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RESEARCH ARTICLE

Improving medication safety in oncology care: impact of clinical pharmacy interventions on optimizing patient safety

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Abstract

Background Adverse drug reactions (ADRs) monitoring in cancer patients is important to ensure early detection, effective management and possible prevention subsequently. *Objectives* This study was conducted to detect and monitor ADRs to anti-cancer agents, and to assess impact of clinical pharmacists (CPs)' interventions in minimizing ADRs to anti-cancer agents. *Setting* Private, specialty oncology care hospital in South India. *Methods* CPs prospectively followed cancer patients admitted to inpatient wards and treated at ambulatory care in order to identify ADRs, for a period of 3 years. Identified/reported ADRs were discussed with concerned oncologists and/or nurses, documented electronically and assessed further for their causality, severity, preventability and grading. Based on study findings during year 1, interventions (educational, therapeutic and system based) were developed by CPs and implemented in order to minimize preventable ADRs. Impact of CPs' interventions was studied during year 2 and year 3. *Main outcome measure(s)* Preventable factors contributing to ADRs and percentage of preventable ADRs before and after CPs' interventions. *Results* A total of 1279 ADRs were reported in 1133 patients from a cohort of 1328 patients. Vomiting (23.22%), alopecia (9.53%), diarrhoea (8.67%) and myelosuppression (7.42%) were the common ADRs reported. Inappropriate administration frequency and regimen of anti-emetics (22%), lack of/suboptimal supportive care (18%) and administration errors (16%) were identified as common contributing (preventable) factors for ADRs in year 1. Percentage of preventable ADRs was 81% during year 1 (pre-intervention), and 45% and 34% in year 2 and year 3 respectively (post-interventions). *Conclusion* Interventions by CPs helped to minimize preventable ADRs to anti-cancer agents.

Keywords Adverse drug reactions · Anti-cancer agents · Clinical pharmacists · India · Oncology care

Impact on practice

- Day-to-day medication safety monitoring in cancer patients helps to identify most common ADRs and their contributing factors.
- Identification of the preventable factors and medication errors (contributing to ADRs) in cancer patients is essential to propose nature and levels of interventions needed to improve medication safety.
- Appropriate pharmacy interventions and team work can minimize preventable ADRs and optimize patient safety in oncology care.

Introduction

In recent decades many developments have taken place in cancer care due to translation of research evidence into clinical practice and the commitment of oncologists and other health professionals. Newer screening methods, diagnostic aids, surgical interventions, chemotherapy regimens, targeted therapies and immunotherapy have reduced the mortality associated with many cancers [1, 2]. Despite this

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cancer patients face challenges associated with drug toxicities, high treatment costs, poor quality of life and changes in their socio-economic circumstances. Adverse drug reactions (ADRs) in cancer patients are very common and known to cause delay in subsequent chemotherapy cycles, medication non-adherence and additional health care expenditure. These ultimately lead to lack of confidence towards treatment and impact overall well-being and quality of life [3–5].

Although the risk of ADRs to anti-cancer agents cannot be completely eliminated, it is possible to minimize this risk. The process of risk assessment, risk monitoring and risk minimization of ADRs is complex. However, it begins with quality ADR detection and monitoring in patient care settings [6]. An ADR reporting program at the hospital level helps to develop an understanding of common ADRs, drugs involved in causing these ADRs, severity of reactions and preventable risk factors leading to ADRs within the practice setting. A pharmacovigilance and/or drug and therapeutics committee at the hospital may assist in monitoring the quality and safe use of medicines and support strategies to improve medication safety [7, 8].

All anti-cancer agents require safety monitoring during initiation and continuation of therapy [6]. Clinical pharmacists can contribute by working with oncologists, nurses and patients to prevent ADRs and improve the quality of ADR reporting and management. Clinical pharmacists can provide appropriate medication counselling before treatment is initiated and during subsequent treatments. This can also help in the early detection of ADRs to anti-cancer agents [7]. A retrospective study reported that comprehensive medication therapy management including patient education provided by clinical pharmacists is effective in delivering early interventions, resulting in decreased rates of adverse effects, medication non-adherence, drug interactions, and medication errors [9]. Patient knowledge, attitudes and practices to deal with cancer and medications amongst patients at a Chinese cancer hospital significantly improved with education provided by clinical pharmacists compared to a control group. They also reported that patient engagement with pharmacists led to a decrease in the incidence of delayed chemotherapy-induced nausea and vomiting (CINV) in adult cancer outpatients [10]. Pharmacists have also been shown to improve the detection and management of cancer treatment-induced bone loss and osteoporosis in patients receiving systemic therapy for breast or prostate cancer [11].

Spontaneous reporting and active surveillance systems have traditionally been used for detection and monitoring of ADRs [6]. Active surveillance may be more beneficial for medication safety evaluation in cancer patients because many ADRs related to anti-cancer agents either require hospitalization or prolonged ambulatory care. However, spontaneous reporting helps in identification of unsolicited adverse drug events from health care professionals involved in cancer care. Many observational studies have reported on the pattern of ADRs to anti-cancer agents. Vomiting, myelosuppression, febrile neutropenia, extravasations, hypersensitivity reactions and alopecia are commonly reported in these studies [12–14]. As many of these ADRs are predictable they may be prevented or minimised if the patient receives optimal medical care. However very few studies have attempted to identify correctable clinical factors and medication errors leading to ADRs to anti-cancer agents.

