Pattern of Adverse Drug Reactions Due to Cancer Chemotherapy in Tertiary Care Teaching Hospital in Bangladesh

Sneegdha Poddar[1], Razia Sultana[1], Rebeka Sultana[2], Maruf Mohammad Akbor[2], Mohammad Abul Kalam Azad[3] and Abul Hasnat[2]

[1]Department of Pharmacy, Stamford University Bangladesh, Dhaka, Bangladesh
[2]Department of Clinical Pharmacy and Pharmacology, University of Dhaka, Dhaka-1000, Bangladesh
[3]Department of Pharmaceutical Technology, University of Dhaka, Dhaka-1000, Bangladesh

ABSTRACT: The objective of the present study was to evaluate the pattern of adverse drug reactions (ADRs) occurring in cancer patients treated with chemotherapy in tertiary care hospitals in Bangladesh. A prospective hospital based study over a period of six month was carried out in the Department of oncology, Bangabandhu Sheikh Mujib Medical University and Dhaka Medical College Hospital. The data were subjected to descriptive analysis. A total of 50 patients having ADRs due to cancer chemotherapy were randomly selected. Adverse drug reactions were mostly occurred in the age group between 41-50 years (26%). Considering socio-economic status of cancer patients married persons (82%) have significantly higher risk than unmarried (18%). Prevalence of breast cancer (20%), cervical cancer (14%) and leukemia (16%) were higher and they were treated mostly by adjuvant chemotherapy (46%) and secondly by chemotherapy (38%) alone. In most cases ADRs were developed in patients receiving alkylating agents (40%) and antimetabolites (40%) as anticancer therapy. The five certain ADRs observed in the current study were nausea, stomatitis, alopecia, myelosuppression and increased ESR level in both male and female patients. Moreover, hematological system was affected severely by alkylating agents and antimetabolites. Similar studies covering more patients from different regions are needed to validate our findings.

Key words: ADRs, Cancer, Chemotherapy, Tertiary hospital, Bangladesh.

INTRODUCTION

Adverse drug reactions (ADRs) constitute a major clinical problem in terms of human suffering and increased healthcare costs.[1] An adverse drug reaction (ADR) is any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use. World Health Organization (WHO) defines an ADR as "any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy".[2]

Correspondence to:
Abul Hasnat
Tel. 02-8612069; Fax-02-8615583
E-mail: ahasnat99@yahoo.com

Dhaka Univ. J. Pharm. Sci. **8**(1): 11-16, 2009 (June)

A study demonstrated that adverse drug events extended the hospital stay by nearly two days and increased the cost of hospitalization by about $ 2000.[3] It has been found that the total cost of the drug related morbidity and mortality exceeds the cost of medications themselves.[4] The practice of cancer medicine has changed dramatically in the past four decades, as curative treatments have been identified for a number of previously fatal malignancies such as testicular cancer, lymphomas, and leukemia. Chemotherapy is employed as part of a multimodal approach to the treatment of many tumors.[5] The acute effects of frequent administration of antineoplastic drugs include nausea and vomiting,

often via a central mechanism, and sometimes extremely severe. Many of the adverse effects of antineoplastics are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells.[6] Common adverse drug reactions (ADRs) due to cancer chemotherapy are alopecia, nausea and vomiting, myelosuppression, haemorrhagic cystitis, mucositis, increased toxicity with impaired renal function, cardiac toxicity, hot flushes, electrolyte imbalance, deep vein thrombosis etc.[7] A recent study from a South Indian tertiary care teaching hospital has reported antineoplastic agents as the common class of drugs causing the ADRs accounting for a total of 21.8% of the reported ADRs.[8] Compromising dose intensity of drug or by delaying the doses ADRs can be minimized. But the dosage regimen and method of administration of some anticancer drugs can greatly affect their efficacy and toxicity.[9] The commonly used anticancer drugs in Bangladesh are alkylating agents, cytotoxic antibiotics, antimetabolites, vinca alkaloids, etoposide and several other antineoplastic drugs.[10] The safety profile of cancer chemotherapy is not available in Bangladesh. So the objective of the present study was carried out to evaluate the pattern of adverse drug reactions (ADRs) occurring in cancer patients treated with chemotherapy in tertiary care hospitals in Bangladesh.

