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Research Article

Causality Assessment in Cancer Chemotherapy-induced Adverse Drug Reactions in a Tertiary-care Centre in North India

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Abstract

Aims and Objectives: To determine the causality of ADRs of anticancer drugs administered to the patients of various cancers in a tertiary care centre.

Study Design: In this prospective study, causality of ADRs occurring in patients on cancer chemotherapy in a tertiary care centre in north India, over a period of one year was assessed employing Naranjo Prabability Scale.

Results: Out of a total 268 ADRs in 102 patients, most frequently reported ADR was alopecia (16.04%) followed by nausea (14.55%), constipation (11.94%) and vomiting (11.57%) which together constituted 54.1% of the total ADRs. Majority of the drugs were observed to cause 'probable' (61%) followed by 'definite' (13%), possible (9%) and 'doubtful' (7%) causality.

Conclusion: Wide variation in ADR-related causality amongst our series as well as series from some other centers warrant conduction of further well-planned studies.

Keywords: *Adverse Drug Reaction (ADR); Anticancer Drugs; Cancer Chemotherapy; Causality; Naranjo Probability Scale; Pharmacovigilance*

Introduction

According to the World Health Organisation (WHO) definition, an Adverse Drug Reaction (ADR) is "any noxious and unintended response to a drug that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or modification of physiological function" [1,2]. Today, ADRs are considered to be a robust public health problem worldwide, causing significant proportion of morbidity, hospital admissions, and even deaths. Hence, it is essential to recognize ADRs and to establish a causal relationship between the drug and the adverse event [3].

Until recently, the importance of ADR monitoring remained less understood in the resource-limited countries including India, leading to their under-reporting. India's National Pharmacovigilance Programme (NPvP), coordinated by Central Drugs Standard Control Organisation (CDSCO), was officially launched at New Delhi in 2004. However, it became operational in 2005 only [4,5].

Since emergence of pharmacovigilance in the Indian subcontinent in letter and spirit is a recent phenomenon, at present there is a paucity of data regarding the causality of ADRs associated with cancer chemotherapy in the region. The present study was, therefore, designed to evaluate the causality of ADRs occurring in cancer patients treated with chemotherapy in a tertiary care hospital in Jammu and Kashmir, India.

Materials and Methods

Study design

The present prospective study, spread over a period of one year, was conducted in the Regional Cancer Centre, Department of Radiation Oncology, Government Medical College and Associated Hospitals, Jammu, Jammu and Kashmir, India, with the approval of the Institutional Ethics Committee and Institutional Review Board.

The patients were enrolled for the study after taking their written informed consent. In case of children, their parents' consent was taken. Inclusion Criteria: All patients suffering from various cancers registered with Department of Radiation Oncology and put on cancer chemotherapy as the only therapy at a given time regardless of age and sex. Exclusion Criteria: Patients receiving concomitant chemo-radiotherapy.

Methodology

All hospitalised and outpatients suffering from various cancers registered with the Department of Radiation Oncology and put on anticancer drugs as the only therapy at a given time were studied for ADR casualty. Only 102 patients could be followed throughout the administration of the planned treatment cycles and for 1 month thereafter. Out of those 102, 90 patients developed at least one ADR and 12 developed no ADR at all.

A specially predesigned proforma, Adverse Drug Event Reporting Forma (as per the Government of India's CDSCO) was used for recording the data.

ADR monitoring was done in a systematic manner and the ADRs were reported by adopting both spontaneous and intensive reporting methods.

Casualty assessment was done using Naranjo Probability Scale [6] and categorized as 'definite' ('highly probable'), 'probable', 'possible' or 'doubtful'.

Plan of analysis

All the data collected was coded in numerical terms and was entered in excel data sheets. It was analysed with the help of computer software Microsoft Excel and SPSS for windows.

Observations

Out of a total of 116 patients enrolled in the study, only 102 could be followed throughout the administration of the planned treatment cycles and for 1 month thereafter.

Most frequently reported ADRs were alopecia (16.04%) followed by nausea (14.55%), constipation (11.94%) and vomiting (11.57%) which together constituted 54.1% of the total of 268 ADRs.

Table 1 presents the causality rating of drugs and the causality rating on causality assessment by Naranjo Probability Scale. Majority of the drugs were observed to cause 'probable' (61%) followed by 'definite' (13), possible (9) and 'doubtful' (7%) causality.

