RESEARCH PAPER

Evaluation of Neuroprotective Therapies in Chemotherapy Induced Peripheral Neuropathy: A 12 Month Prospective Clinical Study

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ABSTRACT

Background: Chemotherapy induced peripheral neuropathy (CIPN) is a frequent, dose dependent adverse effect of anti neoplastic agents, with reported incidence rates of 68.1% at one month, 60% at three months, and 30% at six months of therapy. CIPN leads to sensory, motor, and autonomic nerve dysfunction, causing paresthesia, numbness, pain, and impaired quality of life. Despite its burden, effective preventive and therapeutic options remain limited.

Aim: To evaluate the therapeutic management patterns of CIPN and assess treatment outcomes among cancer patients receiving chemotherapy.

Methodology: A prospective observational study was conducted over 12 months in the Medical Oncology wards of Ramaiah Medical College, Bangalore. A total of 148 patients receiving chemotherapy were enrolled based on predefined inclusion and exclusion criteria. CIPN was screened using the eViQ tool, and severity was graded using CTCAE v3.0. Treatment outcomes were categorized as complete response, partial response, or no response following the use of neuroprotective agents.

Results: Among 148 patients, 62 (41.89%) developed CIPN, predominantly grade 2 (69.35%) and grade 3 (30.64%). Of these, 48 (77.41%) received treatment. Gabapentin was the most prescribed therapy (58.33%), followed by multivitamins and calcium/magnesium supplements. After three months, 93.75% of treated patients showed symptom improvement. Complete response rates were highest with calcium/magnesium therapy (87.5%), followed by meganeuron (71.42%) and gabapentin (67.85%).

Conclusion: CIPN remains a significant complication of chemotherapy, adversely affecting patient well being. Although no definitive standard therapy exists, gabapentin, multivitamins, and calcium/magnesium supplementation demonstrated meaningful symptomatic improvement. Further comparative and long term studies are warranted to establish optimal, evidence based management strategies.

Keywords: Chemotherapy induced peripheral neuropathy, CIPN, Neuroprotective therapy, Gabapentin, CTCAE, eViQ.

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INTRODUCTION: Chemotherapy-induced peripheral neuropathy (CIPN) is a common, dose-dependent, and disabling adverse event [(1)]. Incidence rate was, 68.1% (57.7-78.4) at the first month of chemotherapy, 60% (36.4-81.6) at 3 months, and 30.0% (6.4-53.5) at 6 months of chemotherapy or more [(2)]. CIPN negatively affects the nerve function which results in the degeneration of peripheral sensory, motor, and autonomic nerves. It causes unusual sensations (paresthesia's), numbness, and balance problems or pain. Neuromyotonia like symptoms such as myalgia, myopathy, and muscle cramps are also seen [(3)].

Most often, CIPN is associated with platinum compounds, taxanes, and plant alkaloids [(1),(4),(5)].Several other factors that are influence the incidence of CIPN are alcohol abuse, autoimmune disease, diabetes mellitus, poison exposure, infectious disease, inherited disorders, trauma, vitamin deficiencies, tumors, bone marrow disorders, patient receiving neurotoxic anti-neoplastic agents that include patient age, dose intensity therapy duration, cumulative dose, co-administering neurotoxic anti-neoplastic agents [(1),(6)]. Progression of the neurotoxic symptoms is proportional to duration and dose of chemotherapeutic therapy. By doing dose alteration and cessation of

treatment can resolve it either partially or completely [7].

Disease burden and quality of life of the patients are completely imbalanced by the CIPN. Unfortunately, neuropathic pain prevention and treatment remains challenging for health care professionals and patients [8]. It is challenging to decide appropriate treatment for managing neuropathic pain. Few pharmacological agents that have neuroprotective action such as calcium and magnesium supplements, gabapentin, pregabalin, vitamin – E, lamotrigine, alpha-lipoic acid, glutamine, amitriptyline reduces the symptoms of CIPN [7].