Aims of the study

This study comprised of two phases. In the first observational phase, the research aimed to identify, monitor, and document ADRs to anti-cancer agents reported by clinical pharmacists and other health care professionals. Following a comprehensive assessment of these ADRs, the second interventional phase of the study aimed to design, implement, and assess the impact of clinical pharmacy interventions intended to minimize preventable ADRs at the practice site.

Ethics approval

This study was approved by the institutional ethical committee of JSS College of Pharmacy, Mysore, India. (Candidate number 13PPM009, Date of approval: 15-Dec-2012).

Methods

Study design

This was a prospective observational single centre study with the first phase collecting ADR data over 1 year (July 2013–June 2014) followed by an interventional phase over a period of 2 years (July 2014 to June 2016).

Study site

The study was conducted at a private specialty oncology care hospital in south India. The study site has 50 in-patient beds, 20 beds/chairs at a chemotherapy ambulatory care centre, and medical, surgical and radiotherapy oncology units. The hospital does not have paediatric oncology or a bone marrow transplant unit. An ADR reporting and monitoring program was initiated as an integral part of routine oncology pharmacy services at the hospital in July 2013.

ADR reporting and documentation

Existing active surveillance and spontaneous reporting systems were adapted to identify ADRs. During active surveillance, clinical pharmacists followed the patients admitted

to in-patient wards of medical oncology, radiation oncology and ambulatory care units. Paper-based medical records were reviewed, and patients and their care givers were interviewed to identify possible ADRs. Prior to study initiation health care professionals including oncologists, residents and nurses were briefed on the aims and potential benefits of the study. ADR notification forms were made available at every nursing station, and health care professionals were encouraged to drop completed forms into ADR drop boxes available at every nursing station and/or bring the observed ADR(s) to the notice of clinical pharmacists to complete further documentation.

Pharmacists discussed all identified ADRs with the concerned oncologists and nurses, with the aim to confirm and authenticate these before documentation on ADR notification forms (Supplementary material I) and electronically in Microsoft® Excel 2010 format

Each reported ADR was coded by system organ class using World Health Organization (WHO) Adverse Reaction Terminology 2007. Reported ADRs were assessed for causality, preventability, severity and Common Terminology Criteria for Adverse Events (CTCAE) grades using CTCAE 4.0 criteria [15]. The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) and Naranjo probability scales were used to assess causality of the reaction to the suspected drug(s). Using the WHO-UMC scale, causality was assessed as "Certain", "Probable", "Possible", "Unlikely", "Conditional" and "Unassessable" [16]. As per the Naranjo scale causality was assessed as "Definite" (score > 9), "Probable" (score 5–8) and "Possible" (score 1–4) [17]. The severity of the ADRs was assessed using the Hartwig Scale where ADRs were categorized as "Mild" (level 1, 2), "Moderate" (level 3, 4, 5), and "Severe" (level 6, 7). [18] The modified Schumock and Thornton criteria were used for determining the preventability of the ADRs and classified as "Definitely Preventable", "Partially Preventable" and "Not Preventable" [19]. Causality, preventability and severity were assessed by clinical pharmacists independently with mutual cooperation from physicians as required, and grading per CTCAE criteria was done by physicians. In cases where consensus could not be reached with regard to detection and reporting of ADRs, the oncologist's opinion on causality prevailed.

Developing clinical pharmacy interventions

All ADRs reported in the first year of the study were assessed by a clinical pharmacist in consultation with physician(s) to understand if the ADR(s) occurred due to any discrepancies in medication use processes and to ascertain if reported ADR(s) were clinically preventable. For the purpose of this study, a preventable factor was considered to be any discrepancy in the medication use process which was potentially preventable by ensuring standards of medical and pharmaceutical care.

Using observations and assessment of ADR reports during the first phase of the study, clinical pharmacists identified the need for interventions at various levels in order to improve the safe use of medications. With joint cooperation from physicians and hospital administration, it was decided to provide interventions at specific levels in order to achieve meaningful changes in patient care. Interventions were primarily developed by clinical pharmacists with mutual support from the hospital's chief physician. The implementation strategy was prepared by clinical pharmacists in liaison with medical unit heads, nursing chief and hospital administration.

We developed interventions of three types; (1) structured educational interventions to nurses (2) therapeutic and educational interventions to physicians and (3) system-based interventions to hospital administration. Educational interventions to nurses were provided in the form of group educational sessions which covered many aspects including basic principles of cancer care, haematological malignancies, pain management, medication errors and common anti-cancer drugs. Each session related to anti-cancer drugs involved teaching and discussion of selected anti-cancer drugs, related ADRs, safe administration and handling of drugs, common medication errors reported by clinical pharmacists related to those drugs, followed by group discussion and a quiz. Interventions to physicians were mainly therapeutic in nature, mainly to ensure the most appropriate medication orders of anti-cancer agents, pre-medications and other supportive care like antibiotics and myeloid growth factor. These interventions were provided either during ward rounds, one-to-one meetings or ward seminars. The delivery mode depended on the experience/rapport of clinical pharmacists with specific physician(s) and the physician's preference. Some physicians encouraged pharmacists to deliver ward seminars for the benefit of the entire team of healthcare professionals. Seminar topics were selected by pharmacists and the concerned ward physician considering observations from ADR reports and mutual needs at the study site. System-based interventions were provided to hospital administration where inputs and approval were required to revise and implement medication use and management processes, including administrative support for education and training of nurses, drug administration audits, medication counselling and additional pharmacy staffing needs.

