International Journal of Research in Pharmacology & Pharmacotherapeutics

***ISSN Print: 2278-2648*** ***IJRPP |Vol.3 | Issue 3 | July-Sep-2014***
***ISSN Online: 2278-2656*** ***Journal Home page: www.ijrpp.com***

***Research article*** ***Open Access***

# Neurological adverse drug reactions of anticancer drugs

**[*]M Palaniappan[1], SK Srinivasamurthy[1], B Dubashi,[2] SA Dhkar,[3] A Chandrasekaran.[1]**

[1]Department of Clinical Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research, (JIPMER) Pondichery, India.

[2]Department of Medical oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, (JIPMER) Pondichery, India.

[3]Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research, (JIPMER) Pondichery, India.

***Corresponding author: Muthiah Palaniappan,**
**E-mail id: krplmuthu@gmail.com**

## ABSTRACT

**Aim:** The aim of this study was to analyze the neurological adverse drug reactions of anticancer drugs that were reported to adverse drug reaction monitoring centre.

**Methods:**The entire neurological adverse drug reactions (ADRs) reported with anticancer drugs, received through spontaneous reporting system and active surveillance method from January 2012 to September 2013 were analyzed for demographic profile, ADR pattern, severity and causality assessment.

**Results:** During the study period, a total of 1418 anticancer drug related ADRs were obtained from 1076 patients; among them 84 (5.9%) reactions were neurological. Totally 77 patients developed 84 neurological ADRs. Among them 42 were males (54.5%) and 35 were females (45.5%). CAPOX (Capecitabine and oxaliplatin) was the leading drug regimen among agents causing neurological ADRs accounting for 15.5%. The most frequently reported ADR was neuropathy (72.6%). According to WHO causality assessment of ADRs, majority of the reports come under possible (89.6%) category. Hartwig severity scale showed that 57.1% of the reactions were moderately severe.

**Conclusion:** The frequency of neurological adverse drug reactions of anticancer drugs obtained was found to be 5.9%. Capecitabine and oxaliplatin regimen is the major causative agent among the anticancer drugs for neurological ADRs. Our study provided the analysis of neurological ADRs occurring due to anticancer agents.

**Keywords:** Adverse drug reactions, anticancer drugs, Neurological, neurotoxicity.

## INTRODUCTION

Adverse drug reactions (ADRs) are a major clinical problem in terms of morbidity, mortality and increased healthcare costs.(1) Antineoplastic agents are the common drug class causing the ADRs, and it was found to be total of 21.8% of the reported ADRs in a study(2). In India, the crude incidence rates of

cancer varied between 57.5 and 78.6 per 100,000 men; and between 57.7 and 89.7 per 10,000 women in urban registry areas. In urban areas the age standardized incidence rates range from 108.0 to 143.4 per 100,000 women; and from 98.7 to 138.3 per 100,000 men (3). Neurologic dysfunction is a well-recognized adverse effect of anticancer drugs. Neurotoxicity is a usual and often dose-limiting complication of chemotherapy treatment. (4) Subacute and delayed toxicities likewise occur and can greatly affect cancer patients' quality of life. (5) Central nervous system toxicity is the one of the most common complications of chemotherapeutic drugs. (6) Hence our study was designed to analyze the neurological adverse drug reactions of anticancer drugs.

## METHODS

The study was conducted by the department of clinical pharmacology and Medical Oncology, Jawaharlal Institute of Post graduate Medical Education and Research (JIPMER), Puducherry, India. This study analyzed the neurological adverse drug reactions of anticancer drugs that were reported to adverse drug reaction monitoring centre (AMC), department of Pharmacology, JIPMER spontaneously and also by active surveillance method. Spontaneous reporting is the core data-generating system of pharmacovigilance, to identify and report any adverse events voluntarily by the healthcare professionals (7). Active surveillance a tool for pharmacovigilance, in counterpoint to passive surveillance, searches completely to determine the number of adverse events through a continuous preorganized process. (8).

Spontaneous ADR reporting was done by various healthcare professionals from the hospital including physicians, pharmacists and nurses. Among them neurological ADRS of anticancer drugs were included in the study. Active surveillance was done by reviewing the medical records and interviewing the cancer patients in order to find the adverse drug reactions. The total study period was 21 months from January 2012 to September 2013. During this period all the neurological adverse drug reactions caused by anticancer drugs reported to the AMC were included for the study.

The ADRs were reported in a Suspected Adverse Drug Reaction Reporting form, provided by Central Drugs Standard Control Organization (CDSCO), Ministry of Health & Family Welfare, and Government of India. The ADRs were analyzed for their types of ADR, drug characteristics and causality. The causality of ADRs were analyzed using WHO Causality Assessment Scale and were categorized as certain, probable, possible, unlikely, unclassified as well as unclassifiable (9). The severity of ADRs was analyzed using modified Hartwig Siegel's severity assessment scale as mild, moderate and severe (10).

