Original Article

An observational study to monitor and report radiation-related adverse events by a clinical pharmacist to achieve a better therapeutic outcome and suggest preventive measures in a tertiary care teaching hospital

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Abstract

Objectives: This study was conducted to investigate the potential role of clinical pharmacists in monitoring and developing a reporting system of radiation-related adverse events (RRAEs) in cancer patients and provided suggestive measures to prevent RRAEs to achieve a better therapeutic outcome for improving patient health-related quality of life.

Methodology: This study was a prospective observational study conducted for a period of 2 years at a private academic oncology teaching care hospital. Patients on radiation therapy or chemoradiation therapy were enrolled and followed by clinical pharmacists on daily basis to identify adverse event(s) if any. Upon identification, adverse events were discussed with concerned radiation oncologists for authentication and graded as defined by the radiation therapy oncology group. Enrolled patients were also followed to ensure if they were provided adequate supportive care for RRAEs.

Results: A total of 715 patients were followed during the study period. A total of 422 RRAEs were identified in patients who were on radiation therapy or chemoradiation therapy. The most common reported events were fatigue ($n = 64$, 15.16%), followed by mucositis ($n = 55$, 13.03%), diarrhea ($n = 37$, 8.76%), vomiting ($n = 31$, 7.34%), gastritis ($n = 29$, 6.87%), and dryness of the mouth ($n = 22$, 5.21%). Among the study patients who developed RRAEs, majority ($n = 253$, 60%) of them received a combination of chemotherapy and radiation therapy and 169 (40%) of 442 patients received radiotherapy alone. Cisplatin weekly monotherapy or cisplatin-based chemotherapy was commonly used pharmacological treatment in patients on chemoradiation therapy. Clinical pharmacists intervened to initiate adequate supportive care for nearly 20% ($n = 84$) patients.

Conclusions: Clinical pharmacists may be contributing to monitoring and development of reporting systems for radiation-related toxicities/RRAEs in cancer patients. Teamwork of clinical pharmacists with radiation oncologists can improve the safety reporting of radiation and can ensure required medical and supportive care to manage RRAEs.

Keywords: Clinical pharmacists, radiotherapy, radiation-related adverse events, supportive care

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INTRODUCTION

Cancer is a term used for diseases that are characterized by uncontrolled cellular growth, local tissue invasion, and distant metastases. Cancer appears to occur when the growth of cells in the body is out of control and cells divide too quickly. Cancer cells can also invade neighboring tissues as well as travel to other parts of the body. It can also occur when cells forget how to die.[1] Cancer is a major cause of morbidity and mortality in developing and developed countries alike. Therefore, the goal of cancer treatment is first to eradicate the cancer. As per the Global cancer statistics 2018 (GLOBOCAN) estimates, 18.1 million newer cancer cases and 9.6 million deaths related to cancer in both sexes worldwide.[2] In 2018, the incidence of breast cancer in India was reported as 40.7/100,000 persons in the GBD study compared with 24.7/100,000 people as per the GLOBOAN 2018 estimates.[3] There is no specific information about the prevalence of radiation-related adverse events (RRAEs) in India as well as worldwide. Most of the study subjects were given radiation therapy or chemoradiation therapy for head-and-neck cancers and cancer of the cervix. Admission due to these cancers on the study site is higher among the study subjects, majority of the patients received chemoradiation therapy than radiotherapy alone. Concurrent radiation and chemotherapy appear to be efficacious due to their synergistic action; however, this also results in an added number of adverse events in cancer patients. Radiation therapy is one of the important modalities of treatment for many cancers. Radiation therapy may cause side effects by damaging or destroying normal cells like cancer chemotherapy agents. Nature and extent of radiation toxicities are different than that of chemotherapy agents.[4] A study conducted by Maduro *et al*. has well-demonstrated acute and delayed toxicities due to radiation in patients with cervical cancer.[5] Nature and extent of RRAEs depend on the type of radiation therapy, dose of radiation (Gy), duration of treatment, hydration status, type of cancer, and/or any other patient-specific factor(s). Radiation toxicities may be potentiated when patients are receiving concurrent chemotherapy.[6] A study conducted by Silveira *et al*. and team showed that the quality of life was impaired in patients who received chemotherapy concurrent to radiotherapy for breast cancer.[7] A study conducted by Kassam *et al*. also reported impairment in quality of life when chemotherapy is given concurrently with radiation therapy for patients with gastric cancer.[8] In common, radiation therapy-induced events contribute to the poor quality of life of the patients and may demand additional medical care and treatment cost. Due to these known facts, it is essential to timely detect and monitor such radiation toxicities in cancer patients. In a developing country like India where a smaller number of radiation oncologists have a relatively higher patient load, it is difficult to follow each and every patient to identify RRAEs after initiation of radiation therapy. Due to this reality, many times, RRAEs remain undetected or are not detected on time. Conventionally, clinical pharmacists are involved in monitoring patient drug safety by routinely monitoring adverse drug reactions. Hence, most probably with properly structured training, they may be able to identify RRAEs in consultation with radiation oncologists and for the development of reporting system. In this study, we are report adverse events that might be due to radiotherapy as well as chemotherapy also.

