ORIGINAL ARTICLE

PATTERN OF ADVERSE DRUG REACTIONS DUE TO CANCER CHEMOTHERAPY IN A TERTIARY CARE TEACHING HOSPITAL IN NEPAL

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ABSTRACT

Use of cancer chemotherapeutic drugs is associated with several adverse drug reactions (ADRs) ranging from mild nausea to fatal myelosuppression. Data regarding safety profile of cancer chemotherapy is lacking in Nepal.

To study the pattern of ADRs caused by cancer chemotherapeutic drugs in Manipal Teaching Hospital (MTH), Pokhara, Nepal.

Hospitalized patients treated with cancer chemotherapy drugs from 1st January to 30th June 2006, was studied retrospectively. Necessary information was collected from the patients' hospital records.

Total 60 patients underwent chemotherapy among which 25 (41.67%) developed ADRs. More than half (60 %) were male and 40 % were of age group 61-70 years. The mean ± SD age was 57.8 ± 11.54 years. More than half of the patients (56%) who developed ADRs were on adjuvant chemotherapy. Alkylating agents were responsible for the ADRs in nearly half of the patients (52%) followed by antimetabolites (20%). Cisplatin was the individual drug responsible for 44% of the ADRs. The onset of the ADR was within a day in 44% of the patients.

Thirty six percent of patients developing ADRs stayed in the hospital for 1-4 days. Hematological system was affected primarily (40.47% of the patients), followed by the gastrointestinal tract (33.33%). Grade I neutropenia was the most common ADR affecting 28.6% of the patients, followed by emesis (21.4%). Increased dose of antiemetics was needed in 38.5% of the patients to manage the ADRs. Levamisole was the drug used primarily (30.43%) for managing ADRs.

Male patients and age group 61-70 years were highly predisposed to ADRs. Cisplatin was the common drug responsible for ADRs. Levamisole was commonly used in managing the ADRs. Similar studies covering more patients form different regions are needed to validate our findings.

Keywords: Cancer chemotherapeutic drug, antiemetics, cisplatin, ADR.

INTRODUCTION

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" (Lee and Thomas, 2003). A study demonstrated that adverse drug events extended the hospital stay by nearly two days and increased the cost of hospitalization by about $ 2000 (Classen *et al.,* 1997). It has been found that the total cost of the drug related morbidity and mortality exceeds the cost of medications themselves (Smith, 1993). 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 (Chabner *et al.,* 2006). Chemotherapy is employed as part of a multimodal approach to the treatment of many tumors (Chabner *et al.,* 2006). The acute effects of antineoplastic administration frequently include nausea and vomiting, often via a central mechanism, and sometimes extremely severe (Sweetman, 2002). 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: antineoplastic therapy is made possible only by increased sensitivity or less effective recovery of malignant cells compared with normal cells (Sweetman, 2002).

The commonly used cancer drugs in Nepal are cisplatin, cyclophosphamide, doxorubicin, fluorouracil, lomustine, methotrexate, mitomycin, procarbazine, vincristine, vinblastine, prednisolone, stilboestrol, ethinyloestradiol, norethisterone, medroxyprogesterone, tamoxifen and azathioprine (Nepalese National Formulary, 1997). Compromising dose intensity of cancer drug therapy by delaying or reducing doses can compromise outcomes of therapy. Dose regimen and method of administration of

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some anticancer drugs can greatly affect their efficacy and toxicity (Balmer *et al.,* 2005).

Common ADRs due to cancer drugs are alopecia, nausea and vomiting, myelosupression, hemorrhagic cystitis (alkylating agents), mucositis, increased toxicity with impaired renal function, cardiac toxicity, hot flushes, electrolyte imbalance, deep vein thrombosis etc (Beers and Berkow, 1999). 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 (Jose and Rao, 2006). The safety profile on cancer medicines is not available in Nepal. Hence, the present study was carried out with the following objectives.

1. To study the demographic details of the patients who had developed ADRs during chemotherapy
2. To study the pattern of ADRs occurring in the patients treated with chemotherapy in Manipal Teaching Hospital (MTH), Pokhara, Nepal.
3. To identify the drugs used in managing ADRs and the duration of their use

Methodology

The details of the study methodology are mentioned below.

Study site

Department of Radiotherapy and Oncology, Manipal Teaching Hospital (MTH), Phulbari, Pokhara. MTH is a 550 bedded tertiary care hospital located in Western Nepal. MTH runs a separate Radiology and Oncology unit which is supported by a separate ward, outpatient department, and day care unit and radiotherapy setup.

Study duration

All the patients treated with cancer chemotherapy drugs during 1st January to 30th June 2006.

Study type

Retrospective study.

Inclusion and exclusion criteria

All the patients who underwent chemotherapy at the Oncology department of MTH during the study period were studied. Any patient who developed at least one ADR during the treatment period was included. The patients who did not develop any ADRs were excluded from the study.

