ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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To Study the Pattern, Causality, Severity and Predictability of Adverse Drug Reactions in Patients on Cancer Chemotherapy: Descriptive Research-Qualitative Study

Kanser Kemoterapisi Alan Hastalarda Advers İlaç Reaksiyonlarının Modeli, Nedenselliği, Şiddeti ve Öngörülebilirliği: Betimsel Araştırma-Nitel Çalışma

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ABSTRACT Objective: To study the pattern of adverse drug reactions (ADRs) in patients receiving cancer chemotherapy. **Material and Methods:** The present prospective open label observational study assessed the new and old patients suffering from any of (breast, lung, colon, ovary, lymphoma) cancer on chemotherapy attending medical oncology department after taking their consent and patients who developed at least 1 adverse drug reaction during the treatment period. **Results:** It was found that the incidence of ADRs was more in females than males. The majority (77%) of ADRs were reported in age group of 31-60 years. The higher number of (30%) patients were of breast cancer. The most common organ system involved in ADRs because of cancer chemotherapy was skin and epidermis, having (45%) ADRs. The most recurrent ADR was pain in injection site (22.5%) followed by other adverse effects. The most common drug responsible for highest number of ADRs (18.1%) was docetaxel. As per World Health Organization Uppsala Monitoring System Causality Scale, majority (52.5%) ADRs were of possible category. According to Naranjo Algorithm Scale, (55%) of ADRs were of probable category. As per Hartwig and Siegel scale of severity assessment, highest number of ADRs (29.1%) of level 2 (100%) of the ADRs were predictable as per Rawlins and Thompson Scale. **Conclusion:** It is important to identify and evaluate the ADRs at an early stage, so that quality of life of cancer patients on cancer chemotherapy can be improvised.

Keywords: Drug-related side effects and adverse reactions; drug therapy; antineoplastic agents

ÖZET Amaç: Kanser kemoterapisi alan hastalarda advers ilaç reaksiyonlarının (AİR) modelinin araştırılması. **Gereç ve Yöntemler:** Bu prospektif açık etiketli gözlemsel çalışmada medikal onkoloji bölümüde kemoterapi alan, herhangi bir kanserle (meme, akciğer, kolon, over, lenfoma) savaşan eski ve yeni hastalar ve tedavi süresince en az bir kez advers ilaç reaksiyonu gelişmiş olan hastalar onamları alındıktan sonra değerlendirildi. **Bulgular:** AİR'nin kadınlarda erkeklerden daha sık görüldüğü bulundu. AİR'nin çoğu (%77) 31-60 yaş grubunda bildirildi. Hastaların çoğunluğu (%30) meme kanseri hastasıydı. Kanser kemoterapisi nedeniyle gelişen AİR'den en çok etkilenen organ sistemi cilt ve epidermisti (%45). En sık tekrarlanan AİR enjeksiyon bölgesinde ağrı idi (%22,5), ardından diğerleri geliyordu. En fazla AİR'na neden olan ilaç docetaksel idi (%18,1). Dünya Sağlık Örgütü Uppsala Gözlem Sistemi Nedensellik Skalasına göre, AİR'nın çoğunluğu (%52,5) muhtemel katregorideydi. Naranjo Algoritm Skalasına göre ise AİR'nın %55'i kuvvetle muhtemel kategorisindeydi. Hartwig ve Siegel şiddet değerlendirme ölçeğine göre, AİR'lerin 2. seviyesindeki (%100) en yüksek AİR sayısı (%29,1) Rawlins ve Thompson Ölçeğine göre tahmin edilebilirdi. **Sonuç:** AİR'larının erken dönemde saptanması ve değerlendirilmesi kanser hastalarının yaşam kalitesinin artırılması açısından önemlidir.

