Low Level Energy Laser and Chemotherapy-Induced Peripheral Neuropathy

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ABSTRACT

Pupose: Chemotherapy-induced peripheral neuropathy (CIPN) is a significant concern with cancer patients. It has a negative impact on quality of life and can be a dose limiting side effect of anti-tumor treatment, leading to decreased treatment efficacy. The goal of this study is to investigate the LLEL to improve CIPN.

Methods: Charts from 52 unique patients suffering from chemotherapy-induced peripheral neuropathy were reviewed from Southwestern Regional Medical Center. Sensory and Motor Neuropathy grade was assessed using the WHO classification criteria (Grade 1-4). All patients were treated with an 830 nm wavelength laser multiple times per week. Energy delivered (joules) was determined based on severity (3 joules per 33 sec cycle). Treatment time estimates ranged from 10-25 minutes. Side effects of treatment and concomitant medications and therapies were recorded at each visit. Pain was recorded prior and following treatment on a 1-10 scale. Functional impairment was recorded and all data was charted in an electronic healthcare record.

Results: Medical records were evaluated over a twelve month period. In many patients, pain relief was noted immediately after receiving treatment. LLEL contributed to a reduction in pain and numbness, with the number and duration of treatments corresponding to the severity of the neuropathy.

Conclusions: Low level energy laser is an exciting new tool that significantly improves quality of life for many cancer patients. It is beneficial in treating chemotherapy induced peripheral neuropathy and was shown to provide significant pain relief for some patients. No side effects were noted with LLEL therapy. This is a therapy that should be made available to oncology patients experiencing neuropathy.

INTRODUCTION/BACKGROUND

Peripheral neuropathy, is defined as the condition arising from the damage and dysfunction of the peripheral nerves—the motor, sensory and autonomic nerves that connect the brain and spinal cord to the rest of the body. It is a common complication of cancer and its treatment that can lead to serious clinical consequences for the patient including reduced quality of life, interference with activities of daily living, disability, and potentially shorter survival. Among the various types of neuropathies seen in cancer patients, CIPN is the most widely reported.[1] CIPN can cause treatment delays, dose reductions, or even discontinuation of therapy, which can affect outcomes and compromise survival.

SIGNS AND SYMPTOMS

The severity of peripheral neuropathy ranges from discomfort to being severely debilitating, with symptoms beginning suddenly or slowly progressing over time. Initially, patients often feel abnormal sensations like paresthesia and dysesthesia (numbness, tingling, abnormal touch sensations), or cold sensitivity in the hand and/or feet. Pain is often reported and may be described as burning, freezing, shock-like, or electric. Normal touch can be perceived as painful (allodynia), with sensations that are excruciating painful (hyperpathia). Motor symptoms, if present, are generally mild. These may manifest as weakness in the lower limbs or diminished ankle reflexes. Some patients experience altered proprioception, which can lead to a greater incidence of accidents or falls. Many complain of difficulty in walking, dropping things, or feeling like they are wearing gloves and stockings when they are not. Autonomic impairment may be evidenced by constipation after use of vinca alkaloids, orthostasis, urinary dysfunction, and sexual dysfunction.[2,3] CIPN has a number of diagnostic features that can help physicians differentiate it from other neuropathies (e.g., PND, carpal tunnel syndrome, diabetic neuropathy, metabolic neuropathy). These include:

- Symmetrical, distal, length-dependent "glove and stocking" distribution
- Predominantly sensory symptoms (especially pain), both in frequency and severity, rather than motor symptoms
- Onset after administration of chemotherapy, which may be progressive, rapid, or "coasting"
- Dose-dependent

CHEMOTHERAPEUTICS

Table 1 is a general list of chemotherapeutic drugs frequently associated with symptomatic neuropathy.[1,4] These include platinum-containing agents, vinca alkaloids, and taxanes. Many of these drugs (e.g., paclitaxel and cisplatin) are widely used in a variety of cancers and the onset dose is an approximation of the cumulative dose when neuropathy typically starts to occur. Often the severity of neuropathy increases with dose and duration until cessation of treatment. A notable exception is the platinum agents, for which symptoms may progress for weeks to months after treatment completion. This is called the *coasting effect*.[5] Another exception to the typical pattern of CIPN is oxaliplatin, which is unique in that two patterns have been observed: cumulative persistent (dose-limiting) and acute transient (cold-induced) neuropathy.[6,7] Symptoms of CIPN usually improve with time for most drugs, although long-term sequelae can occur. As shown in Table 1, the frequency of documented neuropathic events ranges widely for many agents. One main reason is that the severity and frequency of the adverse effects heavily depends on the dose, duration and schedule.