MATERIALS AND METHODS

The study was carried out in the department of oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) & Dhaka Medical College Hospital (DMCH). The duration of the study was six months (August 15, 2007 to February 20, 2008) and done by prospective manner.

Inclusion and exclusion criteria. All the patients who underwent chemotherapy at the oncology department of BSMMU and DMCH during the study period were studied. Any patient who developed at least one ADR during the treatment period was included and ADRs were screened according to WHO guidelines.[11]

Operational modality. Hospitalized patients treated with chemotherapy in BSMMU & DMCH were studied prospectively. Patients who have suffered from ADRs before and after (within one month) stating chemotherapy were identified by the first author and reconfirmed by the corresponding author during their hospital stay. Only certain and probable ADRs (based on WHO causality definitions) were included in the study. [11] The study protocol was approved by the institutional ethical review Board before starting the study. The socio-economical, biophysical, clinical and treatment data were collected from the inpatient case records using a specially designed data collection form which include age, gender, education level, occupation, smoking habit, completed diagnoses, comorbid factors, hematological changes (hemoglobin, ESR level), serum creatinine, duration of hospital stay and the outcome. Data collected on adverse drug reactions included drugs received, nature of ADR, drugs implicated, signs and symptoms of extravasations, in accordance with the data collection form. Collected data were analyzed by SPSS for descriptive statistics.

RESULTS AND DISCUSSION

Among the 50 patients, 24 male (48%) and 26 (52%) female patients had suffered from ADRs within one month after receiving cancer chemotherapy. According to the causality assessment, 5 ADRs were classified as ‘certain’ and 12 as ‘probable’ associations with the drug. The prevalence of adverse drug reactions mostly occurred in the age group between 41-50 years (26%) and in female patients (52%) compared to male patients (48%). The male-to-female ratio was 1: 1.1. (Figure 1)

Socio-economic status. From Table 1, it was found that married (82%) persons are more susceptible to cancer than unmarried (18%). Among the study population, (64%) are living in rural area and 32% are businessman. This study also shows that illiterate persons (32%) have higher risk for developing ADRs than the educated.

Biophysical characteristics. Among the biophysical characteristics the most significant changes that occur in the patients average BMI level before (21.46 kg/m²) and after (18.56 kg/m²) chemotherapy and shown in Table 2. BMI level decreased by 13.52% after chemotherapy has started.

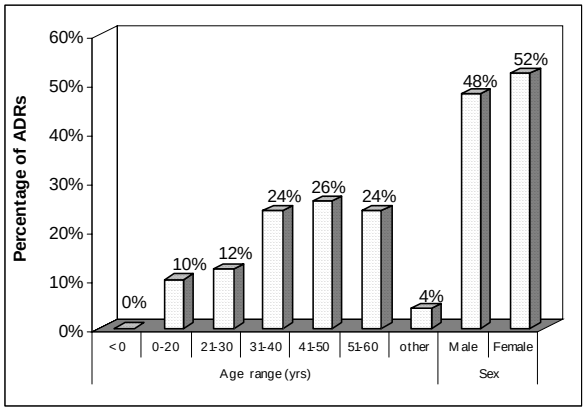


Figure 1. Prevalence of ADRs in different age group and gender receiving chemotherapy.

Cancers and Treatment. The prevalence rate of different types of cancer that have been encountered in this study. It has been found that patients are mostly affected by breast cancer (20%), leukemia (16%) and cervical cancer (14%) (Figure 2).

Among different kinds of anticancer therapy highest percentage of peoples (46%) were found to be treated with adjuvant chemotherapy. The suspected anticancer drugs that cause ADRs are presented in Figure 3 which shows antimetabolites (40%) and alkylating agents (40%) are mostly responsible for adverse effect. 16% people were treated with platinum.