Anahtar Kelimeler: İlaca bağlı yan etkiler ve advers reaksiyonlar; ilaç tedavisi; antineoplastik ajanlar

Cancer is one of the leading causes of morbidity and mortality in both developed and developing countries.[1] There are different modalities available for cancer treatment like chemotherapy, radiotherapy, surgery, hormonal therapy, immunotherapy, biologic therapy and cryosurgery.[2] Chemotherapy regimens are immensely complex and cancer patients are a susceptible population with little tolerance.[3] As anti-

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cancer drugs have narrow therapeutic index, adverse drug reactions (ADRs) to these medications are high compared to other classes of drugs.[4] In general, the prevalence of ADRs leading to hospital admission is 3% to 6% and represented 5% to 10% of hospital expenditure.[5] Also, recent studies have determined that ADRs are 4th to 6th leading cause of death among cancer patients treated with chemotherapy.[6] It has also been estimated that about 35% of hospitalized patients experience their ADRs during their stay and incidence of fatal ADRs is 0.23% to 0.4%.[7] ADRs of cancer chemotherapy may also result in slackened quality of life, increased physician visits, health costs, long hospitalizations, and even death. ADRs of drugs continue to remain as an important public health issue.[8] Hence it is important to recognize the causality, severity and predictability of ADRs occurring with anticancer drugs to enhance the quality of life of patients and to reduce the cost of ADRs related hospitalization among cancer patients on chemotherapy.[9]

Therefore, the present study was planned to study the pattern, causality, severity and predictability of ADRs in cancer patients on chemotherapy.

AIMS AND OBJECTIVES

AIM

To study the pattern of ADRs in patients receiving cancer chemotherapy.

OBJECTIVE

1. To assess the causality of ADRs using World Health Organization Uppsala Monitoring Center (WHO-UMC) and Naranjo Algorithm Scale.

2. To assess the severity of ADRs using Hartwig and Siegel Scale.

3. To assess the predictability of ADRs using Thompson and Rawlins Scale.

MATERIAL AND METHODS

This was a prospective open label observational study. Patients of 5 most common cancers attending medical oncology department were enrolled in the study after taking their consent. The study was carried out in Department of Pharmacology in association with the Department of Medical Oncology, VMMC Safdarjung Hospital New Delhi. The study was in accordance with the principles of the Declaration of Helsinki, the protocol number of this retrospective study (IEC/VMMC/SJH/Project /2020-02/CC-30) was obtained from the Institutional Ethics Committee of Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi-10029 for approval (no: date: August 10, 2020).

Inclusion Criteria:

1. New and old patients suffering from any of (breast, lung, colon, ovary, lymphoma) cancer on cancer chemotherapy were included in the study.

2. The patients on cancer chemotherapy who developed at least 1 ADR during the treatment period.

Exclusion Criteria:

1. Cancer patients who did not develop any ADR after taking 1 or more chemotherapeutic agent.

2. Cancer patients undergoing/undergone some surgical procedure or on radiotherapy while receiving anticancer drugs.

The patient related information, demographic details, clinical and treatment data, age, sex, suspected drug causing ADR treatment details (dose, frequency, date of starting and stopping) describing of the event, onset and ablation of event, information on challenging and dechallenging, concomitant medical product used were reported in the "Suspected Adverse Drug Reaction Reporting Form" by Pharmacovigilance program of India, Ministry of Health and Welfare. Causality of ADR in relation to drug was done using WHO-UMC Causality Scale and Naranjo Algorithm Scale.[4] ADRs were/categorized like certain/probable/possible/unlikely/unclassified/unclassifiable as per WHO-UMC. Naranjo Probability Scale was used to evaluate the relationship between suspected ADR and the drug. This scale consists of a questionnaire which contains 10 questions with the options yes, no, and do not know and the score was given for each option. The total score calculated from this questionnaire defines the category as >9: definite, 5-8: probable, and 1-4: possible.[3] The severity of the ADR was assessed using modified Hartwig and Siegel Scale. Predictability of the ADR was done and was characterized as type a dose-dependent and type B idiosyncratic with no clear dose dependent and not

predictability from as per system introduced by Rawlins and Thompson.[10] The data were analyzed using descriptive statistics. The percentage and frequency of occurrence of ADR due to particular drugs/particular regimens affecting particular organ system were expressed as percentage using SPSS Statistics for Windows, version 16 (x.0) (SPSS Inc., Chicago, Ill., USA.