Drugs	Highly Probable/Definite	Probable	Possible	Doubtful
Epirubicin	0	40	1	0
5-FU	1	122	4	0
Cyclophosphamide	0	81	4	0
Gemcitabine	2	21	0	0
Carboplatin	0	38	1	0
Ifosfamide	3	6	1	0
Etoposide	3	42	1	0
Doxorubicin	4	42	0	0
Cisplatin	0	36	4	0
Capecitabine	2	16	0	0
Hydroxyurea	5	1	0	0
Paclitaxel	2	16	1	0
Bleomycin	0	14	3	4
Oxaliplatin	0	35	4	0
Vinblastin	0	6	2	0
Dacarbazine	0	6	2	0
Methotrexate	0	9	1	0
Vincristine	0	7	0	0
Docetaxel	6	0	0	0
Cladribine	0	0	0	0
Irinotecan	0	3	0	0
Leucovorin	0	9	1	60
Prednisolone	0	3	0	0

Table 1: *Drugs and the causality rating.*

Note: The numerical values are more than the actual number of ADRs observed during the study i.e. 268. This is because most of the drugs were given as combinations but to take out the causality these have been linked separately with each ADR caused by the combination.

Out of the total drugs causing alopecia, the commonest ADR observed in this study, 5 drugs were assessed to have a definite causal relationship whereas 17 had a probable relationship and 22 a doubtful relationship. Reports of alopecia with the drugs ifosfamide, etoposide, doxorubicin, and paclitaxel were probable in certain cases and definite in others as they had been given in combination in certain cases and as monotherapy in others. Similar was the case with other ADRs.

The causality of leucovorin with various ADRs remained doubtful. The FEC regimen (5-FU+Epirubicin + Cyclophosphamide i.e. 2+1+3, respectively) and the CapOx Regimen (Capecitabine+Oxaliplatin i.e. 10+14, respectively) were found to be associated with majority of the probable ADRs

Table 2 shows the ADRs caused by various regimens. Alopecia, nausea and constipation were seen to have occurred because of almost every regimen used. Epirubicin; Paclitaxel+ Cisplatin+ 5-FU+ Leucovorin; Paclitaxel; Gemcitabine; Cisplatin and Cladribine were found to have caused no ADR in certain patients while the same drugs caused a number of ADRs in others.

Drug Combinations used	ADRs caused by them
Cyclophosphamide, Methotrexate, 5-FU	Nausea, Vomiting, Anorexia, Allergy, Alopecia
Cyclophosphamide, Doxorubicin, 5-FU	Constipation, Headache, Anorexia, Pruritus, Nail changes, Alopecia
5-FU, Epirubicin, Cyclophosphamide	Alopecia, Irregular menses, Mucositis, Taste alteration, Constipation, Nausea, Vomiting, Anaemia, Neutropenia, Headache, Fatigue, Skin rash
Doxorubicin	Alopecia, Nausea
Doxorubicin, Cyclophosphamide	Nausea, Anaemia, Alopecia, Vomiting, Fatigue
Docetaxel	Alopecia, Constipation, Abdominal pain, Fatigue
Epirubicin, Cyclophosphamide	Alopecia, Dizziness, Nausea, Vomiting, Constipation, Anorexia
Paclitaxel, Carboplatin	Thrombocytopenia
Etoposide	Alopecia, Nausea
Epirubicin, Oxaliplatin, 5- FU, Leucovorin	Anaemia, Nail changes
Paclitaxel, Cisplatin, 5- FU, Leucovorin	Constipation, Alopecia, Musculoskeletal pain, Fatigue, Headache
Paclitaxel	Alopecia, Nail changes
Oxaliplatin, 5- FU, Leucovorin	Alopecia, Nausea, Fatigue, Constipation, Vomiting, Irregular menses, Diarrhoea, Anorexia, Fatigue, Headache
5- FU, Leucovorin	Nausea, Vomiting, Fatigue, Dry skin, Anorexia, Irregular menses, Constipation, Alopecia, Diarrhoea
Irinotecan, 5- FU, Leucovorin	Alopecia, Constipation, Anorexia
Cisplatin, 5- FU**, Leucovorin	Nausea, Constipation, Fatigue, Dysphagia, Dry skin
Gemcitabine, 5- FU**, Leucovorin	Nausea, Vomiting, Anorexia, Constipation
Oxaliplatin, Capecitabine	Nausea, Vomiting, Constipation, Deranged LFTs, Neuropathy, Taste alteration, Fatigue, Anorexia, Alopecia
Capecitabine	Thrombocytopenia, Fatigue
Ifosfamide	Alopecia, Anaemia, Thrombocytopenia
Vincristine, Cyclophosphamide, Doxorubicin	Nausea, Vomiting
Cisplatin, etoposide	Constipation, Diarrhoea, Anorexia, Taste alteration, Abdominal pain, Fatigue, Alopecia
Carboplatin, etoposide	Nausea, Vomiting, Allergy, Xerostomia, Constipation, Alopecia, Fatigue
Gemcitabine, Carboplatin	Constipation, Alopecia, Fatigue, Anorexia, Nausea
Etoposide,5- FU, Leucovorin	Constipation
5-FU, Cisplatin	Nausea, Vomiting
Gemcitabine, Carboplatin	Constipation, Alopecia, Dizziness, Nausea, Vomiting
Gemcitabine	Constipation, Taste alteration

