–16]

Oxaliplatin-induced allergic reactions were noted most frequently in our study, whereas other studies showed cisplatin, 5-fluracil, taxanes-induced reactions to be more common;[10,12–14,16,17] this could alert us to administer antihistaminics as additional premedication for oxaliplatin-containing regimens. The majority of our patients had grade I to II reactions which were easily managed, similar to the study conducted in northeast Indian states where the reactions are

Table 4 Suspected drug with their severity

Sl. no.	Causative drug	Number anaphylactic reactions (%)			Allergic reactions (%)			GI reactions (%)			No. of sessions (%)
		Grade I	II	III	Grade I	II	III	Grade I	II	III	
1	Oxaliplatin	21 (25.30%)			14(32.56%)			6(15.38%)			28 (23.73%)
		1	14	6	0	8	6	0	3	3	
2	Paclitaxel	16 (19.28%)			4(09.30%)			6(15.38%)			21(17.80%)
		1	11	4	1	1	2	0	4	2	
3	Carboplatin	9 (10.84%)			9(20.93%)			3(07.69%)			14(11.86%)
		0	9	0	1	7	1	0	1	2	
4	Rituximab	9 (10.84%)			4(09.30%)			7(17.95%)			13(11.02%)
		0	7	2	0	2	2	0	5	2	
5	Docetaxel	7 (08.43%)			3(06.98%)			2(05.13%)			9(07.63%)
		3	1	3	2	1	0	0	1	1	
6	Trastuzumab	7 (08.43%)			0(00.00)			0(00.00)			8(06.78%)
		6	1	0	0	0	0	0	0	0	
7	5-flurouracil	3 (03.61%)			1(02.33%)			5(12.82%)			6(5.08%)
		1	1	1	0	0	1	2	2	1	
8	Leucovorin	0 (00.00%)			2(04.65%)			4(10.26%)			6(05.08%)
		0	0	0	1	1	0	0	1	3	
9	Irinotecan	1 (01.20%)			0(00.00)			3(07.69%)			4(03.39%)
		0	1	0	0	0	0	0	2	1	
10	Fosaprepitant	1 (01.20%)			2(04.65%)			1(2.56%)			3(02.54%)
		0	0	1	0	1	1	0	1	0	
11	Others	9 (10.84%)			4(09.30%)			2(05.13%)			6(05.08%)
		0	3	6	1	2	1	0	1	1	
	Total	83 (100.00)			43 (100.00)			39(100.00)			118 (100.00)
		12	48	23	6	23	14	2	21	16	

Abbreviation: GI, gastrointestinal.

mostly seen in grade I and II which may be due to chemotherapy.[10] Among patients with grade III reactions, one patient who developed anaphylactic reaction required overnight observation in the hospital; no patient died due to reaction. However, a 61-year-old lady who was diagnosed to have carcinoma of the stomach on FLOT (5-fluracil + lecovorin + oxaliplatin + docetaxel) chemotherapy was noted to have recurrent allergic reactions to oxaliplatin inspite of administering additional premedications. This observation stresses that in a minority of patients management is likely to be challenging, and constant monitoring is important. Most of the drug reactions occurred within 2 hours from the start of infusion; this could be due to sequential administration of drugs, allergy-inducing drug being administered later in the line.

Table 5 Time to reaction (minutes)

Sl. no	Onset of time (minutes)	No. of sessions	Percentage
1	Start of infusion (< 5 to 30 min)	61	51.69
2	During of infusion (>30 min to 2 h)	29	24.58
3	End of infusion (<5 to 30 min)	9	7.63
4	After of infusion (before discharge)	19	16.10
	Total	118	100.00

The reactions observed after the completion of infusion are mostly GI reactions, which could be easily managed with antacids or antiemetics.

Limitations of the Study

We included all day-care chemotherapy administrations in the study period and restricted this analysis only to acute drug reactions which are expected to occur on the day of administration. However, we did not precisely analyze the time gap between premedication and the actual administration of chemotherapy drug; the duration of infusion of each drug and extravasation reactions were also not included.

Benefits of the Study

Overall, our study presented the acute reactions encountered in the present-day medical oncology practice and highlighted the unexpected drugs to be associated with allergic reactions. Our analysis also stresses the importance of constant monitoring and appropriate use of human resources in the day-care units to monitor and manage the ADRs. All ADRs in the day-care setting should be strictly documented in the future to examine if there is a changing trend in the present-day practice that will be of practical importance to the country.

Conclusions

Acute allergic, anaphylactic, and GI reactions in the day-care chemotherapy setting are not uncommon and could be easily managed in most of the cases. Grade II and III reactions are most commonly observed, with oxaliplatin being the most frequent drug associated with ADR in the day-care setting. No grade IV reaction was encountered. Constant monitoring and prompt corrective action prevent serious adverse events.

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None.

Conflict of Interest
None declared.

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