Pattern and impact of drugs targeted toward toxicity amelioration in patients receiving cancer chemotherapy

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INTRODUCTION

Groundbreaking discoveries during the latter half of the 20th century have put us in a position to be able to use medical knowledge to both enhance and augment life. Unfortunately, noncommunicable diseases (NCDs) continue to be on the rise.[1] According to Thakur JS, et al. the share of NCDs in total mortality has been catapulted from 40% in 1990 to a projected 67% in 2020.[2] Among all NCDs, cancer accounting for about 7.6 million deaths per year is second only to cardiovascular diseases. Treating

Abstract

Background: Drug therapy today is remarkably safe and efficacious. Still, some drugs - particularly anticancer drugs - are fraught with numerous adverse drug reactions (ADRs), severely jeopardizing quality of life of cancer patients. Fortunately, most of these ADRs are preventable provided adequate prophylactic drugs are administered along with chemotherapy.

Aims: The aim of this study is to assess the pattern and impact of cytoprotective prophylactic drugs on anticancer ADRs in patients receiving cancer chemotherapy.

Subjects and Methods: We included 200 patients receiving anticancer therapy for the first time. Patient details and for each cycle: details of baseline investigations, anticancer treatment given, ADRs observed and interventions done to prevent and manage the ADRs were recorded. Preventability and predictability scales were applied to assess the impact of drugs and strategies toward toxicity amelioration. Data were analyzed using descriptive statistics.

Results: Adjuvant drugs were administered prophylactically along with anticancer drugs for the prevention of nausea and vomiting, gastritis, immediate allergic reactions, nephrotoxicity, ototoxicity, hemorrhagic cystitis, and other anticipated ADRs. About 94.80% reactions were found to be predictable and 5.20% unpredictable. Maximum reactions (56.47%) were probably preventable. Paracetamol, filgrastim, mucaine, etc., were used to manage a variety of ADRs.

Conclusions: Although the predictability of ADRs was almost 95%, we could prevent only about 56% of them. Surprisingly, we have no ADRs that appear definitely preventable. This could be due to less attention being paid to the ADRs that could have been prevented by the appropriate use of prophylactic measures.

Keywords: Adverse drug reactions, anticancer drugs, predictability, preventability, toxicity amelioration
cancer is a daunting task. Several types of treatment modalities need to be combined. Available therapeutic options are surgery, chemotherapy, radiation therapy, and immunotherapy.\[4\] Chemotherapy is the most commonly employed. However, chemotherapy is curative in only about 5% of cancer patients. Still, it is routinely given to more than 50% patients, with the appearance of several adverse effects.\[4\] The reasons for this colossal toxicity probably are (a) the close structural and functional resemblance of cancer cells with normal cells, (b) cancer cells are more plastic and adapt to environmental changes; manifesting as resistance to chemotherapy, (c) entry of drugs into the tumor depends on vascular supply; blood supply is poor inside tumor with resultant poor drug concentration. Anticancer drug development, therefore, is a priority research area. New drugs with limited efficacy and unacceptable toxicity are being continually added, sometimes within 6 months.\[5-7\]

Consequently, many adverse drug reactions (ADRs) which could otherwise have been detected in rigorous clinical trials are missed.\[8\]

Thus, both existing and upcoming anticancer drugs are potential sources of clinical toxicity, and physical, emotional, and financial trauma, making the quality of life of patients severely compromised.\[8,9\] Studies in India and China on anticancer drugs have reported ADRs in 22%–100% individuals.\[11\]

Despite this grim picture, it is very much possible to prevent these ADRs and to treat them adequately with approaches such as dose reduction, use of alternate drugs, growth factors, and cytoprotective agents. Several strategies such as the use of antiemetics, mannitol, and antiallergic drugs along with anticancer drug infusion have been in place for many years. Careful and appropriate usage of these practices remarkably reduces the burden of anticancer ADRs. Therefore, it is of vital importance to know how much and how well these strategies are employed in hospital settings and also to find out the remaining lacunae and ways to manage them for all inclusive patient management.