Etoposide, Cisplatin, Bleomycin	Nausea, Vomiting, Constipation, Striae, Allergy, Headache, Anorexia, Alopecia, Fatigue, Abdominal pain, Diarrhoea
Hydroxyurea	Nausea, Vomiting, Constipation, Fatigue, Allergy, Somnolence
Cyclophosphamide, Cisplatin	Nausea, Vomiting
Paclitaxel, Carboplatin	Fatigue, Alopecia, Anorexia, Thrombocytopenia, Nausea
Doxorubicin, Bleomycin, Vinblastin, Dacarbazine	Fatigue, Injection site reaction, Alopecia, Irregular menses, Neutropenia, Anorexia
Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone	Nausea, Vomiting, Abdominal pain

***Table 2**: ADRs caused by various regimens.*

Table 3 lists the drug regimens that caused no ADR in certain patients.

Epirubicin
Paclitaxel, Cisplatin, 5-FU, Leucovorin
Paclitaxel
Gemcitabine
Cisplatin
Cladribine

***Table 3:** Drug regimens causing no ADRs in certain patients.*

Discussion

The term, causality, denotes the relationship between ADRs and particular drugs. Causality assessment is used to determine the likelihood of a drug causing a suspected ADR. The causal relationship between majority of the drugs and the ADRs caused by them is followed by the relationship being 'definite', 'probable', 'possible' and 'doubtful'. The grade of causality for each ADR remains low perhaps because of a combination of drugs given in most of the cases [7].

In our study, causality assessment using the Naranjo Probability Scale showed that the majority of the drugs were observed to cause 'probable' (61%) followed by 'definite' (13%), 'possible' (9%) and 'doubtful' (7%) ADRs.

A review of the literature based on studies carried out in Indian subcontinent shows a wide variation in the frequency of causality of ADRs in cancer chemotherapy. In series by Surendiran., *et al*. [7], almost 62% of the ADRs were categorized as probable and 38% as possible. Wasgleng., *et al*. from Shilong [8], employing the same scale, found that 13.2% of cases showed probable and 86.7% possible association. Khandelwal and colleagues [9] reported 100% and Goyal and colleagues [10] reported 61% of probable scores using the same scale. In the series by Chopra et al from New Delhi [11], 80% ADRs were possible and 20% probable. As high as 80% ADRs in Singh and Chopra's series [12] were of possible causality. In Saini., *et al*.'s experience [13], 64.67% ADRs were probable whereas 35.33% were possible with cancer chemotherapy. Behera., *et al*.'s study [14], conducted at the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry (Pudchurry), revealed the following causality of the ADRs: 90.9% possible, 2.36% certain, 2.08% unlikely, and 0.18% unclassified. In a retrospective study by Sharma., *et al*. [15], amongst 500 ADRs encountered by their group, 65.6% were probable and 34.4% possible. Table 4 lists a comparative causality observations of ADRs in various studies from Indian subcontinent.

Author(s)	Definite	Probable	Possible	Doubtful	Remarks
Surindiran., *et al*. [7]	-	-	62%	38%	-
Wahlong., *et al*. [8]	-	13.6%	36.2%	-	-
Khandelwal., *et al*. [9]	-	100%	-	-	-
Goyal., *et al*. [10]	-	61%	-	-	-
Chopra., *et al*. [11]	-	-	20%	18%	-
Singh and Chopra [12]	-	61%	80%	-	-
Saini., *et al*. [13]	-	64.67%	35.33	-	-
Behera [14]	-	-	90.9%	-	2.08% unlikely 0.18% unclassified
Sharma., *et al*. [15]	-	65.6%	34.4%	-	-
Gupte., *et al*. (Present study)	13%	61%	9%	7%	-

***Table 4**: Causality of cancer chemotherapy ADRs in various studies from Indian subcontinent.*

Out of the total drugs causing alopecia, 4 drugs have been assessed to have a definite causal relationship whereas 17 drugs have been observed to have a probable relationship. Doubtful relationship has been found in 22 drugs. In a sheer 1% drugs, "highly probable" causality was found.

An interesting observation made in this study was that some of the patients developed multiple ADRs. On the other hand in 12 patients, there was absolutely no ADR. This could well be the outcome of genetic differences. More work needs to be carried out to elucidate this aspect.

Conclusion

Only limited available data, including ours, on causality pattern of chemotherapeutic drugs employed in cancer patients from Indian subcontinent show a wide variation, warranting more work in the field.

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Conflicts of Interest

There is no conflict of interest.

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