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Analysis of risk factors associated with common terminology criteria for adverse event in cancer chemotherapy patients

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***Abstract*---**Background: Chemotherapeutic drugs are commonly associated with various harmful consequences which can remarkably reduce quality life of patient and lengthen the hospital admission. The objective of this study was to evaluate the frequency and its associated factors affecting cancer chemotherapy-related side effects in cancer patients. Methods: Patient case report form was used to gather information on the patient's demographics and adverse drug reactions (ADRSs) to chemotherapy medications. ADRs were analyzed for toxicity grade using National Cancer Institute Common Terminology NCI-CTCAE version 4.0. Causality Assessment and Predictability of ADRs were analyzed using World Health Organization' (WHO) Causality assessment scale and Council for International Organization of Medical Sciences (CIOMS) method respectively. Utilizing the chi square test and descriptive statistics, the relationship between the grade of ADRs and the patient's characteristics was

investigated. Results: A total of 120 patients were included in the study. Mean age of participant was 46.87 (SD-10.1). Majority (60%) participants were female. 81.7% of total patient received poly-chemotherapy in their treatment modality. Total 412 numbers of ADRs were noted. The most frequent adverse drug reactions were observed to be nausea and vomiting (17.7%), neutropenia and alopecia. On NCI-CTCAE grading maximum number of ADR was assessed as “Grade 2” ADR (33%). Causality assessment shows 46% of ADRs were “Probable”. Up on Predictability assessment, majority (81%) of ADRs were “Predictable”. Significant association between sex and occurrence of “Grade 3& 4” toxicity was found. Conclusion: Incidence of chemotherapy induced side effects among cancer patients is high. Early detection and spontaneous reporting of ADRs and identifying their nature may support managing the problem and improve their quality of life.

***Keywords*---**chemotherapy, adverse drug reaction, NCI-CTCAE, causality.

Introduction

Cardiovascular disease is the world's biggest cause of mortality, with cancer coming in second(1). A study in 2016 says that 8.3 % death in India is due to the cancer disease, which is 112.8 % higher than a study of 1990. Additionally, India's crude cancer incidence rate increased by 28.2% from 634 per 100,000 in 1990 to 812 per 100,000 in 2016. In terms of states, Kerala and Mizoram had the highest incidence rates of crude cancer, followed by Delhi, Haryana,Goa, Karnataka, Uttarakhand, Himachal Pradeshand Assam(2). Modernization and the adoption of unhealthy lifestyles, such as smoking, eating meals rich in fat and poor in fiber, are largely responsible for the increased prevalence of cancer in emerging nations (3). Cancers of the lung, breast, cervix, mouth, tongue and uterus are often reported cases in India (4). Treatment modalities of cancer depend on leading site as well as grading and staging of tumor and patient demographic profile. The principal goal is to provide utmost beneficial care and treatment at lowest risk by using chemotherapy, hormonal therapy, surgical method, radiation therapy and monoclonal antibodies (5). The use of chemotherapy in the treatment of cancer patients improves patient outcomes, but it also comes with a host of side effects (6). Chemotherapeutic medications cause toxicity as a side effect of their therapeutic activity and may reduce the quality of life for patients (7). The prevalence of adverse drug reactions (ADRs) suffered by oncology patients is significant among the anticancer medications now in use. Due to their non-specificity and tendency to harm the majority of the body's rapidly reproducing cells, these ADRs may sometimes be the limiting factor in determining the end points for treatment procedures (8).

Vomiting, nausea, alopecia, cardiovascular toxicity, myelosuppression, hemorrhagic cystitis, mucositis and electrolyte imbalance are the most frequent side effects of cancer chemotherapy(9). Pharmacovigilance in oncology(Onco-Pharmacovigilance) have been developed for ADR monitoring produced by

different chemotherapeutic drugs (10). Early detection of an adverse medication response is important because the limited therapeutic index of antineoplastic medicines makes it difficult to offer an ameliorative treatment to counteract their toxic effects (11). Patients getting many chemotherapeutic drugs in the first few months need to have their toxicity assessed carefully since it might play a part in the development of negative side effects(12).The correct treatment of adverse medication reactions has been deemed to benefit from early detection by antineoplastic medicines. Consequently, it was intended for this research to examine the ADR profiles of anticancer medications in patients using chemotherapy medications at a tertiary care facility.