**SUBJECTS AND METHODS**

Patients being prescribed cancer chemotherapy for the first time, over a period of 12 months were included in the study. They were followed up every 21 days for at least 6 months, for occurrence of any adverse events. Patient’s demographic details and for each cycle: details of baseline investigations, anticancer treatment given, ADRs observed and interventions done to prevent and manage the ADRs were recorded. ADRs were classified as predictable or not predictable on the basis of modified guidelines developed by the Council for International Organizations of Medical Sciences.\[12\] Preventability of the ADRs according to the modified Schumock–Thornton criteria was analyzed and categorized as definitely preventable, probably preventable, or not preventable.\[13\]

**Criteria for determining predictability of an adverse drug reaction (based on the Council of International Organization of Medical Sciences’ guidelines)**

**Patients who have had the drug on a previous occasion**
If the drug was previously well tolerated at the same dose and route of administration, the ADR is not predictable; if there was a history of allergy to or previous reaction to the drug, the ADR is predictable.

**Patients who have never had the drug previously**

The incidence of the ADR reported in product information or other literature determines its predictability.

| Incidence Rate | Incidence Description | Predictability |
|----------------|-----------------------|----------------|
| ≥1/10          | Very common           | Predictable    |
| ≥1/100 and < 1/10 | Common               | Predictable    |
| ≥1/1000 and <1/100 | Uncommon            | Not Predictable|
| ≥1/10,000 and <1/1000 | Rare               | Not Predictable|
| <1/10,000       | Very rare             | Not Predictable|

**Preventability assessment of the adverse drug reactions (modified Schumock–Thornton criteria)**

A. Definitely preventable: Answering “yes” to one or more of the following implies that the ADR is definitely preventable.
   - Was there a history of allergy or previous reactions to the drug?
   - Was the drug involved inappropriate for the patient’s age, weight, or disease status?

B. Probable preventable: Answering “yes” to one or more of the following implies that the ADR is probably preventable.
   - Was required therapeutic drug monitoring or other necessary laboratory tests not done?
   - Was a documented drug interaction involved in the ADR?
   - Was poor compliance involved in the ADR?
   - If a preventive measure was administered, was it adequate and/or inappropriate? Answer no if this question is not applicable.

If answers are all negative to the above, then proceed to section B
If answers are all negative to the above, then proceed to section C.

C. Not preventable: The ADR could not have been avoided by any reasonable means

Descriptive statistics was used to present the data.

RESULTS

A total of 200 newly diagnosed patients with 128 females and 72 males were included in the study. Mean weight of the 200 patients was 54.85 ± 12.62 kg. Mean age of all patients was 50.37 ± 13.77 years [Table 1]. Most of the patients fell in the age group of 51–60 years [Table 2]. Overall, breast cancer (47%) followed by lung cancer (10%) was the most common type of cancer [Table 2]. Cyclophosphamide followed by fluorouracil (5-FU), and epirubicin were the most commonly used drugs [Figure 1]. Baseline characteristics were comparable [Table 3].

All patients suffered from ADRs [Table 4]. Overall, a mean of 4.71 ± 2.55 ADRs was present. All patients at the end of follow-up were alive except for the one male patient with lung cancer who died after his second cycle of chemotherapy. Of the many reactions observed,
alopecia and nausea and vomiting were the most common [Figure 2].

When the predictability of ADRs was analyzed, 94.80% reactions were found to be predictable and 5.20% unpredictable. The important reactions that were found to be unpredictable were anasarca, pharyngitis, allergic phenomena, breathlessness, sedation, hiccups, and death [Table 5].

Modified Schumock–Thornton criteria were used to assess the preventability of ADRs. 56.47% reactions were probably preventable, and 43.53% reactions were not preventable [Table 5].

Drugs were used prophylactically for the prevention of nausea and vomiting, gastritis, immediate allergic reactions, nephrotoxicity, ototoxicity, hemorrhagic cystitis, and gastrointestinal tract (GIT) toxicity [Table 6]. All 200 patients received ondansetron (8 mg intravenous [IV] drip), and dexamethasone (8 mg IV drip) in 100 ml normal saline (NS) for the prevention of nausea and vomiting; 33.5% patients did not report any nausea and vomiting. All the patients also received ranitidine (50 mg IV drip) in 100 ml NS, for the prevention of gastritis; 76% patients did not report any gastritis. Mannitol (20% in 100 ml NS), MgSO₄ (1amp - 2 ml), and KCl (1amp - 10 ml) along with cisplatin-containing regimens were administered to 54 patients for the prevention of nephrotoxicity and ototoxicity. None of the patients receiving cisplatin reported any ototoxicity and only 1 reported edema-whole body, which was taken as a subjective sign of nephrotoxicity. Mesna was used to prevent hemorrhagic cystitis in patients receiving ifosfamide-containing regimens. Out of three patients in this group, none reported any hemorrhagic cystitis. Pheniramine (1amp - 2 ml) was used in 62/200 patients receiving cyclophosphamide, epirubicin, docetaxel, 5-FU, cisplatin, carboplatin, and paclitaxel-containing regimens; 85% had no allergic reactions. Leucovorin was used in FOLFOX regimens with 5-FU and oxaliplatin for Ca colon. None of the patients receiving methotrexate reported any bone marrow toxicity