After adoption of these interventions, the patterns of ADRs (including preventable factors and percentage of preventable ADRs) were documented and studied during the subsequent 2 years. Interventions were repeated and reinforced on a needs basis after observing ADR reports during this period. Since interventions were developed and provided based on preventable factors reported in the first year of the

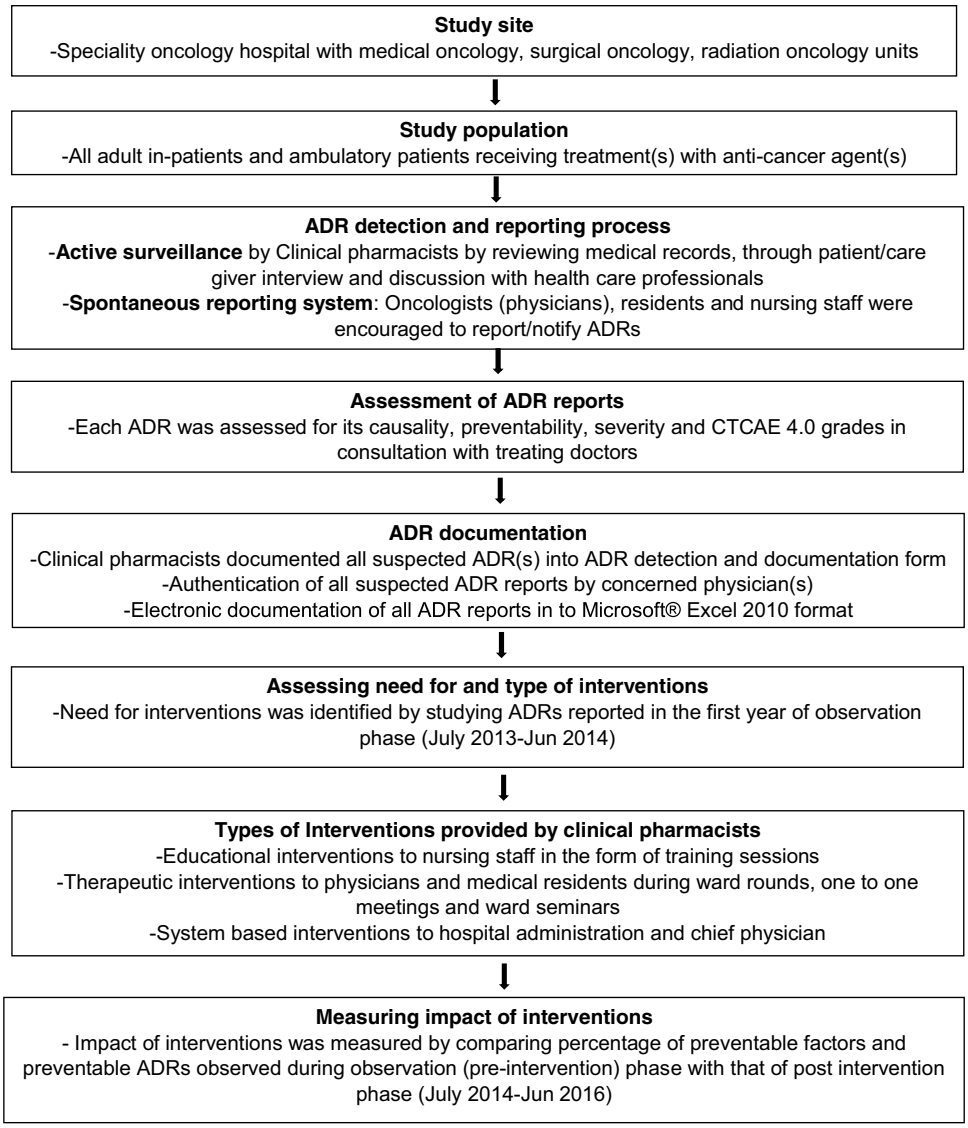

Fig. 1 Adverse drug reaction(s) reporting process and flow of interventions

study, the impact of interventions was studied by comparing the percentage of preventable factors and preventable ADRs observed in year 1 (observation period) with that of years 2 and 3 (intervention period). A methodological protocol and the flow of interventions has been provided in Fig. 1.

We did not conduct a study specific survey to collect feedback of HCPs regarding interventions provided by clinical pharmacists to prevent ADRs. However a validated scheduled survey of HCPs regarding oncology pharmacy services (medication therapy management) provided by clinical pharmacists was done [20].

Results

A total of 1279 ADRs were reported in 1133 patients from a cohort of 1328 patients over 3 years from July 2013 to June 2016. Most of the ADRs (n = 342, 30.18%) were seen in the age group 40–49 years and 50–59 years (n = 301, 26.56%). The treatment modality for the majority of patients (n = 580, 51.20%) was chemotherapy followed by chemo-radiation therapy (n = 435, 38.40%) and biologicals/targeted therapies (n = 118, 10.41%). The majority of patients who developed ADRs were on adjuvant chemotherapy (n = 642, 56.66%) followed by neo-adjuvant therapy (n = 387, 34.15%) and palliative care (n = 104, 9.17%). The majority of ADRs were reported in patients with head and neck cancers (n = 232, 20.47%), cervical cancer (n = 228, 20.12%) and breast cancer (n = 180, 15.88%) (Table 1).