Aim of the study

This study was conducted to investigate the potential role of clinical pharmacists in monitoring and developing a reporting system of RRAEs in cancer patients and provided suggestive measures to prevent RRAEs to achieve a better therapeutic outcome for improving patient health-related quality of life and reduced burden of the patient due to prolongation of hospital admission and cost of the treatment due to RRAEs. As per our knowledge, still now, reporting system of RRAEs is not developed, in our study there is a need for development of reporting system for RRAEs like for drugs having a safety reporting system like pharmacovigilance. Clinical pharmacist must be a part of a system for reporting an RRAE. This is the first long-term study conducted to assess the RRAEs in all types of cancer patients.

METHODOLOGY

It was a prospective observational study conducted for a period of 2 years (January 2017 to January 2019) at a private academic oncology care hospital setting at a medical university. The study obtained approval from the Institutional Human Ethical Committee. Patient informed consent was also obtained from an individual patient who was enrolled in the study. Patients who are not receiving radiation therapy were excluded from the study. All cancer patients who were on radiotherapy and/or chemoradiotherapy were enrolled in a study and followed on daily basis by clinical pharmacists to identify RRAE(s) if any. Identified adverse events were discussed with concerned radiation oncologists for authentication of RRAEs. All the identified RRAEs were reported and coded as per the international medical terminology by clinical pharmacists and graded by radiation oncologists as per Radiation Therapy Oncology Group (RTOG) and preventive measures suggested by the clinical pharmacist. Clinical pharmacists collected information regarding the type of cancer, chemotherapy prescribed (if applicable),

type of radiation therapy, duration, and dose of radiation therapy. There is no specific information related to causality, seriousness, severity, and preventability related to RRAEs. Clinical pharmacists also followed patients to understand if identified events were treated by concerned radiation oncologist(s). Interventions were made by clinical pharmacists to concerned radiation oncologists to initiate symptomatic and/or specific treatment for all untreated RRAE(s). All the relevant data collected and recorded electronically. Descriptive statistics used for the analysis of the data. As per our knowledge, there is no specific long-term study conducted related to RRAEs in all types of cancer patients who are receiving radiation therapy or chemoradiation therapy.