RESULTS

In this study, 300 patients of 5 most common cancers on chemotherapy attending Medical Oncology of Safdarjung Hospital were enrolled to study the pattern of ADRs. A total of 480 ADRs were collected from these patients. The analysis of ADR has been done on the basis of age, sex, number, type of ADR, organ involved, causality assessment, severity and predictability.

a) Demographic characteristics of the patients: The incidence of ADRs was more in females as compared males as depicted in the Figure 1. Majority (77%) of the ADRs were reported in the age group in 31-60 years. Only 11% ADRs occurred in the age more than 60 years and 12% of ADRs occurred less than 31 years of age as shown in Figure 2.

b) Type of cancer and number of patients: Out of 300 patients included for various cancer on chemotherapy, maximum 90 (30%) patients were of breast cancer and minimum 18 (6%) patients were of colon cancer as shown in Table 1.

c) Organ system wise distribution of ADRs: There were total 480 ADRs reported in 300 patients of cancer on chemotherapy. The most common organ system involved in ADRs because of cancer chemotherapy was skin and epidermis having 216 (45%) ADRs, followed by peripheral nervous system [108 (22.5%)], gastrointestinal system [84 (17.5%)], vascular system [51 (10.6%)], central nervous system [12 (2.5%)] ADRs and blood [9 (1.8%)] ADRs as shown in Table 2.

d) Type of most common ADRs due to anticancer drugs: Out of total 480 ADRs reported, majority of ADRs (108) were pain at the injection site (22.5%) followed by other adverse effects. Other less common ADRs were bone marrow suppression 6 (1.2%), diarrhea 6 (1.2%), severe anemia 3 (.6%) and skin erection 3 (0.6%) as shown in Table 3.

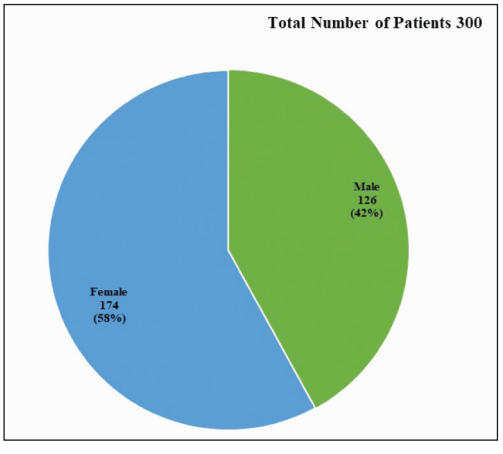

FIGURE 1: Showing sex distribution of adverse drug reactions in patients on cancer chemotherapy.

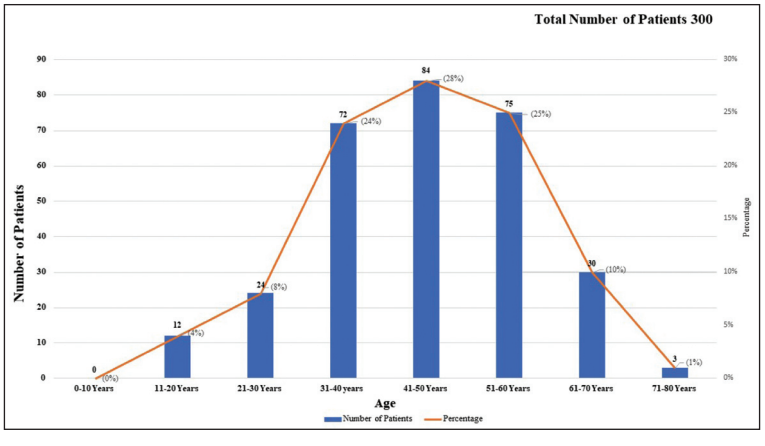

FIGURE 2: Showing age, number and percentage of patients on cancer chemotherapy.

TABLE 1: Showing the type of cancer, number and percentage of the patients included in the study.