Table 1 Demographic details of study patients who developed ADRs

Patient demographics	N (%)
Age (years)	
Below 18	24 (2.11%)
18–29	40 (3.53%)
30–39	170 (15.0%)
40–49	342 (30.18%)
50–59	301 (26.56%)
60–69	148 (13.06%)
70–79	88 (7.76%)
80 and above	20 (1.76%)
Gender	
Male	585 (51.63%)
Female	548 (48.36%)
Treatment modalities	
Chemotherapy	580 (51.20%)
Chemotherapy + Radiation therapy	435 (38.40%)
Biologicals/targeted agents	118 (10.41%)
Phase of therapy	
Adjuvant	642 (56.66%)
Neo-adjuvant	387 (34.15%)
Palliative	104 (9.17%)
Cancers in study population	
Breast	180 (15.88%)
Lung	116 (10.24%)
Colorectal	124 (10.94%)
Head and neck	232 (20.47%)
Stomach	74 (6.53%)
Cervix	228 (20.12%)
Leukaemia	62 (5.47%)
Non-Hodgkin's lymphoma	32 (2.82%)
Others	85 (7.50%)

Vomiting (n = 297, 23.22%), alopecia (n = 122, 9.53%), diarrhoea (n = 111, 8.67%), myelosuppression (n = 95, 7.42%) and skin rashes and pigmentation (n = 76, 5.94%) were the most common ADRs reported during the study period (Fig. 1). Gastrointestinal system disorders (n = 408, 31.89%), skin and appendages disorders (n = 261, 20.40%) and central and peripheral nervous system disorders (n = 99, 7.74%) were the most commonly involved with ADRs (Fig. 2). Cisplatin monotherapy concurrent with radiation (n = 177), Leucovorin +5-Fluorouracil + Oxaliplatin (FOLFOX-4) (n = 148), Paclitaxel monotherapy (n = 132) and Paclitaxel + Cisplatin (n = 124) were the most common chemotherapy regimens associated with ADRs (Fig. 3). Cetuximab (n = 26), Bevacizumab (n = 24), Rituximab (n = 23), Sorafinib (n = 17), Gefitinib (n = 15), Imatinib (n = 13) and Trastuzumab (n = 12) were the targeted agents mostly associated with ADRs.

As per the WHO-UMC scale, the majority of ADRs (n = 846, 66.14%) were classified as "Probable" and the remaining (n = 433, 33.85%) as "Possible". Using the Naranjo scale, the majority of ADRs (n = 894, 69.89%) were classified as "Probable" and the remaining (n = 385, 30.10%) as "Possible". ADR severity was graded as moderate (n = 588, 45.97%), in nature followed by mild (n = 433, 33.85%) and severe (n = 258, 20.17%). Most of the ADRs were "Partially Preventable" (n = 464, 36.27%) followed by "Definitely Preventable" (n = 355, 27.75%) and the remaining (n = 460, 35.96%) were "Not Preventable" in nature. Applying CTCAE criteria, most of the ADRs were categorised as Grade 1 (n = 602, 47.06%) and Grade 2 (n = 365, 28.53%). However, 208 (16.26%) were categorised as Grade 3 and 48 (3.75%) were categorised as Grade 4. No ADR was categorised as Grade 5 (Table 2).

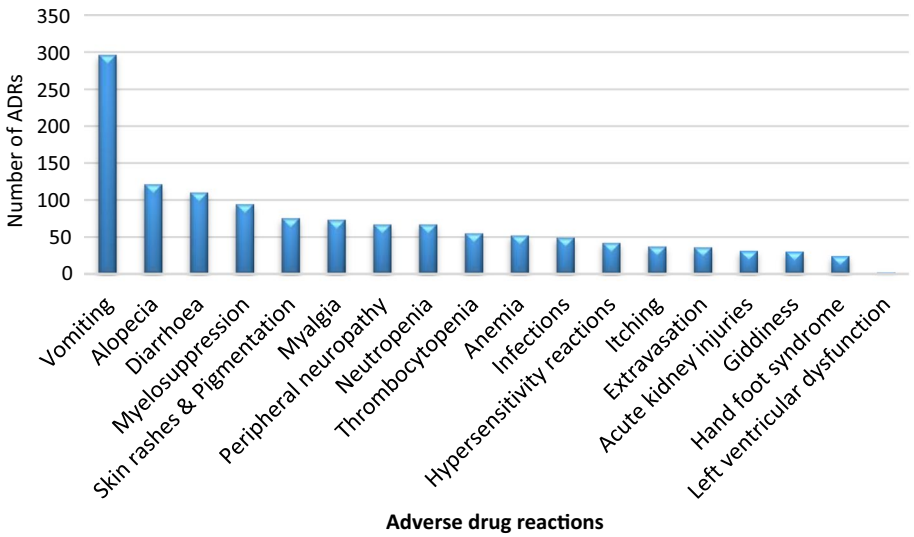

Fig. 2 ADRs to anti-cancer agents reported during July 2013 to June 2016

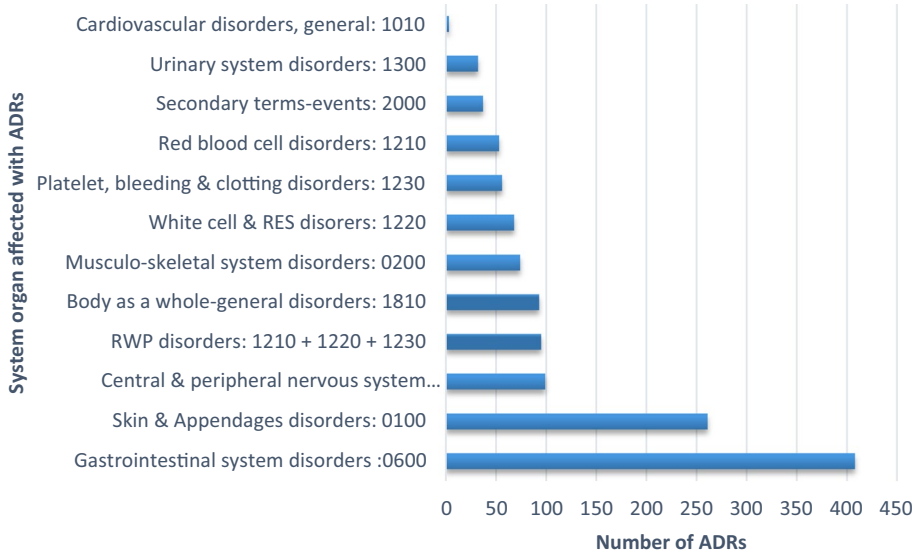

Fig. 3 System Organ affected with ADRs to anti-cancer agents (as per WHO Adverse Reaction Terminology 2007). RWP: Red blood cell disorders + White cell and RES disorders + Platelets, bleeding and clotting disorders