Intravenous calcium and magnesium supplements helps in preventing platinum compounds (oxaliplatin, cisplatin) induced peripheral neuropathy by increasing the concentration of extracellular calcium and decrease the hyperexcitebility of peripheral neurons [9],[10].Gabapentin and pregabalin are anti-epileptic drugs, which is effective in treating many forms of neuropathies. These drugs prevent release of excitatory neurotransmitters and decrease sensitivity and irritability of nociceptive neurons by inhibiting $\alpha_{2\text{-}\delta 1}$ subunit of voltage gated calcium channels [11]. Vitamin E acts as neuroprotective agent in presence of neurological damage caused by platinum compounds [12]. Lamotrigine inhibits the concentration and voltage dependent sodium channels therapy decrease the release of excitatory neurotramitters especially glutamate and aspartate, thus decreases the neuropathic pain [13]. Alpha-lipoic acid reduces the oxidative stress produced during peripheral neuropathy caused by chemotherapy [14]. Glutamine is non-essential amino acid which provides neuroprotective action during CIPN and also controls tumor growth [15].The purpose of this research is to study the management of CIPN and its treatment outcomes.

MATERIALS AND METHODS:

The study was conducted prospectively on patients admitted to the Medical Oncology wards. Following approval by the Human Ethics Committee and the Institutional Scientific Committee of Ramaiah Medical College, Bangalore, the research was carried out over a period of 12 months. Samples were recruited based on predetermined inclusion and exclusion criteria. A total of 148 patients were enrolled as study subjects. Inclusion criteria encompassed patients over 18 years of age who had confirmed histological malignancy, had undergone at least one cycle of chemotherapy, developed CIPN, and provided informed consent to participate, with normal hematological, renal, and hepatic functions. Exclusion criteria included patients who developed peripheral neuropathy due to radiotherapy or diabetes mellitus, those with a history of peripheral neuropathy, patients who had not received treatment for CIPN, and pregnant women at the time of the study.

After enrollment, subjects were assessed by using the eViQ screening tool and the grade was evaluated using CTCAE v3.0. Outcome measures were assessed in three stages based on symptom severity.

I. Complete response: There was a complete disappearance of CIPN symptoms in subjects after post-prescription neuroprotective agents.
II. Partial response: There was a significant improvement in subjects at post-prescription of neuroprotective agents.
III. No response: No improvement in subjects.

RESULTS:

Between September 2018 to March 2019, 148 cancer patients recruited met the study criteria

BASELINE DEMOGRAPHICS:

GENDER DISTRIBUTION:

In our study of CIPN, a total of 148 cancer patients were enrolled in which the gender distribution was 43 (29.05%) were males and 105 (70.94%) were females.

Table:1 indicates the gender distribution of patients studied in the wards from medical oncology

SEX	**N = 148**	**%**
MALE	43	29.05%
FEMALE	105	70.94%

AGE DISTRIBUTION:

The age distribution among recurited cancer patients is 18-29 : 8 (5.4%), 30-39: 18(12.16%), 40-49: 42(28.37%), 50-59: 28(18.91%), 60-69: 29(19.59%), 70-79: 16(10.81%) and 80-89: 7(4.72%) were included .

Table: 2 Indicates the age distribution of patients studied in the wards from medical oncology

AGE (YEARS)	N = 148	%
18 - 29	8	5.4
30 - 39	18	12.16
40 - 49	42	28.37
50 - 59	28	18.91
60 - 69	29	19.59
70 - 79	16	10.81

80 - 89	7	4.72

DISTRIBUTION OF CANCER:

Among 148 cancer patients 6 (4.05%) were lung, 18 (12.16%) were gastrointestinal, 21 (14.18%) were gynecologic, 8 (5.40%) were rectum , 8 (5.40%) were prostate, 2 (1.35%) were genitourinary, 16 (10.81%) were oral cavity, 6 (4.05%) were multiple myeloma , 46(31.08%) were breast, and 17 (11.48%) patients were of other cancers.

