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Research Article

Role of Duloxetine as Adjuvant in Chemotherapy Induced Peripheral Neuropathic Pain-An Update

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of many anticancer drugs such as platinum compounds, antitubulins (taxanes and vinca alkaloids), bortezomib and thalidomide [1]. CIPN may manifest as sensory symptoms in hands and feet, typically in a "glove and stocking" pattern; pain, numbness, tingling etc; or motor symptoms such as weakness, deficits in the cranial nerve or autonomic neuropathy [2]. Various pharmacological agents have been evaluated for management of CIPN and have been reported to have variable effects. These agents include amitriptyline, nortriptyline, venlafaxine, gabapentin, pregabaline, lamotrigine, gel mixture of baclofen, amitriptyline and ketamine. These agents have shown variable effects for management of CIPN. The studies have observed to have limited success because of insignificant relief in pain and paresthesia or no difference in pain scores with these drugs [3-7] (Table 1).

Need of newer drug for CIPN

Due to the potential harm, limited data available regarding efficacy and increase cost, new drugs are always introduced into clinical research. Duloxetine is mainly prescribed for generalized anxiety disorder and major depression. Duloxetine has recently been reported for its role in management of CIPN.

Mechanism of action: Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI). Reuptake of serotonin and norepinephrine (NE) is inhibited by duloxetine in the central nervous system. Duloxetine increases dopamine level specifically in the prefrontal cortex, via the inhibition of NE reuptake pumps (NET) which is believed to mediate reuptake of DA and NE [7]. Inhibition of

Table 1: Pharmacological agents for CIPN.

Study	Pharmacological agent and dosage	Study outcome and results	Adverse effects
Hammack et al. 2002 [5]	Nortriptyline (N) 25 mg daily with dose escalation of 25 mg/week up to target maximum dosage of100 mg during treatment period	No significant reduction in paresthesia (49 vs 55 [scale, 0-100] in placebo arm; P = 0.78)	Dry mouth Dizziness Constipation
Rao et al. 2007 [3]	Gabapentin (G) 300 mg with dose escalation of 300 mg to a target maximum dosage of2700 mg daily for 6 weeks during treatment period	"Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline, 6 weeks, or 14 weeks between groups	No significant differences in toxicities between groups
Rao et al. 2008 [4]	Lamotrigine 25 mg at bedtime for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then 100 mg twice daily for 2 weeks, then 150 mg twice daily for 2 weeks	"Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline or 10 weeks between groups	No significant differences in toxicities between groups
Barton et al. 2011 [11]	Baclofen, amitriptyline, and ketamine gel,1.31 g of compounded gel containing 10 mg baclofen, 40 mg amitriptyline HCL, and20 mg ketamine twice daily for 4 weeks	EORTC CIPN sensory subscale mean neuropathy change from baseline to 4 weeks: 8.1 vs 3.8 in placebo arm (P = 0.053).	No significant differences in toxicities between groups
Gewandter et al. 2014 [7]	Amitriptyline and ketamine cream 4 g twice daily for 6 weeks	Mean pain, numbness, and tingling score at week 6: no significant reduction in mean score (P = 0.363)	No significant differences in toxicities between groups

BPI-SF -Brief Pain Index-Short Form; CIPN- chemotherapy-induced peripheral neuropathy; EORTC- European Organization for Research and Treatment of Cancer; ENS-ECOG Neuropathy Scale; NRS- Numerical Rating Scale.

serotonin metabolism causes a decrease in pro-inflammatory cytokine activity and an increase in anti-inflammatory cytokines; duloxetine may act through this mechanism in its effect on depression [8]. The analgesic properties of duloxetine in the treatment of and central pain syndromes and diabetic neuropathy are believed to be due to sodium ion channel blockade [9].

Adverse effects: Duloxetine has been reported to be a safer drug without any major adverse effect. However, 10% to 20% of patients do report some minor side effects [10]. The published studies report various side effects with the nausea, somnolence, insomnia, dry mouth, headache and dizziness. Sexual dysfunction is often a side effect [11].

Contraindications: Duloxetine should be avoided in patients with hypersensitivity, concomitant use in patients taking MAOIs, triptans etc, and patients with uncontrolled narrow-angle glaucoma (Table 2).

Discussion

Duloxetine has been approved for the pain associated with diabetic peripheral neuropathy (DPN), based on the positive results of clinical trials [12-14]. However two recent studies Yang et al. (2011), and Smith et al. (2013), used duloxetine in CIPN and they found significant reduction in pain scores in duloxetine group than the placebo [15,16]. In both the studies they used duloxetine 30 mg per day increasing up to 60mg per day for 4-12 weeks. The side effects documented were very minimal fatigue (7%) insomnia (5%) and nausea (5%). In addition to a decrease in pain, data from the trial also supported that duloxetine decreased numbness and tingling symptoms [15]. Based on the results of this study, the ASCO clinical practice guidelines categorized this drug for use in patients with cancer experiencing CIPN under moderate recommendation, moderate benefit, intermediate strength of evidence and low harm [17,18].

Conclusion

There is great interest in interventions to treat CIPN, as well as to characterize this treatment-related adverse effect. Although treatment and prevention options for CIPN are limited at present, the use of duloxetine for painful CIPN has been recommended at a dose of 30-60 mg per day for 4-12 weeks. However further studies are required to prove its efficacy in clinical practice.

Clinical application of this knowledge for routine clinical practice

Chemotherapy-induced peripheral neuropathy (CIPN) remains a major issue affecting quality of life in cancer patients receiving chemotherapy. The drug armamentarium for CIPN management have limited outcome. The newer role of Duloxetine for CIPN is emerging and would prove useful for better neuropathic pain management. Its dose needs to be titrated as per response and the suggested dose is 30-60 mg/day. This needs to be continued for 4-12 weeks for optimal response.

Table 2: Overview of clinical studies for role of Duloxetine in CIPN.

Study	dosage	study design	Drug causing CIPN	outcome and results	Adverse effects
Yang et al. 2011[14]	Duloxetine (D) 30 mg daily increasing upto 60mg daily for 12 weeks	single-arm open-labeled pilot study of 39 patients	chronic oxaliplatin-induced neuropathy	Nine patients (23.1%) discontinued duloxetine because of adverse events. 19 patients (63.3%) had a VAS score improvement. 9 patients (47.4%) showed a simultaneous grade improvement, and the other 10 patients (52.6%) had a stable grade according to NCI-CTCAE v3.0	dizziness/ giddiness/ nausea, somnolence, restlessness or insomnia and urinary hesitancy
Smith et al. 2013 [10]	Duloxetine (D) 30 mg daily for 1 week, then 60 mg daily for 4 weeks during treatment period	Total: 220 Group A (D/PL): 109 Group B (PL/D): 111 Double-blind crossover study after 5 weeks	Paclitaxel, docetaxel, nanoparticle albumin-bound paclitaxel, cisplatin, oxaliplatin	Reduction in average pain as measured by BPI-SF: in initial treatment period, larger mean reduction in BPISF pain score in duloxetine group than placebo group (1.06 vs 0.34 [scale, 0-10]; P = .003)with moderately large effect size(0.513).	Fatigue (7%) Insomnia (5%) Nausea (5%)

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