RESULTS

A total of 715 patients were followed during the study period of the study site. A total of 422 RRAEs were identified in patients who were on radiation therapy or chemoradiation therapy. Majority of the events were reported in the age group of 41–50 years (28.43%) followed by 51–60 years (25.59%) and 61–70 years (22.27%). A total of 264 (62.55%) events were reported in female patients and 158 (37.44%) events were reported in male patients. Among the enrolled study subjects, 69.43% of patients (n = 293) were treated under private insurance or self-payment and 30.56% of patients (n = 129) were treated under government schemes. Most of the study subjects were given radiation therapy or chemoradiation therapy for head-and-neck cancers (n = 169, 40.04%) and cervical cancers (n = 129, 30.56%). Among the study patients who developed RRAEs, majority (n = 253, 60%) of them received a combination of chemotherapy and radiation therapy and 169 (40%) of 442 patients received radiotherapy alone. Cisplatin weekly monotherapy or cisplatin-based chemotherapy was commonly used pharmacological treatment in patients on chemoradiation therapy. The most common reported events were fatigue (n = 64, 15.16%), followed by mucositis (n = 55, 13.03%), diarrhea (n = 37, 8.76%), vomiting (n = 31, 7.34%), gastritis (n = 29, 6.87%), and dryness of th mouth (n = 22, 5.21%) [Table 1]. Majority (n = 379, 89.81%) reported events were acute in nature, whereas 43 (10.18%) of 442 events were delayed in nature. Most of the adverse events observed during the study were acute in onset. Since delayed adverse events appear only after few weeks to months in comparison to acute events, acute event occurs within 30 min of receiving therapy and chronic or delayed events occur after 24 h of receiving therapy. Majority of RRAEs were reported in patients who received unfractionated external radiotherapy (n = 232), followed by intracoronary radiation therapy (n = 65), intensive-modulated radiation therapy (IMRT) (n = 59), three-dimensional conformal radiation therapy (n = 45), and intraluminal radiation therapy (n = 21). However, we did not study the correlation between the dose of radiation and reported RRAEs. Most of the reported Grade 1 events were fatigue, vomiting, gastritis, mucositis, dryness of the mouth, and insomnia. Most of the reported Grade 2 events were fatigue, diarrhea, mucositis, vomiting, gastritis, and dryness of the mouth. However, Grade 3 and 4 events were vomiting, diarrhea, fatigue, gastritis, proctalgia, mucositis, dryness of mouth dermatitis, thrombocytopenia, and leukopenia. Most of the Grade 3 and Grade 4 events were reported in patients on external radiation therapy and on chemoradiation therapy. Table 2 describes grading of the most common RRAEs as per the RTOG scale. However, RRAEs like burning sensation and bowel dysfunction were not graded because RTOG does not provide grading of the mentioned RRAEs. Among the patients who developed RRAEs, around 80.09% (n = 338) were started on symptomatic or specific treatment for the respective event(s). However, 19.90% (n = 84) of patients were not started with any symptomatic or specific care for the reported RRAEs. The most common untreated RRAEs were fatigue followed by proctalgia, gastritis, pain, mucositis, and burning sensation. Few patients with dermatitis, burning micturition, dryness of the mouth, insomnia, dehydration, and pyrexia were also untreated. Clinical pharmacists consulted with concerned radiation oncologists to initiate adequate medical and supportive care for all untreated RRAEs. Radiation oncologists prescribed/recommended treatment for all untreated RRAEs after clinical pharmacists' interventions. These interventions were provided in form of reminders to concerned radiation oncologists to issue medication orders or provide instructions for nonpharmacological treatment to manage RRAEs (n = 44), drug information to the concerned clinician to manage RRAE (n = 20), dosage adjustments of supportive care used to manage RRAEs (n = 10), patient counseling (n = 4), and by improving availability of medicines required to treat RRAEs (n = 2). With our experience in monitoring RRAEs, we developed a training module for clinical pharmacists to guide them on radiation safety reporting. It is recommended for clinical pharmacists at the study site to undergo this training if they want to participate in radiation safety reporting. For drug safety reporting system already available worldwide but need to be develop RRAEs reporting system worldwide.

Table 1: List of radiation-related adverse events and graded as per radiation therapy oncology group grades in study patients

IMT Code	Event	*n* (%)	Grade	*n* (%)
001423	Fatigue	64 (15.16)	1	30 (46.87)
			2	30 (46.87)
			3	4 (6.25)
018489	Mucositis	55 (13.03)	1	25 (45.45)
			2	15 (27.27)
			3	15 (27.27)
021197	Diarrhea	37 (8.76)	1	14 (37.83)
			2	10 (27.02)
			3	10 (27.02)
			4	3 (8.10)
021162	Vomiting	31 (7.34)	1	15 (48.38)
			2	10 (32.25)
			3	5 (16.12)
			4	1 (3.22)
000925	Gastritis	29 (6.87)	1	10 (34.48)
			2	10 (34.48)
			3	9 (31.03)
017574	Dryness of the mouth (xerostomia)	22 (5.21)	1	10 (45.45)
			2	8 (36.36)
			3	4 (18.18)
001140	Insomnia	21 (4.97)	1	15 (71.42)
			2	3 (14.28)
			3	3 (14.28)
004966	Dehydration	17 (4.02)	1	1 (5.88)
			2	2 (11.76)
			3	13 (76.47)
			4	1 (5.88)
008304	Proctalgia	16 (3.79)	1	2 (12.5)
			2	2 (12.5)
			3	12 (75)
900180	Pain	14 (3.31)	1	8 (57.14)
			2	2 (14.28)
			3	4 (28.57)
02247	Dermatitis	14 (3.31)	1	1 (7.14)
			2	2 (14.28)
			3	11 (78.57)
017797	Thrombocytopenia	13 (3.08)	1	1 (7.69)
			2	2 (15.38)
			3	7 (53.84)
			4	3 (23.07)
000759	Skin erythema	12 (2.84)	1	6 (50)
			2	4 (33.33)
			3	2 (16.66)
010407	Leukopenia	12 (2.84)	1	2 (16.66)
			2	2 (16.66)
			3	6 (50)
			4	2 (16.66)
020341	Proctitis	11 (2.60)	1	4 (36.36)
			2	4 (36.36)
			3	3 (27.27)
00180	Pyrexia	11 (2.60)	1	5 (45.45)
			2	2 (18.18)
			3	4 (36.36)
NA	Burning sensation	11 (2.60)	1	8 (72.72)
			2	2 (18.18)
			3	1 (9.09)
000706	Painful urination	7 (1.65)	1	4 (57.14)
			2	2 (28.57)
			3	1 (14.28)
010451	Anemia	7 (1.65)	1	1 (14.28)
			2	1 (14.28)
			3	3 (42.85)
			4	2 (28.57)
005765	Neutropenia	3 (0.71)	3	2 (66.66)
			4	1 (33.33)
900190	Sexual dysfunction	3 (0.71)	3	3 (100)
018172	Neurotoxicity	3 (0.71)	3	2 (66.66)
			4	1 (33.33)
001215	Cardiac dysfunction	2 (0.47)	3	1 (50)
			4	1 (50)
900188	Secondary cancer	2 (0.47)	3	1 (50)
			4	1 (50)
019204	Ototoxicity	2 (0.47)	3	2 (100)
024832	Cognitive impairment	1 (0.23)	4	1 (100)
008571	Pulmonary fibrosis	1 (0.23)	4	1 (100)
NA	Bowel dysfunction	1 (0.23)	4	1 (100)

