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CHEMOTHERAPY INDUCED NEUROPATHY: PATHO-PHYSIOLOGY AND POSSIBLE NEURO-PROTECTIVE STRATEGIES

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Abstract:

With the advent of effective and intensive chemotherapy, we are able to achieve better response rates as well as improved survival but the side effects remain a constraint. This article intends to discuss one of the side effects of chemotherapy i.e. neuropathy; culprit agents, mechanism and therapeutic strategies to manage it.

INTRODUCTION

Chemotherapy is an invariable component in the management of most of the cancers, at one stage or the other. Neurotoxicity is the dose limiting side effects of many chemotherapeutic agents. Patients usually complain of tingling, numbness and pain in distal extremities. Some patients also develop motor and autonomic symptoms. Some patients remain symptomatic even after discontinuation of offending drugs.[1]

Incidence, severity of chemotherapy induced neuropathy depends upon specific anticancer drug used. Clinical assessment of neuropathy is difficult. Difference between physician's diagnosis of chemotherapy induced neuropathy using NCI-CTC (National Cancer Institute-Common Toxicity Criteria) and patients self-reported intensity and severity using PNQ (Patient Neurotoxicity Questionnaire) has been reported.[2]

As chemotherapeutic agents are being increasingly used, survival of cancer patients has

improved remarkably. Thus the number of patients struggling with these neurotoxic adverse effects is also on rise. Physicians usually under-estimate the severity of chemotherapy induced neuropathy as reviewed in a study.[3]

There is no specific treatment for chemotherapy induced neuropathy. Patients with distressing symptoms are required to reduce the dose or stop their anticancer drug which may affect the disease course and may further increase their problems. Patients with chemotherapy induced neuropathy bear higher healthcare cost than cancer patients without neuropathy.[4]

CAUSATIVE AGENTS

Platinum analogues

Cisplatin: Cisplatin is used as an anticancer agent in solid tumours of lung, ovary, bladder, testes, head and neck, oesophagus, stomach, colon, pancreas, breast and prostate.[5] Neuropathic symptoms usually occur following a total cumulative drug dose of more than 400-500 mg/m2, i.e. after three to six months of treatment.[1] Symptomatology includes paraesthesia and dysaesthesia in distal extremities. Some patients may develop sensory ataxia and Lhermitte's phenomenon.[6] Neuropathy is usually reversible after discontinuation of drug but recovery is very slow.

Oxaliplatin: Usually two patterns of symptoms are seen. First is early acute nerve hyperexcitabilty which is observed with in few hours and second is a chronic, cumulative neuropathy occur after repetition of chemotherapy cycles.[7]

Early features include cold induced dysesthesia in hands and circumoral area and numbness, tingling and cramps in extremities. This occurs in more than 90% patients. These symptoms are generally self limiting and resolve within few days. However, they reappear on subsequent administration of drug with increased severity. Neurophysiological studies revealed neuromyotonic discharges in first 24 to 48 hours which suggest peripheral nerve hyperexcitability which is probably due to oxaliplatin induced channelopathy.[7]

After multiple cycles of chemotherapy, 50-70% patients develop persistent distal symmetrical sensory symptoms. Usually severe symptoms develop after a cumulative dose of 874mg/m^2. Median time of recovery is around 13 weeks after discontinuing the treatment.[8,9] In some patients, due to coasting effects, neuropathic symptoms may progress even after stopping the drug.

Carboplatin: This platinum analogue is less toxic. Neuropathy similar to cisplatin appears but with higher cumulative doses, usually 600mg/m^2 or more.[10]

Vinca alkaloids: Around 50% of the patients receiving vincristine develop sensory motor peripheral neuropathy. Symptoms appear after a cumulative dose of 12mg. After a cumulative dose of 30-50mg, the drug has to be stopped because of higher risk of irreversible neuropathy. Neuropathic symptoms include numbness, tingling, dysaesthesia in hands and feet along with loss of deep tendon reflexes. More severe cases may develop distal muscle weakness. One-third of patients may develop autonomic symptoms.[11-13]

Taxanes: Paclitaxel is used for various solid tumours e.g. ovary, breast, head & neck and lung carcinomas.[14] Neuropathy usually occurs after a cumulative dose of 1400mg/m^2. Neuropathic symptoms also depend on larger dose in each cycle (>200mg/m^2) and infusion duration (short duration). Clinical presentation includes paraesthesia, numbness, tingling, burning and

allodynia in distal extremities. Perioral numbness, loss of tendon reflexes and vibration sensation can also be seen. Motor symptoms rarely occur in severe cases.[15,16]

Thalidomide: It is used for treatment of multiple myeloma, Waldenstrom's macroglobulinemia, myelodysplastic syndromes, acute myeloid leukemia.[17] Around 20-40% of the patients develop neuropathy. After seven months of therapy, 100% patients may develop these symptoms. Clinical features include parasthesia, tingling, dysesthesia and slight loss of tactile sensations.[18,19]

PATHOPHYSIOLOGY

Platinum analogues

Various studies suggested that both cisplatin and oxaliplatin have strong affinity to dorsal root ganglia where it causes structural changes in DNA. When DNA damage exceeds the repairing capacity of cell, it undergoes apoptosis leading to cell death.[20,21]

