Adverse drug reaction profile of microtubule-damaging antineoplastic drugs: A focused pharmacovigilance study in India

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Abstract:
Objectives: The aim of the study was to analyze the adverse drug reaction (ADR) profile of microtubule-damaging antineoplastic drugs (taxanes and vinca alkaloids) and to look for unexpected ADRs among the local population. Focused study on these drugs, rampantly used in oncology department for a wide variety of tumors including early and advanced malignancies, would enable better treatment care by physicians.

Materials and Methods: Data on ADRs were collected from the cancer patients belonging to both gender and of all ages, on taxanes- or vinca-based cancer chemotherapy and reported in the Indian Pharmacopoeia Commission form. Causality was assessed using the WHO criteria and Naranjo's Algorithm. Preventability and severity of ADRs were also assessed.

Results: A total of 97 ADRs were reported among 488 patients on microtubule-damaging anticancer drugs admitted over a period of 1 year. The incidence rate was 19.87%. Gastrointestinal system (40.2%) was the most affected followed by bone marrow (33%) and skin (8.2%). The highest incidence of ADRs was reported among paclitaxel (54.6%), and vincristine (39.2%). Most of the reported ADRs were of milder nature and preventable. The WHO causality assessment scale indicated 71.1% possible reactions.

Conclusions: This study showed that most ADRs are preventable with effective ADR monitoring. There is a great need to create awareness among healthcare professionals regarding the importance of the pharmacovigilance system. Judicious use of the preventive measures will lead to a reduction in the incidence of ADRs due to the drug armamentarium, thereby enabling additional economic benefit to the patient and society.

Key words: Adverse drug reactions, focused pharmacovigilance, taxanes, vinca alkaloids

The National Pharmacovigilance Programme of India has recently taken increased efforts in improvising the observational methods of adverse drug reaction (ADR) detection, where, the spontaneous reporting schemes provide the major source of information.[1]

New ADRs are often discovered when drugs are used in larger or different populations than studied during initial clinical trials. An efficiently operating hospital-based reporting program may be helpful in providing an insight into the potential problems of drug usage in an institution. Through these efforts, problems can be identified and resolved, resulting in continuous improvement in patient care. The aim of the study was to analyze the ADR profile of taxanes and vinca alkaloids-based chemotherapy regimen in the cancer ward of our tertiary care hospital.

Materials and Methods

This prospective study was conducted among 488 patients admitted to oncology ward of our Hospital, over a period of 1 year, after obtaining the approval of the Institutional Ethics Committee (IEC 176/2012). It was an observational, focused pharmacovigilance study carried out as a part of the pharmacovigilance program of the hospital from January 1, 2013, to December 31, 2013.

After obtaining informed consent, data on ADRs were collected from the cancer patients belonging to both gender and of all ages, who...
were receiving either taxane – based or vinca-based cancer chemotherapy under any standard regimen. Those patients who did not receive drugs belonging to either of these groups as part of drug regimen were excluded from the study. No change in the treatment decision, schedule, or duration of cancer chemotherapy was made as a part of the study.

The patients who were admitted following the infusion were monitored for adverse effects till their discharge from hospital. The drug effects which were described by the patients and effects which were diagnosed and documented by the physician during the infusion visit and the follow-up period were recorded. No invasive investigation was suggested as a part of the study.

Patients demography, drug, dose, type of ADR, severity, causality, and outcome of the treatment of ADR were noted and reported in the Indian Pharmacopoeia Commission (IPC) form.[5] Causality was assessed using the WHO criteria and Naranjo’s Algorithm.[8] The WHO causality assessment scale[9] is the one recommended by the WHO Uppsala Monitoring Center and classifies ADR as certain, probable, possible, unlikely, conditional, and unassessable. The Naranjo’s Algorithm is a questionnaire – based scale consisting of ten objective questions with three types of answers, yes, no, or do not know. Scores are given accordingly, and the drug reaction can be classified as definite, probable, possible, and doubtful based on the total score. In Naranjo’s Algorithm, if there were alternate causes particularly other drugs in case of multi-drug regimen then the score for that question would be negative.

Preventability and severity of ADRs were assessed by modified Schumock and Thornton scale[10] and modified Hartwig et al. scale[11] respectively. The modified Schumock and Thornton scale classifies ADRs as definitely preventable, probably preventable, and not preventable based on a set of questions for each level. The modified Hartwig and Siegel scale classify the severity of ADR as mild, moderate, or severe with various levels according to factors such as requirements for change in treatment, duration of hospital stay, and disability produced by the ADR.