Adverse Drug Reactions. Among the five certain ADRs, most of the patients (52%) have risk for severe vomiting during chemotherapy (Figure 4). Stomatitis (20%) is one of the common ADRs during cancer chemotherapy. Myelosuppression is another certain ADR observed in the current study and a higher percentage of people (16%) suffering from bleeding during chemotherapy. Alopecia is a very certain ADRs during chemotherapy and 29 people (58%) were found to have alopecia after giving chemotherapy. In the present study a higher percentage of people 15 (30%) have alopecia with total baldness after chemotherapy (Figure 4). The most significant changes were observed in the ESR level (mm in 1st hr) within one month after chemotherapy has been started. It was also revealed that male patients have 151.85 % increased ESR level whether female patients have 337.62 % increased level of ESR during chemotherapy. The other probable ADRs associated with chemotherapy are abnormal renal function (16%), impaired hepatic function (6%), emesis (52%), itching (24%), inflammation (20%), headache (10%), swelling (24%), neutropenia (30%), diarrhoea and constipation

Table 1. Socio-economical parameters of cancer patients

Marital status	Number (n=50)	%	Family expense	Number (n=50)	%
Married	41	82	Lower middle	12	24
Unmarried	9	18	Upper middle	30	60
			Poor	8	16
Place of living			**Smoking**		
Rural	32	64	Never	29	56
Urban	16	32	Ex smoker	13	26
Other	2	4	Current smoker	8	16
Educational status			**Occupation**		
Illiterate	16	32	Clerical	4	8
Can read only	8	16	Businessman	15	30
Can write a letter	2	4	Student	2	4
SSC	12	24	Professional	4	8
HSC	4	8	Technical	2	4
Graduate or higher	8	16	Skilled worker	6	12
			Unemployed	4	8
			House wife	9	18
			Farmer	4	8

(20%), skin disorder (4%), thrombocytopenia (10%) and paralysis (2%). To compensate these ADRs different classes of drugs were found to be used like proton pump inhibitor (46%), vitamin (44%), antibiotic (36%), antiemetic (28%), H_2-receptor blocker (22%), antiseptic disinfectant (20%), corticosteroids (14%), anti-anemic (14%), blood transfusion (12%), sedatives (12%), opoid analgesic (8%), antispasmodic (4%), antidepressant (2%) and antidiarrhoeal (2%) in the present study.