Oxaliplatin induced early acute neurotoxicity is supposed to be due to channelopathy. Recent evidence suggests that oxaliplatin has specific effect on voltage gated channels although exact mechanism is not known.[22-24] Earlier, it was hypothesized that an oxaliplatin metabolite, oxalate was the cause of transient dysfunction of ion channels by chelating intracellular calcium ions.[25] But, it has never been demonstrated that intracellular calcium concentration is lowered in oxaliplatin toxicity.[26]

Oxalate usually leads to renal damage along with neurological dysfunction but it is not seen in oxaliplatin toxicity.[27] Recently a new mechanism for oxaliplatin induced nerve hyper-excitability has been proposed. According to this oxaliplatin causes impairment of fast potassium channel functioning in myelinated axon internodes.[28] This leads to formation of after discharges in response to a saltatory action potential.

Transient receptor potential (TRP) channels are related to mechano-sensation and temperature perception. They have been extensively studied in animal studies. Some experimental studies suggest that sensitization of TRPV1 and TRPA1 is associated with hot and cold hypersensitivity in oxaliplatin induced neuropathy.[28]

Vinca alkaloids and taxanes

Both exert their action by inhibiting the formation of mitotic spindles but the basic difference in their mechanism of action is that vinca alkaloids inhibit microtubule formation while taxanes excessively stabilise the microtubules.[1,29] Oxidative stress is supposed to play an important role in paclitaxel induced neuropathy.[30]

In experimental studies it has been shown that pharmacological inhibition of reactive oxygen species may prevent mechanical hypersensitivity and pain.[31] In some studies activation of satellite glial cells in the dorsal root ganglia has been demonstrated while in other studies, accumulation of macrophages in dorsal root ganglia has been shown to play a role.[32-33]

Thalidomide

Exact mechanism is still unknown but studies have suggested that this drug is anti-angiogenic which leads to decreased blood flow to dorsal root ganglia by inducing micro-vascular changes in vasa nervosum.[34] Alternate hypothesis suggest that there is dysregulation of neurotrophin sensitivity attributable to inhibition of NF- κB.[35]

THERAPEUTIC STRATEGIES

Symptomatic therapy

Tricyclic antidepressants and anticonvulsants have been used with variable efficacy but these drugs are not free of side effects.[36] A recent trial suggested superior efficacy of duloxetine in suppressing the symptoms of oxaliplatin induced neuropathy.[37]

NEUROPROTECTIVE THERAPY

Many options have been tried with a great hope but only few of them have shown some efficacy in combating the neural damage due to chemotherapeutic agents.

Amifostine: It is an antioxidant tried for the prevention of cisplatin and paclitaxel induced neuropathy.[38-44] Although, some studies have demonstrated good results but serious side effects like hypotension have posed a risk to its use in many of the patients. The efficacy of this agent could not be reproduced in further trials.[39-41,44]

Glutathione: Promising results have been shown in a few small randomised placebo control trials while other studies could not demonstrate its efficacy in preventing neurotoxicity. This warrants the need for further studies.[45-47]

Calcium/Magnesium infusion: Earlier studies suggested their role as neuro-protective agents in preventing oxaliplatin induced neuropathy but a recent phase III trial could not reproduce the previous findings.[48-52]

Vitamin E: Its role has been investigated for cisplatin and paclitaxel induced neurotoxicity. There are conflicting results in different studies.[53-56]

Glutamine: There are inconsistent results regarding its role as a neuro-protective agent.[57- 60]

Erythropoietin: It has neurotrophic properties in addition to its role in erythropoiesis. The receptors are present on nerve axons, Schwann cells and dorsal root ganglia which increase after injury and thus form the basis of treatment with this agent. Large clinical trials are needed to establish its role in neuro-protection.[61,64]

Acetyl-L-Carnitine: Many trials have investigated its role in cisplatin and paclitaxel induced neuropathy with one study suggesting improvement in sensory and motor neuropathy but large scale trials are needed for the confirmation of these results.[65-67]

PHARMACOGENOMICS

Pharmacogenomics is the study of genetic variations that influence individual response to drugs. It may help in identifying people at high risk of developing chemotherapy induced neuropathy.[68] Neurotoxic effects associated with specific genes have been studied in patients receiving platinum analogues, taxanes, thalidomide and bortezomib.[69]

Some genes e.g. ***GSTP1, GSTM1, GSTM3, ERCC1, ABCB1, CYP2C8, CYP3A5, ITGB3, AGXT*** are studied in detail for their toxic effects. Some studies showed their association with chemotherapy induced neuropathy but some failed to demonstrate that association.[69] In future carefully done large scale studies may help in identifying people at high risk of developing chemotherapy induced neuropathy.

CONCLUSION

As cancer survival is increasing with the advent of newer chemotherapeutic agents, the number of patients with chemotherapy induced neuropathy is also increasing. There is still no specific therapy and protocol available for management of this distressing condition. As our understanding about the pathophysiology of chemotherapy induced neuropathy is increasing, we shall probably be able to achieve the target of effective therapy for neuro-protection in such condition.

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