## RESULTS

During the study period, a total of 1076 anticancer drug related ADR reports were received with 1418 ADRs, Totally 77 patients developed 84 (5.9% )neurological ADRs. Among them 42 were males (54.5%) and 35 were females (45.5%). The age of the patients ranged from 5 to 71 years and the median age was 42 years. The patient's included cases of acute lymphoblastic leukemia (19.5%), Non Hodgkin's lymphoma (15.6%), multiple myeloma (15.6%), stomach cancer (14.3%), ovarian cancer (11.7%), colon cancer (7.8%), breast cancer (3.9%), and others (11.7%)

CAPOX regimen (oxaliplatin and capecitabine) is contributed of most of neurological ADRs. They together involved in causing 15.5% of the neurological ADRs. It was followed by CHOP regimen, that is cyclophosphamide, adriamycin, vincristine, prednisolone which was involved in 13.1% of the neurological ADRs. Drugs involved in neurological ADRs are shown in table 1.

**Table 1. Drugs involved in neurological ADRs**

| Drugs | No. of ADRs (n=84) | % (95% CI) |
|---|---|---|
| Oxaliplartin, Capecitabine | 13 | 15.5 (8.5 - 25) |
| Cyclophosphamide, Adriamycin, Vincristine, Prednisolone | 11 | 13.1 (6.7 – 22.2) |
| Paclitaxel, Carboplatin | 8 | 9.5 (4.2 – 17.9) |
| Bortezomib, Dexamethasone | 7 | 8.3 (3.4 – 16.4) |
| ARA C, Methotrexate, Cyclophosphamide, 6 MP | 7 | 8.3 (3.4 – 16.4) |
| L Asparaginase, Vincristine, ARA C, Methotrexate | 5 | 6.0 (2 – 13.3) |
| 5 FU, Oxaliplatin, Leucovorin | 2 | 2.4 (0.3 – 8.3) |
| Adriamycin, Vinblastine, Bleomycin, Dacarbazine | 2 | 2.4 (0.3 – 8.3) |
| Docetaxel | 2 | 2.4 (0.3 – 8.3) |
| Carboplatin | 2 | 2.4 (0.3 – 8.3) |
| Vincristine, Rituximab, Cyclophosphamide, Prednisolone | 2 | 2.4 (0.3 – 8.3) |
| Vincristine, Adriamycin, Dexamethasone | 2 | 2.4 (0.3 – 8.3) |
| Vincristine, Etoposide, Cyclophosphamide, Prednisolone | 2 | 2.4 (0.3 – 8.3) |
| Others | 19 | 22.6 (14.2 – 33.1) |

ARA C: Cytarabine, 6 MP: Mercaptopurine, 5 FU: Fluorouracil; CI: Confidence interval

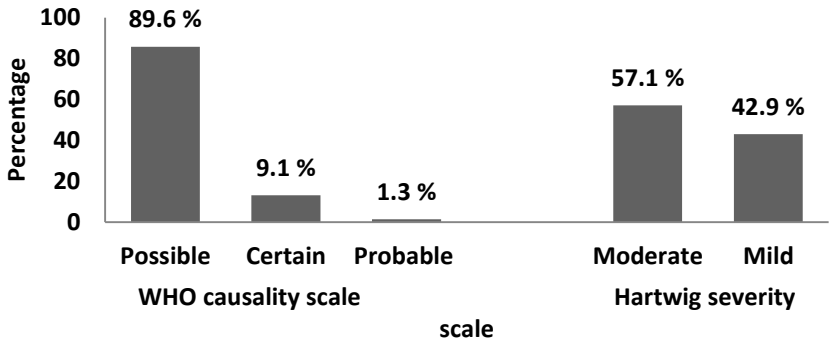
Among the ADRs most frequently reported ADR was neuropathy, totally 62 cases were reported (72.6%), most of them were grade 2 (54.1%). It was most commonly reported with CAPOX regimen with 11 cases, followed by paclitaxel and carboplatin regimen with 8 cases. Other neurological ADRs reported are shown in table 2. According to WHO causality assessment of ADRs, majority of the ADRs were classified as possible (89.6%). Modified Hartwig severity scale showed that 57.1% of the reactions were moderately severe. Assessment of ADRs are shown in figure 1.

