ORIGINAL ARTICLE

Reporting and Monitoring of Radiation Related Adverse Events by Clinical Pharmacists in Cancer Patients: A Pilot Study

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ABSTRACT

Objectives: This study was conducted to investigate the role of clinical pharmacists in radiation related adverse events detection and monitoring in cancer patients. **Methods:** This was a prospective interventional study conducted at private academic oncology care setting for a period of six months. Patients on radiation therapy or chemo-radiation 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 per defined by Radiation Therapy Oncology Group (RTOG). Enrolled patients were also followed to ensure if they were provided adequate supportive care. **Results:** A total of 226 radiation related adverse events (RRAEs) were reported from 254 patients followed during the study period. Among the study subjects, majority of them received chemo-radiation (n=126, 56%) than radiotherapy (n=100, 44%) alone. The most common reported events were fatigue (n=39, 17.2%) followed by mucositis (n=29, 12.8%), pain (n=23, 10.17%), diarrhoea (n=23, 10.17%), gastritis (n=22, 9.7%), proctalgia (n=20, 8.8%) and vomiting (n=18, 7.9%). Among the study patients who developed adverse events, majority (n=126, 56%) of them received a combination of chemotherapy and radiation therapy and 100 (44%) of 226 patients received radiotherapy alone. Weekly cisplatin monotherapy was the most common chemotherapy prescribed concurrently to radiotherapy. Clinical pharmacists intervened to initiate adequate supportive care for 32% (n=72) patients. **Conclusions:** Clinical pharmacists may contribute for identifying radiation related toxicities in cancer patients. Team work of clinical pharmacists with radiation oncologists can improve the radiation safety reporting and can ensure required medical and supportive care to manage RRAEs.

Key words: Radiotherapy; adverse events; clinical pharmacists; supportive care

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Access this article online

Website: www.jbclinpharm.org

Quick Response Code:

INTRODUCTION

Radiation therapy is one of the important modalities of treatment for many cancers. Patients with some cancers like head and neck, cervix and brain respond well to radiotherapy whereas patients with cancers like lung and colorectal respond well when radiation therapy is given concurrent to chemotherapy.[1] However, radiotherapy 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.[2] Most radiation toxicities like vomiting, diarrhea, mucositis and fatigue are temporary and acute in nature whereas many like fibrosis, cardiac dysfunction, cognitive impairment and sexual dysfunctions occur months to years following treatments. Few toxicities like burning micturition, dermatitis are also associated with cumulative effects of radiation therapy on repeated treatments.[3-6] A study conducted by Maduro JH have well demonstrated acute and delayed toxicities due to radiation in patients with cervical cancer.[7]

Nature and extent of radiation related adverse events (RRAEs) depend on type of radiation therapy, dose of radiation (Gy), duration of treatment, hydration status, type of cancer and/or any other patient specific factor(s).[3,8] Also, these events impact negatively on patients' daily activities like eating, liquid intake, sleep, exercise, work and hence lead to poor quality of life.[8,9] Radiation toxicities may be potentiated when patients are receiving concurrent chemotherapy.[10] A study conducted by Caroline FS et.al and team showed that quality of life was impaired in patients received chemotherapy concurrent to radiotherapy for gynecological and breast cancer.[11] A study conducted by Kassam Z *et al.* also reported impairment in quality of life when chemotherapy is given concurrent to radiation therapy for patients with gastric cancer.[12] In common, RRAEs contributes for poor quality of life and may demand additional medical care.[11,12] Due to these known facts, it is essential to timely identify and monitor such radiation toxicities in cancer patients.

In a country like India where radiation oncologists have relatively higher patient load, it is difficult to follow 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. Traditionally, clinical pharmacists are involved in monitoring patient drug safety by routinely detecting and monitoring adverse drug reactions. So, probably with structured training they may be able to identify RRAEs in consultation with radiation oncologists. Hence, this study was conducted to investigate the potential role of clinical pharmacists in detection and monitoring of RRAEs.

