Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial

Peter A. Argenta, MD [a,*], Karla V. Ballman, PhD [b], Melissa A. Geller, MD [a], Linda F. Carson, MD [a], Rahel Ghebre, MD [a], Sally A. Mullany, MD [a], Deanna G.K. Teoh, MD [a], Boris J.N. Winterhoff, MD [a], Colleen L. Rivard, MD [a], Britt K. Erickson, MD [a]

[a] Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Women's Health, University of Minnesota, Minneapolis, MN, United States
[b] Division of Biostatistics and Epidemiology, Department of Healthcare Policy and Research, Weill Cornell Medical School, New York, NY, United States

ARTICLE INFO

Article history:
Received 5 September 2016
Received in revised form 1 November 2016
Accepted 5 November 2016
Available online xxxx

ABSTRACT

Background. Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer therapy with few efficacious treatments.

Methods. We enrolled 70 patients with CIPN in a randomized, double-blinded, sham-controlled, cross-over trial to determine if photobiomodulation (PBM) ± physiotherapy reduced the symptoms of neuropathy compared to sham treatment. At the conclusion of follow-up, sham-arm patients could cross-over into a third arm combining PBM and physiotherapy to determine if multimodal treatment had additive effects. Treatment included 30 minute sessions 3-times weekly for 6 weeks using either PBM or sham therapy. Neuropathy was assessed using the modified total neuropathy score (mTNS) at initiation and 4, 8, and 16 weeks after initiating treatment.

Results. Sham-treated patients experienced no significant change in mTNS scores at any point during the primary analysis. PBM patients experienced significant reduction in mTNS scores at all time points. Mean changes in mTNS score (and corresponding percent drop from baseline) for sham and PBM-group patients respectively were −0.1 (−0.7%) and −4.2 (−32.4%) at 4 weeks ($p < 0.001$), 0.2 (0.0%) and −6.8 (−52.6%) at 8 weeks ($p < 0.001$), and 0.0 (0.1%) and −5.0 (−38.8%) at 16 weeks ($p < 0.001$). Patients who crossed over into the PBM/PT-group experienced similar results to those treated primarily; changes in mTNS score from baseline were −5.5 (−40.6%) 4 weeks ($p < 0.001$), −6.9 (−50.9%) at 8 weeks ($p < 0.001$), and −4.9 (−35.9%) at 16 weeks ($p < 0.001$). The addition of physiotherapy did not improve outcomes over PBM alone.

Conclusion and relevance. Among patients with CIPN, PBM produced significant reduction in neuropathy symptoms.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side-effect of many modern chemotherapeutic agents. It typically manifests as numbness, paresthesia, pain, and/or burning, though motor dysfunction (typically weakness) and/or autonomic dysfunction can also occur [1,2]. The reported prevalence of CIPN following neurotoxic chemotherapy is 20–51%, but estimates vary considerably depending on the agents assessed, the severity threshold, and mechanism of detection; but because sensory symptoms are not overt, underreporting of both the prevalence and magnitude of CIPN is likely [3,4].

Once present, regression of CIPN symptoms is slow. Lingering or permanent symptoms are common and can significantly impair quality of life [5,6]. Unfortunately, multiple trials focusing on mitigation of lingering symptoms, especially pain, have been disappointing, with a 2009 National Comprehensive Cancer Network Taskforce unable to recommend any directed therapy [7,8]. Since then, Smith and colleagues have reported the only positive, large, placebo-controlled trial examining pharmacologic treatment for CIPN, observing modest symptom-improvement in platinum-treated patients with painful CIPN who were treated for 5 weeks with duloxetine, a serotonin and norepinephrine re-uptake inhibitor [9].

