Chemotherapy Induced Painful Peripheral Neuropathy: A Treatment Option

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Abstract

BACKGROUND: Cancer diagnosis and treatment are tragic issues for patients. Besides the psychological aspects associated with therapeutic interventions, chemotherapy-induced painful peripheral neuropathy (CIPPN) is one of the long-term side effects of intravenous chemotherapeutic agents used to treat cancers. This type of neuropathic pain has not effectively responded to medications for peripheral neuropathy treatment. Duloxetine is effective in decreasing CIPPN. This evidence-based research investigates the practice changes that can be implemented to reduce the pain ratings of survivors with CIPPN.

METHODS: In this practice improvement project, patients with CIPPN who reported a rating of ≥3 on the pain scale with the current pain regimen were given duloxetine 30 mg daily for one week and increased to 60 mg daily. The goal is to implement practice changes to decrease painful peripheral neuropathy induced by chemotherapy in cancer survivors.

INTERVENTION: Lewin's Change Theory was used, which provided fundamental principles for change. Lewin's Change Theory consists of 3 stages: Unfreezing, Change, and Refreezing. The change was implemented with evidence-based research to prove the effectiveness of duloxetine to improve CIPPN using the Plan-Do-Study-Act (PDSA) model for treatment.

RESULTS: A total of 9 patients with CIPPN who rated their pain greater or equal to 3 on the pain scale initiated treatment with duloxetine. The project ran for 7 weeks from 1/17/2022 to 3/9/2022. Patients were identified in the first 4 weeks and were asked to revisit 3 weeks later for effective evaluation. The provider contracted COVID-19 during this period, which caused a delay in project completion and reduced the patient population. The mean pain rating was 7.25 for 9 patients on a traditional peripheral neuropathy regimen. However, the duloxetine mean pain

rating was 3.125 for 8 patients. A total 4.125-point reduction in pain was noted with duloxetine compared to other therapies.

CONCLUSION**:** Duloxetine was effective in decreasing pain scores in patients with CIPPN compared with other neuropathy regimens. Pain relief provides a sense of well-being and helps patients function physically and mentally.

Keywords: chemotherapy-induced painful peripheral neuropathy, treatment, duloxetine

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Cancer is one of the most feared diseases globally owing to the medical diagnosis and its relationship with poor prognosis and mortality. Cancer treatment is also linked to a considerable fear due to it's severe and debilitating side effects. Cytopenia, nausea, vomiting, diarrhea, constipation, mucositis, skin toxicity, alopecia, anorexia, fatigue, and peripheral neuropathy are just a few of the side effects patients expect with treatment or chemotherapy regimens. If these side effects are associated with medication to treat a disease such as hypertension, most patients would not consider the side effects. With a change in diagnosis to cancer, almost all patients accept these side effects without a second thought. Most of the treatment side effects are temporary and resolve within 6-8 weeks of treatment. However, some toxicities take longer than 8 weeks post-treatment to resolve, and in some cases, the effects are permanent.

Chemotherapy-induced painful peripheral neuropathy (CIPPN) is one of these effects directly related to the amount of chemotherapy received. CIPPN is defined as damage to peripheral nerves leading to abnormal sensory function, pain, and or loss of motor control (Zhang et al., 2017). The pain is commonly present in the hands and feet, leading to numbness, tingling, altered touch sensation, impaired vibration, paresthesia, and dysesthesias induced by touch and warm or cool temperatures. Painful sensations are spontaneous burning, shooting or electric shock-like pain, mechanical, thermal allodynia, or hyperalgesia (Zajączkowska et. al., 2019). CIPPN develops as a glove and stocking neuropathy. Although in more severe cases, it can spread proximally to most of the limbs (Colvin, 2019). The severity of symptoms is directly associated with the amount of treatment received. Minimizing neurologic damage, with dose reduction or discontinuation of treatment, can often be problematic due to a phenomenon known

as “coasting”, in which symptoms fail to show until chemotherapy has been completed, and nerve damage has occurred (Colvin, 2019).

