

Chemotherapy-Induced Adverse Drug Reactions in Pediatric Oncology

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ABSTRACT

Background: Chemotherapy accounts to high vulnerability toward Adverse Events (AEs) as it involves highly complicated regimens. Objective of the study is to identify, assess, grade and categorize chemotherapy-induced adverse drug reactions in pediatric oncology. **Materials and Methods:**

A 6 months Prospective-observational study was conducted in pediatric hematology oncology department. 0-15 years of hospitalized patients receiving chemotherapy for cancer were enrolled. Demographic details, cytotoxic drugs used and AEs that occurred were collected in a self-designed patient profile form. AEs were studied using CTCAE version 4.03 and Naranjo's Scale of Probability. After each cycle, follow ups were taken.

Result: A total of 50 patients, of which 33 male and 17 female patients were included in the study and a total of 332 AEs were observed. AEs were segregated into organ class and the number of events observed were, Gastrointestinal (123), General Disorders (107), Musculoskeletal (23), Blood and Lymphatic (42), Eye and ear (4), Nervous (17), Respiratory (16). Drugs suspected to cause the AEs were; Vincristine 65, Daunorubicin 130, Methotrexate 107, Cyclophosphamide 42, and L' Asparaginase 54. ADR may

be caused by more than one chemotherapeutic drug. Using Naranjo's Scale we observed, 6 were definite, 159 were probable and 167 were possible. On using CTCAE, out of 332 AEs, 167 were characterized as Grade 1, 114 as Grade 2, 51 as Grade 3 and 1 as Grade 5. **Conclusion:** Using CTCAE, most AEs were suspected to have been caused because of Daunorubicin and Methotrexate, but the severe AEs (neurotoxicity, pulmonary toxicity) were due to Vincristine, Methotrexate, and Cyclophosphamide.

Key words: Chemotherapy, Pediatric cancer, Chemotherapy, ADRs, CTCAE, Organ Toxicities.

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INTRODUCTION

Paediatric patients, who are diagnosed with cancer and are receiving chemotherapy, are highly susceptible to serious ADRs. Chemotherapy associated Adverse Drug reactions have become a significant factor in remission of Cancer. Drug toxicity is bound to occur more drastically in paediatric patients having smaller body sizes and larger surface area, than in adults. Majority of ADRs are caused by chemotherapeutic agents (drugs used for the treatment of cancer) and there is a surplus of evidence indicating the same. Among the paediatric cancer patients 22% hospitalization are caused by ADRs¹ and 44.2% of ADRs in general lead to hospitalization.² The drug regimen comprising doxorubicin, vincristine and cyclophosphamide, was associated with haematological disorders (8.4%) namely anaemia (mild anaemia to anaemia of grade 2 level), and febrile neutropenia.³

Drug regimens have been designed to destroy maximum number of tumour cells by treating with Chemotherapy agents. These agents, cause DNA damage and disrupt DNA replication in proliferating cells. Adverse Drug Reactions are caused due to damage to proliferating cells in healthy tissues pose serious constraints on the use of chemotherapy.⁴

Assessment tools like **CTCAE criteria** (Common Terminology Criteria for Adverse Events), and **Naranjo's Probability Scale** are used to study these ADRs to have an understanding of the suspected drugs that could've caused the event and the organ systems that are most affected. CTCAE gives a better association of the events and the organ systems involved along with their severity while Naranjo's Scale of Probability is an algorithm to look for a causal relationship with the drug.

This study could help in learning the extent of severity of the observed ADRs, and helped in comparing the impact of chemotherapy on individual organ systems and assessing the toxicities of the each drug involved in chemotherapy. This study observes the tolerability of the drugs in each cycle and is based on the safety aspects of the chemotherapeutic drugs. Overall, it can be said that, in order to ensure the safety of paediatric patients diagnosed with Cancer, a better understanding of the Adverse Drug reactions is a very significant factor.

METHODOLOGY

The present prospective observational study was conducted in Bharati Hospital and Research Centre (Paediatric Haematology/ Oncology Unit) for a period of 6 months. The sample consisted of 50 patients, who met the following inclusion criteria: Patients of 0 – 15 years of age, and patient diagnosed with cancer and undergoing chemotherapy. Those excluded from the study were; patients other than paediatric age group, patients with more than one malignancy and non-co-operative patients. The Study was designed to obtain a pattern of Adverse Drug Reaction occurring in the paediatric patient population diagnosed with cancer. Approval was taken from the ethics committee after the completion of protocol design. The cases were actively selected among the hospitalized patients. The data collected from patient files, patient or/and parent interviews were recorded in a self-designed patient profile form. The data included patient's information and the adverse events reported by doctor or/and the patient.

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CTCAE Criteria (version 4.03) and Naranjo's Probability Scale were used to assess these events in order to reach to a conclusive data of the organ systems that were affected and the drugs suspected to have caused the Adverse Event. Determination of the frequency of the ADRs was done using the Kruskal Wallis Test of Significance.