NA=Not available

DISCUSSION

The role of the clinical pharmacist is well known and accepted worldwide in detecting, monitoring, and improving the safe use of drugs in cancer patients. However, clinical pharmacists are not routinely involved in detecting monitoring and reporting of radiation-related toxicities in cancer patients. This study discusses the potential role of clinical pharmacists in detection and monitoring of RRAEs in cancer patients. In this study, we observed, females developed a higher number of RRAEs which may be due to a greater number of patients enrolled with cervical cancer. Most of the events were reported in patients with head-and-neck cancers and cervical cancers. This may be due to the higher number of study subjects recruited with those two cancers due to its higher prevalence in our practice.[9] Concurrent radiation and chemotherapy appear to be efficacious due to its synergistic action.[10] However, this also results in an added number of adverse events in cancer patients, the reason being that some of the chemotherapy agents such as cisplatin and 5-fluorouracil, are radiosensitive in nature. In our study, we also found a greater number of RRAEs in patients with chemoradiation therapy than patients with radiotherapy alone. Most of our patients received weekly cisplatin monotherapy concurrent with radiotherapy. Few patients also received radiotherapy with cisplatin + paclitaxel, FOLFOX-4, carboplatin + paclitaxel, capecitabine monotherapy, and gemcitabine monotherapy. Majority of our patients received unfractionated external radiation therapy compared to other types of radiotherapies and a higher number of RRAEs were reported in those patients. The reason for the higher utility of unfractionated external radiation therapy in our practice is economic considerations as unfractionated therapy is more affordable than other types of radiotherapies. Patients treated under government cancer care programs in our practice are usually provided with unfractionated therapy due to limited financial

Table 2: Demographics details of study participants who developed radiation-related adverse events

Demographic details	Number of patients (%)
Age	
20-30	9 (2.13)
31-40	62 (14.69)
41-50	120 (28.43)
51-60	108 (25.59)
61-70	94 (22.27)
71-80	29 (6.87)
Gender	
Male	158 (37.44)
Female	264 (62.55)
Payment scheme	
Self-payment/private insurance	293 (69.43)
Government schemes	129 (30.56)
Types of cancers	
Head and neck	169 (40.04)
Cervix	129 (30.56)
Colorectal	22 (5.21)
Lung	19 (4.50)
Breast	12 (2.84)
Endometrium	10 (2.36)
Bladder	16 (3.79)
Vaginal vault	13 (3.08)
Others	32 (7.58)