Aim of the study

This study was conducted to investigate the role of clinical pharmacists in detection and monitoring of RRAEs in patients on radiotherapy and chemo-radiotherapy.

Cite this article as: Patel H, Paul AA, Hadia R, Islam B, Gurumurthy P. Reporting and Monitoring of Radiation Related Adverse Events by Clinical Pharmacists in Cancer Patients: A Pilot Study. J Basic Clin Pharma 2017;8:S70-S73.

METHODS

It was a prospective interventional study conducted for a period of six months at a private academic oncology care setting. All cancer patients who were on radiation therapy and/or chemo-radiation therapy were followed on daily basis by clinical pharmacists to identify RRAE(s) if any. Identified adverse events were discussed with concerned radiation oncologists for authentication. All the identified RRAEs were reported and coded as per International Medical Terminology (IMT) by clinical pharmacists and graded by radiation oncologists as per Radiation Therapy Oncology Group (RTOG). Clinical pharmacists collected information regarding the type of cancer, chemotherapy prescribed (if applicable), type of radiation therapy, duration and dose of radiation therapy. 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).

RESULTS

A total of 254 patients were followed during the study period at radiation therapy unit and wards of the study site. A total of 226 RRAEs were identified in patients who were on radiation therapy or chemo radiation therapy. Majority of the events were reported in age group of 51-60 years (32.7%) followed by 41-50 years (26.9%) and 61-70 years (23.9%). A total of 117 (51.7%) events were reported in female patients and 109 (48.2%) events were reported in male patients. Among enrolled study subjects, 62.3% of patients (n=141) were treated under private insurance or self-payment and 37.6% of patients (n=85) were treated under government schemes. Most of the study subjects were given radiation therapy or chemo radiation therapy for head and neck cancers (n=89, 39.3%) and cervical cancer (n=74, 32.7%) (Table 1). Among the study patients who developed RRAEs, majority (n=126, 56%) of them received a combination of chemotherapy and radiation therapy and 100 (44%) of 226 patients received radiotherapy alone. Cisplatin weekly monotherapy or Cisplatin based chemotherapy was commonly used pharmacological treatments in patients on chemo-radiation therapy.

The most common reported events were fatigue (n=39, 17.2%) followed by mucositis (n=29, 12.8%), pain (n=23, 10.17%), diarrhea (n=23, 10.17%), gastritis (n=22, 9.7%), proctalgia (n=20, 8.8%) and vomiting (n=18, 7.9%) [Tables 2]. Majority (n=212, 93.8%) reported events were acute in nature whereas 14 (6.19%) of 226 events were delayed in nature. Majority RRAEs were reported in patients who received unfractionated external radiotherapy (n= 142) followed by ICRT (intracoronary radiation therapy) (n=28), IMRT (Intensive modulated radiation therapy) (n=27), 3D CRT (three dimensional conformal radiation therapy) (n=21) and ILRT (intra luminal radiation therapy) (n=8). However, we did not study the correlation between dose of radiation and reported RRAEs.

Most of the reported grade 1 events were fatigue, vomiting, gastritis and mucositis. Most of the reported grade 2 events were fatigue, diarrhea, dermatitis and mucositis. However, grade 3 and 4 events were vomiting, diarrhea, fatigue, gastritis, proctalgia and mucositis. Most of the grade 3 and grade 4 events were reported in patients on external radiation therapy and on chemo radiation therapy. Table 3 describes grading of the most common RRAEs as per RTOG scale. However, RRAEs like pain, burning micturition, dehydration and pyrexia were not graded because RTOG does not provide grading of the mentioned RRAEs.