Often chemotherapy regimens include more than one potentially neurotoxic drug and it is important to realize the additive or synergistic effects of different drug combinations remain largely unknown. Cancer patients may also have preexisting peripheral nervous system dysfunction such as radiculopathy from degenerative disease or neuropathy from diabetes or other causes. This can predispose them to manifesting earlier and more severe neuropathic symptoms when challenged with a neurotoxic chemotherapeutic or other cancer-related insult.[8]

NEUROTOXICITY MECHANISMS OF CHEMOTHERAPY

Neuropathy arises from damage to the peripheral nerves. Within the peripheral nervous system, the motor axons (nerve fibers) are large and myelinated, and the sensory and autonomic axons are mostly small and unmyelinated or thinly myelinated.

Most neurotoxic drugs (taxanes and vinca alkaloids) used in chemotherapy cause axonal damage, a condition termed axonopathy. Primary nerve toxicity of the platinum drugs seems to occur at the dorsal root ganglion (DRG), resulting in neuronopathy. Small sensory fibers are affected early and most frequently by chemotherapeutic agents. Because these nerves have little capacity for regeneration, damage to them is responsible for the predominance of sensory symptoms found in CIPN.

Common Chemotherapeutic Agents Known to Cause Neuropathy

Compound	Incidence	Onset Dose	Symptoms	Recovery
Cisplatin	28%-100%	300 mg/m2	Symmetrical painful paresthesia/ numbness in stocking-glove distribution, sensory ataxia with gait dysfunction	Partial, symptoms may progress for months after discontinuation
Carboplatin	6%-42%	800-1600 mg/m2	Similar to Cisplatin but milder	Similar to Cisplatin
Oxaliplatin (acute)	85%-95%	Any	Cold induced painful dysesthesia	Resolution within a week
Oxaliplatin (chronic)	FOLFOX 10%-18%	750-850 mg/m2	Similar to Cisplatin	Resolution in 3 months, may persist long term
Vincristine, vinblastine, vinorelbine	30%-47%	4-10 mg	Symmetrical tingling paresthesia, loss of ankle stretch reflexes, constipation, weakness, gait dysfunction	Resolution usually within 3 months, may persist with Vincristine
Paclitaxel	57%-83%	100-300 mg/m2	Similar to Cisplatin with added decreased vibration or proprioception	Resolution usually within 3 months, may persist
Abraxane	73%	Unclear	Similar to Paclitaxel	Resolution usually within 3 weeks
Docetaxel	11%-64%	75-100 mg/m2	Similar to Paclitaxel	Resolution usually within 3 months, may persist

Table 1 – Common chemotherapeutic drugs associated with neuropathy

LOW LEVEL ENERGY LASER (LLEL) DEVICE

All patients were treated with a diode laser, with a continuous wavelength (A) 830 nm (infrared) and an output of 90mW, 30 mW at each of the three aperatures. Treatment time (t) for each application patient is given by the equation t(sec)= energy (J/[cm^2]) x surface area([cm^2])/power (W). This means that the longer the irradiation is used the greater the energy is released. Energy delivered (joules) was determined based on severity and number of lesions (3 joules per 33 sec cycle). This laser belongs to the class III-B for safety measure, which means that the direct beam is dangerous for direct eye contact but is not hazardous for diffuse reflections. As a protective measure, patients are asked to wear appropriate goggles that are effective in the 800-850 nm wavelengths. Patients were assessed for response to the laser based according to standardized grading criteria by evaluating development and improvement of CIPN symptoms. The impact of laser therapy on pain control was evaluated using the visual analogue scale.

LLEL MECHANISM OF ACTION

The mechanism by which LLEL affects cells is not well understood but it seems to be based on bio-stimulation.[9] It is believed that low level radiation is absorbed by intracellular photoreceptors in the membrane of the mitochondria. Low level energy laser (LLEL) has been shown to repair, regenerate, and accelerate tissue healing. It accelerates functions of cytochrome enzymes, increases ATP and Nitric Oxide (NO), enhances cellular metabolism, improves microcirculation and resultant nerve function. Recent evidence suggests immune cells play a role in neuropathic pain at the periphery. Several studies have shown that LLEL has modulatory effects on inflammatory markers (PGE_2, TNF-α, IL-1β, plasminogen activator), reduces the inflammatory process itself and modulates leukocyte activity (macrophages, lymphocytes, neutrophils). The specific parameters of laser therapy that can affect biological response include: 1. Wavelength (nm), 2. Laser power (mW), 3. Amount of energy to be delivered to tissues per square area (J/[cm^2]), and 4. Rate of energy (intensity). [10]

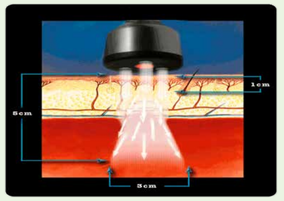

Figure 1 - LLEL tissue penetration.

PATIENTS AND METHODS

Chemotherapy experienced patients diagnosed with cancer between the ages of 18 and 80 with symptoms of peripheral neuropathy had charts reviewed. There were no ECOG performance status restrictions. Response to the laser therapy was assessed for 52 patients (32 female, 20 male) based on the **World Health Organization (WHO) CIPN Grading Score**.[11] The WHO scale is based on sensory and motor symptoms. A single score that grades the severity of the condition from Grade 1 (paresthesias and/or decreased tendon reflexes) to Grade 4 (paralysis) is utilized.