Operational modality

Hospitalized patients treated with chemotherapy from 1st January to 30th June 2006, in MTH, Pokhara was studied retrospectively. Information on age, sex, diagnosis, treatment, suspected drugs causing ADRs, duration of hospital stay, system affected by the ADRs, type of ADRs, outcome of the ADRs and drugs used to manage the ADRs were analyzed. The SPSS package, version 9.5 was used to carryout the descriptive statistics.

Results

During the study period, a total of 60 patents received cancer chemotherapy among which 25 of them developed an ADR with an incidence of 41.67%.

Age and sex distribution of the patients (n=25)

Among the 25 patients, men were 15 (60%) and female 10 (40%). The mean ± SD age of the patients who developed ADRs is 57.8 ± 11.54 years. Majority [40% (n=10)] of the patients developing the ADRs were in the age group of 61-70 years followed by 51-60 years 8 (32%), 41-50 years 4 (16%), more than 70 years 2 (8%) and 21-30 years 1 (4%).

Clinical diagnosis of the patients

Among the patients, higher incidence of ADRs was seen in the patients undergoing treatment for lung cancer and stomach cancer. The details regarding the diagnosis of the patients who developed the ADRs are listed in table 1.

Table 1. Diagnosis of the patients developing the ADRs (n=25)

Diagnosis	No. of reports	Percentage
Lung cancer	5	20
Stomach cancer	4	16
Breast cancer	3	12
Cervical cancer	3	12
Colorectal cancer	3	12
Gall bladder cancer	2	8
Ovarian cancer	2	8
Head and neck cancer	2	8
Acute myeloid leukemia	1	4

Treatment type

Most commonly ADRs were noted in the patients undergoing adjuvant chemotherapy. The details regarding the treatment type of the patients developing ADRs is mentioned in table 2.

Table 2: Treatment type of the patients developing the ADRs (n=25)

Treatment type	No. of reports	Percentage
Adjuvant chemotherapy	14	56
Palliative chemotherapy	5	20
Chemotherapy and radiotherapy	4	16
Chemotherapy alone	1	4
Neo adjuvant chemotherapy	1	4

Drug category causing ADRs
Among the various classes, majority of the ADRs were caused by alkylating agents 13 (52%) followed by antimetabolites 5 (20%), antitumour antibiotics 4 (16%) and mitotic spindle agents 3 (12%).

Drugs causing the ADRs
Cisplatin was the drug responsible for causing 11 (44%) of the ADRs followed by doxorubicin 6 (24%), 5 fluorouracil 5 (20%), docetaxel 2 (8%) and paclitaxel 1 (4%).

Duration of use of the suspected drugs
Among the total ADRs, 11 (44%) of them developed with in a day of drug therapy, 8 (32%) during the third day, 5 (20%) during the fifth day and one (4%) during the fourth day of drug therapy.

Duration of hospital stay
The mean ± SD duration of the hospital stays was 3.0 ± 1.75 days. Among the total patients 9 (36%) stayed in the hospital for 1-2 days and another 9 (36%) stayed for 3-4 days and 6 (24%) stayed for 5-6 days. One patient (4%) stayed for more than six days.

System affected by the ADRs
Hematological system was affected in 11 (40.47%) of the patients followed by GIT 9 (33.33%), dermatological 2 (22.22%) and renal system 1(3.70%).

Types of ADRs
Grade I neutropenia was the most commonly seen ADR in the study population. The details are listed in Table 3.

Table 3: Type of adverse drug reactions

Reaction type	No.of reports (n=28)	Percentage
Grade -I neutropenia	8	28.6
Emesis	6	21.4
Hair loss	4	14.3
Diarrhoea	2	7.1
Thrombocytopenia	1	3.6
Genaralized Itching	1	3.6
Grade II Neutropenia	1	3.6
Grade III Neutropenia	1	3.6
Allergic reaction	1	3.6
Constipation	1	3.6
Oral candidiasis	1	3.6
Increased creatinine	1	3.6

Outcome of the ADRs
The outcome of the ADRs is listed in table 4.

Drugs to manage the ADRs
Levamisole was the common drug used for managing the ADRs (Grade I neutropenia). The other drugs used in management of the ADRs are listed in Table 5.