Increasing study of non-pharmacologic therapies has revealed multiple strategies with potential efficacy in reducing the burden of CIPN [10,11]. Photobiomodulation (PBM) employs non-ionizing, low power, laser light therapy and has been shown in pre-clinical and small trials to improve neural function. In animal models PBM demonstrates alleviation of oxaliplatin-induced mechanical and cold allodynia as well as both nerve regeneration and improved motor recovery after nerve crush injury [12,13]. In humans, two small, sham-controlled studies

* Corresponding author at: MMC 396, 420 Delaware St SE, Minneapolis, MN 55455, United States.
E-mail address: argenta@umn.edu (P.A. Argenta).

http://dx.doi.org/10.1016/j.ygyno.2016.11.013
0090-8258/

demonstrated that PBM reduced weekly pain scores among patients with diabetic sensorimotor polyneuropathy [14] and improved carpal tunnel syndrome-related numbness and tingling [15].

Similarly, multiple trials for patients with diabetic neuropathy suggest that manipulative therapies may be effective at reducing the sensory deficits and improving function either alone or in combination with other treatments [16,17]. Physical therapy and massage-based therapies (physiotherapy, PT) are well-tolerated, relatively low-cost treatments, advocated for the treatment of CIPN based on reports from small case series, though neither has been studied directly in prospective randomized trials [18].

We sought to investigate whether PBM reduced neuropathy symptoms for patients with CIPN; and to determine if the addition of PT to PBM could further improve results.

2. Methods

2.1. Study design

After obtaining approval of our Institutional Review Board and the Cancer Research Protocol Committee of the University of Minnesota, we conducted a prospective, double-blind, randomized, sham-controlled study of PBM for the treatment of lower extremity CIPN (clinicaltrials.gov: NCT02000908). The primary hypothesis was that PBM would be more effective than sham in reducing the symptoms of CIPN as measured by the modified total neuropathy score (mTNS). Secondary outcomes included assessment of: time to onset of treatment effect, time to maximum effect, durability of response, and response to the addition of physiotherapy to PBM. Accrual occurred between April 2014 and June 2015.

2.2. Patients

Patients were recruited from the Gynecologic Oncology Clinic at the University of Minnesota owing to a high baseline prevalence of CIPN in this population. All adult patients with self-reported peripheral neuropathy (PN) and a history of chemotherapy exposure were considered eligible. Patients with a diagnosis of PN prior to chemotherapy or who were on pharmacologic treatment for PN prior to enrollment were considered eligible, but agreed not to initiate new therapy or dose modifications during the study period. Active cytotoxic treatment for cancer (within 30 days of enrollment) was considered an exclusion; the protocol allowed for continued inclusion of patients who relapsed requiring chemotherapy during the study.

We intended a three-pronged analysis comparing no-treatment (Sham-group) to both a PBM treated group and a group receiving the combination of PBM and PT. Randomization was performed centrally, without stratification, using block randomization with blocks of variable sizes and opaque, sequentially-numbered envelopes. Patients, their treating oncologist, and assessing personnel were blinded to treatment assignment. At the conclusion of initial treatment and follow-up (week 16), patients were unblinded and Sham-group patients were offered crossover into the PBM/PT arm.

All patients signed written consent before initiation of treatment. Patients were not offered inducements, financial or otherwise.

2.3. Intervention

All patients underwent treatment 3 times per week for 6 weeks (18 total treatments). Treatments were specified to be delivered every other day, but deviations to accommodate patients' availability, were not considered protocol violations. A standardized treatment plan of 30 min per visit was used, irrespective of the degree of impairment, to reduce potential for artifact from variable treatment durations. Treatments were delivered using a handheld wand at a distance of 1 cm from the skin for 1–12 min over any of up to 36 specified zones, for total treatment time of 30 min. Power varied from 6.75 to 12 W per specific zone. Waveform and wavelengths varied during each session and included pulsed waveforms at 20,000 Hz or continuous waveforms with wavelengths of 800–970 nm. The power, wavelength, waveform, duration per zone and number of treatment zones were assigned using a proprietary, deterministic algorithm driven by the input of patient reported symptoms (numbness, pain, tingling, hot/cold alteration, tightness) taken at each visit and signs (pinwheel, vibration, light touch) assessed at every 3rd visit (a typical plan is demonstrated in Fig. 1).