Table 2 Grading of reported ADRs as per CTCAE 4.0 criteria

Name of the ADR	CTCAE grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Vomiting	158	84	43	12	0
Alopecia	89	33	–	–	–
Diarrhoea	70	22	13	6	0
Myelosuppression	42	35	12	6	0
Skin rashes and pigmentation	52	17	7	0	–
Myalgia	12	44	18	–	–
Peripheral neuropathy	49	14	5	0	0
Neutropenia	–	–	55	13	0
Anaemia	28	15	10	0	0
Infections	–	14	28	8	0
Hypersensitivity reactions and anaphylaxis	22	12	6	3	0
Itching	28	10	0	–	–
Extravasation	–	37	0	0	0
Acute kidney injuries	14	10	8	0	0
Giddiness	22	9	0	–	–
Hand foot syndrome	16	9	0	–	–
Left ventricular dysfunction	–	–	3	0	0

CTCAE Common Terminology Criteria for Adverse Events

ADRs to anti-cancer agents reported during the study period are shown in Fig. 2. System organ classes affected by ADRs are provided in Fig. 3, and common treatment regimens associated with ADRs are summarised in Fig. 4. During Year 1 a total of 568 ADRs were reported in 448 patients from a cohort of 520 patients. The most common ADRs were vomiting (n = 151, 26.6%) followed by alopecia (n = 56, 9.8%), diarrhoea (n = 48, 8.45%), myalgia (n = 38, 6.70%), myelosuppression (n = 35, 6.2%) and neutropenia (n = 30, 5.3%). Many ADRs were attributed to inappropriate administration frequency and inappropriate selection of anti-emetics (n = 125, 22%), lack of/suboptimal supportive care (n = 102, 18%), and administration errors (n = 90, 16%) (Fig. 5).

Educational interventions provided to nurses and system-based interventions are summarized in Table 3. A total of 25 ward seminars were delivered to oncology treatment team. Therapeutic interventions provided to physicians included: (1) ensuring appropriate prescribing of anti-emetics, (2) ensuring prophylaxis for delayed emesis (3) ensuring

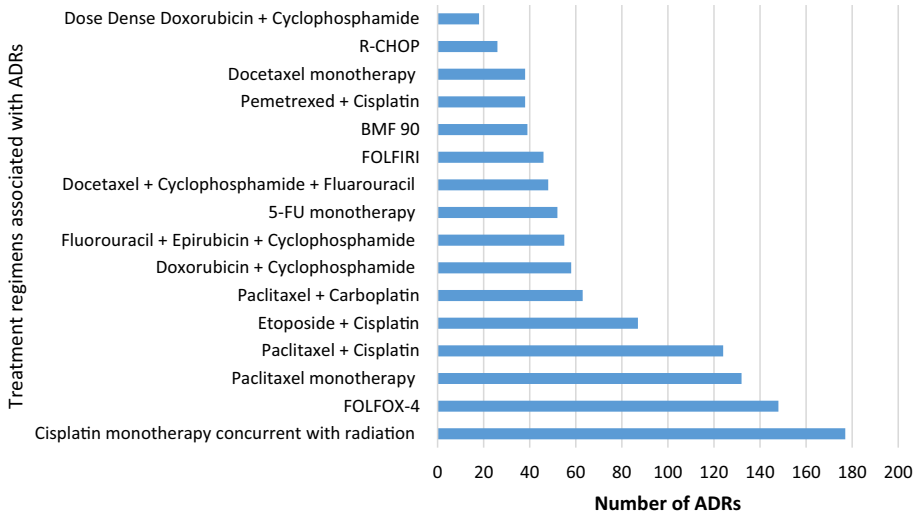

Fig. 4 Common treatment regimens associated with ADRs (July 2013 to June 2016)

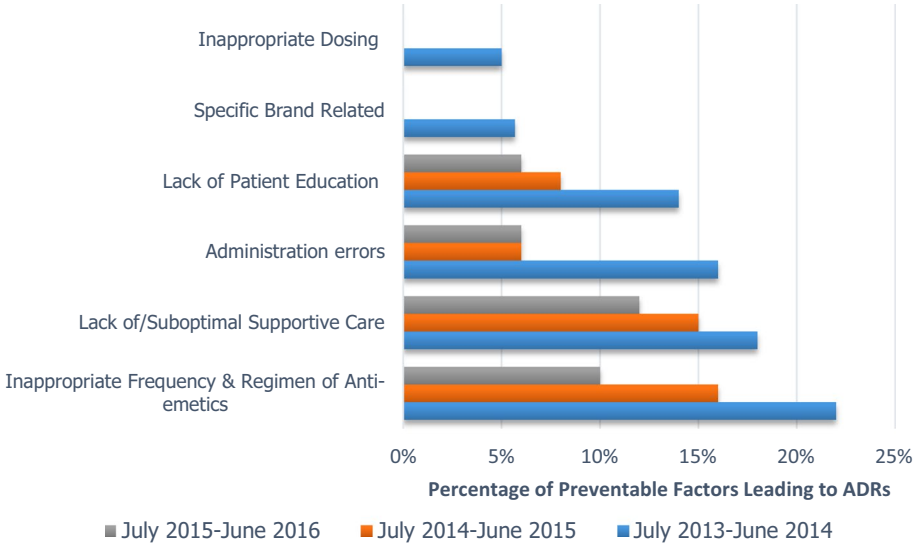

Fig. 5 Changes in preventable factors leading to ADRs to anti-cancer agents over Years 1, 2 and 3