S.No.	Type of cancer	Number n=300	Percentage
1.	Breast	90	30%
2.	Ovary	84	28%
3.	Lung	81	27%
4.	Lymphoma	27	9%
5.	Colon	18	6%

TABLE 2: Showing organ system wise distribution of ADRs in patients on cancer chemotherapy.

No.	System organ class	No. of ADR	Percentage
1	Skin and epidermis	216	45%
2	Peripheral nervous system	108	22.5%
3	Gastrointestinal system (GIS)	84	17.5%
4	Vascular system	51	10.6%
5	Central nervous system	12	2.5%
6	Blood	9	1.8%

ADRs: Adverse drug reactions.

e) Type of drugs and numbers of ADRs: The most common drug responsible for the highest number of ADRs was docetaxel 87 (18.1%) and the fluorouracil (5-FU), 6 (1.2%) was the least common drug responsible for adverse drug effects as shown in Table 4.

TABLE 3: Showing most common cancer ADRs due to anti-cancer drugs.

1.	Pain in injection site	108	22.5%
2	Dryness	66	13.7%
3	Rashes	66	13.7%
4	Swelling	51	10.6%
5	Itching	45	9.3%
6	Vomiting	42	8.7%
7	Ulcers in mouth	36	7.5%
8	Pimples	36	7.5%
9	Anxiety	12	2.5%
10	Bone marrow	6	1.2%
11	Diarrhea	6	1.2%
12	Severe anemia	3	0.6%
13	Skin erection	3	0.6%

ADRs: Adverse drug reactions.

TABLE 4: Showing number and percentages of ADRs caused by different anti-cancer drugs.

S.NO.	Drugs	No. of ADRs	Percentage of ADRs
1	Docetaxel [SP Accure Labs Pvt. Ltd. (SPAL), India]	87	18.1%
2.	Paclitaxel [SP Accure Labs Pvt. Ltd. (SPAL), India]	69	14.3%
3.	Cisplatin [SP Accure Labs Pvt. Ltd. (SPAL), India]	66	13.7%
4.	Carboplatin (GLS Pharma Ltd., India)	63	13.1%
5.	Gemcitabine (Neon Laboratories, India)	30	6.25%
6.	Etoposide [Parenteral Drugs (India) Limited, India]	21	4.3%
7.	Vinblastine (Neon Laboratories, India)	9	1.8%
8.	Adriamycin (Neon Laboratories, India)	9	1.8%
9.	Cyclophosphamide (GLS Pharma Ltd., India)	12	2.5%
10.	5-FU (Actiza Pharmaceutical Private Limited, India)	6	1.2%
11.	Other drug	108	22.5%
	Epirubicin (Hetero Healthcare Ltd, India)		
	Trastuzumab (Lupin Limited, India)		
	Pld (Neon Laboratories, India)		
	Pemetrexed (Zuvius Life Sciences Private Limited, India)		
	Doxorubicin (Neon Laboratories, India)		
	Vincristine (Neon Laboratories, India)		
	Rituximab (Neon Laboratories, India)		
	Bleomycin (Zuvius Life Sciences Private Limited, India)		
	Dacarbazine (Zuvius Life Sciences Private Limited, India)		
	Oxaliplatin [SP Accure Labs Pvt. Ltd. (SPAL), India]		
	Capecitabine (Cipla, India)		
	Irinotecan (Zuvius Life Sciences Private Limited, India)		
	Leucovorin (Biozenta Laboratories)		

5-FU: 5-Fluorouracil; ADRs: Adverse drug reactions.

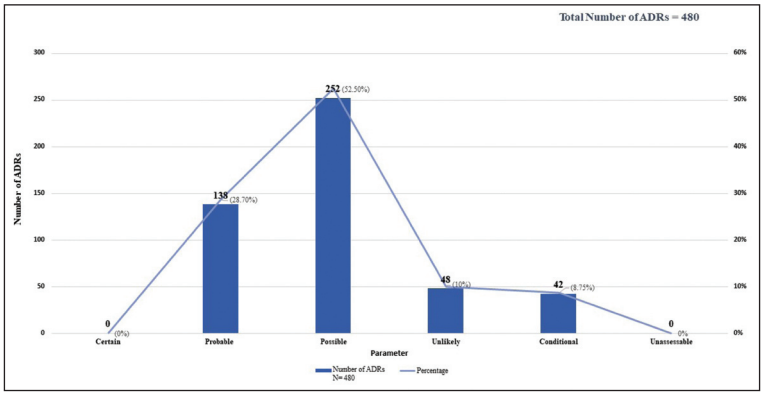

FIGURE 3: Showing World Health Organization Uppsala Monitoring Center causality assessment of adverse drug reactions in cancer patients on chemotherapy.