Table: 3 Indicates cancer distribution of patients studied in the wards from medical oncology

TYPE OF CANCER	N = 148	%
Lung	6	4.05
Gastrointestinal	18	12.16
Gynecologic	21	14.18
Rectum	8	5.40
Prostate	8	5.40
Genitourinary	2	1.35
Oral cavity	16	10.81
Breast	46	31.08
Multiple myeloma	6	4.05
Others	17	11.48

INCIDENCE OF PERIPHERAL NEUROPATHY (PN)

Among 148 cancer patients who underwent cancer chemotherapy, 62 (41.89%) had developed peripheral neuropathy whereas 86 (58.10%) did not show any symptoms of peripheral neuropathy

Table: 4 indicates the incidence of peripheral neuropathy in the studied sample from medical oncology wards

STATE	N = 148	%
Patients with PN	62	41.89
Patients without PN	86	58.10

GRADING OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY ACCORDING TO CTCAE

The grading of CIPN was done according to the CTCAE scale which showed 43 (69.35%) in grade 2, 14 (30.64%) in grade 3, and 0 (0.0%) in both grade 4 and grade 5.

Grading of CIPN according to the CTCAE scale among the studied sample in the medical oncology wards

S.No	Grading of CIPN based on CTCAE v 0.3	N	Percent (%)
1	Grade 2	43	69.35
2	Grade 3	14	30.64
3	Grade 4	0	0.0
4	Grade 5	0	0.0

CIPN PATIENTS UNDERWENT TREATMENT:

Among 62 CIPN patients, 48 (77.41%) have received treatment for CIPN, whereas 15 (22.58%) did not receive treatment for CIPN

Patients who underwent treatment for CIPN among the studied sample in the medical oncology wards

S.No	Chemotherapy treatment assessment	N	Percent (%)
1	CIPN with treatment	48	77.41
2	CIPN without treatment	15	22.58

PRESCRIBING PATTERN FOR CIPN

The prescribing pattern of CIPN included 28 (58.33%) were gabapentin, 7(14.58 %) were meganeuron, 8 (16.66%) were calcium & shelcal and 5 (10.41%) were nerving.

SYMPTOM ASSESSMENT AFTER THREE MONTHS OF TREATMENT FOR CIPN

Among 48 CIPN patients who received treatment 45 (93.75%) had a reduction in symptoms and 3 (6.25%) did not show any progress in symptoms reduction.

Table: 8 Indicates assessment of symptoms after three months of treatment for CIPN

DRUG	STATE	N = 48	%
Gabapentin (N= 28)	Complete Response	19	67.85
	Partial Response	4	14.28
	No Response	5	17.85
Meganeuron (N = 7)	Complete Response	5	71.42
	Partial Response	0	0
	No Response	2	28.5
Calcimax&Shelcal (N = 8)	Complete Response	7	87.5
	Partial Response	1	12.5

	No Response	0	0
Nervigen (N = 5)	Complete Response	1	20
	Partial Response	0	0
	No Response	4	80

DISCUSSION:

Chemotherapy-induced peripheral neuropathy is a commonly reported adverse event by patients receiving anti-neoplastic drugs for the treatment of cancer which affects the long-term quality of life as well as anti-cancer treatment outcomes [16]. In our study, a total of 148 subjects with varying age groups and cancer were included. Our study showed that out of 148 subjects about 41.89% (N= 62) of participants developed CIPN after being treated with anti-neoplastic agents, among them the majority of subjects showed grade -2 (69.35%) and grade-3 (30.64%) respectively. Unfortunately, due to a lack of clinical data or evidence, the routine usage of agents for the management and prevention of CIPN is either conflicting or insufficient. Therefore, the therapeutic approach is focused on symptomatic management of neuropathic pain.