Therapy rooms were equipped with an activated laser and a sham heat probe. Patients wore opaque, laser-protective goggles both before and throughout treatment for safety and to maintain blinding. All treatments took place at a single center (Realief Neuropathy Centers, St. Louis Park, MN) and were delivered by one of six certified laser technicians.

2.4. PBM-group

Patients in the PBM-group received treatment consisting of cutaneous application of a class IV therapeutic laser (Eltech K1200, Treviso, Italy) over surface areas for dwell times dictated by the treatment plan.

2.5. Sham-group

Therapy with a class IV laser is known to produce a sense of warmth; therefore, patients in the Sham-group patients were exposed to a ceramic heat probe (ConAir Corporation, East Windsor Township, NJ). Areas of treatment and dwell times were determined using the same algorithm as the PBM-group.

2.6. PBM/PT-group

Patients in the PT/PBM-group received a combination of PBM and physiotherapy. Physiotherapy consisted of manual soft tissue mobilization at each treatment visit (15 min per treatment), followed by instructions for at-home toe, ankle and foot stretches, to be performed twice a day.

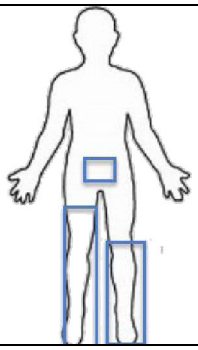
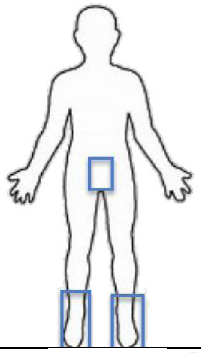
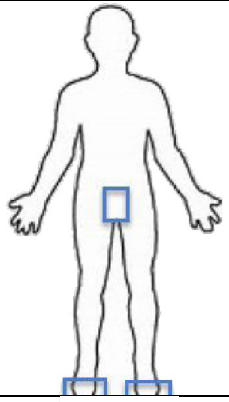
2.7. Data collection

Demographic data was collected at initiation visit and included: age, race, body mass index, disease type and stage, medical co-morbidities, medications, and previous chemotherapy exposures. All patients underwent assessment using the modified total neuropathy score (mTNS). Patients were assessed by one of two evaluators trained to assess the mTNS and blinded to treatment assignment, at induction, and at 4, 8, and 16 weeks following initiation of treatment. The mTNS is a validated tool that assesses six domains of sensory and motor neuropathy, providing a single score from 0 to 24 with higher scores indicating worsening neuropathy (Table 1). It is expedient to deliver, demonstrates consistent reproducibility and correlation with the total neuropathy score (TNS), previously the gold standard of neuropathy assessment [19–21].

2.8. Statistics

Our primary endpoint was a reduction in neuropathy as measured by the mTNS from pre-treatment baseline to 8 weeks following initiation of therapy. In the initial phase we used an external control (PBM-group vs Sham-group). In the crossover PBM/PT-group served as their own control with the mTNS score at the end of the sham treatment serving as their baseline. A reduction of mTNS by 30% from baseline at 8 weeks was felt to be clinically significant. Based on this we determined that 30 patients per arm would provide an 80% power (2 sided α of

Please cite this article as: P.A. Argenta, et al., The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.013