Among the patients who developed RRAEs, around 68% (n=154) were started on symptomatic or specific treatment for the respective event(s). However, 32% (n=72) of patients were not started with any symptomatic or specific care for the reported RRAEs. The most common untreated RRAEs were fatigue (32%) followed by proctalgia (14.5%), gastritis (8.1%), pain (6.5%), mucositis (4.2%) and burning sensation (4.2%). Few patients with dermatitis, burning micturition, dryness of mouth, edema, insomnia, vertigo, chest pain, myalgia, dehydration and pyrexia were also untreated [Figure 1]. Clinical pharmacists consulted to concerned radiation oncologists to initiate adequate medical and supportive care for all 72 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 non-pharmacological treatment to manage RRAEs (n=32), drug information to concerned clinician to manage RRAE (n=14), dosage adjustments of supportive care used to manage RRAEs (n=12), patient counselling (n=10) and by improving availability of medicines required to treat RRAEs (n=4).

With our experience in reporting RRAEs, we developed training module for clinical pharmacists to guide them on radiation safety

Table 1: Demographics of study patients who developed RRAEs

Demographic details	N (%)
Age	
20-30	10 (4.4%)
31-40	14 (6.19%)
41-50	61 (26.99%)
51-60	74 (32.7%)
61-70	54 (23.9%)
71-80	13 (5.7%)
Gender	
Male	109 (48.23%)
Female	117 (51.76%)
Payment Scheme	
Self-payment/Private Insurance	141(62.38%)
Government schemes	85(37.61%)
Type of Cancers	
Head And Neck	89 (39.38%)
Cervix	74 (32.7%)
Colorectal	11 (4.86%)
Lung	10 (4.4%)
Breast	08 (3.54%)
Endometrium	05 (2.21%)
Bladder	09 (3.98%)
Vaginal vault	06 (2.65%)
Others	14 (8.79%)

Table 2: List of RRAEs observed in study patients

IMT Code	Event	Number (%)
001423	Fatigue	39 (17.25%)
018489	Mucositis	29 (12.8%)
021197	Diarrhea	23 (10.17%)
900180	Pain	23 (10.17%)
000925	Gastritis	22 (9.7%)
008304	Proctalgia	20 (8.8%)
021162	Vomiting	18 (7.9%)
Not available	Burning Micturition	07 (3.09%)
02247	Dermatitis	07 (3.09%)
00180	Pyrexia	06 (2.65%)
004966	Dehydration	05 (2.21%)
	Others	27 (11.9%)

Table 3: RTOG grades for commonly reported RRAEs

Event	Grade	N (%)
Vomiting	1	10 (55.5%)
	2	5 (27.77%)
	3	2 (11.1%)
	4	1 (5.55%)
Diarrhea	1	5 (21.7%)
	2	15 (62.2%)
	3	3 (13.1%)
Fatigue	1	18(46.15%)
	2	19(48.7%)
	3	1(2.5%)
	4	1(2.5%)
Gastritis	1	10 (45.45%)
	2	11(50%)
	3	1(4.55%)
Proctalgia	1	13 (65%)
	2	6(30%)
	3	1 (5%)
Mucositis	1	9 (31.03%)
	2	16(55.1%)
	3	4(13.7%)
Dermatitis	1	2 (28.57%)
	2	4 (57.14%)
	3	1(14.28%)

Table 4: Training sessions to guide clinical pharmacists for Radiation Related Adverse Event Reporting

Session	Duration
Basics of Radiotherapy, Types and Subtypes	1 hour
Radiotherapy as treatment for common cancers	1 hour
Radio sensitizing agents/Concurrent Chemotherapy	2 hours
Types of radiation related toxicities	1 hour
Grading of radiation toxicities (IMT & RTOG)	1 hour
Managing radiation toxicities	2 hours
Visit to radiotherapy unit and instruments	2 hours