Patients, as part of the Cancer Treatment Centers of America (CTCA) integrative model of care, met with a variety of health care professionals during their course of treatment and were offered some of the following recommendations or concomitant medications:

- Pain Management Physicians/Medical Oncologists: Gabapentin, 5% Lidocaine patch, Opiods, Pregabalin and Tricyclic antidepressents
- Naturopathic Physicians: supplements including L-glutamine, Vitamin E, Alpha lipoic acid, Acupuncture, Acetyl L-carnitine, Vitamin B6, Topical Capsaicin
- Registered Dieticians: Healthy diet with control of glucose level and ideal weight management
- Occupational and Physical Therapists: Task modification using adaptive equipment (bigger utensils, velcro shoe laces); gait training and extremity strengthening to improve balance and function; assistive devices such as canes, walkers and orthotics; electrical nerve stimulation (TENS) therapy (rebuilder); massage therapy
- Mind Body Medicine: Counseling and visualization exercises
- Patient Education and Care Management: Educated on foot/hand care as a mainstay of treatment; watching for skin abrasions and blisters, selecting good sturdy footwear; avoid or protect against thermal stress; use of light nights, slip-fall hazards; educated patients on higher risk for falls

The laser was to be applied every 48 hours, repeating the procedure at each visit until symptoms resolved. During each treatment session 18-36 joules were administered to the patient (approximately 10 min-25 min). Most patients received 1-4 treatments, yet some received greater than 10 treatments.

RESULTS

A total of 52 adults were treated with the LLEL. Some patients suffered from progressive symptoms due to ongoing chemotherapy. There were different grades I-III, with the majority grade I or II. At each new visit the scoring in pain and severity was recorded. All patients tolerated the laser treatment without any adverse effects or reactions.

As Figure 2 shows, 36 patients reported improvement of CIPN symptoms within 1-4 treatments, often within a single week. Overall, 40 patients showed improvement of symptoms, while 12 patients showed no improvement.

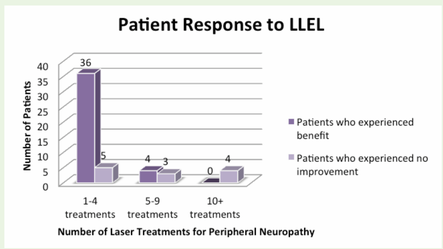

Figure 2 - Patient response to LLEL treatment.

As Figure 3 shows, the majority of patients with CIPN were breast cancer patients on taxane based regimes. Additionally, 77% (40 of 52) patients were on a taxane based chemotherapy regime.

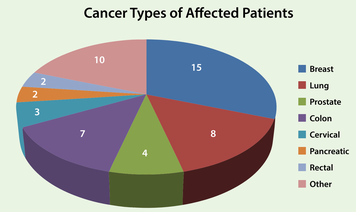

Figure 3 – Cancer Types of Affected Patients

DISCUSSION

Because CTCA delivers an integrative patient centered model of care, all patients received integrative medical interventions including: massage, acupuncture, naturopathic supplementation, prescription medication, rebuilder/physical therapy, patient education, nutrition, physical and occupational therapy.

We found there was consistency with patient compliance and integrative medicine engagement across disciplines. Of note, patients that did not see benefits lacked compliance with other recommendations. For example, they continued to smoke and were also noncompliant with physical exercise or diet recommendations. At least half of the patients were on prescription pain medications. There is some research to show benefit using the laser preventatively before peripheral neuropathy symptoms appear and we did not use it that way in this study. We could have utilized neurophysiologic tests such as electromyography, nerve conduction studies, and quantitative sensory tests to further examine peripheral nerve function, laboratory tests to look for metabolic disturbances and nutritional deficiencies and imaging tests to look for other possible causes of nerve damage. We had three providers administering the laser therapy.

CONCLUSIONS

The three main effects applicable to LLEL are: 1) an immediate analgesic effect, 2) an anti-inflammatory impact and 3) a faster wound healing. Based on these properties and results of other studies, it can be concluded that in the present review the GaAlAs 830nm diode laser can assist in managing CIPN. However, it was a small patient sample and a more extended study would be helpful to further confirm this promising result.

FUTURE DISCUSSION

A couple of items could help increase the strength of a future study: 1. Assigning patients randomly and equally to an active laser group or a placebo laser group (control group). 2. The use of analgesic or adjuvant analgesic medications (e.g. opiates, antidepressants, anticonvulsants, local anesthetics) and integrative therapies could be allowed, but should be unchanged for at least four weeks before entering the study and during the study. 3. Assigning one provider to deliver the laser therapy would help allow for greater consistency of care delivered. 4. Protocol design allowing standardized areas to be treated for CIPN.

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