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Cancer Chemotherapy-Induced Adverse Drug Reactions: A Prospective Study of Role of Socio-Demographic Factors

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Abstract

Background: Cancer chemotherapy is known to be accompanied by adverse drug reactions (ADRs). There is a paucity of documented studies concerning the factors predisposing to these ADRs in the English medical literature.

Objective: To evaluate the role played by socio-demographic factors in predisposition to ADRs in patients on cancer chemotherapy.

Material and Methods: In this prospective and observational study, outcome of relationship between socio-demographic factors and ADRs occurring in patients receiving cancer chemotherapy in a regional oncology center in Jammu and Kashmir, India over a period of one year was studied.

Results: Overall, 90% of the 102 cancer patients expressed ADRs to chemotherapy. As many as 268 ADRs were reported in the study participants. The most common adverse effects were alopecia, nausea, constipation and vomiting. The mean age of the participants was 46.84 ± 15.18 years. The mean age of

males (48.53 ± 15.46 years) was slightly higher as compared to that of females (45.53 ± 14.89 years). Aged patients had higher frequency of ADRs than young ones. Females were observed to express ADRs more often than males. Illiterate patients expressed more ADRs compared to educated patients.

Conclusion: Knowledge of socio-demographic factors may assist clinicians to address these factors in prediction of predisposition to ADRs in cancer chemotherapy.

Keywords

Adverse drug reactions; Chemotherapy; Pharmacogenomics; Pharmacovigilance; Socio-demographic factors

Introduction

According to the World Health Organization (WHO), cancer has snowballed as a top cause of death world over [1]. In 2020, it caused almost 10 million deaths [2]. Conservative estimates show that around 70% of deaths from cancer occur in low- and middle-income countries [3]. Most importantly, cancer burden is on an increase globally [1]. Over and above huge morbidity and mortality, cancer is accompanied by huge socio-economic repercussions not only in relation to patients but also their caretakers, families and the health-care systems as such. In many countries such as India, Bangladesh, Pakistan, Afghanistan, Sri Lanka, and Nepal, its burden has more than doubled up in the past two to three decades [1-3].

Adverse drug reactions (ADRs), ranking among the top global public health problems, occur much more frequently in patients on cancer chemotherapy. Such ADRs result in 6.5%-10.9% of hospitalization with a mortality of 0.15%-2.9% [4]. Moreover, these ADRs are a source of additional economic burden on the nations across the board.

The concept of “drug safety” is universally acknowledged. To ensure this goal, we have at our command the “pharmacovigilance” which is by and large well-established in the prosperous countries [5,6]. In the resource-limited countries, its organized application and practice in letter and spirit is a relatively recent development and is in the thick of “evolving process". As a matter of fact, it is still undergoing teething troubles in most of these countries.

Whereas studies on various aspects of ADRs related to chemotherapy in subjects suffering from malignancies are in progress, there is a paucity of studies concerning role of socio-demographic factors in predisposition for ADRs from cancer chemotherapy, especially from the Indian subcontinent. This prospective observational study was designed to determine the role played by socio-demographic factors in the development of ADRs in cancer patients receiving chemotherapy.

Material and Methods

The present prospective study, spread over a period of one year, was conducted in the Regional Cancer Centre, Government Medical College, Jammu, Jammu and Kashmir, India, with the approval of the

Institutional Ethics Committee and Institutional Review Board. The patients were enrolled for the study after taking their written informed consent.

Inclusion Criteria: All patients suffering from various cancers registered with the Regional Oncology Center attached to the Government Medical College, Jammu, Jammu and Kashmir, India and put on cancer chemotherapy as the only therapy at a given time regardless of age and sex. .
Exclusion Criteria: Patients receiving concomitant chemo-radiotherapy.

Methodology

All the participating patients were studied for the outcome of the cancer chemotherapy, occurrence of ADRs and the relationship between socio-demographic factors and ADRs.Only 102 patients could be followed throughout the administration of the planned treatment cycles and for 1 month thereafter. Out of those 102 patients, only 90 developed at least one ADR.

A specially predesigned proforma, Adverse Drug Event Reporting Form (as per the Government of India's CDSCO) was employed for recording the data. ADR monitoring was done in a systematic manner. The ADRs were reported by adopting both spontaneous and intensive reporting methods.