Currently available options for the prevention and management of CIPN are clearly inadequate whereas in our study showed that gabapentin, Ca/Mg therapy, multivitamins were the treatment of choice. Out of 62 patients who developed peripheral neuropathy, about 77.41 % (N = 48) received treatment for the management of neuropathic pain, were gabapentin being majorly used (N=28, 58.33%) followed by multivitamins (Nervigen (N=5, 10.41%) & meganeuron (N=7, 14.58%) and calcium & magnesium supplements (N=8,16.66%).Gabapentin, an anticonvulsant that shows an anti-nociceptive effect through the blockade of voltage-gated calcium channels at presynaptic terminals and the downregulation of excitatory neurotransmitters [17],[18].In this study, 58,33% (N=28) of patients with peripheral neuropathy induced by chemotherapy received gabapentin therapy and followed up after three months, showed that the majority of patients who received gabapentin had complete prognosis or response of symptoms (N= 19, 67.85%), 14.28 % (N=4) of patients had partial response whereas, 17.85% (N=5) showed no response to therapy. Caraceni A et al., administered gabapentin therapy for aweek over twenty-two cancer patients with neuropathic pain induced by chemotherapy showed a decrease in intensity and frequency of neuropathic symptoms. Overall, 90% (N=20) of patients who received gabapentin therapy judged the drug effectiveness in symptom reduction [19].

Oneschuk et al conducted a retrospective medical chart review of 45 cancer patients with neuropathic pain induced by chemotherapy to reveal the “real-life” therapeutic approach; results showed that 49% (N= 22) of patients had received gabapentin therapy at a cumulative daily dose of 100–3,000 mg (median: 900 mg), whereas therapy had been stopped in 46 % (N=10) of patients among who received the therapy. The study concluded that the change in pain scores was not significantly different in those who continued gabapentin compared with those who discontinued it [20].Despite the absence of evidence, gabapentin is gradually incorporated into the therapeutic regimen for the management and prevention of neuropathic pain induced by chemotherapy.

Calcimax(Calcium, Magnesium & Vitamin D3) &Shelcal (Calcium) supplementation is one of the most commonly used prescriptions for the management and prevention of neuropathic pain induced by CIPN [21]. This supplementation promotes the ability to modify the properties of voltage-gated calcium channels. In particular, it provides a hyperpolarization effect on the cell membrane due to an increase in extracellular concentration level[22]. In this study, 16.66% (N= 8) of patients received oral calcium and magnesium supplementation, where 87.5 % (N=7) of patients showed complete response, as well as 12.5% (N=1) of patients, showed partial response. Axel Grothey et al. conducted a study of administration of intravenous calcium and magnesium supplementation in oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer patients, showed effective therapy in reducing symptoms with less adverse effects [23]. Knijn, N et al. performed a phase-3 clinical trial on 720 advanced colorectal cancer patients, out f this, 551 patients who had received a Ca/Mg infusion before chemotherapy, shown a great reduction in the incidence of neuropathic pain induced by oxaliplatin[24]. Further studies to be conducted for oral calcium and magnesium supplementation in neuropathic pain had to be evaluated because to prove effectiveness, to provide a convenient way for treatment as well as to provide less expensive therapy.

Multivitamins such as meganeuron and nervijenwere basically used in treating neuropathic pain caused by damage to neurons [25]. Significant deficiency of vitamin B12 can cause neuropathic pain in the periphery. This is because in malignant patients there will elevate B12 dependent metabolites (methylmalonic acid/MMA, homocysteine) which may cause neuropathic pain by imposing oxidative stress [25]. Similar study showed that MMA levels were elevated in 38% of cancer patients and homocysteine

levels were elevated in 23 % of cancer subjects who had developed neuropathy. Six subjects who were treated with cyanocobalamin, found reduction of MMA values [25]. Our study results had shown consistency with the above study, with 5 out of 7 subjects who were treated with meganeuron showed complete response which is reciprocal with subjects who were treated with nervijen.

CONCLUSION:

Peripheral neuropathy is a side effect of anti-neoplastic agents. It can affect the patient's quality of life as well as may prolong the cancer treatment. Although there is no established treatment of choice for the treatment of chemotherapy-induced peripheral neuropathy, it is evident that multivitamins, Ca/Mg therapy, and anticonvulsants can prevent this symptom. However, health care professionals, manufacturers must encourage comparative efficacy studies to provide better treatment outcome by minimizing side effects.

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