CIPPN has been identified in approximately 68% of individuals a month after the initiation of chemotherapy and in 30% of individuals 6 months after treatment (Custodio & Knowlton 2020). Acute development of neuropathy during treatment causes pain and discomfort, which often requires dose reduction or treatment cessation, thereby impacting progression-free and overall survival (Colvin, 2019). Approximately 30% of patients are still with CIPPN a year or more after chemotherapy (Colvin, 2019). According to The National Cancer Institute, (2017), 40% of women, who were part of a large clinical trial and received taxane-based chemotherapy to treat breast cancer, still experienced neuropathy two years after treatment. Patients who are treated with taxanes, platinum drugs, and vinca alkaloids have a high likelihood of having chemotherapy-induced peripheral neuropathy (CIPN) (Staff et. al., 2017). These drugs are commonly used for treating colon, breast, lung, ovarian, and testicular cancers. A multicenter study in France in 2020 that focused on colon cancer survivors showed that almost 40% of patients had neuropathy one year after treatment, and 27% were still experiencing peripheral 5 years after treatment (Selvy et al., 2017).

Thus, CIPPN can cause long-term functional disability 1-5 years after treatment. Survey findings presented at the American Society of Clinical Oncology (ASCO) 2020 annual meeting showed that out of 986 patients surveyed, 23% reported moderate-to-severe problems with hand function, and 28% reported moderate-to-severe walking difficulties related to pain (Battaglini et al., 2020). This impairment can lead to difficulties in daily activities, job-related functions, and activities geared toward health improvement or maintenance. Patients with CIPPN have also experienced an increased incidence of falls, have higher body mass index (BMI) scores, and have

more comorbid health conditions (Battaglini et al., 2020). According to The Global BMI Mortality Collaboration (2016), these comorbidities are the risk factors associated with increased mortality.

Long-term CIPPN can also lead to a negative effect on mental health and overall quality of life. Selvy et al. (2020) found that long-term CIPPN can impact anxiety, lead to depression, inadequate sleep, and alter emotional functioning. In another study, high Patient Neurotoxicity Questionnaire grades were significantly associated with poor psychological status and poor sleep quality (Hong et al., 2014). With many factors affecting physical and emotional health, it is no surprise that survivors with CIPPN reported a poorer quality of life (Kerckhove et al., 2017). A combination of these factors contributes to a vicious cycle of deterioration in mental and physical health.

The financial impact associated with increased healthcare costs is also noted in patients with CIPPN. A study collected data from a third-party payor/employer to assess healthcare and work loss costs of CIPPN patients with breast, ovarian, head/neck, or non-small cell lung cancer. The outcomes of the study revealed that average healthcare costs were $17,344 higher for CIPPN cases than for non-CIPPN controls, with outpatient costs being the highest component (with cases having excess costs of $8,092) (Pike et al., 2012). This cost was estimated within 3-12 months of undergoing chemotherapy. These costs are expected to rise with patients reporting CIPPN up to 8 years after treatment and can increase with rising cancer diagnoses and survival rates. Apart from the cost increase, the study also found that on average each CIPPN case had 12 more outpatient visits than controls and spent more days in the hospital (Pike et al., 2012).

Currently, no preventative treatment is available for CIPPN. Methods to reduce the incidence and severity of CIPPN include dose reduction or termination of treatment. However,

this option could also impact progression-free and overall survival (Colvin, 2019). Steroid therapy is also used to minimize neuropathy. Despite these efforts, a common complaint when providing care for survivors treated with neurotoxic chemotherapy patients are long-term CIPPN. Providers often attempt to use other medications to treat CIPPN, particularly using other medications to treat neuropathic conditions such as nerve injury, post-herpetic neuralgia, polyneuropathy, and painful diabetic peripheral neuropathy; even though CIPPN differs from other forms of neuropathy when considering pathophysiology and symptoms (Kerckhove et al., 2017). Medications often used include gabapentin, pregabalin, amitriptyline, and other controlled substances. Sleeping aides and anxiolytics are often used to treat conditions commonly associated with uncontrolled CIPPN.

However, in May 2020, ASCO updated its guidelines regarding the treatment approaches for chemotherapy-induced peripheral neuropathy (CIPN) based on a targeted, systematic review by an expert panel. A summary of the recommendations reconfirmed that:

> No agents are recommended for the prevention of CIPN. The use of acetyl-l-carnitine for the prevention of CIPN in patients with cancer should be discouraged. Furthermore, clinicians should assess the appropriateness of dose delaying, dose reduction, substitutions, or stopping chemotherapy in patients who develop intolerable neuropathy and/or functional impairment. Duloxetine is the only agent that has appropriate evidence to support its use for patients with established painful CIPN (Loprinzi et al., 2020, p. 3325).