The evaluation of the socio-demographic factors in predisposition for ADRs was in terms of below parameters:

1. Age
2. Gender
3. Residential background: Urban or rural
4. Educational/literacy status

Statistical Analysis

The collected data was coded in numerical terms and was entered in excel data sheets. It was analyzed with the help of computer software Microsoft Excel and SPSS for windows.

Results

The present observational study was spread over a period of 1 year. A total of 116 patients were enrolled in the study. Out of these, 14 were lost to follow up-9 patients stopped the treatment in between, 4 patients shifted their further treatment to the private clinics and 1 patient died because of the disease. Eventually, only 102 patients could be followed throughout the administration of the planned treatment cycles and for 1 month thereafter.

Table 1 lists the frequency of various diagnoses in the 102 cases. Among the participants studied, nearly 1/4 (27.45%) had breast carcinoma and nearly 1/6 had rectal (10.78%) and lung (9.80%) carcinoma each. One case each of nasopharyngeal carcinoma, Chronic Myeloid Leukaemia, renal cell carcinoma, alveolar carcinoma, testicular tumor and ileocaecal carcinoma was seen (0.98% each).(Table 2) provides the highlights of the socio-demographic profile of the patients.

Diagnosis	Frequency(n)	Percentage (%)
Breast Ca*	**28**	**27.45**
Lung Ca*	**10**	**9.80**
Stomach Ca*	7	6.86
Rectum Ca*	**11**	**10.78**
Ewing's Sarcoma	4	3.92
Ependymoma	2	1.96
Gall Bladder Ca*	5	4.90
Nasopharyngeal Ca*	1	0.98
CML**	1	0.98
Dysgerminoma Ovary/Ovarian Cancer	3	2.94
Hodgkin's Lymphoma	3	2.94
EsophagealCa*	5	4.90
Colon Ca*	8	7.84
Renal Cell Ca*	1	0.98
Duodenum Ca*	2	1.96
Pancreatic Ca*	2	1.96
Alveolar Ca*	1	0.98
Hairy Cell Leukemia	2	1.96
Ca Cervix	2	1.96
Testicular tumour (embryonal cell Ca*)	1	0.98
Non Hodgkin Lymphoma	2	1.96
IleocaecalCa*	1	0.98
Total	102	100

Table 1: Distribution of the patients according to the frequency of their diagnosis (N=102).
Note: *Ca stands for Carcinoma; **CML stands for Chronic Myeloid Leukaemia.

No. of patients (n)	No. of patients (n)	Percentage (%)
1-10	1	0.98
11-20	7	6.86
21-30	2	1.96
31-40	23	22.55
41-50	**27**	**26.47**
51-60	**27**	**26.47**
61-70	12	11.76
71-80	2	1.96
81-90	1	0.98

Gender	No. of patients (n)	Percentage (%)
Male	49	48.04
Female	53	51.96
Residence	**No. of patients (n)**	**Percentage (%)**
Rural	68	66.67
Urban	34	33.34
Education	**No. of patients (n)**	**Percentage (%)**
Illiterate	55	53.92
Literate	47	46.08

Table 2: The socio-demographic profile of the patients (N=102).

Note: Mean age of all patients under study = 46.84 ± 15.18 years; Mean age of males = 48.53 ± 15.46 years; Mean age of females = 45.53 ± 14.89 years; Mean age of rural patients = 47.04 ± 14.43 years; Mean age of urban patients = 46.44 ± 16.79 years.

Age

The mean age of the patients studied was 46.84 ± 15.18 years. The mean age of males (48.53 ± 15.46 years) was observed to be slightly higher as compared to that of females (45.53 ± 14.89 years). More than half (52.94%) of the study participants of both sexes were aged between 41-60 years. The youngest patient was a 3 years old male and the oldest was a female aged 88 years. Obviously, both very young and very old patients were more vulnerable to ADRs compared to other age groups (Table 3).

Age group (years)	Breast Ca*1	Lung Ca*1	Stomach Ca*1	Rectal Ca*1	Ewing's Sa*2	Spindlemona	Gall Bladder Ca*1	Nasopharyngeal	CML*3	Dysgerminoma/OC*	HL*5	Esophageal Ca*1	Colonic Ca*1	Renal Ca*1	Duodenal C*1	Pancreatic Ca*1	Alveolar Ca*1	HCL*6	Ca*1 Cervix	Testicular T*7	NHL*8	Ileocaecal Ca*1	Total
1-10	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
20-Nov	0	0	0	0	2	0	0	1	0	2	2	0	0	0	0	0	0	0	0	0	0	0	7
21-30	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
31-40	4	2	0	5	1	0	0	0	1	0	1	3	2	1	0	0	0	0	2	0	0	1	23
41-60	10	3	1	3	0	0	1	0	0	1	0	0	3	0	0	0	0	1	0	1	0	0	27
51-60	8	5	4	1	0	0	1	0	0	0	0	1	1	0	1	2	0	1	0	0	2	0	27
61-70	0	1	2	1	0	1	2	0	0	0	0	1	3	0	1	0	0	0	0	0	0	0	12
71-80	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
81-90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Total	28	10	7	11	4	2	5	1	1	3	3	5	9	1	2	2	1	2	2	1	2	1	103