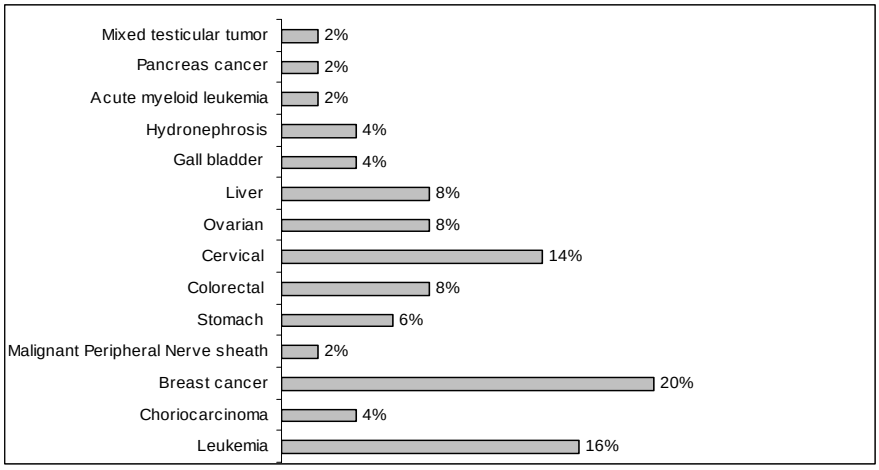


Figure 2. Different types of cancer observed in this study

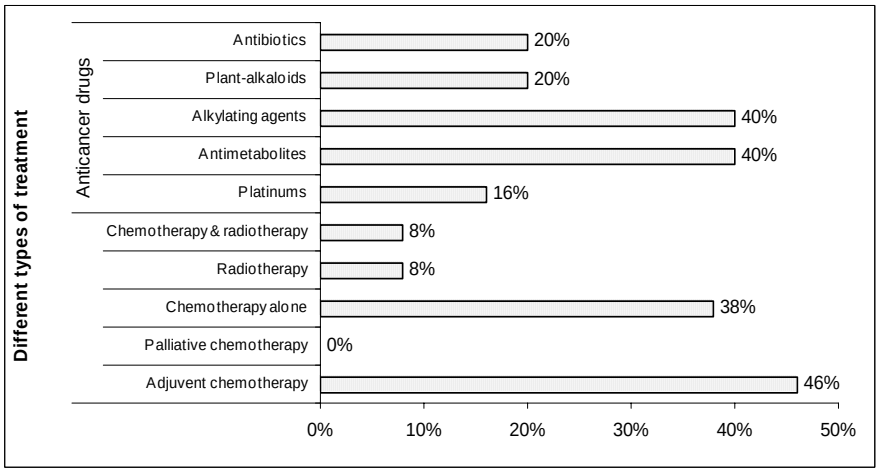


Figure 3. Different types of treatment applied for treating cancer patients

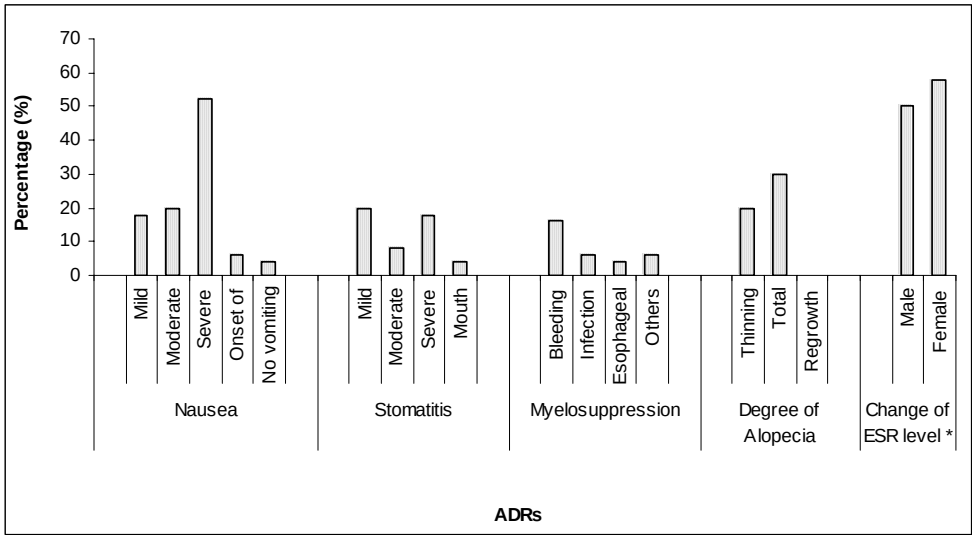
Table 2. Biophysical characterization of 50 patients during chemotherapy

Bio Physical Characteristics	Normal	Abnormal	
Pulse	40%	60%	
Temperature (°F)	84%	16%	
BP	56%	40%	
BMI (Mean)	BFC (kg/m²)	DC (kg/m²)	% Decreased
N=50	21.46	18.55	13.52

N=Number of patients encountered ADRs, BFC= Before Chemotherapy, DC=During Chemotherapy (within one months after starting of chemotherapy)

The findings of the current study are similar to another study conducted by Blacker et al in 1993 where adverse drug reactions are known to occur commonly in female population than the males.[12] The reasons for the increased incidence of ADRs in female may be due to the different stages like puberty, pregnancy etc. During these periods an alteration occurred in the pharmacokinetics of the drugs.[13] Among the biophysical characteristics a decreased BMI (Body Mass Index) was observed. When age group is taken into consideration then

elderly patients (Between 41-50 yrs) encountered majority (26%) of the ADRs. This finding is similar with Jose *et al.* where the incidence of ADRs among elderly and older adults were significantly higher than other age groups but no difference (like this study) were observed in gender group.[8] This may be due to the low metabolizing capacity and reduced excretory functions leading to accumulation of drugs in the body and thus increasing the risk of ADRs.[14] in elder patients. As a result extra precautions should be taken while using chemotherapy in the elderly population. Lao *et al.* also found the constipation as the most common ADR followed by nausea with or without vomiting.[15-17] The decrease of ESR level in the cancer patient receiving chemotherapy in the present study is in agreement with previous finding.[18] While destroying cancer cells, chemotherapy can also damage rapidly dividing cells of bone marrow resulting in myelosuppression by affecting WBCs, platelets and RBCs. Neutropenia resulting from chemotherapy may be life threatening. Thrombocytopenia when suspected clinically or diagnosed by laboratory investigations has to be managed with platelet transfusion when indicated. Anaemia due to chemotherapy can be managed by antianaemics and blood transfusion. More than 80% of patients receiving chemotherapy experience these side effects in the present study. The most common mechanism of chemotherapy induced nausea and vomiting may be by activation of CTZ (Chemoreceptor trigger zone). The use of newer anti-emetics agents significantly decreased the incidence of nausea and vomiting though they have failed to prevent this completely. In the current study, in majority of the cases the dose of anti-emetic was increased in order to manage this ADR. Since vomiting is a common problem associated with cancer chemotherapy, strategies should be made to prevent and manage the vomiting in patients undergoing cancer chemotherapy.