A randomized, double-blind, placebo-controlled crossover study of 231 patients aged ⩾ 25 years was conducted in 2013. Patients were randomized to receive either duloxetine followed by placebo or placebo followed by duloxetine. Individuals receiving duloxetine as initial

treatment reported a larger decrease in the mean average pain compared with placebo-treated patients. In addition, 59% of duloxetine-treated patients, compared with 38% of placebo-treated patients, reported a decrease in pain (Smith, et al., 2013). Other studies reported improved quality of life and daily functioning in the duloxetine group compared with the placebo group (Smith, et. al., 2013). A meta-analysis of 10 studies, 6 randomized-controlled studies, and 4 observational studies found that CIPN improved after treatment with serotonin and norepinephrine reuptake inhibitors (Song et al., 2020). Another study provides biological evidence to support the use of duloxetine as the first standard treatment for painful CIPN; the study thereby shows that duloxetine does not affect the antitumor activity of chemotherapies oxaliplatin and paclitaxel (Meng et al., 2019).

In a random-control clinical trial that compared venlafaxine with duloxetine for CIPPN control, patients were assigned to three pharmacotherapy medications: venlafaxine, duloxetine, and placebo to evaluate neuropathic pain on day 1, week 2, and week 4. Duloxetine was more effective than venlafaxine in decreasing motor neuropathy and neuropathic pain grade (Farshchian et al., 2018). In another systematic review, duloxetine is considered to have moderate benefits. However, no conclusive evidence has been reported for tricyclic antidepressants as amitriptyline showed no benefit; nortriptyline had insufficient evidence (Hou et al., 2018). Further research with larger sample sizes, long-term follow-up, standardized outcome measurements, and standardized treatment timing was recommended. An open-label, randomized, crossover study, involving 34 patients in Japan compared duloxetine with vitamin B12. The study found significant differences in pain between the duloxetine group 4 weeks after administration (Hirayama et al., 2015).

In the French study discussed previously, the prevalence of CIPPN was 36.5% in 406 patients, and none of the patients were treated with duloxetine (Selvy et al., 2020). Only 3.2%, 1.6%, and 1.6% were treated with pregabalin, gabapentin, and amitriptyline, respectively. ASCO does not recommend any of these medications.

Locally, pregabalin, gabapentin, and controlled substances such as tramadol are also used as treatment options. Many patients also seek non-pharmaceutical or alternative methods, such as physical and massage therapy, to treat CIPPN. Sometimes, patients seek treatment out of the United States to seek the service of naturopathic practitioners. Overall, a failure in the management of these patients is observed. During a 10-day reflective practice, CIPPN was a common complaint of many survivors. The most prevalent treatment was a combination of tramadol and physical therapy, often initiated by an oncologist. This treatment was normally continued by the nurse practitioner during surveillance management. However, these treatments failed to completely resolve symptoms as patients often reported dissatisfaction with the treatment outcomes. The primary question is: “What practice change is to be implemented in reducing pain ratings in survivors with CIPPN?”

Method

The healthcare provider started the practice improvement project based on a 10-day reflective practice log to determine the major need among established patients. Three possible areas of improvement were identified. During the reflective practice log, three PICOT questions were developed based on the areas that required improvement. It was noted that a large percentage of patients continued to report a significant amount of CIPPN despite using tramadol and physical therapy as the pain regimen. Next, a literature review was conducted to search for evidence-based interventions to improve treatment outcomes of CIPPN. A significant amount of

evidence supported the use of duloxetine for the CIPPN treatment, which was the only recommended medication by ASCO.

Lewin's Change Theory was applied to bring the research into practice. Lewin's 3-Stage Model of Change provides a significant understanding of how changes occur, which involves three steps: Unfreezing, Change, and Refreezing (Petripin, 2020). During the practice improvement project, the use of tramadol and physical therapy as the treatment option for CIPPN was unfrozen. Using evidence-based research, a practice change was implemented to prove that duloxetine was effective for treating CIPPN. Refreezing involves the continued use of duloxetine for treating CIPPN. The Plan-Do-Study-Act (PDSA) method helps test implemented changes (PDSA, 2020). The model was utilized to guide the practice improvement project through the change and to evaluate the outcome.