Table 3: Distribution of diagnosis of patients according to age (N =102).

Note: *1Ca stands for Carcinoma; *2Sa stands for Sarcoma; *3CML stands for Chronic Myeloid Leukaemia; *40C stands for Ovarian Cancer; *5HL stands for Hodgkin's Lymphoma; *6HCL stands for Hairy Cell Leukaemia; *7T stands for Tumor; *8 NHL stands for Non Hodgkin's Lymphoma.

Gender

The female participants in the study were more in number as compared to males (M:F= 0.9:1). Over half (52.83%) of all the malignancies in females were contributed by Breast Carcinoma. Other malignancies dominant in females were Rectal Carcinoma (13.21%), Gall Bladder carcinoma (7.55%), Dysgerminoma Ovary/Ovarian Cancer (5.66%) and Hodgkin's Lymphoma (5.66%). In comparison, Lung (20.41%), Stomach (12.24%), Esophageal (10.20%) and Colonic Carcinomas (14.29%) were more commonly seen in males (Table 4).

Diagnosis	Male n (%)	Female n (%)

Breast Ca	0 (0.00)	**28 (52.83)**
Lung Ca	**10 (20.41)**	0 (0.00)
Stomach Ca	**6 (12.24)**	1 (1.89)
Rectal Cancer	4 (8.16)	**7 (13.21)**
Ewing's Sarcoma	3 (6.12)	1 (1.89)
Ependymoma	2 (4.08)	0 (0.00)
Gall Bladder Cancer	1 (2.04)	**4 (7.55)**
Nasopharyngeal Cancer	1 (2.04)	0 (0.00)
Chronic Myeloid Leukemia	1 (2.04)	0 (0.00)
Dysgerminoma Ovary/Ovarian Cancer	0 (0.00)	**3 (5.66)**
Hodgkin's Lymphoma	0 (0.00)	**3 (5.66)**
EsophagealCa	**5 (10.20)**	0 (0.00)
Colonic Cancer	**7 (14.29)**	1 (1.89)
Renal Cell Cancer	1 (2.04)	0 (0.00)
Duodenal Cancer	2 (4.08)	0 (0.00)
Pancreatic Cancer	2 (4.08)	0 (0.00)
Alveolar Cancer	0 (0.00)	1 (1.89)
Hairy Cell Leukemia	0 (0.00)	**2 (3.77)**
Cancer Cervix	0 (0.00)	**2 (3.77)**
Testicular tumour (embryonal cell Ca)	1 (2.04)	0 (0.00)
Non Hodgkin Lymphoma	2 (4.08)	0 (0.00)
Ileocaecal Ca	1(2.04)	0 (0.00)
Total	49 (100)	53 (100)

Table 4: Distribution of the diagnosis of the patients according to their gender (N=102).

Urban/Rural Background

The study sample showed an overall rural predominance. Rural:Urban ratio was 2:1. The mean age of the rural population was slightly higher as compared to that of the urban population (47.04 ± 14.43 and 46.44 ± 16.79 years, respectively).

Literacy

Out of the total patients studied, 55.92% were illiterate and the rest (46.08%) were literate (had at least primary education).

Discussion

ADRs are defined as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.” Thus, ADRs are harm directly caused by the medicinal agent at normal doses and h during normal use. According to Leach and Roy, [7] socio-demographic factors that could have a bearing on the frequency and severity of ADRs, include age, gender, residence and educational status.

Broadly speaking, the factors that stand established for playing an important role in the occurrence of ADRs are either patient-related or drug related. Though favorably speculated, the contribution of socio-demographic factors in predisposing to ADRs in cancer patients receiving chemotherapy remain to be adequately studied.

Our prospective observational study, spread over a period of one year, was designed to evaluate the role of socio-demographic factors as “predisposing indices” in development of ADRs in cancer patients on chemotherapy.