Methodology

Collection of data and study tool

It was observational research with 2-year follow-up duration. This study was authorized by the institution's research ethics committee. IEC-SU/2017/1226(5), held in the Santosh Hospitaland Medical College, Santosh university, in Ghaziabad (NCR), India. Using a standard case report form, data on the patient's demographic profile, medicines taken, and adverse drug reactions (ADRs) were acquired from the patient and their in-patient file. Patients administered anticancer medication for the first time who were hospitalized or referred for treatment were included in the research. Patients with concomitant medical conditions, overprescribing, unintended and intentional overdosing, and a history of drug abuse/addiction are excluded from the research. In addition to noting the concurrent medicine administered, pertinent biochemical data were also noted. The severity of reported ADRwas assessed using National Cancer Institute Common Terminology (NCI-CTCAE) version 4.0(13). Assessments of reported ADRs were also done for causality by using WHO Causality Assessment scale. It is a probabilistic method used for the evaluation of the causal relationship between a suspected drug and ADR. Causality is categorized as “Certain”,“Probable”, “Possible”, “Unlikely”, “Unclassified,” and “Unclassifiable” (14). Predictability Assessment of ADRs was classified as “Predictable” or “Not Predictable” on the basis of modified guidelines developed by the Council for International Organizations of Medical Sciences (15).

Statistical analysis

Software called SPSS (version 25) was used for data cleansing, input, and analysis. Patient demographic data, NCI-CTCAE grade (13), Causality Assessment (14), and Predictability were all subjected to descriptive statistics such as percentage and frequency distribution (15).Grades of ADR and patient variables were compared using the Pearson chi-square test.

Results

Features of patients' demographics

A total of 120 samples were included in the study. The mean age of the total patient participated in the study was 46.87 (Standard Deviation SD 10.1),

minimum age was found to be 18 years and maximum 75 years. 79(65.8%) patients were categorized in age 18-50 years. The average weight of the total study population was 55.33 kilograms. Out of 120 patients, gender female was 72(60%) and majority of patient 109(90.8%) were married. Frequency of occupation were calculated, 72(42.5%) were homemaker followed by 21(17.5%) laborers. (Table I.)

TableI.Patient's demographic characteristics (N=120)	
Variables	Frequency (%)
Age (years)	
18-50	79 (65.8)
51-Above	41 (34.2)
Sex	
Female	72 (60)
Male	48 (40)
Religion	
Muslim	48 (40)
Hindu	72 (60)
Marital status	
Unmarried	11 (9.2)
Married	109(90.8)
Occupation	
Labor	21 (17.5)
Homemaker	51 (42.5)
Job	13 (10.8)
Business	19 (15.8)
Student	7 (5.8)
Unemployed	4 (3.3)
Elderly	5 (4.2)

Anticancer medication dosages and side effect profiles for treatments

Most commonly administered chemotherapy regimen were combination of Carboplatin & Paclitaxel 17(14.2%), CAF-Cyclophosphamide, Doxorubicin &Flurouracil 16(13.3%) and Cisplatin & Paclitaxel 14(11.7%). Majority of the patient 98(81.7%) received poly-chemotherapy as their treatment modalities. Breast cancer 28(23%) was found to be the leading site in this study followed by gastric 19(15.8%), colorectal 16(13.13%), ovarian15(12.5%), lung 10(8.3%) and another carcinoma 25(20.8%). Details are described in TableII. A total of 412 chemotherapy related ADRs were detected. Most common ADR was found out to be Nausea & Vomiting 73(17.7%) followed by Alopecia and Neutropenia (TableIV).

Table II. Cancer, treatment regimen and adverse effect profile of chemotherapy drug (N=120)	
Cancer type	Frequency (%)
Breast	28 (23.3)
Gastric	19 (15.8)
Colorectal	16 (13.3)
Ovarian	15 (12.5)

Lung	10 (8.3)
Leukemia	7 (5.8)
Others	25 (20.8)
Chemotherapy agent	
Mon chemotherapy	22 (18.3)
Polychemotherapy	98 (81.7)
Grade ADR	
Grade 1 and 2 ADR	65 (54.2)
Grade 3 and 4 ADR	55 (45.8)

Assessment of ADRs due to chemotherapy

A total of 412 chemotherapy related adverse effects were assessed for, causality severity as well as predictability. Severity of the documented ADRs assessed using NCI-CTCAE scale. Maximum number of ADR was found out be “Grade 2” ADR 136(33%) followed by 126(30.68%) “Grade 1” ADR, 96(22.8%) “Grade 3” ADR and 54(13.1%) “Grade 4 ADR”. Severe ADR (Grade4) observed maximum with alopecia followed by nausea & vomiting, neutropenia and anemia. (TableIV).According to WHO-UMC Probability scale Causality assessment was done. Out of which, 189 (46%) ADRs were analyzed as “Probable”. 182(42%) and 41(10%) ADRs were noted as “Possible” and “Unlikely” respectively. No“Certain” ADR was found as re-challenge were not done. (TableIII).Predictability assessment (based on the Council of International Organization of Medical Sciences’ guidelines) were performed and it was found out to be 332(81%) ADRs were “Predictable”.