### Table 3: Number of drugs prescribed and number of adverse drug reactions in males and females

| Sex            | Mean±SD | Number of drugs prescribed | Number of ADRs  |
|----------------|---------|----------------------------|-----------------|
| Male           | 6.8±1.57| 4.73±2.54                  |                 |
| Female         | 6.85±1.51| 4.71±2.55                  |                 |
| Total (male + female) | 6.8±1.51| 4.71±2.55                  |                 |

ADR = Adverse drug reactions, SD = Standard deviation

Figure 1: Anticancer drugs used in various cancers (n = 200). Cyclophosphamide was the most commonly used drug. Platinum compounds were also quite frequently used

Figure 2: Distribution of adverse events (n = 200). Alopecia, nausea, vomiting, and peripheral nervous system manifestations were the most common adverse drug reactions
and 50% of these patients reported GIT toxicity in the form of diarrhea, constipation, etc. Doses were adequate and as per standard guidelines.

Several ADRs appearing in a variety of patients were treated symptomatically. Ondansetron and dexamethasone for the treatment of nausea and vomiting were given in 132 patients while aprepitant was administered in three patients for nausea and vomiting not responding to ondansetron and dexamethasone [Table 7]. Musculoskeletal pain, headache, fever, and pharyngitis were treated with Paracetamol in 97 (48.5%) patients. Sixty-five (32.5%) patients presenting with gastritis were treated with ranitidine or pantoprazole. Cyproheptadine was used to treat anorexia in 45 (22.5%) patients. Liquid paraffin and milk of magnesia were used for the treatment of constipation in 41 patients (20.5%), oral ulceration was treated by the use of mucaine gel in 31 (15.5%) patients. For the treatment of neutropenia in 22 patients, filgrastim was used. In four patients, the brand of filgrastim used was changed from X-grast to neupogen in view of the intractable myalgias and bone pain being experienced by patients who were taking X-grast. Anemia was treated by blood transfusions, erythropoietin, and packed red blood cells in two patients each. For the treatment of diarrhea, metronidazole was used in 18 patients whereas ciprofloxacin and levofloxacin were used in one patient each.

### DISCUSSION

About 94.80% reactions were predictable, and 5.20% were unpredictable, in agreement with a variety of studies conducted in India and Bangladesh where the range of reactions that are unpredictable has been from 3% to 7%.14

Most of the reactions that appeared unpredictable were allergic and idiosyncratic reactions such as rash, pruritis, injection site reactions, etc. For some drugs that are prone to cause allergy (paclitaxel, carboplatin, etc.), antiallergic medication is usually given prophylactically as was given in this study. Risk factors for allergies are not well known which stresses the importance of active anticancer drug monitoring.

Modified Schumock–Thornton criteria classified 56.47% reactions as probably preventable and 43.53% reactions as not preventable in contrast to a study conducted in India which classified most reactions as not preventable.15,16 Nausea and vomiting, alopecia, fever, diarrhea, and constipation were classified as probably preventable. The reactions that were classified as not preventable were allergic reactions, burning and tingling sensation, alteration in taste sensation, anorexia, and a few others.

It seems a sorry situation where out of about 95% reactions that are predictable we can prevent and that too probably, only 56%. Surprisingly, we have no ADRs that appear definitely preventable. This could be due to less attention being paid to the ADRs that could have been prevented by the appropriate use of prophylactic measures; establishing the huge scope for research and betterment in this area. This further stresses on the importance of having proper pharmacovigilance and dedicated preventive measures in
place, to bridge this enormous gap between predictability and preventability.

The preventability of alopecia (using cooling caps, tourniquets), nausea and vomiting (by using newer drugs such as palonosetron, aprepitant, and the older ones in appropriate dosages and durations), peripheral nervous system manifestations (by vitamin supplementation, neurotrophic agent usage etc.), and many other ADRs could have been easily increased by appropriate prophylactic measures.