ADRs-Age Relationship

Age is a known independent risk factor for ADRs. Most of the ADRs in the present study were encountered in relatively older patients, a finding that is in keeping with the observations made by other workers [8,9].

An analysis of our patients showed that out of the 268 ADRs, as many as 180 occurred in patients aged > 50 years. Many studies from around the world show an impressive correlation between increasing age and ADR rate [10-13].

The factors contributing to development of ADRs in older age group could include reduced renal function and metabolizing capacity of the body. According to Leech and Roy [7], ADRs are logically considered to be more frequent in the elderly due to polypharmacy, poor compliance, concurrent medical illnesses, including poor nutritional status and alteration of pharmacokinetic and pharmacodynamic parameters**.**

A study by Caamano, *et al.* [13] led to the conclusion that special attention should be paid to avoid ADRs in elderly people with nutritional problems, renal failure or those who are using two drugs or more. Additional precautions should be taken with people with cognitive impairment who have a reduced capacity to report their symptoms.

ADRs-gender Relationship

In our study, female patients suffered from larger number of ADRs as compared to male patients– an observation also made by several researchers [3, 14-16]. Gender-related differences in drug disposition could be responsible for this discriminatory observation. It has been suggested that pharmacological, immunological and hormonal differences, more consumption of drugs by women, and more perception of ADRs by women may explain some gender differences [1,17,18].

Interestingly, in a study by Wahlang, *et al.* [18] from India's North-East, ADRs were seen more frequently in male participants who accounted for 61.43% (n = 43) than in female participants who accounted for 38.57% (n = 27).

Urban/Rural Residential Background

Half of the participants studied belonged to the urban areas as compared to the rural (rural: urban = 2:1). Nearly 78% of the participants in rural areas belonged to the age group 31-60 years as compared to 70.6% of the participants in urban areas. The mean age of the rural population was slightly higher as compared to that of the urban population was (47.04 ± 14.43 and 46.44 ± 16.79 respectively).A slightly higher proportion of females (37.73%) belonged to urban areas as compared to males (28.57%).

There was no significant relationship between occurrence of ADRs on one hand and rural or urban background. However, more ADRs were encountered in illiterate participants. Similar observations were documented by Poddar, *et al.* [10] from Bangladesh. This highlights the importance of the intensive method of reporting the ADRs which involves voluntary questioning of the patients.

Literacy

In our study frequency of ADRs was inversely related to the educational status, the illiterate patients demonstrating higher incidence. The literature is nearly defunct on this aspect.

Finally, it is felt that knowledge of socio-demographic factors may be of value in prediction of predisposition to ADRs in cancer chemotherapy and provide appropriate counseling to the concerned patients and families. The knowledge also enables healthcare professionals to choose the most appropriate chemotherapy for a particular patient. However, more studies on larger number of patients, with inclusion of such social characteristics as smoking, alcohol drinking, substance abuse, etc. need to be carried out for better inputs. This observation should not be interpreted to undermine the importance of the pharmacogenomics that emphasizes the genetic predisposition of ADRs. This innovative state of the art new science is emerging as the best strategy in the decision making process of drug selection [18].

Clinical Relevance

Bearing in mind the sociodemographic indices can help the clinicians in predicting the occurrence of ADRs secondary to cancer chemotherapy, there by contribute to taking a sensible decision about the suitability of chemotherapeutic agent(s) to be administered to individual cases as well as provide counseling to the concerned patients and their families. .

Limitations of the Study

1. The period of study was just one year.
2. Such social indices as smoking, alcohol drinking and substance abuse were not included.

Summary and Conclusion

In this prospective study, an overwhelming proportion (90%) of the 102 cancer patients expressed ADRs

(258 in number) to chemotherapy. The most commonly involved system was gastrointestinal tract followed by skin and mucous membranes. Most frequently encountered ADRs were alopecia, nausea, constipation and vomiting. The mean age of the participants was 46.84 ± 15.18 years. The mean age of males (48.53 ± 15.46 years) was slightly higher as compared to that of females (45.53 ± 14.89 years). Aged patients had higher frequency of ADRs than young ones. Females were observed to express ADRs more often than males. Illiterate patients expressed more ADRs compared to educated patients. In conclusion, knowledge of socio-demographic factors may assist clinicians to address these factors in predisposition to ADRs in cancer chemotherapy and provide appropriate counseling.

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