appropriate/quality supportive care like myeloid growth factors, antibiotics to prevent and manage neutropenia (4) ensuring correct dosing of anti-cancer agents per body surface area or otherwise as applicable (5) ensuring dose adjustment in patients with abnormal laboratory investigations (renal impairment, blood toxicities) and (6) advising on avoidance of product brands observed to cause adverse events frequently. Documenting numbers and percentages of therapeutic interventions was not feasible because the interventions were repeated based on need either during ward rounds and/or one-to-one meetings. Table 4 provides a summary of preventable factors for which therapeutic and educational interventions were developed. Interventions are described in more detail in supplementary material II.

After providing these interventions to nurses and physicians, during Year 2 a total of 402 ADRs were reported in 360 patients from a cohort of 422 patients. Common ADRs during this period were vomiting (n = 82, 20.40%), alopecia (n = 44, 10.94%), diarrhoea (n = 37, 9.20%), myelosuppression (n = 36, 8.95%) and skin rashes (n = 26, 6.46%). Some ADRs during this period were contributed by inappropriate anti-emetic regimen (n = 64, 15.92%), lack of/suboptimal supportive care (n = 60, 14.92%) and inability to provide patient counselling (due to workload) (n = 32, 7.96%). However, no vomiting was reported due to inappropriate frequency of anti-emetics as observed during Year 1. During Year 2 the proportion of ADRs due to administration errors and lack of patient education also reduced compared to Year 1. No myelosuppression or neutropenia was observed due to inappropriate dosing as observed during Year 1 (Fig. 5).

During Year 3 a total of 309 ADRs were reported in 325 patients from a cohort of 386 patients. Common reported ADRs were vomiting (n = 64, 20.71%), diarrhoea (n = 26, 8.41%), and myelosuppression (n = 24, 7.76%). Some ADRs were contributed by lack of/suboptimal supportive care (n = 37, 12%), inappropriate anti-emetic regimen

Table 3 Educational and system based interventions provided by clinical pharmacists

Educational interventions provided to nursing staff (in the form of training sessions)

- General principles of cancer chemotherapy and role of health care professionals (2 sessions)
- Common anti-cancer drugs, administration and safe handling of those drugs and their important practice points (15 sessions covering different classes of drugs)
- Detection of common adverse drug reactions to anti-cancer agents (4 sessions with workshop)
- Detection and Management of Adverse drug reactions to biologicals (2 sessions with workshop)
- Medication errors reporting and prevention (demonstration of hospital data) (2 sessions)
- Pain management in cancer patients (2 sessions)
- Role of multidisciplinary team in palliative care (2 sessions)
- Acute care required for hematological malignancies (3 sessions)
- Patient counselling: Need, techniques and communication skills (1 session)

Educational interventions (Ward seminars) provided to Oncology treatment team

1. Oxaliplatin induced hypersensitivity reactions and its management
2. Newer anti-emetics and their comparative efficacy
3. Comparative safety & efficacy of Cetuximab versus Panitumumab in metastatic colorectal cancer
4. Pain management: General and Special Population
5. Supportive care in hematological malignancies
6. Management of drug induced neutropenia
7. Management of drug induced deep vein thrombosis
8. Administration guidelines for selected newer drugs
9. Medication errors: Hospital survey and possible prevention strategies
10. Patient oriented medication errors in hospital and possible prevention strategies
11. Comparative safety and efficacy of various endocrine therapies for breast cancer
12. Common toxicities and their management associated with the use of tyrosine kinase inhibitors
13. Radiosensitive chemotherapy agents
14. Comparative safety and efficacy of Pregabalin and Gabapentin for Peripheral neuropathy
15. Newer drug monographs (04 sessions)

Summary of system based interventions provided to hospital administration

- Demonstrated the need for education and training of nursing staff on safe and responsible administration of anti-cancer agents (Action plan was provided which included summary of education sessions which can help nurses to improve their practice).
- Recommended strict implementation of drug administration guidelines (as provided by pharmacists) by nurses. Recommended periodic audits of drug administration process at chemotherapy center to ensure compliance of procedures by nurses.
- Recommended to expand chemotherapy center to accommodate more number of patients to avoid inconvenience to patients and nurses
- Requested to permit the pharmacists to prescribe anti-emetics to prevent delayed emesis in case if physician did not prescribe it, so that patient don't miss delayed prophylaxis of anti-emetics.
- Demonstrated the need for strengthening the coordination among treatment team to ensure that patient medication counselling are conducted consistently and on time for all patients (as needed)
- Requested to provide additional pharmacy staff to efficiently conduct patient medication counselling and medication therapy review
- Recommended to review/revise hospital antibiotic policy periodically and advised strict implementation of antibiotic policy within hospital to improve rational use of antibiotics in the hospital
- Recommended to timely review pharmacy inventory (by pharmacy technicians) to avoid out of stock situation for pain medicines, antibiotics and other medications requiring longer administrative/transportation time
- Recommended to guide pharmacy & therapeutic committee to limit use of products from specific manufacturers (generic) noted to cause adverse events frequently compared to the generic of another manufacturers (as per local observations).