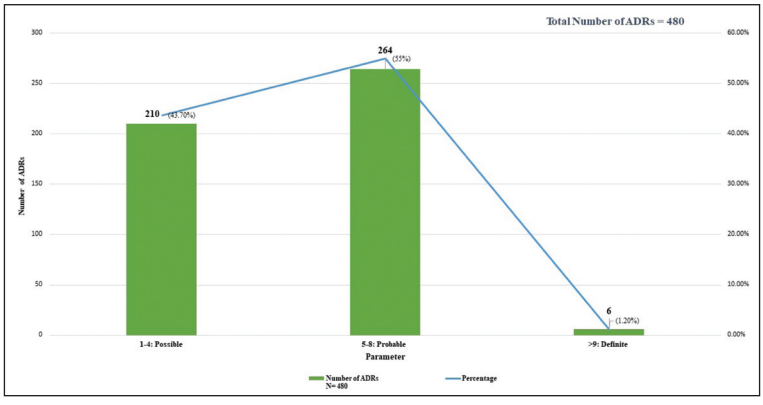

FIGURE 4: Showing Naranjo Algorithm Scale for causality assessment of adverse drug reactions in cancer patients on chemotherapy.

CAUSALITY

WHO-UMC Scale: In the present study, according to WHO-UMC Causality Scale, out of 480 ADRs, majority of the ADRs were of possible category 252 (52.5%), followed by probable 138 (28.7%), unlikely 48 (10%) and conditional 42 (8.7%) as shown in Figure 3.

Naranjo Algorithm Scale: According to Naranjo Algorithm Scale, out of 480 ADRs, 264 (55%) ADRs were of probable category, 210 (43.7%) possible and 6 (1.2%) definite as shown in Figure 4.

Severity Assessment

According Hartwig and Siegel Scale of severity assessment, out of 480 ADRs, the highest were 140 (29.1%) of level 2, 101 (21%) were level 3, 100 (20.8%) were level 5, 74 (15.4%) were level 1 and 65 (13.5%) were level 4 as shown in Figure 5.

Predictability of ADRs by Rawlins and Thompson: Out of 480 ADRs, all the ADRs were predictable and none of ADRs were unpredictable with respect to Rawlins and Thompson classification as shown in Figure 6.

DISCUSSION

Cancer chemotherapy has high potential to cause adverse drug reactions. So, it is very important to identify them at an early stage to improve the quality of life of cancer patients on chemotherapy experiencing ADRs. In our study, we collected ADRs from the patients of 5 most common cancer (breast, ovary, lung, lymphoma and colon) on cancer chemotherapy attending Medical Oncology Department of Safdarjung Hospital. Four hundred and eighty ADRs from 300 patients of cancer-on-cancer chemotherapy were collected over the period of 6 months. This can be com-

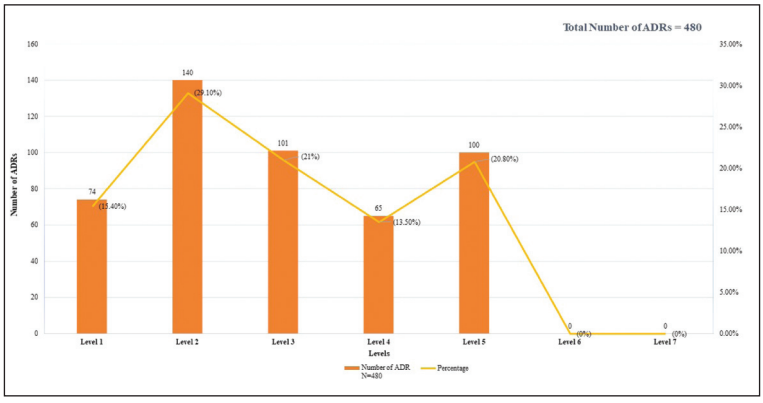

FIGURE 5: Showing Hartwing and Siegel Scale of severity assessment of adverse drug reactions in cancer patients on chemotherapy.