Treatment 1/18 360s @ 7.75W - Spine: L2-S2 180s @ 6.75W - Left Leg: popliteal fossa and fibula 240s @ 6.75W - Left Leg: popliteal fossa 300s @ 6.75W - Left Foot: malleoli 120s @ 6.75W - Right Leg: fibula 300s @ 6.75W - Right Leg: popliteal fossa 300s @ 6.75W - Right Foot: malleoli	
Treatments 2 – 8, data not shown	...
Treatment 9/18 360s @ 12.0W - Spine: L3-S2 240s @ 12.0W - Left Leg 480s @ 12.0W - Left Foot: malleoli 240s @ 12.0W - Right Leg 480s @ 12.0W - Right Foot: malleoli	
Treatments 10 – 17, data not shown	...
Treatment 18/18 360s @ 12.0W - Spine: L3-S2 720s @ 12.0W - Left Foot: malleoli 720s @ 12.0W - Right Foot: malleoli	

s - seconds; W – watts; L – lumbar; S – sacral

Fig. 1. Treatment parameters for treatments 1, 9, and 18 of 18 treatments. This treatment plan demonstrates the evolving distribution of treatment zones during the course of treatment with representative data from the initial, middle, and end of treatment. Treatment duration was held constant at 1800 s. The surface area requiring treatment decreases with time, corresponding to improvement of symptoms and allowing for greater attention to the most refractory (distal) areas.

≤0.05) to detect a 30% change in mTNS score. Assuming that some patients would decline cross-over, 70 patients were randomized 3:4 to either the PBM- or Sham-groups.

Secondary endpoints were analyzed using chi-squared, two-group *t*-tests, and Fisher's exact test, as appropriate. Analysis was by intention to treat and all available data from patients (until study completion or withdrawal) were included. All statistical tests are two-sided using a 0.05 level of significance. The statistical analysis was performed using R version 3.2.1 (© 2015 The R Foundation for Statistical Computing).

Table 1
Modified total neuropathy score, adapted from Cornblath et al. [21].

	Score				
Parameter	0	1	2	3	4
Sensory symptoms	None	Limited to fingers and toes	Symptoms extend to wrist/ankle	Symptoms extend to knee/elbow	Symptoms extend beyond knee/elbow or are disabling
Motor symptoms	None	Slight difficulty (independent)	Moderate difficulty (independent)	Requires assistance	Paralysis
Pin sensitivity	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced beyond elbow/knee
Vibration sensitivity	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced beyond elbow/knee
Motor/strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Reduced at ankle	Absent at ankle, normal at knee	Absent at ankle, reduced at knee	All reflexes absent

Please cite this article as: P.A. Argenta, et al., The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.013

3. Results

Seventy patients were recruited between April 2014 and May 2015. Thirty were assigned to the PBM-group and 40 were assigned to the Sham-group. Patient demographics are included in Table 2. Patients were generally well matched for baseline characteristics and exposures. Notably the population was all female and largely non-Hispanic white (98%). The former we attribute to the fact that the trial accrued through the Gynecologic Oncology Clinic. Though men were not specifically excluded from enrolling, the prevalence of CIPN among patients receiving chemotherapy for gynecologic malignancies is high; additionally the location of enrollment in a women's center may have led referring physicians to erroneously conclude that the trial was for women only.

Patient compliance was high with 29 patients (97%) in the PBM-group and 40 patients (100%) in the Sham group receiving >95% of scheduled treatments. Two patients withdrew from the study; both were from the PBM-group (one withdrew consent after completing treatment but prior to follow-up; one patient recurred during treatment and withdrew after week 4 to focus on treatment, Fig. 2).

There were no observed complications among patients treated with PBM. One patient in the control group experienced a second degree superficial burn when inadvertent contact was made between a heat probe and the patient's skin. This was treated with topical antibiotics and the patient tolerated the remainder of planned treatment without event.

Table 2
Patient characteristics.