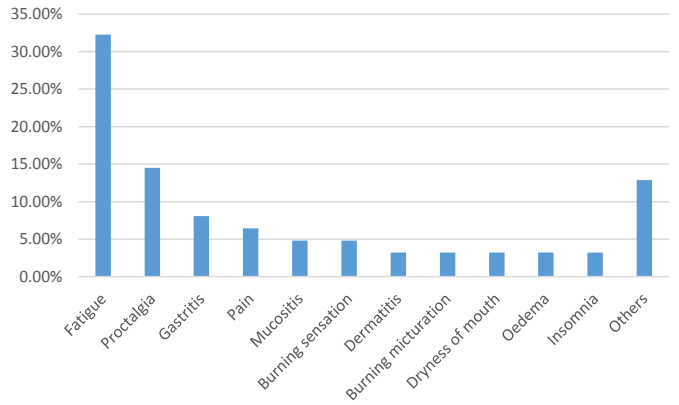

Figure 1: List of untreated RRAEs for which clinical pharmacists intervened to provide medical and supportive care

reporting [Table 4]. It is recommended for clinical pharmacists at the study site to undergo this training if they want to participate in radiation safety reporting.

DISCUSSION

The role of clinical pharmacist is well known and accepted in monitoring and improving safe use of drugs in cancer patients. However, clinical pharmacists are not routinely involved in monitoring of radiation toxicities in cancer patients. This study discusses potential role of clinical pharmacists in detection and monitoring of RRAEs in cancer patients. In this study we observed, females developed higher number of RRAEs which may be due to more number of patients enrolled with cervical cancer. The most of the events were reported in patients with head and neck cancers and cervical cancer. This may be due to higher number of study subjects recruited with those two cancers due to its higher prevalence in our practice.[13] Concurrent radiation and chemotherapy appear to be efficacious due to its synergistic action.[10] However this also results in added number of adverse events in cancer patients, the reason being that some of the chemotherapy agents like cisplatin, fluorouracil is radiosensitive in nature. In our study we also found more number of RRAEs in patients with chemo radiation 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 higher number of RRAEs were reported in those patients. The reason for 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 coverage of those schemes and inability of our patients to manage out of pocket expenditures. Higher number of RRAEs is reported with use of unfractionated therapy is 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.[14] MRI scan studies done by van De Bunt *et al.* and Dosimetric analysis done by collecting CT results before and after treatment by Portelance *et al.* shows that IMRT is superior to external radiation therapy in normal tissue sparing function.[15,16] We could not study the correlation between doses of radiation received by each patients to that of reported RRAEs.

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,[17] we could not follow all the patients for delayed events. In a critical review on radiotherapy-related fatigue by Jereczek-Fossa BA 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 breast, lung and prostate.[18] 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 cancer and lung cancer. Mucositis accounted to 12% of the events of which all of them occurred in head and neck cancer patients. Similar results was reported in a systematic review which consisted of 31 Randomized control trails where the mean incidence of developing mucositis in head and neck cancer was 80%.[19] 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 nearly 32% of RRAEs were undetected where patients needed symptomatic and/or specific medical care. Clinical pharmacists 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 non-pharmacological 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. Non-pharmacological 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 mouth washes and gargles. Whereas, for dermatitis we recommended certain local ointments containing steroids, anti-histamines and soothing agents. Dosage adjustments were provided for patients who had renal impairment. For example, patient with gastritis and dehydration had elevated serum creatinine and hence, patient needs renal dosage adjustment if 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 like Tramadol, 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 same can be authenticated and treated further by radiation oncologists as needed. Such 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 chemo radiation therapy. This pilot study highlighted the potential role of clinical pharmacists in monitoring RRAEs. However, such concept is newer and may require training of clinical pharmacist before they are assigned such responsibilities. We developed training module for clinical pharmacists and same was implemented. However, the impact of training was not measured systematically. Structured training of clinical 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 activity after presentation of these results at study site.

CONCLUSION

Patients on external radiation therapy were found with 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 for 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 control group to investigate the role of clinical pharmacists in RRAE reporting.

Funding

No funding was received for this study from any source.

Conflicts of interest

None to declare.

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