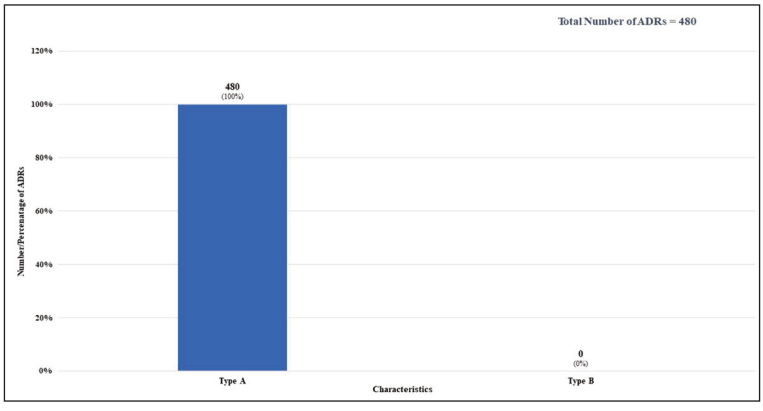

FIGURE 6: Showing predictability of ADRs by Rawline and Thompson classification in cancer patients on chemotherapy. ADRs: Adverse drug reactions.

pared with 2,209 ADRs collected from 1,869 patients in a study conducted by Behera et.al. In our study, out of 300 patients, 126 (42%) males and 174 (58%) females experienced ADRs due to cancer chemotherapy. These findings are similarly to the study in which out of 1,869 patients, 1,327 (60.07%) females and 882 (39.93%) males experienced ADRs.[9] In our study, the incidence of ADRs were highest (28%) in age group of 41-50 years which is similar to the study conducted by Chopra et.al in which the maximum number of ADRs i.e., 162 (27.4%) were in age group of 41-50 years.[3]

In our study, out of 300 patients included for various cancer on cancer chemotherapy, 90 (30%) patients were of breast cancer, 84 (28%) patients were of ovary cancer, 181 (27%) patients were of lung cancer, 27 (9%) patients were of lymphoma and 18 (6%) patients were of colon cancer. This can be compared with the study conducted by Chopra et al., in which 192 (32.5%) patients of breast cancer, 24 (4.1%) patients of carcinoma colon and 6 (1%) patients of lymphoma experienced ADRs.[3] In another study by Saini et.al., out of 174 patients, 91 (52.3%) patients of breast cancer and 61 (35.05%) patients of lung cancer experienced ADRs. So, it has been observed that in most of the studies, the breast cancer patients are highest in number, so adverse effects experienced by these patients on cancer chemotherapy are also maximum in number.[11] In our study, the most common organ system involved in ADRs because of cancer chemotherapy was skin and epidermis with 216 (45%) ADRs. This finding shows a contrast with the study in which total of 2,207 ADRs were observed out of which 535 (24.22%) ADRs involved blood system.[9] In our study, out of 480 ADRs, 108 ADRs were pain at the injection site (22.5%) followed by dryness [66 (13.7%)], rashes [66 (13.7%)], swelling [51 (10.6%)], itching [45 (9.3%)]. Less common