The Brief Pain Inventory-Short Form (BPI-SF) tool measures pain, it's severity and the impact of pain on daily activities (MDAnderson, 2020). BPI-SF assesses pain at 4 different intervals and measures the interference of pain on 7 different functional activities. BPI-SF can also be used to assess peripheral neuropathy (Cleeland, 2009). BPI-SF is composed of a 9-item self-administered questionnaire that patients were asked to complete during follow-up appointments. For this project, only the pain rating or question 5 was used to analyze data. Question 5 of the pain questionnaire is structured as follows: Please rate your pain by circling the one number that best describes your average pain intensity. Patients rate their pain on a scale from 0-10 with 0 rated "no pain" and 10 rated "Pain as bad as you can imagine" (Cleeland, 2009).

The project lasted 7 weeks from January 17, 2022 to March 9, 2022. Patients already scheduled for follow-up appointments and those examined during this period were screened by

the provider. Inclusion criteria were patients aged 21-80 years, with a CIPPN pain rating of 3/10 or greater. Patients on antidepressants, or those that had been on antidepressants within 14 days were excluded. Those with a history of suicidal ideation or attempt were also excluded from participating. Patients were identified and those who met the inclusion criteria were included in the project during the first 4 weeks. A total of 12 patients met the inclusion criteria. However, 3 patients did not agree to start the medication, and patients who agreed to start duloxetine were included in the project. Survivors were instructed to take duloxetine 30 mg daily for one week and were instructed to increase the dosage to 60 mg daily thereafter. Patients were asked to discontinue their current pain regimen within the first week of initiating duloxetine monotherapy. Patients were scheduled to return 3 weeks later to evaluate the effectiveness of duloxetine.

Analysis

A total of 9 patients agreed to start duloxetine monotherapy. During the first 4 weeks of the project, the provider contracted COVID-19 in week 2, causing a project delay and a reduction in the patient population, because some patients agreed to be consulted via telemedicine, and others rescheduled and preferred in-person visits at a later day. The project included 2 men and 7 females. The average age of the patient was 52.2 years. All the patients were Hispanic. Patients were diagnosed with breast, colon, lung, ovarian, and testicular cancers. Neurotoxic chemotherapies used for these patients included oxaliplatin, paclitaxel, and cisplatin. Two patients undergoing CIPPN treatment with gabapentin and tramadol either completed the physical therapy or had not undergone physical therapy treatment. Seven patients were treated with tramadol alone and had either completed physical therapy or had not undergone any physical therapy treatment. None of the patients reported previous painful peripheral neuropathy

before chemotherapy. Only one patient had a medical history of type-2 diabetes mellitus and did not report neuropathy associated with diabetes.

Some of the ethical considerations included the risk of developing known side effects of duloxetine. A full review of medication included the medication side effects per manufacturer, and patients were educated about the side effects with printed education sheets in their preferred language, using “Clinical Pharmacology” patient medication education sheets. Patients were also educated about duloxetine’s co-indication for depression and anxiety. The exclusion criteria were patients not meeting the inclusion criteria, especially those on a current antidepressant or those recently on-off antidepressant within the past 14 days. Patients who reported a present or history of suicidal ideation or suicide attempt were also excluded. Pregnant patients were excluded. All patients had the right to refuse treatment.

Results

All 8 patients who took duloxetine reported a decrease in pain within the 3-week evaluation timeframe. Using BPI-SF, the mean pain rating on a traditional peripheral neuropathy regimen for 9 patients was 7.25/10. The highest pain rating was a 10/10, and the lowest was a 3/10 on the pain scale. The patient with the highest rating on the pain scale just completed therapy within 3 months. Patients with lower pain scores completed treatment over one year. The standard deviation in pain rating was +/- 1.13.

The mean pain rating for taking duloxetine 60 mg daily was 3.125 for 8 patients. The largest differences in pain rating were noted in two patients with pain rating from 8/10 to 2/10 and 10/10 to 5/10. Both patients completed treatment within 6 months. The rest of the patients had completed therapy over 6 months. The standard deviation in pain rating was +/- 0.84. A 4.125-point reduction is noted in pain when using duloxetine compared with other therapies.