Table III. Causality assessment scale				
Number of adverse drug reaction				
WHO causality assessment scales				
ADRs	Probable	Possible	Unlikely	Total
Nausea and Vomiting	18	55	0	73
Alopecia	6	51	0	57
Anemia	33	1	0	34
Neutropenia	56	0	0	56
Thrombocytopenia	33	1	0	34
Fever	40	4	0	44
Anaphylaxis	0	4	7	11
Anorexia	0	4	9	13
Diarrhea	0	25	0	25
Constipation	0	4	4	8
Mucositis	5	22	0	27
Dizziness	0	0	6	6
Headache	0	1	4	5
Ototoxicity	0	2	5	7
Hemorrhagic cystitis	0	3	0	3
Hyperpigmentation	0	2	4	6
Hand foot syndrome	0	3	2	5

Table IV. Chemotherapy induced ADRs (Grading according to NCI-CTCAE)					
Type of ADRs	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)
Nausea &Vomiting	10 (13.7)	37(50.7)	13 (17.8)	13 (17.8)	73 (17.7)
Alopecia	0	0	34 (59.6)	23 (40.4)	57 (13.8
Anemia	10 (29.9)	14 (41.2)	5 (14.7)	5 (14.7)	34 (8.2)
Neutropenia	11 (19.6)	22 (39.3)	16 (28.6)	7 (12.5)	56(13.6)
Thrombocytopenia	7 (21.9)	12 (37.5)	12 (37.5)	1 (3.1)	32 (7.8)
Fever	27 (61.4)	8 (18.2)	6 (13.6)	3 (6.8)	44(10.7)
Anaphylaxis	11 (100)	0	0	0	11 (2.7)
Anorexia	5 (38.5)	7 (53.8)	1 (7.7)	0	13 (3.2)
Diarrhea	5 (20)	14 (56)	4 (16)	2 (8)	25 (6)
Constipation	7 (87.5)	1 (12.5)	0	0	8 (1.9)
Mucositis	8 (29.6)	14 (51.9)	5 (18.5)	0	27 (6.6)
Dizziness	6 (100)	0	0	0	6 (1.4)
Headache	2 (40)	3 (60)	0	0	5 (1.2)
Ototoxicity	7 (100)	0	0	0	7 (1.7)
Hemorrhagic-					
Cystitis	1 (33.3)	2 (66.7)			3 (0.7)
Hyperpigmentation	6 (100)	0	0	0	6 (1.4)
Hand foot syndrome	3 (60)	2 (40)	0	0	5 (1.2)
Overall	126(30.58)	136 (33)	96 (22.8)	54 (13.1)	412 (100)

Factors associated with the severity of ADRs

On performing chi (x) square analysis, there is a significant association between grading of toxicity and gender of the patient (p=.00039). Age group and number of chemotherapies are not significantly associated with the grading of toxicity (TableV).

TableV. Association between patient character and grade 3&4 ADR produced N=120				
Variables	Patients (%)	Grade 1&2 ADR (%)	Grade 3&4 ADR (%)	p-value
Age group				
18-50	79 (65.8)	46 (58.2)	33 (41.8)	
>51	41 (34.2)	19 (46.3)	22 (53.7)	0.21
Sex				
Male	48 (40)	37 (77.1)	11 (22.9)	
Female	72 (60)	28 (38.9)	44 (61.1)	0.0009
Number of Chemotherapy				
Monotherapy	22 (18.3)	13 (59.1)	9 (40.9)	
Polytherapy	98 (81.7)	52 (53.1)	46 (46.9)	0.6

Discussion

Chemotherapy for cancer may have a lot of unpleasant side effects that must be addressed as soon as possible. Side effects from chemotherapy drugs, such as cytokine release syndrome, can manifest in a sudden, unexpected manner. Quick diagnosis is essential since these conditions may be lethal (16). Therefore, complete knowledge of aggravating risk factor and identification of adverse effect play important role in reduction in suffering and improvement of quality of life.

Pharmacovigilance practice is one of the most important methods for identification of ADRs and improves the safe use of medicines (17).

Our study suggests that age group 18-50 years produces 58.2% of “Grade 1 and 2” ADR & 41.8% of “Grade 3and 4” ADRs, while age group 51< produces 46.3% of “Grade 1 and 2” ADRs & 53.7% of “Grade3and 4” ADRs, which reveals severe toxicities are markedly greater in upper age group.Age is mentioned as contributing risk factor for the development of cancer as aged person are also suffering from different concomitant disease condition (18). Physiological changes occurred due to aging can also modify pharmacodynamic and pharmacokinetic parameter of anticancer drugs (19). According to another research, older cancer patients who take more than two medications for their therapy are at twice the risk of side effects. The likelihood of non-compliance and non-adherence to treatment rises with age and co-morbidities, particularly in elderly and juvenile patients(20).