Note: Ward seminar topics were decided based on observational data and mutual requests from physicians. Attendees were physicians, nurses, residents and interns. Total of 25 ward seminars were delivered and in this table some examples are provided to reflect the nature of educational interventions. Refer supplementary material II for detailed explanation of clinical pharmacy interventions

Note: All the system based interventions were provided in detail with examples to hospital administration

(n = 31, 10%) and inability to provide patient education (due to workload) (n = 24, 8%) (Fig. 5). However, we found considerable reductions in proportions of ADRs due to inappropriate anti-emetics use, lack of/suboptimal supportive care, administration errors and inappropriate dosing from Year 1 through to Year 3. A total of 81% of ADRs were preventable during year 1 and this reduced to 46% and 34% in years 2 and year 3 respectively (relative

Table 4 Types of preventable factors for which therapeutic interventions and educational interventions provided by clinical pharmacists

Type of preventable factor	Description of preventable factor and reason for interventions
Inappropriate frequency of anti-emetics	Anti-emetics were administered just 5 to 10 min before chemotherapy to manage patient load at chemotherapy centre
Inappropriate anti-emetic regimen	Patients receiving highly emetogenic chemotherapy drugs (e.g. Dose dense AC, DCF, ECF, Paclitaxel + Carboplatin) were prescribed with combinations of (5-HT3 antagonist + Dexamethasone) or (Metoclopramide + Dexamethasone) either orally or intravenously. NK-1 receptor antagonist (e.g. Aprepitant, Fosaprepitant) was not prescribed due to routine prescribing practice and higher cost of innovator's product Due to high workload of clinicians, written medication orders were not completed for some patients and hence, some patients were not prescribed and dispensed anti-emetics to prevent delayed emesis
Inappropriate dosing of anti-cancer drugs	Due to high workload of clinicians, latest body surface area (BSA) was not calculated during subsequent visits for some patients. Use of first cycle BSA led to either sub therapeutic dose or over dose (mostly over dose). A few patients with over dose developed neutropenia in our observations Some patients were given chemotherapy at doses higher than recommended limit. E.g. Patients with serum creatinine higher than 1.5 mg/dl, either needs dose adjustment of cisplatin or cycle to be held. But we noted that patients with higher serum creatinine received doses of cisplatin as normal patients, leading to prolonged renal toxicities
Lack of/suboptimal supportive care	Some patients who developed lower white blood cells and neutrophil count during subsequent cycles, were not provided with myeloid growth factors on time due to out of pocket expenses and shortage of generic products. This led to further worsening of neutropenia in few patients Some patients were prescribed sub-therapeutic dose of Filgrastim. E.g.: Single subcutaneous dose (300 mcg) against actual need of 3–4 doses Some patients were attempted myeloid growth factors administration by nurse within 24 h of last chemotherapy dose (against order of administering it only after 24 h of last chemotherapy dose) Patients who needed antibiotic prophylaxis to prevent further neutropenia and infections were not given appropriate antibiotic therapy due to traditional prescribing practice and out of pocket expense Some patients received multiple antibiotics with overlapping anti-microbial coverage. Adherence to hospital antibiotic policy was limited Many patients with moderate to severe cancer pain were not prescribed with opioid analgesics due to shortage at pharmacy inventory. These patients were provided tramadol and NSAIDs like Diclofenac, Ibuprofen
Inappropriate drug administration It was noted that most of the nurses at study site holds either diploma nursing certificate or general nursing qualification and training. Most of the nurses had not undergone any specialty training to provide oncology nursing care. Hence, their skills and knowledge to handle anti-cancer agents were limited	Administration procedures of chemotherapy drugs and biologicals deviated from instructions given by clinicians and pharmacists. A common deviation was faster infusion rate than recommended to manage patient load and patients' pressure to complete infusion faster. E.g. Infusion ordered to complete within 3 h, was completed in less than 2 h
Lack of patient education Due to high patient load and growing awareness about pharmacists' role among patients, in our practice patient counselling by clinical pharmacists is not mandatory before starting chemotherapy cycle and during discharge (for in-patients)	Patients were counselled based on convenience of pharmacists and patients. Even though patients were prescribed/dispensed with anti-emetics to prevent delayed emesis, we found that many patients had developed delayed emesis at home. We realized that patients were not correctly educated and counselled on use of anti-emetics to prevent delayed emesis. Our interactions with many patients during subsequent visits informed us that patients were taking anti-emetics only after experiencing emesis and not as a prophylaxis
Use of generic from specific manufacturer	ADRs like hypersensitivity reactions in few patients were believed to be common with use of generic from specific manufacturer compared to generics from other manufacturers. E.g. Frequent hypersensitivity reactions with use of Paclitaxel from specific manufacturer

This table provides summary of types of preventable factors and related scenario for which therapeutic and educational interventions were identified and provided. Details of therapeutic interventions provided by clinical pharmacists are available as supplementary material II

reduction of 35% and 47% respectively compared to year 1).

A survey to collect feedback on oncology pharmacy services was responded by all medical staff (oncologists, general physicians and residents) of the study site (n = 10).

Most responders expressed that the medication therapy management service was useful in developing chemotherapy protocols for individual patients (n = 7), to ensure correct dosing of anti-cancer drugs (n = 8) and to identify and resolve medication related problems before these reach patients (n = 10). Responders also indicated that drug therapy review by clinical pharmacists brought improvement in medication reconciliation (n = 10), drug safety monitoring (n = 8). Most responders believed that clinical pharmacists can act as trainers for nursing staff to improve safe handling of anti-cancer drugs (n = 10) [20].