This was uploaded weekly on the VigiFlow database[12] for assessment by National Coordinating Centre, IPC which was reported to Uppsala monitoring center – a WHO program for International drug monitoring.

**Results**

A total of 488 patients on microtubule-damaging anticancer drugs (taxanes and vinca alkaloids) were admitted to oncology ward during the above period. Among them, 97 ADRs were reported. The incidence rate of these ADRs was 19.87%. Majority of ADRs occurred in the age group of 41–60 years (n = 45, 46.4%) with a female preponderance (n = 67, 69.1%). However, more than one ADR was observed in most patients. Of the 180 male patients, 19 (10.56%) reported with ADRs and similarly of the 308 female patients, 39 (12.66%) reported with ADRs. The observations for sex distribution of ADRs were analyzed statistically using Chi-square test. The sex wise difference in the occurrence of ADRs was statistically not significant (P = 0.481).

Of the ADRs reported, 73 (75.3%) were from those being treated for an early stage of the tumor, whereas 24 (24.7%) were from patients being treated for an advanced malignancy. Of the total reactions, 34 (35.1%) were from those who received anticancer drugs as the primary modality of treatment, 42 (43.3%) were from those who received the drugs as adjuvant therapy, 16 (16.5%) from those who received as neoadjuvant therapy, and 5 (5.2%) of the reactions were from those who received as palliative care. Only 21 (21.6%) reactions were from those who received these drugs as monotherapy, while 75 (77.3%) reactions were from those who received these drugs as a part of a regimen. Most of the patients received more than one cycle of chemotherapy during the study. The median cycle number at which ADRs were reported is 3 (interquartile range [IQR] 1–5). Results revealed that gastrointestinal system 39 (40.2%) was the most affected organ system followed by bone marrow 32 (33%), skin 8 (8.2%), kidney, central nervous system and others 6 (6.2%) [Figure 1].

The various indications for the use of taxanes were tumors of head and neck, lung, peritoneal, and gynecological tumors. The most common indication was adenocarcinoma of the lung. The frequently reported ADRs among taxanes were anemia 11 (18.6%), diarrhea 10 (16.9%), candidiasis 7 (11.9%) followed by peripheral neuropathy 4 (6.8%) [Figure 2]. The most common drug causing these ADRs was paclitaxel 53 (54.6%).

The various indications for the use of vinca alkaloids were tumors of head and neck and childhood tumors. The most common indication was rhabdomyosarcoma. The frequently reported ADRs among vinca alkaloids were febrile neutropenia 9 (23.7%), candidiasis 8 (21.1%), vomiting 6 (15.8%), followed by anemia 3 (7.9%), and obstipation 3 (7.9%) [Figure 3]. The most common drug causing these ADRs was vincristine 38 (92.9%).

Most of the reported ADRs were Type A reactions as per the ADR classification by Rawlin and Thomson. Predictability analysis showed that 43 (44.3%) of the reactions were not predictable while 54 (55.7%) were predictable. According to modified Shumock and Thornton scale, most of the reactions belonged to the category of “probably preventable” (n = 50, 51.5%), followed by 27 (27.8%) of the reactions “not preventable” while reactions like vomiting and neutropenia belonged to the category “definitely preventable” (n = 20, 20.6%). Based on modified Hartwig and Siegel scale of severity assessment, most of the reactions were of “mild level 1” severity, except for candidiasis and febrile neutropenia, which were of “moderate level 3” severity.

The WHO causality assessment scale indicated 28 (28.9%) “probable” and 69 (71.1%) “possible” but no “certain” reactions. Naranjo’s Algorithm indicated 48 (49.5%) “probable” with score ranging from 5 to 8 and 49 (50.5%) “possible” reactions with a score ranging from 1 to 4 [Table 1]. However, the grade of causality for each ADR remained low due to the presence of co-administered drugs. Of the reported cases, 69 (71.1%) received either specific or symptomatic treatment while 28 (28.9%) required no treatment. The median duration of hospital stay of those who required admission was 7.50 (IQR 0–20). From the study, it was found that 85 (87.5%) recovered
from the reaction, although none had fatal ADRs. The remaining 12 (12.4%) cases either continued to have the reaction during the study or else their reaction treatment outcome was unknown.