RESULTS

Amongst the total number of patients (n=50) included in the study, 66% of patients were of male (n=33) and 34% of patients were female (n=17). The patients included in the study are organized according to the age groups classified by WHO within the paediatric population, considering the entire paediatric population as one whole group the average age of the patients is 5.948 years with a standard deviation of 4.34. Within this classification of pediatric patients, (n=24) 48% diagnosed with Cancer were from the age of 2 to 6 years old (Young child group), followed by 20% (n=10) were infants (1 month – 2 years), 18% (n=9) were child (6 – 12 years old)

In Table 1, the Organ Systems are classified according to the MedDRA hierarchy as is followed by the CTCAE. Every Adverse Event presented by the patient is put under the associated organ system. The most affected organ system is gastrointestinal system (37.04%) by 123 Adverse Events occurrence in 4 cycles in total, followed by General System Disorders 107 (32.20%), Musculoskeletal System Disorders 23 (6.92%), Blood and Lymphatic System disorders 42 (12.65%), Nervous System Disorders 17 (5.12%), Respiratory System Disorders 16 (4.82%) and the least affected organs are the ears and eyes comprised of 1.20% of the total events in the four cycles of the treatment. The most observed Adverse Systems are nausea, vomiting and fever seen in 48 patients out of 50, followed by febrile neutropenia forming 25 from observed cases and the least observed event was the ear and the eye pain reported by the patients a total of 4 cases out of 50 patients

To test the hypotheses of the occurrence of complaints is same on an average, The Null Hypothesis, H_0 : The occurrence of complaints is same on an average. Vs. The Alternative Hypothesis, H_a : The occurrence of complaints is not same on an average. The test used is Kruskal-Wallis test. Chi-Square value of 662.536, with df37, P value 0.000. Since p value < 0.05, the level of significance; there is strong evidence to reject the null hypothesis.

Therefore, the occurrence of complaints is not same on an average. Thus order from highest severity to lowest occurrence is as given in list below

As shown in Table 2, CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline as set by NCI (National Cancer Institute). Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe or medically significant but not immediately life-threatening, Grade 4 Life-threatening consequences, Grade 5 Death related to AE.⁵ Most of the events associated with general and gastrointestinal system disorders are graded as mild or moderate. While the blood and lymphatic system disorders were severe because of the febrile neutropenia.

To check for the aforementioned adverse events' association with the drugs, Naranjo's probability Scale was used and the results found were from the total of 332 events, 6 had a definite relation with the drugs, 157 were probable and 169 were possible. Table 3 further gives the details of the probability of the relationship for each organ system.

Since the relationship of the events with the drugs is established, the drugs suspected to have caused the Adverse Drug Reactions are mentioned in Table 4.

Ranking for Frequency of Events

Order	Complaints	Order	Complaints	Order	Complaints
1	Nausea vomiting	13	Irritability	25	Seizure
2	Fever	14	Arthralgia	26	Gingivitis
3	Febrile Neutropenia	15	Headache	27	Mucositis
4	Diarrhoea	16	Constipation	28	Intracranial bleed
5	Flu-like symptoms	17	Tachypnoea	29	Dysphagia
6	Rash	18	Pneumonia	30	Leukocytosis
7	Anaemia	19	Back pain	31	Ear pain
8	Mouth ulcer	20	Pleural Effusion	32	Tremor
9	Abdominal pain	21	Gastritis	33	Vertigo
10	Dry mouth	22	Facial pain	34	Conjunctivitis
11	Fatigue	23	Eye pain		
12	Myalgia	24	Dizziness		

Table 1: List of Adverse Events.

Organ System	Disorders (n = number of patients)
Gastrointestinal System Disorders	Abdominal pain (n=14), Constipation (n=7), Diarrhoea (n=18), Dry mouth (n=12), Dysphagia (n=1), Gingivitis (n=2), Gastritis (n=3), Mucositis (n=2), Mouth ulcer (n=16), Nausea vomiting (n=48).
General System Disorders	Fever (n=48), Fatigue (n=11), Flu-like symptoms (n=18), Facial Pain (n=3), Rash (n=18), Irritability (n=9).
Musculoskeletal System Disorders	Arthralgia (n=8), Back pain (n=4), Myalgia (n=11).
Eye and Ear Disorders	Ear pain (n=1), Vertigo (n=0), Conjunctivitis (n=0), Eye pain (n=3).
Blood and Lymphatic System Disorders	Anemia (n=17), Febrile Neutropenia (n=25).
Nervous System Disorders	Dizziness (n=3), Headache (n=8), Seizure (n=3), Intracranial bleed (n=2), Tremor (n=1).
Respiratory System Disorders	Tachypnoea (n=7), Pleural Effusion (n=4), Pneumonia (n=5).

Table 2: CTCAE Grades for each system.