Discussion

ADRs in cancer patients are often predictable and a collaborative approach for medication safety monitoring helps in the early detection and management of adverse events following anti-cancer treatments. To our knowledge, this is the first interventional study from India which has studied clinically correctable factors and medication errors leading to ADRs to anti-cancer agents.

The majority of the reported ADRs were in patients with head and neck cancers, cervical cancer and breast cancer which may be due to higher patient numbers of these cancers treated at the study hospital. Though we did not conduct a statistical analysis, there was no significant change in patient population, treatment modalities and treatment selection throughout the study and it is unlikely that these factors impacted the incidence of ADRs during the observational and interventional periods.

From the observations during year 1 it was apparent that ADRs like vomiting, alopecia, diarrhoea, myelosuppression and febrile neutropenia were common as reported in published studies [12–14]. However, we found that many of these reported ADRs were clinically preventable in nature. Vomiting, neutropenia, renal toxicities, and hypersensitivity reactions in some patients were associated with inappropriate medication use. For example, some patients undergoing highly emetogenic chemotherapy were prescribed inadequate anti-emetics based on standard recommendations [21–23]. We also identified that anti-emetics were administered by nurses less than 10 min prior to chemotherapy administration. Such a narrow time gap between anti-emetics and chemotherapy does not provide therapeutic benefit and resulted in vomiting in some patients. Toutounji et al. [24] have reported similar findings and have demonstrated that patients who are prescribed inappropriate anti-emetics regimens are likely to have higher rates of nausea and vomiting. Hence nausea and vomiting in most patients are preventable provided an appropriate anti-emetic regimen is used.

We noticed that administration rates of anti-cancer agents for some patients were too fast or changed by nurses contrary to directions of oncologists or pharmacists. Fast infusion rates of chemotherapy agents are known to cause various toxicities including hypersensitivity reactions. In the Indian health care system there is a shortage of skilled nurses trained in the area of oncology. Moreover, typically nurses are overloaded by high patient numbers and the need to provide additional patient support services. A needs based structured training program on safe and quality use of anti-cancer agents can help nurses to strengthen their understanding and may improve their skills [20]. A study by LeBaron et al. [25] studied challenges faced by nurses practicing in oncology and palliative care in a south Indian hospital and recommended similar types of periodic training for nurses to improve patient care. A multi-centre study in academic cancer hospitals in Turkey by oncology nurses also reported a heavy workload (49.7%) and insufficient number of nursing staff (36.5%) as the most common reasons for higher medication and administration errors (50.5%) [26]. The extent of administration errors in oncology practice in India due to shortage of trained nurses has not been studied in depth, and further studies are needed to investigate this in other oncology care settings in the country.

There are many studies describing common ADRs to anti-cancer agents from India [7, 27, 28]. Saini et al. [27] and Chopra et al. [7] showed similar patterns of ADRs as we found. A study conducted by Vijayalaxmi et al. [28] reported similar ADRs but in a small cohort (n = 55). However none of these studies investigated medication errors and administration procedures which led to ADRs.

Lau et al. [29] identified common ADRs in one Australian cancer centre where many ADRs like vomiting and myelosuppression were due to inappropriate pre-medications and preventive measures. At a hematology oncology department prescribing errors (mainly dosing errors) and inappropriate pre-medication and supportive care like anti-emetics were common causes of ADRs [30]. These ADRs were preventable if standardized chemotherapy order forms (SCOF) were followed. In our practice utilization of SCOF was also limited which allowed many prescribing errors and treatment disparities among patients usually expected to receive similar treatments. Adoption of SCOF by oncology physicians and hospitals would help to standardize the approach for medication use which may help to prevent ADRs.

During the post-implementation period we noted that the percentage of many preventable factors had reduced and this may have helped to minimize the number of preventable ADRs. This may be attributed to educational and therapeutic interventions provided to nurses and physicians. System based interventions were well accepted by hospital administration who provided administrative support to strengthen overall medication use processes and transition of care among HCPs. ADR reporting and monitoring by clinical pharmacists led to many improvements in patient

care processes including dose calculations, drug administration, patient medication counselling and other quality supportive care in some patients. Feedback from physicians on pharmacy interventions was encouraging and reflected their acceptance of these. Future cost-effectiveness analyses are indicated to explore the potential and actual cost savings of offering such interventions. In combination with cost-effectiveness data, our results may be useful in advocating for the need of clinical pharmacist services in oncology practice settings within emerging health care systems.

Despite interventions certain preventable factors persisted during the post-implementation period in a few patients, including lack of/suboptimal supportive care and inappropriate anti emetic regimens. Due to limited insurance coverage and higher out of pocket expenses, optimal supportive care (e.g. anti-emetics, growth factors, opioids, antibiotics) remains a challenge in our practice. In India patients treated under public cancer schemes have limited financial support and access to a restricted formulary which does not allow for the use of quality supportive care. Patient education was strengthened at our hospital but it can be further improved by additional nursing and pharmacy staffing. Since use of many newer agents are limited in our practice due to economic considerations, we could not study the safety of many newer agents (biologicals).

Conclusions

Pharmacist co-ordinated medication safety monitoring can identify preventable factors contributing to anti-cancer treatment related ADRs. Clinical pharmacy interventions can help to reduce preventable ADRs and contribute to improvements in medication safety and patient care in the oncology setting.

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