Of the nine patients who agreed to start duloxetine, one patient could not obtain authorization from insurance within the allotted time frame and was excluded from the project. One patient started duloxetine and reported pain relief while on medication for 3 weeks. However, the patient discontinued the medication owing to worsening anxiety levels. Another patient also reported pain relief during treatment with duloxetine but discontinued medication after 3 weeks due to nausea and decreased appetite. One patient reported pain relief with duloxetine 30 mg daily but had extreme fatigue and experienced sleepiness disorder when the dosage was increased to 60 mg. The patient reverted to take 30 mg daily without consulting the provider, and his sleepiness disorder and fatigue reduced. Five patients reported pain relief of varying degrees and continued duloxetine 60 mg daily. Three of the five patients were assessed at 5 weeks of initiation, rather than 3 weeks because they rescheduled their appointments.

Discussion

All patients with CIPPN who started duloxetine reported a decrease in pain, as validated by previous studies. The largest difference in pain scale numbers was noted in patients who completed treatment within 6 months of treatment, compared with those who completed treatment over 1 year. Based on the findings in the practice improvement project, duloxetine initiation for patients with CIPPN is a practice change that must be implemented closer to completion of treatment to decrease long-term pain. These patients were also assessed at 5 weeks rather than 3 weeks. Another practice change is to evaluate the post-intervention pain level, possibly 5 to 6 weeks after therapeutic initiation. Differences were noted in women treated with the neurotoxic chemotherapeutic agent oxaliplatin for colon cancer and those treated with paclitaxel for breast cancer. Practice changes should also focus on breast and colon cancer survivors treated with these agents.

One patient was unable to obtain medication because of insurance denial. Short-term follow-up appointments may assist the patient in obtaining medication and improve treatment adherence. The Centers for Disease Control (CDC) has developed procedures to reduce barriers to obtaining medication and increase medication adherence (Neiman et al., 2017). For example, a follow-up appointment at 1-2 weeks would evaluate the patients' ability to obtain and start medication and ensure an increase in dosage. These short-term appointments could also be used as a reminder that side effects often improve and resolve with time to improve adherence. The CDC also reports that access to providers and implementation of team-based care improve medication adherence (Neiman et al., 2017). Short-term follow-up appointments would improve access to a provider and collaboration with a nursing could to assist with follow-up would also improve medication acquisition and adherence.

One patient discontinued the medication because of nausea. Short-term supportive therapy could be implemented to assist with treatment adherence. One study investigated low-dose olanzapine in patients taking duloxetine for major depressive disorder and confirmed that the medication was effective in reducing the severity of nausea and vomiting related to duloxetine (Zhong, 2014). Other patients diagnosed with nausea, while on duloxetine, could be managed using this strategy to ensure that patients follow medication prescriptions.

One patient decreased the duloxetine dose from 60 mg daily to 30 mg without consulting the provider and still had pain relief. Previous studies should be consulted to validate CIPPN management following this dosage.

Although the BPI-SF asses physical function, and other types of neuropathies, only the pain portion was utilized to document the patients experience after treatment. The impact of

physical activities on other neuropathic symptoms, such as numbness, could be evaluated during follow-up appointments.

Limitations

Some limitations were identified in this project. A local surge in COVID-19 contraction directly reduced the number of sampled patients during the assessment because these patients were not allowed to enter the clinic, and many did not have access to telemedicine. Moreover, the nurse practitioner contracted COVID-19 during the second week of the project, which also limited the number of patients since the provider had to work from home and see patients via telemedicine. Patients who could not be consulted via telemedicine were rescheduled for their follow up appointment in person after the project allotted time frame.

The project's short time frame is another limitation. The time frame for the intervention evaluation was 3 weeks. Recommended evaluation of patient outcome was 4 weeks. The short time frame did not allow patients who wanted to reschedule the time to be included in the project. Insurance denial of medication was another limitation. One patient did not inform the provider of the insurance denial until the follow-up for the therapeutic evaluation. At that point, it was too late to evaluate patient pain and be included in the project. If a prior medical authorization was required, time was not enough for approval.

Lastly, differences in patient follow-up times could also impact pain score ranges, with smaller ranges in pain improvement noted for 3-week follow-up appointments compared to 5-week follow-up appointments.

Conclusion

This evidence-based research supports the use of duloxetine medication to treat patients with treat CIPPN and improve health outcomes. This improved outcome had a direct and

positive impact on physical and mental health. Improvement in physical and mental health offers survivors a sense of well-being and improved quality of life. Resolution and/or reduction in pain can reduce health costs and outpatient or hospital visits related to uncontrolled pain. Finally, duloxetine minimizes the use of controlled substances, an important factor to consider in the opioid epidemic across the nation.

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