Characteristics	PBM-group	Sham-group	Total
Age (years)			
≤50	2 (6.7%)	2 (5.0%)	4 (5.7%)
51–60	7 (23.3%)	10 (25.0%)	17 (24.3%)
61–70	14 (46.7%)	18 (45.0%)	32 (45.7%)
71–80	7 (23.3%)	9 (22.5%)	16 (22.8%)
>80	0	1 (2.5%)	1 (1.4%)
Gender			
Female	30 (100%)	40 (100%)	70 (100%)
Race			
White	29 (96.7%)	38 (95.0%)	67 (95.7%)
Black	0	1 (2.5%)	1 (1.4%)
Asian	1 (3.3%)	0	1 (1.4%)
Native American	0	1 (2.5%)	1 (1.4%)
Cancer diagnosis			
Gynecologic	21 (70%)	26 (65%)	
Ovarian	19 (63.3%)	15 (37.5%)	34 (48.6%)
Uterine	2 (6.7%)	9 (22.5%)	11 (15.7%)
Cervical	0	2 (5.0%)	2 (2.9%)
Breast	4 (13.3%)	6 (15.0%)	9 (14.3%)
Hematologic	3 (10.0%)	1 (2.5%)	4 (5.7%)
Colon	0	5 (12.5%)	5 (7.1%)
Other	2 (6.7%)	2 (5.0%)	4 (5.7%)
Exposure			
Taxane			
Yes	24 (82.8%)	30 (75.0%)	54 (78.3%)
No	5 (17.2%)	10 (25.0%)	15 (21.7%)
Unknown	1	0	1
Platinum			
Yes	24 (85.7%)	35 (87.5%)	59 (86.8%)
No	4 (14.3%)	5 (12.5%)	9 (13.2%)
Unknown	2	0	2
Chemotherapy-free interval (months)			
Median (min, max)	6.5 (1, 276)	11 (0, 118)	7.5 (0, 276)
≤6	15 (50.0%)	17 (42.5%)	32 (45.7%)
7–12	6 (20.0%)	4 (10.0%)	10 (14.3%)
13–24	3 (10.0%)	7 (17.5%)	10 (14.3%)
25–36	2 (6.7%)	2 (5.0%)	4 (5.7%)
>36	4 (13.3%)	10 (25.0%)	14 (20.0%)
Current treatment			
Gabapentin/duloxetine	8 (26.7%)	13 (32.5%)	21 (30.0%)
Vitamin B	15 (50.0%)	10 (25.0%)	25 (35.7%)
Any pharmacologic treatment	23 (76.7%)	20 (50.0%)	43 (61.4%)

3.1. Primary endpoint

The primary endpoint was the change in mTNS score from pre-treatment baseline to 8 weeks after treatment initiation. Negative values indicate reduction in neuropathy while positive scores indicate worsening neuropathy. Patients treated with PBM had a mean change in mTNS of −6.8 points (−52.6%) at 8 weeks, corresponding to a statistically significant improvement (p-value < 0.001). Patients Sham-group patients experienced a mean mTNS change of +0.2 (+1.5%), indicating no evidence of an improvement ($p = 0.44$, Fig. 3A).

Thirty-eight of the 40 Sham-group patients (95.0%) elected crossover to the PBM/PT-group; 36 (94.7%) of these completed treatment. Two patients dropped out after crossover (one recurred and one withdrew consent). The mean change in the mTNS score 8 weeks after initiation of PBM/PT was −6.9 points (−50.9%), indicating significant improvement ($p < 0.001$). The difference in mean mTNS reductions at 8 weeks following PBM or PBM/PT was 0.1 ($p = 0.85$), indicating the addition of PT to PBM did not improve neuropathy more than PBM alone (Fig. 3A).

In absolute measures, 6 (15.0%) patients in the control group and 63 (96.9%) patients in the treatment groups (27 in PBM group + 36 in PBM/PT group) had some improvement in their mTNS score at 8 weeks. Using our pre-defined cutoff of 30% as a meaningful reduction in mTNS score, 1 patient (3.3%) in the control group experienced a meaningful reduction in mTNS compared to 61 patients (89.7%) in the treatment groups (27 PBM-group and 34 PBM/PT-group patients). Therefore the number needed to treat to achieve a meaningful reduction in mTNS score by this definition is 1.2 patients.