**Table 2. Neurological ADRs due to anticancer agents.**

| ADRs | | | No. of ADRs (n=84) | % (95% CI) |
|---|---|---|---|---|
| Neuropathy | Grade I | 13 | 61 | 72.6 (61.8 – 81.8) |
| | Grade II | 33 | | |
| | Grade III | 15 | | |
| Giddiness | | | 6 | 7.1 (2.7 – 14.9) |
| Cerebral vein thrombosis | | | 4 | 4.8 (1.3 – 11.7) |
| Seizure | | | 3 | 3.6 (0.7 – 10.1) |
| Superior sagittal sinus & torcula thrombosis | | | 1 | 1.2 (0.03 – 6.4) |
| Arachnoiditis | | | 1 | 1.2 (0.03 – 6.4) |
| Cerebellar ataxia | | | 1 | 1.2 (0.03 – 6.4) |
| Embolic stroke | | | 1 | 1.2 (0.03 – 6.4) |
| Meningitis | | | 1 | 1.2 (0.03 – 6.4) |
| Motor weakness of finger | | | 1 | 1.2 (0.03 – 6.4) |
| Palsy facial | | | 1 | 1.2 (0.03 – 6.4) |
| Perioral numbness | | | 1 | 1.2 (0.03 – 6.4) |
| Syncope | | | 1 | 1.2 (0.03 – 6.4) |
| Vertigo | | | 1 | 1.2 (0.03 – 6.4) |

CI: Confidence Interval

**Figure 1. Assessment of neurological ADRs due to anticancer agents for causality and severity.**




## DISCUSSION

In our study we have found that overall frequency of neurological ADRs of anticancer drugs was 84 (5.9%) among reported 1418 ADRs due to anticancer agents. CAPOX regimen is the leading drug regimen attributed to neurological ADRs. They together involved in causing 15.5% of the neurological ADRs. Neuropathy was most common ADR reported (72.6%). The mechanism of oxaliplatin-induced peripheral neuropathy may be related to calcium chelation by oxaliplatin induced oxalate. Further oxaliplatin can alter the voltage-gated sodium channels through a pathway involving calcium ions. Further, decreased cellular metabolism and axoplasmatic transport resulting from the accumulation of oxaliplatin in the dorsal root ganglia cells could also contribute. (11) Capecitabine is reported to cause peripheral neuropathy, but the mechanism is unknown.(12) Earlier report also suggested concomitant use of oxaliplatin and capecitabine in causation of neuropathy.(13) A study by Storey et al found that the Incidence of chronic peripheral neuropathy may be more common with capecitabine and oxaliplatin regimen. (14). Therefore, oxaliplatin and capecitabine might be additive in causing neuropathy.

The drugs in CHOP regimen together accounted for 13.1% of the neurological ADRs, many were neuropathy. Among CHOP Vincristine is most frequently reported to cause neuropathy, but mechanism behind reaction is unknown. (15) Cyclophosphamide is also reported to cause neuropathy, by an unknown mechanism.(16) Adriamycin has also been reported with other drugs in causing neuropathy. (17) Thus vincristine would have taken major role in neuropathy than the other drugs in the regimen, or the other drugs may be attributed with vincristine in neuropathy.

Following CHOP regimen, paclitaxel and carboplatin together involved in 9.5% of neurological ADRs. All of these reactions were found to be neuropathies. Degeneration of sciatic nerve and the selective dysfunction of high-diameter myelinated fibers may be attributable to paclitaxel-induced neuropathy. (18) Carboplatin is also reported to cause neuropathy, (19) but the mechanism is unknown. A study by Argyriou et al found that the evidence of paclitaxel and carboplatin-induced peripheral neuropathy was found in 14 of the 21 patients (66.6 %). (20) Therefore both paclitaxel and carboplatin might be involved in causing neuropathy. A study by Olivier et al found severe neuropathy in the three patients treated with high dose carboplatin in combination with ifosfamide and etoposide. (19)

Bortezomib and dexamethasone regiemen also been involved in causing neurological ADRs.. The frequency of bortezomib induced neurological ADRs were 8.3%. Most of the neurological ADRs found with bortezomib was neuropathy. The mechanism of bortezomib induced neuropathy is not clearly known. The accumulation of bortezomib in the dorsal root ganglia cells, mitochondrial-mediated dysregulation of Ca (++) homeostasis, and dysregulation of neurotrophins might be contributed to the pathogenesis of bortezomib induced neuropathy. Proteasome inhibitor class effect might be increasingly recognized as the mechanism of bortezomib induced neuropathy. (21)

According to Modified Hartwig severity scale 53 % of the ADRs were found to be moderately severe. Any ADR is classified as moderately severe when the suspected drug is withheld or an antidote or other treatment was required or increase length of stay by at least 1 day or the ADR was the reason for the admission. (10) In our study patients, many of them were treated for the ADRs. Mostly treatment was given for neuropathy mainly with gabapentin or amitriptylline. Thus it is important to indentify neurological ADRs in patients on follow-up with chemotherapeutics. As most of these ADRs are of unknown mechanism, exploring further to indentify the pathways involved by *in-vitro* and animal studies would pave the way for better treatment in follow-up patients.