coverage of those schemes and inability of our patients to manage out-of-pocket expenditures. The higher number of RRAEs is reported with the use of unfractionated therapy due to its higher exposure to body tissues and its ability to spare normal tissues is inferior compare to other therapies. In a randomized trial in comparison to radiation side effects of conformal and conventional radiotherapy in prostate cancer, conformal techniques significantly lowered the risk of radiation-induced proctitis after radiotherapy for prostate cancer.[11] MRI scan studies done by van de Bunt *et al*. and Dosimetric analysis done by collecting computed tomography results before and after treatment by Portelance *et al*. show that IMRT is superior to external radiation therapy in normal tissue sparing function.[12,13] We could not study the correlation between doses of radiation received by each patient to that of reported RRAEs. In a critical review on radiotherapy-related fatigue by Jereczek-Fossa *et al*., radiotherapy-induced fatigue was a common early and chronic side effect of radiation reported in up to 80% and 30% of patients during radiation therapy and at follow-up visits, respectively. The fatigue was reported higher in patients with cancer of the breast, lung, and prostate.[14] In our study also, the most commonly observed adverse event was fatigue. However, it was reported more in patients with head-and-neck cancers, cervical cancers, and lung cancers. Mucositis accounted for 13% of the events of which all of them occurred in head-and-neck cancer patients. Similar results were reported in a systematic review which consisted of 31 randomized control trials where the mean incidence of developing mucositis in head-and-neck cancer was 80%.[15] Hence, mucositis is a frequent and severe toxicity in head-and-neck cancer patients.

In our practice, high workload of radiation oncologists may not allow them to dedicate adequate time for patients to follow radiation toxicities. Due to this reality, many times, RRAEs remain undetected or are not identified on time. We found that nearly 20% of RRAEs were undetected where patients needed symptomatic and/or specific medical care. Clinical pharmacist's interventions led to adequate medical and/or supportive care to manage those RRAEs. Our interventions were in the form of reminders to issue medication orders or instructions for nonpharmacological treatment to manage RRAEs. These reminders were provided to concerned clinicians in coordination with radiation nurses. We needed these reminders to clinicians because of their higher workload which may not allow them to monitor every patient on radiation therapy on daily basis. Nonpharmacological treatments were mainly recommended for patients with fatigue and dry mouth. Drug information queries were requested from clinicians to manage few patients with mucositis, dermatitis, and pain. For example, for mucositis, we provided better formulations of mouthwashes and gargles, whereas for dermatitis, we recommended certain local ointments containing steroids, antihistamines, and soothing agents. Dosage adjustments were provided for patients who had renal impairment. For example, a patient with gastritis and dehydration had elevated serum creatinine, and hence, a patient needs renal dosage adjustment if a patient is prescribed ranitidine for gastritis. Regular availability of morphine is a challenge in our practice. Hence, in the absence of morphine, alternative pain medicines such as tramadol and buprenorphine were recommended considering patient affordability. Patient counseling was mainly done for patients with proctalgia, gastritis, and pain to ensure patient safe and quality use of prescribed supportive care. Collaborative work of clinical pharmacists with radiation oncologists can allow pharmacists to identify RRAEs and the same can be authenticated and treated further by radiation oncologists as needed. Such a collaborative approach can also direct pharmacists to study and report to concerned clinicians about possible involvement of drug(s) causing/potentiating such adverse events in patients on chemoradiation therapy. This pilot study highlighted the potential role of clinical pharmacists in monitoring RRAEs. However, such a concept is newer and may require the training of clinical pharmacists before they are assigned such responsibilities. We developed a training module for clinical pharmacists and the same was implemented. However, the impact of training was not measured systematically. Structured training of clinical oncology pharmacists and their

collaborative work with radiation oncologists may be able to improve reporting of radiation safety in cancer patients. RRAE reporting and monitoring has become one of the daily clinical pharmacy activities after presentation of these results at the study site. After reviewing many previous studies, as per our knowledge, there is no specific long-term study conducted on RRAEs in all types of cancer Patients. Adverse event reporting due to radiation therapy must be performed wherever feasible.

CONCLUSIONS

Patients on external radiation therapy were found with a higher number of RRAEs compared to other types of radiotherapies. Patients who were on radiotherapy concurrent with chemotherapy developed more RRAEs compare to radiotherapy alone. Clinical pharmacists may contribute to radiation safety reporting in consultation with radiation oncologists. Interventions made by clinical pharmacists helped to initiate supportive care to patients untreated for their RRAEs. Further studies should be done with a control group to investigate the role of clinical pharmacists in RRAE reporting. Adverse event reporting due to radiation therapy should be performed on daily basis as a part of patient safety monitoring and clinical pharmacy services wherever feasible.

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Conflicts of interest

There are no conflicts of interest.

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