**Discussion**

An ADR, as defined by the WHO, is “a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man.”[8] According to Lazarou et al. in 1998, ADRs are considered fourth to sixth leading cause of death in the United States with an incidence of 0.13% fatal ADRs requiring hospital admissions.[9]

The plant alkaloids (taxanes and vinca alkaloids), exert their antineoplastic effects by interfering with microtubule function, leading to inhibition of mitosis and apoptosis. Vinca alkaloids cause destabilization of the mitotic spindle, whereas taxanes cause disorganized stabilization of microtubule ultimately resulting in cell cycle arrest.[10] Taxanes are the leading agents in the treatment of various malignancies including breast cancer, ovarian cancer, prostate cancer, Kaposi’s sarcoma, squamous cell carcinoma of the head and neck, esophageal cancer, lung cancer, and bladder cancer.[11] Vinca alkaloids are used in various treatment protocols of hematological malignancies and solid tumors including germ cell cancer, lung cancer, neuroblastoma, Ewing sarcoma, and multiple myeloma.[12]

Taxanes and vinca alkaloids being natural plant products, though apparently considered as safer drugs, like all other drugs they too show some ADRs in various patient conditions.[10]

The incidence rate of adverse reactions in this study was found to be comparatively low when compared to other studies.[13,14] This lower incidence rate could be due to delivering periodic ADR awareness classes to treating physicians and nurses, active involvement of clinical pharmacy and postgraduate students of pharmacology in clinical activities and coordination of quality control unit in the hospital.

In this study, we found that majority of the patients were females (69.1%) which is consistent with findings in other studies.[9,14,15] In India, most common cancer among males is oropharyngeal cancer followed by bronchogenic carcinoma with oropharyngeal cancer having surgical resection and irradiation as the modality of treatment. Thus, there was a proportionately higher ratio of females who were prescribed micro-tubule damaging drugs which account for the predominance of adverse reactions in them.[16] Two other studies showed male predominance while the study by Lazarou et al. showed that gender did not contribute to the heterogeneity of ADRs.[9,16,17]
Analysis of the age-wise distribution showed the predominance of patients in the age group of 41–60 years (46.4%) which is again similar to reports of previous studies. Lazarou et al. showed that age of patients could be attributed to variations in ADR occurrence. The primary indications of the microtubule-damaging drugs were for breast, ovarian, cervical, endometrial carcinomas, and other solid tumors which were more prevalent among geriatric patients. The presence of comorbid illnesses and usage of multiple drugs in them also could attribute to the adverse reactions in them. This could also be because, in elderly patients, the metabolizing capacity and the excretory functions are reduced, leading to accumulation of drugs in the body and thus increasing the risk of ADRs.

In this study, the different treatment plans adopted depend on a variety of factors such as the staging of cancer, cost of the treatment plan, patient and physician-related factors. ADRs occurring only due to chemotherapy were taken into consideration in this study. The causality attributed to the drugs received as a part of a regimen received a lower score on the Naranjo’s Algorithm.

The documented ADRs are mainly affecting the gastrointestinal tract, bone marrow and skin and this study also pointed out the same. The study of Shamma et al. and Astolfi et al. also found the predominance of the gastrointestinal system followed by the skin in ADR occurrence. Cancer chemotherapy damages rapidly dividing cells of bone marrow resulting in myelosuppression thus affecting white blood cells, platelets, and red blood cells. This myelosuppression leads to a lowering of immunity and thus patients on cancer chemotherapy are at a high risk for developing various infections. Nausea and vomiting are prominent with most cytotoxic agents and is caused mainly due to direct stimulation of chemoreceptor trigger zone.

The documented taxanes ADRs are mainly alopecia, anemia, peripheral neuropathy, arthralgia/myalgia, nausea, diarrhea, neutropenia, flushing, rash, thrombocytopenia, and severe hypersensitivity reactions and this study also pointed out the same. Arthralgia and myalgia are dose dependent reactions occurring generally at higher doses. Since patients in this study received the standard dose, there was no report of these adverse effects. The frequency of candidiasis reported is more in this study as the majority of the patients were receiving repeated cycles of chemotherapy infusion. Hyperuricemia and symptomatic hyponatremia were “not predictable,” though there are some reports of it, which cannot be considered conclusive. This again highlights the importance of a continued rigorous screening of drug safety profile.