Drugs were used prophylactically for the prevention of nausea and vomiting, gastritis, immediate allergic reactions, nephrotoxicity, ototoxicity, hemorrhagic cystitis, bone marrow and GIT toxicity. 33.5% and 76% patients did not report any nausea and vomiting and gastritis or dyspepsia, respectively, in the present study. These findings are similar to studies in patients who received aprepitant plus ondansetron compared to those who received only ondansetron and dexamethasone.\(^{17}\) Dexamethasone as recommended by the NCCN was not used in the appropriate dosage or duration in the present study; 8 mg instead of 12 mg and for 4 days instead of 5 days. Ondansetron was universally given in 8 mg IV dosage, irrespective of the emetogenic potential of the drug except to a few patients in the ward. Moreover, aprepitant, an extremely useful drug, was not used universally in all patients receiving high emetogenic potential chemotherapy. If all these guidelines were followed in Toto may be the incidence of nausea and vomiting would have been much less in our study. Obviously, a lot of discrepancy and lack of fixed guidelines for prophylactic antiemesis in chemotherapy induced nausea and vomiting impacts patient care negatively. Should there be a revision of guidelines for prevention of nausea and vomiting associated with a number of chemotherapeutic

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**Table 6: Preventive measures used and their impact on adverse drug reactions**

| ADR                        | Preventive drug used            | Success rate in percentage of patients | Drug given in number of cases | Drug for which given |
|---------------------------|---------------------------------|----------------------------------------|-----------------------------|----------------------|
| Nausea and vomiting       | Ondansetron, dexamethasone      | 33.5                                   | 200                         | ALL                  |
| Nausea and vomiting       | Aprepitant                      | 50                                     | 4                           | ALL                  |
| Gastritis                 | Ranitidine or Pantoprazole      | 76                                     | 200                         | ALL                  |
| Nephrotoxicity            | Mannitol, MgSO\(_4\), KCl      | 99.5                                   | 54                          | 54 - cisplatin       |
| Ototoxicity               | Mannitol, MgSO\(_4\), KCl      | 100                                    | 54                          | 54 - cisplatin       |
| Hemorrhagic cystitis      | Mesna                           | 100                                    | 3                           | Ifosfamide - 3       |
| Allergic phenomena        | Pheniramine                     | 85                                     | 62                          | Cyclophosphamide, epirubicin, docetaxel, 5-FU, paclitaxel, cisplatin, carboplatin containing regimens |

5-FU = Fluorouracil, ADR = Adverse drug reaction, ALL = Acute lymphoblastic leukemia

**Table 7: Treatment of adverse drug reactions**

| Drug given for treatment of ADR | ADR                                      | Number of cases |
|---------------------------------|------------------------------------------|-----------------|
| Ondansetron, dexamethasone      | Nausea and vomiting                      | 132             |
| Paracetamol                     | Musculoskeletal pain, headache, fever, pharyngitis | 97              |
| Ranitidine/pantoprazole         | Gastritis                                | 65              |
| Cyproheptadine                  | Anorexia                                 | 45              |
| Liquid paraffin, milk of magnesium | Constipation                        | 44              |
| Mucaine gel                     | Oral ulceration                           | 31              |
| Filgrastim, pegylatedfilgrastim | Neutropenia                              | 22              |
| Metronidazole                   | Diarrhea                                 | 18              |
| X-grast to neupogen             | Myalgia                                  | 4               |
| Aprepitant                      | Nausea and vomiting                      | 3               |
| Blood transfusion               | Anemia                                   | 2               |
| Erythropoietin                  | Anemia                                   | 2               |
| PRBCs                           | Anemia                                   | 2               |
| Phenergan                       | Palpitations, restlessness                | 2               |
| Topical steroids                | Rash, pruritus                           | 2               |
| Ciprofloxacin                   | Diarrhea                                 | 1               |
| Levofloxacin                    | Diarrhea                                 | 1               |
| Azithromycin                    | Pharyngitis                              | 1               |
| Ibuprofen                       | Pharyngitis                              | 1               |
| Tramadol                        | Pain in abdomen                           | 1               |
| Calamine                        | Rash                                     | 1               |
| Sodium picosulfate              | Constipation                             | 1               |
| Cetirizine                      | Pruritus                                 | 1               |
| Expectorant                     | Wet cough                                | 2               |