3.2. Secondary outcomes

There was a statistically significant difference between the PMB and Sham treated patients by the week 4 assessment (−4.2 vs −0.1 respectively, $p < 0.001$, Fig. 3A). The separation between the PBM- and Sham-groups increased through week 8, with the difference between the mTNS score at week 8 significantly greater than the week 4 value ($p < 0.001$). By week 16 (10 weeks after completion of treatment) there was some regression of effect with the mean change in mTNS score for PBM patients being −5.0, which was significantly different from the baseline value ($p < 0.001$) and comparable to the week 4 value ($p = 0.20$, Fig. 3A).

Patients in the PBM/PT-group, experienced results nearly identical to the PBM-group, with significant reduction in neuropathy at week 4 (change in mTNS = −5.5, $p < 0.001$), further reduction peaking 8 weeks after initiation ($p < 0.001$) and modest regression by week 16. There remained significant improvement at 16 weeks compared to treatment initiation which was again comparable to that seen after 4 weeks of treatment ($p = 0.16$).

3.3. Exploratory analyses

To determine if the efficacy of PBM was affected by specific chemotherapy exposures, we performed secondary analyses based on prior treatment with taxane, platinum, or both. Most patients had received a taxane or platinum drug prior to enrolling with 24 out of 30 (80%) in the PBM, and 26 out of 40 (65%) in the Sham-group having received both (Table 2). For patients with previous taxane exposure, the mean change in mTNS at eight weeks compared to baseline for those treated with PBM was −7.0 compared to a mean change in mTNS score of 0.2 for the control arm ($p < 0.0001$). Similar results were observed for patients exposed to platinum and both taxane and platinum.

As some spontaneous regression of CIPN symptoms is expected after recent chemotherapy exposure, we sought to determine if the duration of neuropathy was associated with response to PBM. Patients were classified as having “recently acquired neuropathy” if they enrolled within 6 months of their last chemotherapy administration, or “chronic

Please cite this article as: P.A. Argenta, et al., The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.013