Organ System Disorders	CTCAE Grading				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal System	70	45	8	0	0
General System Disorders	61	44	2	0	0
Musculoskeletal System	16	6	1	0	0
Eye and Ear Disorders	2	1	1	0	0
Blood and Lymphatic System	7	9	25	0	1
Nervous System	7	7	3	0	0
Respiratory System	3	3	9	0	1

Table 3: Drugs Associated with the Events

Organ System Disorders	Naranjo's Scale			
	Definite	Probable	Possible	Doubtful
Gastrointestinal System	0	54	69	0
General System Disorders	0	46	61	0
Musculoskeletal System	0	12	11	0
Eye and Ear Disorders	0	0	4	0
Blood and Lymphatic System	1	25	16	0
Nervous System	4	9	4	0
Respiratory System	1	11	4	0

Table 4: Drugs Affecting the Organ System

Organ System Disorders	DRUGS									
	VCR	DNM	MTX	CTX	6- MP	L- ASP	Cytarabine	Cisplatin	5-FU	Etoposide
Gastrointestinal System	11	67	59	21	2	0	12	4	2	16
General Disorders	2	41	0	2	0	50	3	1	0	4
Musculoskeletal System	18	0	0	0	0	0	0	0	0	0
Eye and Ear Disorders	1	0	0	0	0	0	0	0	0	0
Blood and Lymphatic System	20	22	35	11	2	1	4	0	0	4
Nervous System	13	0	9	0	0	2	1	0	0	0
Respiratory System	0	0	4	8	0	1	0	3	0	0

VCR – Vincristine, DNM – Daunorubicin, MTX – Methotrexate, CTX – Cyclophosphamide, 6-MP – 6 Mercaptopurine, L-ASP – LAsparginase, 5-FU – 5-Fluorouracil.

DISCUSSION

In this study, it was observed that there were more children of the age group of 2-6 years (n=24) diagnosed with cancer and followed by the infant group (n=10). This data can be supported by a similar incidence study conducted in United States by National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. In their Study it was observed most Cancer incidences were from the age of 0-4 followed by age groups 5-9 and 10-14, and the incidences were observed more in male population than female.⁶

In this study, amongst the adverse symptoms 281(84.64%) were graded 1 and 2 while 51(15.36%) were grade 3 to 5. Another cross-sectional study conducted was by Sewunet Admasu Belachew, at Gondar University Referral Hospital Oncology Centre. The reported ADRs were assessed for causality using the World Health Organization's causality assessment scale and Naranjo's algorithm. The severities of the reported reactions were also assessed using National Cancer Institute Common Terminology CTCAE version 4.0. Accordingly, 70.1% of the reported ADRs (both hematologic and non-hematologic) were grades 3-5 and the rest 29.9% were grades 1-2.⁷

From those mentioned 332 ADRs, The Adverse Drug Reactions most commonly noted was involving the Gastrointestinal System 37.04% of total ADRs. The second most observed ADRs were General Disorders which comprised of 32.2% of the total ADRs. Musculoskeletal System Disorders 6.9%, Blood and Lymphatic System Disorders 12.65%, Eye and Ear Disorders 1.2%, Nervous System Disorders 5.12%, Respiratory System Disorders 4.82%. In another similar study conducted by S. MALLIK, it was found Haematological system was affected in 40.47% of the patients followed by GIT (33.33%), dermatological (22.22%).⁸ In yet another study, the most common ADR reported was nausea and vomiting

(23%). Gastroenterology (40.1%) was the most affected system. About 50.2% of the ADRs required treatment and 12.9% ADRs were considered serious.⁹

In this study, Naranjo's Causality assessment showed 1.80% as definite, 47.28% as probable, and 50.9% as possible. In a similar study conducted by Julie Birdie Wahlang, Naranjo's causality assessment showed 86.7% possible (score 4) and 13.2% probable (score 5-6).³

Like any other medical field, oncology health care team also needs a pharmacist who can provide their services for the better patient care. These services include comprehensive medication reviews integrating chemotherapy, supportive care and ambulatory treatment for co-morbidities, medication information for the medical staff and patients, therapeutic drug monitoring, support measures for pain management, chemotherapy side-effects prophylaxis and treatment, elaboration of therapeutic guidelines, optimal use of economic resources.¹⁰

LIMITATIONS

Since duration of the study was shorter, long term effects of the therapy could not be assessed. It could be possible that some data might be missed out because the parents/caregivers weren't co-operative sometimes. Any chemotherapeutic agent, other than the suspected chemotherapeutic drug, may be responsible for an ADR since the conclusive evidence of a causal relationship lacks and also because the treatment is given in chemotherapeutic combinations. Extrapolation of the results with the larger population was difficult as the sample size was only 50.

CONCLUSION

The study not only helps patient in reporting the side effects to the Health care professionals, but also improves both nurses' and Doctors' knowl-

edge of the side effects. Under-reporting of symptoms could be reduced, which could, all in all improve the prognosis of the patient. Daunorubicin and Methotrexate have caused most of the ADRs (Gastrointestinal and General Disorders), whereas the more severe ADRs (Neurotoxicity and Pulmonary toxicity) are caused due to Vincristine, Methotrexate and Cyclophosphamide. Gastrointestinal system is the most affected organ system because of the chemotherapeutic agents. To conclude, the Adverse Drug reactions, their assessment and perception about the organ toxicities are more intelligible.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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