ADRs were vomiting [42 (8.7%)], ulcers in mouth 36 (7.5%), pimples [36 (7.5%)], anxiety [12 (2.5%)]. Other less common ADRs were bone marrow suppression [6 (1.2%)], diarrhea [6 (1.2%)], severe anemia [3 (0.6%)] and skin reactions [3 (0.6%)]. The incidence of these ADRs can be compared with the study in which out of 2209 ADRs, 280 ADRs (12.6%) were anemia, followed by 65 (2.94%) vomiting, 39 (1.77%) diarrhea and 38 (1.72%) depicting rash.[9] In another study, out of 509 cases, nausea and vomiting was found in 151 (25.5%) cases, followed by diarrhea in 42 (7.1%) cases, rash in 10 (1.7%) cases, anemia in 6 (1%), oral ulcers in 5 (0.8%) and itching in 3 (0.5%). In our study, the most common drug responsible for highest number of ADRs was docetaxel i.e., 87 (18.1%), followed by paclitaxel in 69 (14.3%), cisplatin in 66 (13.7%), carboplatin in 63 (13.1%), gemcitabine in 30 (6.25%), etoposide in 21 (4.3%), cyclophosphamide in 12 (2.5%), vinblastine in 9 (1.8%), adriamycin in 9 (1.8%) and 5-FU in 6 (1.2%) and other drugs were 108 (22.5%). So, in our study, docetaxel and paclitaxel were the most common offender drugs causing ADRs. In a study conducted by Saini et al., in which 21 (91.5%) patients treated with paclitaxel and 10 (90.9%) patients treated with docetaxel experienced ADRs out of 91 patients who experienced adverse effects on different cancer chemotherapy regimens.[11] In another study, out of 2209 ADRs, 211 (9.55%) ADRs were caused by docetaxel, followed by 189 (8.56%) by gemcitabine, 163 (7.38%) by paclitaxel, 146 (6.61%) by oxaliplatin, 116 (5.2%) by capecitabine, 115 (5.21%) by 5-FU and 68 (3.08%) by vincristine.[9] In our study, according to WHO-UMC Causality Scale, out of 480 ADRs, most of the ADRs were of possible category 252 (52.5%), followed by probable 138 (28.7%), unlikely 48 (10%) and conditional 42 (8.7%). On the contrary, Saini et al. has reported in his study that most of the ADRs were probable [97 (64.67%)] followed by possible [53 (35.33%)].[11] In our study, according to Naranjo Algorithm Scale, out of 480 ADRs, 264 (55%) ADRs were of probable category, 210 (43.7%) possible and 6 (1.2%) definite. Our study findings are similar to the study conducted by Mugada and Samidala in which Naranjo algorithm showed that 76% of the reaction were probable reactions, 20% were possible and 4% were definite.[12] In our study, according Hartwig and Siegel Scale, out of 480 ADRs, 140 (29.1%) were level 2, 101 (21%) were level 3, 100 (20.8%) were level 5, 74 (15.4%) were level 1 and 65 (13.5%) were level 4. According to Hartwig and Siegel Severity Scale, most of the ADRs are mild in severity (58.03%), followed by moderate in severity (41.6%).[12] In our study, out of 480 ADRs, all the ADRs were predictable and none of ADRs were unpredictable by Rawlins and Thompson. In the present study, none of the patients developed fatal ADR and required hospitalization. Moreover, drugs like ondansetron, dexamethasone and ranitidine were given to the patients before chemotherapy to prevent chemotherapy-induced nausea and vomiting.

CONCLUSION

Cancer chemotherapeutic agents are known to cause a variety of ADRs compromising patient's quality of life. So, it is very important to identify and evaluate these ADRs at an early stage to improve quality of life of cancer patients on cancer chemotherapy.

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Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Kamlesh Garg;* ***Design:*** *Kamlesh Garg, Tomar Ashish;* ***Control/Supervision:*** *Kamlesh Garg, Satya Pal Kataria;* ***Data Collection and/or Processing:*** *Tomar Ashish, Satya Pal Kataria;* ***Analysis and/or Interpretation:*** *Kamlesh Garg, Mathur Arushi1, Raveendranath Perumal;* ***Literature Review:*** *Kamlesh Garg, Tomar Ashish, Raveendranath Perumal;* ***Writing the Article:*** *Kamlesh Garg, Tomar Ashish, Raveendranath Perumal;* ***Critical Review:*** *Kamlesh Garg, Satya Pal Kataria, Mathur Arushi1;* ***References and Fundings:*** *Kamlesh Garg, Mathur Arushi1.*

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