Nowadays, older individuals tend to take chemotherapy drugs more often than younger patients, and this might be a risk factor for both more frequent and severe adverse drug reactions (ADRs) (21). ADRs and medication interactions are more common in patients receiving several chemotherapy treatments (22).This study corroborate to previous two studies as adverse effect most often (81.7%)occurs in patient on poly-chemotherapy drugs. In our study 60% of the total participants were females, they mostly suffered with “Grade 3 and4” ADRs (61.1%) that is closed to the result of other study.The severity of ADRs observed in females was noticeably greater, which may be related to changes in hormonal activity over life(6).

Vomiting and nauseousness were the most typical ADRs we discovered in our investigation. Other studies have noted nausea and vomiting as the most typical adverse drug reactions (ADRs) associated with cancer treatment(23,24).In our study most common chemotherapy agent used were found to be combination of Carboplatin and Paclitaxel (14.2%).It may be the cause of the poly-chemotherapeutic group's greater prevalence of ADRs and the fact that vomiting and nausea are the most prevalent ADRs. The mechanistic reason behind most common occurrence of nausea & vomiting may be due to patients experience it acutely up to 24-hour post treatment. It may lead to anticipatory nausea and vomiting if not treated on time. Prior to chemotherapy, three medication regimens are used to treat chemotherapy-induced nausea and vomiting (CINV), including dexamethasone, ondansetron, and neurokinin-1 receptor antagonists (NK1), likeaprepitant (25). The expense and unavailability of aprepitant, one of the key medications indicated to treat CINV, may be the cause of the greater frequency of CINV in our research.

Neutropenia, alopecia, fever, and thrombocytopenia and anemia are the following most frequent adverse chemotherapeutic reaction (ADR) symptoms that were observed in this research. Other study also suggest higher incidence rate of alopecia and its most important cause is administration of polychemotherapy (26).One of the most frequent side effects of chemotherapy is neutropenia(27).Majority of cancer patients may develop neutropenia by chemotherapeutic agents. It can also be caused by lymphocytic leukemia, hairy

cell leukemia and chronic lymphocytic leukemia or solid tumor if they infiltrate the bone marrow. Other risk factor of neutropenia in cancer patients may include older age and patients on poly-chemotherapy regimens. FDA (Food and Drug Administration) approved G-CSF tbo-filgrastim are well tolerated and are advised to use who are more prone (28). Majority of chemotherapeutic drugs like alkylating agents, anthracycline, pyrimidine analog, nitrosourea and others causes myelosuppression in dose dependent manner, it can be prevented by reducing the dose of anticancer medication and by the use of hematopoietic growth factors(29). In some other study myelosuppression as, adverse effect was found out to be the one fourth of its total ADRs. It may be mainly due the use high doses of chemotherapy drugs like methotrexate and ifosfamide (30).

Assessment of causality by WHO-UMC scale revealed that 46% ADRs were “Probable”, 44% ADRs were “Possible” while 10% were “Unlikely”. Anaphylaxis, anorexia, constipation, dizziness, headache, ototoxicity and hyperpigmentation of nail were noted as “Unlikely” ADR on WHO-UMC assessment scale. “Probable” ADRs are comparable to the one study held in Ethiopia (6). Each ADRs produced by chemotherapeutic drugs in our study were assessed for toxicity grade by NCI-CTCAE scale(3). Routine clinical practice of patient reporting outcome-CTCAE plays a major role in evaluation of symptomatic toxicities and also improves the clarity of documentation (31).

Conclusion

The research elucidated the demographic structure of chemotherapeutic medicines' adverse effects. Each patients receiving chemotherapy encountered with at least one ADR. Female patients were more susceptible to adverse effects as compared to male. According to research, breast cancer is the most frequent kind of cancer. Garde 3 and 4 ADRs were more often noted in age group 51<. Mostly patient were on polychemotherapy, and maximum number of patients were at high risk of grade 3 and 4 toxicities. Alopecia and neutropenia were the two most prevalent ADRs associated with cancer treatment, preceded by vomiting and nausea. Causality assessment showed that mostly ADRs observed during the course were Probable and possible. The correlation between ADR pattern and characteristics of patient demonstrates the requirement of paying more interest to the early diagnosis of chemotherapy-induced adverse reactions. By understanding pattern of ADRs, proper use of prophylactic ameliorative therapy can be recommended for each ADR. Further studies regarding patient's characteristics and other lab parameter may attribute for knowing and identification of additional data for risk factor.

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