## CONCLUSION

The frequency of neurological adverse drug reaction with anticancer drugs was found to be 5.9%. Neuropathy was the most frequently observed ADR. 57.1 % of the ADRs were found to be moderately severe. Oxaliplatin and capecitabine were the major causative agents among the anticancer drugs for neurological ADRs. It is important to identify the neurological ADRs especially in the follow-up clinics.

## ACKNOWLEDGEMENT

We acknowledge our reviewer Dr.K Asoke kumar, Head of the Department, Department of Pharmacology, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore.

## CONFLICT OF INTEREST

Conflict of interest declared none.

## REFERENCE

[1] Nerurkar RP, Nadkar MY, Bichile SK. Need for monitoring adverse drug reactions. J Assoc Physicians India. 46, 1998, 673-4.
[2] Jose J., Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res.54, 2006, 226-233.
[3] Cancer Research in ICMR Achievements in Nineties, 1994.
[4] Cavaliere R, Schiff D. Neurologic toxicities of cancer therapies. Curr Neurol Neurosci Rep. 6(3), 2006, 218-26.
[5] Sarah EJ, Hubert B, Russell B, Youmei X, Tao Y, Stephen MM, Frank ML, Qun L. Anti-cancer drug induced neurotoxicity and identification of rho pathway signaling modulators as potential neuroprotectants. Neurotoxicology. 29(4), 2008. 605–612.
[6] Newton HB. Neurological complications of chemotherapy to the central nervous system. Handb Clin Neurol. 105, 2012, 903-16.
[7] Lindquist M. Vigibase, the WHO Global ICSR Database System: Basic Facts. Drug Inf J. 42, 2008, 409-19.
[8] Ich Harmonised Tripartite Guideline, Pharmacovigilance Planning E2E, Current Step 4 version, dated 18 November 2004.
[9] Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf. 17(6), 1997, 374-89.
[10] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 49, 1992, 2229-32.
[11] Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. Cancer Treat Rev. 34(4), 2008, 368-77.
[12] Saif MW, Wood TE, McGee PJ, Diasio RB. Peripheral neuropathy associated with capecitabine. Anticancer Drugs. 15(8), 2004, 767-71.

[13] Jim C, Josep T, Chris T, René B, Charles B, Thierry C, Filippo D, Arie F, Johannes G, Noriaki S, Patrick S, Alberto S, Eric VC, Eduardo D. XELOX (Capecitabine Plus Oxaliplatin): Active First-Line Therapy for Patients With Metastatic Colorectal Cancer. J Clin Oncol. 22, 2004, 2084-2091.

[14] Storey DJ, Sakala M, McLean CM, Phillips HA, Dawson LK, Wall LR, Fallon MT, Clive S. Capecitabine Combined with Oxaliplatin (CapOx) in Clinical Practice: How Significant is Peripheral Neuropathy?. Ann Oncol. 21(8), 2010, 1657-1661.

[15] Verstappen CC, Koeppen S, Heimans JJ, Huijgens PC, Scheulen ME, Strumberg D, Kiburg B, Postma TJ. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. Neurology. 64(6), 2005, 1076-7.

[16] Tschop K, Rommel F, Schmidkonz P, Emmerich B, Schulze J. Neuropathy after cyclophosphamide high dose chemotherapy in a Morbus Werlh of patient. Dtsch Med Wochenschr. 126 (12), 2001, T17-T20.

[17] J B Cavanagh. Sensorimotor neuropathy and cisplatin and adriamycin toxicity. J Neurol Neurosurg Psychiatry. 49(8), 1986, 964–965.

[18] Charity DS, William DF, Alex S. Peripheral Neuropathy Induced by Paclitaxel: Recent Insights and Future Perspectives. Curr Neuropharmaco., 4(2), 2006, 165–172.

[19] Olivier Ha, Jean-Pierre L, Etienne R. Severe neuropathy after high dose carboplatin in three patients receiving multidrug chemotherapy. J Neurol Neurosurg Psychiatry. 64, 1998, 667-669.

[20] Argyriou AA, Polychronopoulos P, Iconomou G, Koutras A, Kalofonos HP, Chroni E. Paclitaxel plus carboplatin-induced peripheral neuropathy. A prospective clinical and electrophysiological study in patients suffering from solid malignancies. J Neurol. 252(12), 2005, 1459-64.

[21] Argyriou AA, Iconomou G, Kalofonos HP. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. Blood. 112(5), 2008, 1593-9