n=Number of ADRs observed in cancer patients within one months after chemotherapy started. %=Percentage of occurrence. *ESR level of Cancer patients measured in mm in 1st hr by westergreen method. *Percentage calculated within male and female. *151.85 and 337.62% increase of ESR level were observed for male and female respectively.

Figure 4. Five different Adverse drug reactions (ADRS) in cancer patient with chemotherapy

CONCLUSION

Chemotherapeutic drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells. However, early detection of drug toxicity helps to modify the doses or the drug regimen to minimize toxic effects. The duration of the study was only for six months, a major limitation of the study. The number of patients developing the ADRs was also less. So, similar studies covering more patients from different regions are needed to validate the findings of this study.

REFERENCES

1. Nerurkar, R.P., Nadkar, M.Y. and Bichile, S.K. 1998. Need for monitoring adverse drug reactions. *J Assoc Physicians India*. **46,** 673-4.
2. Lee, A., and Thomas, S.H.L. 2003. Adverse drug reactions. In: Clinical Pharmacy and Therapeutics Roger (Walker and Clive Eds) 3rd ed. Spain: Churchill Livingstone., pp. 33-34.
3. Classen, D.C., Pestotnik, S.L., Evans, R.S., Lioyd, J.F. and Burke, J.P. 1997. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA*. **277**, 301-6.
4. Smith, D.L. 1993. The effect of patient non- compliance on health care costs. *Med Interface*. **6**, 74-84.
5. Chabner, B.A., Amrein, P.C. and Druker, B.J. 2006. Antineoplastic agents. In: *Goodman and Gilman"s The Pharmacological Basis of Therapeutics.* 11th ed. USA: MaGraw-Hill Companies, Inc., pp.1315
6. Sweetman, S.C. 2002. In: Martindale: *The Complete Drug Reference*. 33rd ed. London, Pharmaceutical Press. pp 645.
7. Beers, M.H. and Berko, R. 1999. *The Merk manual*.17th ed. USA. pp 990-993.
8. Jose, J. and Rao, P.G. 2006. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. *Pharmacol Res*. **54**, 226-233.
9. Balmer, C.M., Valley, A.W. and Iannucci, A. 2005. Cancer Treatment and Chemotherapy. In: *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. USA: McGraw-Hill Companies, Inc. pp. 2279.
10. Rahman, M. H. 2006. Drugs used in malignant disease and immunosuppression. In: *Bangladesh national Formulary*. Directorate of Drug Administration, Dhaka, Chapter 14, pp. 400-430.
11. Edwards, I.R. and Aronson, J.K. 2000. Adverse drug reactions: Definitions, diagnosis and management. *Lancet.* **356**, 1255-1259.
12. Blacker, K., Stern, R. and Wintroub, B.U. 1993. Cutaneous reactions to drugs. In: *Dermatology in general medicine*. New York: McGraw-Hill. pp 1783-1794.
13. Wilson, K. 1984. Sex-related difference in drug disposition. *Clinical. Pharmacokinet*. **9**, 189-202.
14. Bates, D.W. and Leape, L. 2002. Adverse Drug Reaction. In: *Morreli's Clinical Pharmacology.* Boston: McGraw-Hill. pp. 1223-1257.
15. Lau, P.M., Stewart, K. and Dooley, M. 2004. The ten most common adverse drug reactions (ADRs) in oncology patients: do they matter to you. *Support Care Cancer*. **12**, 626-33.
16. Jenns, K. 1994. Importance of nausea. *Cancer Nurs*. **17**, 488.
17. Stewart, D.J. 1991. Nausea and vomiting in cancer patients. In: *Nausea and vomiting: recent research and clinical advances*. Florida: CRC Press. pp.177
18. Yang S.H., Yang, R.S. and Tsai, C.L. 2001. Septic arthritis of the hip joint in cervical cancer patients after radiotherapy: Three case reports. *J. Orthopaedic Surgery.* **9**, 41-45.