ADR = Adverse drug reaction, PRBCs = Packed red blood cells
drugs and regimens, considering the inadequacy of current drugs, doses, and schedules in ameliorating this dreaded toxicity? It needs a serious rethinking. Mannitol, \( \text{MgSO}_4 \) and KCl in cisplatin-containing regimens were administered to 54 patients for the prevention of nephrotoxicity and ototoxicity. None of the patients receiving cisplatin reported any apparent ototoxicity and only 1 reported edema-whole body, which was taken as a subjective sign of possible nephrotoxicity. Studies have reported that although mannitol plus hydration is used to decrease cisplatin-induced nephrotoxicity, there are no compelling data that the addition of mannitol is more nephroprotective than the use of hydration alone.\(^{[18]}\) The role of mannitol in decreasing cisplatin-induced ototoxicity is also controversial with studies reporting varying data. However, the role of anti-oxidants like N-acetyl cysteine, sodium thiosulfate, amifostine, lipoic acid, etc., has been well established; unfortunately none of these were used in this study.\(^{[19]}\) \( \text{MgSO}_4 \) and KCl were given to supplement the possible deficiency caused by nephrotoxic drugs, and to decrease the severity of renal damage without interfering with the anticancer effect of the drug. In fact, among cisplatin-treated cancer patients, those given magnesium had significantly slower disease progression and longer survival times, when compared with patients given a placebo.\(^{[20]}\)

Mesna was used to prevent hemorrhagic cystitis in patients receiving ifosfamide-containing regimens and not in regimens-containing cyclophosphamide because the maximum dose of cyclophosphamide used in the present study was only 1 g.\(^{[21]}\) It is usually given in doses depending on the total dose of chemotherapeutic agent used.\(^{[22]}\) Out of three patients in this group, none reported any hemorrhagic cystitis.

Pheniramine was used in 33% patients receiving cyclophosphamide, epirubicin, docetaxel, 5-FU, cisplatin, carboplatin, and paclitaxel in varying regimens with an overall efficacy of 85%. Pretreatment with corticosteroids (CSs) and antihistaminics are recommended in regimens-containing platinum analogs and biological response modifiers.\(^{[23]}\) CSs and antihistaminics were uniformly used in all patients in this study. Leucovorin is used as a rescue treatment (bone marrow and GIT toxicity) in patients receiving high-dose methotrexate (10 mg/m\(^2\) IV q6 hr in CNS lymphomas). It is not required for cancer patients receiving normal doses (e.g., 3.3 mg/m\(^2\)/day orally or intramuscular for acute lymphoblastic leukemia) as used in this study. Leucovorin was only used along with oxaliplatin in FOLFOX regimen for ca colon in the present study, as recommended.\(^{[24]}\)

Despite preventive antiemesis, 132 patients experienced nausea and vomiting. In case of breakthrough vomiting, the general principle is to add one drug from another class, for example, atypical antipsychotics, cannabinoids, benzodiazepines, phenothiazines, or continue with ondansetron (16 mg PO/IV) and dexamethasone (12 mg PO/IV) (183). However, in this study, no such agents were used. Ondansetron (4 mg BD) and dexamethasone (4 mg BD) were continued in these patients while aprepitant was administered in three patients for nausea and vomiting not responding to ondansetron and dexamethasone. This could be because most patients reported having nausea and vomiting at the time of the next cycle and accepted it as an unavoidable part of therapy. Recently, with the increased use of aprepitant better control of acute and delayed vomiting can be expected.

To conclude, quite a few general, ADR studies have been conducted in India, but very few studies specifically pertaining to the ADRs of anticancer drugs and that too with a sample size of 200 patients. In the present study, active surveillance was done, rigorously for anticancer ADRs. Patients were followed up for 6 months and not just for the duration of chemotherapy; so even ADRs appearing after the cessation of chemotherapy or continuing after that could be analyzed. Apart from the facts already known, this study was able to throw light on some important facts. In the present study, 27 regimens of chemotherapy were prescribed for 200 patients with 29 different types of cancers. This starkly points toward the lack of fixed guidelines in the chemotherapy regimens being used. Even where guidelines do exist (ADR prevention and management), oncologists lack consensus. For some ADRs that can be prevented such as alopecia, etc., no measures are employed. The most important finding in this study was the huge gap between predictability and preventability of ADRs. Possibly the biggest limitation of this study was the fact that it suffered from recall bias.

**CONCLUSIONS**

Oncologists lack consensus and arbitrariness abounds in the management of cancer patients. Appropriate prophylactic measures to prevent ADRs are not taken. Preventability of ADRs, therefore, falls way behind their predictability. This huge gap between predictability and preventability can be remarkably reduced by dedicated and thorough use of cytoprotective adjuvants along with cancer chemotherapy. Routine monitoring in the oncology department to ensure implementation of preventive steps against anticancer ADRs can go a long way to improve the quality of life of cancer patients.
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Conflicts of interest
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