Table 4: Outcome of the adverse drug reactions

Outcomes	No. of reports (n=13)	Percentage
Increased dose of antiemetics	5	38.5
Levamisole	2	15.4
Decreased dose of 5 fluoruracil	2	15.4
Blood transfusion	1	7.7
Death	1	7.7
Decreased dose of cisplatin	1	7.7
Cisplatin-replaced by carboplatin	1	7.7

Table 5: Drugs used to manage the ADRs (n= 23)

Drugs	No. of drugs	Percentage
Tab. Levamisole	7	30.43
Antiemetics	6	26.09
Fusidic acid ointment	1	4.35
Permethrin ointment	1	4.35
Inj. Dexomethasone	1	4.35
Granulocyte colony stimulating factor	1	4.35
Inj. Pheniramine maleate	1	4.35
Inj. Hydrocortisone	1	4.35
Tab. Itraconazole	1	4.35
Tab. Bisacodyl	1	4.35
Syrup Cremafin	1	4.35
Others	1	4.35

DISCUSSION

Our study identified the pattern of ADRs caused by cancer chemotherapeutic agents in a tertiary care teaching hospital of Nepal. In our study males were found to have maximum number of ADRs. Our observation was different from the other researchers. In general, ADRs are known to occur commonly in female population than the males (Blacker *et al.,* 1993). The reasons for the increased incidence of ADRs in female are related to several factors like female undergoes stages like pregnancy, menarchy etc. During these periods there is an alteration in the pharmacokinetics of the drugs (Wilson, 1984). However, one study identified no difference between men and women in the incidence of ADRs (Jose and Rao, 2006). We could not identify the reason for male experiencing higher number of ADRs.

Elderly patients encountered majority of the ADRs. In general the incidence of ADRs is higher in elderly patients. One study identified the incidence of ADRs among elderly adults and older adults were significantly higher than other age groups (Jose and Rao, 2006). The reason could be that in elderly patients, the metabolizing capacity and the excretory functions are generally diminished leading to accumulation of drugs in the body and thus increasing the risk of ADRs (Bates and Leape, 2000). While using chemotherapy in the elderly population, one must be extra cautious.

Alkylating agents were responsible for causing the ADRs. Among the alkylating agents cisplatin was responsible for 44% of the total ADRs. The United States Food and Drug Administration (US FDA) has approved cisplatin in the management of metastatic malignant tumor of testis, metastatic ovarian tumor and in advanced transitional cell carcinoma of bladder (Klasco, 2006). The common ADRs associated with the use of Cisplatin are related to electrolyte imbalance. The serious ADRs are nausea, vomiting, myelosuppression, peripheral neuropathy, ototoxicity and nephrotoxicity. Elderly patients are at a higher risk of myelosuppression, nephrotoxicity, and neurotoxicity due to cisplatin (Klasco, 2006).

We found hematological system (Grade-I neutropenia) as the common ADR in our patients. This was followed by vomiting. One Australian study identified the incidence, predictability, preventability and severity of ADRs in hospitalized oncology patients. The study found constipation as the most common ADR followed by nausea with or without vomiting (Lau *et al.*, 2004). While destroying cancer cells, chemotherapy can also damage rapidly dividing cells of bone marrow resulting in myelosuppression thus affecting WBCs, platelets and the RBCs. Neurropenia resulting from chemotherapy may be lifethreatening. It is managed by Granulocyte Colony Stimulating Factor (G-CSF) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) (Ganser and Karthaus, 1996). Thrombocytopenia when suspected clinically or diagnosed by laboratory investigations has to be managed with platelet transfusion when indicated. Anemia due to chemotherapy induced myelosuppression usually occurs 2-3 weeks after the administration of chemotherapy and can be managed by blood transfusion and erythropoietin (Jun, 2005).

Nausea and vomiting are one of the most common side effects of cancer chemotherapy. More than 50% of patients receiving chemotherapy experience these side effects. The severity of nausea and vomiting depend on the type of chemotherapy regimem and the dosage of individual drugs. The use of newer antiemetics agents has significantly decreased the incidence of nausea and vomiting though they have failed to prevent this completely (Jenns, 1994). The most common mechanism of chemotherapy induced nausea and vomiting is through activation of CTZ (Stewart, 1991). In our study, in majority of the cases the dose of antiemetic was increased in order to mange the ADRs. Since vomiting is a common problem associated with cancer chemotherapy, strategies should be made to prevent and mange the vomiting in patients undergoing cancer chemotherapy.

Levamisole was the common drug used in managing the ADRs. It was used as an immunomodulating drug in the patients developing hematological toxicity. Levamisole is an antihelmentic drug believed to stimulat immune system. It was used in our patients for the treatment of patients who developed afebrile Grade-I neutropenia.

Limitations

Our study had many limitations. The duration of the study was only six months. The number of patients developing the ADRs was less and thus prevented us in applying extensive statistics to the data. Since the number of the patients is low, further studies covering large patient population over a long period is needed to validate our findings.

CONCLUSION

Male patients and patients belonging to the age group 61-70 years had a higher incidence of ADRs. Mostly hematological system was affected by the chemo-therapeutic agents and cisplatin was the common drug causing the ADRs. Levamisole was used in many patients in order to manage the ADRs. The study was its kind in providing a baseline data regarding the safety profile of cancer drugs in Nepal. Similar studies covering more patients form different regions of Nepal are needed to validate our findings.

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