The documented ADRs among vinca alkaloids are alopecia, peripheral neuropathy, constipation, obstipation, abdominal cramps, vomiting, diarrhea, paralytic ileus, urinary retention, polyuria, dysuria, syndrome of inappropriate antidiuretic hormone secretion (SIADH), weight loss, fever, stomatitis, headache and optic atrophy with blindness, and this study pointed out the same. Hyperuricemia and SIADH occur during active cell lysis of highly proliferative tumors of massive burden (e.g., leukemia and lymphoma) by cytotoxic chemotherapy. Thus, the dose of uricosuric acid was increased during vincristine infusion. Lau et al. reported constipation to be the most common ADR. Obstipation is a severe form of constipation associated with fecal impaction and intense abdominal pain.

The most common cancer indication of vinca alkaloids was rhabdomyosarcoma in this study. Most common cancer indication for taxanes was adenocarcinoma of the lung in this study. However, as per a study by Astolfi et al. lung cancer, cervical and breast cancer were found to be the most common.

Vincas by binding to intracellular microtubules causes intracellular edema of sensory axons and dose-dependent peripheral neuropathy. Whereas taxanes by creating leaky axonal membranes are ultimately neurotoxic to Schwann cells, clinically pictured as peripheral neuropathy.

Paclitaxel was the most commonly used drug among taxanes and vincristine among vinca alkaloids in the inpatient settings and hence the higher incidence of ADRs reported with this drug. Nausea, vomiting, and hypersensitivity reactions were not observed in this study due to the use of adequate premedication with parenteral dexamethasone, ranitidine and ondansetron and diphenhydramine, respectively.

Analysis of the type of reported ADRs according to Rawlin and Thompson revealed Type A predominance. This result is in line with the study conducted by Bates et al. and Lazarou et al., but in another study by Suthar and Desai, all the reported reactions were Type B reactions. Type A reactions are dose related and thus were preventable from their known pharmacology and therefore all of them were potentially avoidable. Type B reactions comprise approximately 10–15% of all ADRs and include hypersensitivity drug reactions. With adequate premedication, common ADRs such as nausea, vomiting, glossitis, and candidiasis can be effectively controlled. The incidence of definitely preventable reactions reveals the failure of rational drug use in the hospital. This brings out the need for the treating physician to anticipate and counsel the patient adequately before starting of therapy.

Most of the reactions were of mild to moderate severity and did not warrant stoppage or changing of drug considering the risk-benefit ratio in specific patients. Even though most of them were mild reactions, they resulted in an increased health care cost due to an increased length of stay and need of some medical interventions. Vast majority of the patients recovered from the ADRs. They were not fatal. Surendiran et al. also found that moderate and mild reactions were more reported. While severe reactions were more followed by moderate in a study by Oshikoya et al. Similar studies may be used to identify iatrogenic adverse effects and may help in preventing such occurrences in the future.

In this study, most of the reactions showed a similar causality assessment by both the WHO causality assessment scale and Naranjo’s algorithm except for diarrhea and anemia, which were assessed as “possible” with lower level of causality by the WHO scale, were judged as “probable” with higher level of causality by Naranjo’s algorithm. There were no “certain” reactions as re-challenge was not attempted in any of the patients although some events like neutropenia recurred in
the successive cycles of cancer chemotherapy. The grade of causality remained low due to a number of coadministered drugs. These data correlate with the study of Surendiran et al., Priyadarsini et al. and Shamma et al. and contradict the study by Oshikoya et al. which reported more number of definite reactions.[14,17,25,26]

This study provided basic information regarding the safety profile of microtubule-damaging anticancer drugs in a variety of cancers. It also assessed the causality, severity, predictability, and preventability of ADRs. Similar studies have been done which focused on either multiple drugs used in one field of medicine or only on the causality aspect.[17,27]

To the best of our knowledge, no similar studies have been published from India.

A major limitation of the study is that only one case of alopecia and no case of thrombophlebitis reported though being a very common adverse effect with anticancer medications, there are chances of under-reporting and incomplete documentation of data regarding ADRs in the case records. The fact that all patients were not admitted following the infusion may have led to missing some ADRs, particularly mild ones.

Conclusions

Nevertheless, early detection of these ADRs may help in minimizing the damage by either modifying the dose or changing the offending agent. This knowledge can also prevent the occurrence of similar such reactions in the future. There is a great need to set up an effective ADR monitoring and reporting system in all hospitals and also create awareness among healthcare professionals regarding the importance of this system. Most of the ADRs in hospitalized oncology patients were of milder nature and preventable.

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Conflicts of Interest

There are no conflicts of interest.

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