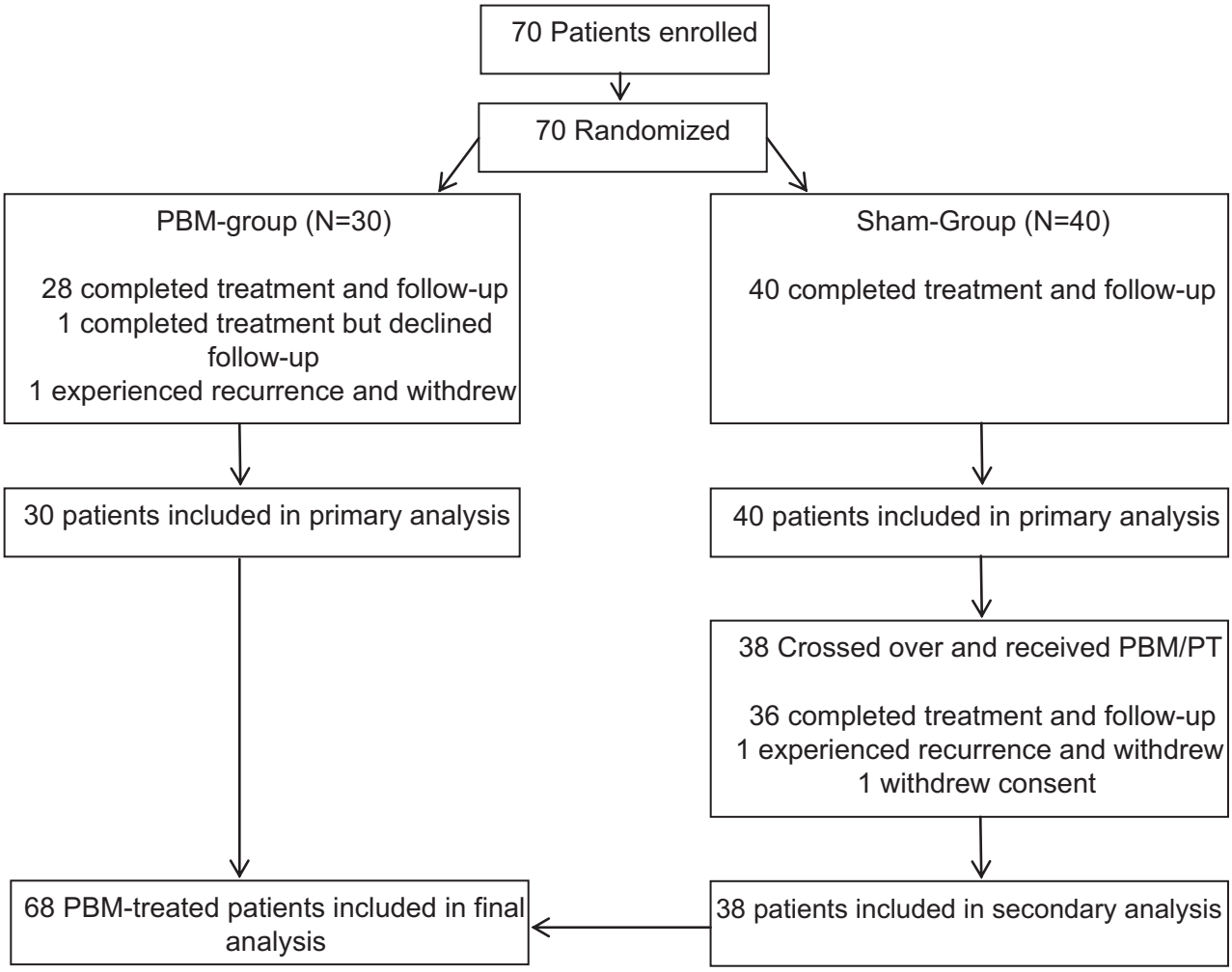


Fig. 2. Patient flow chart*.

neuropathy" if their exposure was ≥7 months prior. Fifteen of 30 patients (50.0%) in the PBM-group had recently acquired neuropathy versus 17 of 40 patients (42.5%) in the Sham-group. Among "recent" patients the mean change in mTNS at eight weeks for the PBM and Sham-groups were −6.7 and −0.4 respectively ($p < 0.0001$). Similarly, for 15 patients (50%) in the PBM group and 23 (57.5%) in the Sham-group with "chronic" CIPN, the mean change in mTNS was −6.9 and +0.61 respectively ($p < 0.0001$). Patients appeared therefore to receive similar benefit from PBM regardless of the reported duration of their neuropathy.

Lastly, we sought to determine if the degree of neuropathy was a predictor of response to PBM therapy. Using the mean of baseline mTNS score from all patients enrolled in the trial, patients were classified as having "greater" (mTNS above the mean) or "lesser" neuropathy (mTNS below the mean). Thirteen out of 30 (43.3%) patients in the PBM group had a "greater" level of neuropathy versus 25 of 40 (62.5%) in the control group. For patients with "greater" neuropathy (mean mTNS = 14.6), the mean change in mTNS at 8 weeks was −8.4 (−56.8%) versus −0.1 (−0.8%) for Sham-group patients (p-value < 0.001). For patients with "lesser" neuropathy (mean mTNS = 11.7), the mean change in mTNS at eight weeks −5.5 (−47.2%) versus +0.7 (+6.2%) for the Sham-group (p-value < 0.001). These data suggest that patients with more or less severe neuropathy symptoms experience significant benefit from treatment albeit not equally.

Evaluation of mTNS subscales demonstrates that benefit did not accrue evenly across all measures (Fig. 3B–F). Sensory and reflex deficits were more impaired at baseline, while motor/strength was less impaired. Gross improvements were observed in the subjective and objective measures of sensation, accounting for a majority of the global mTNS response seen. Negligible changes were seen in reflexes or motor symptoms, however modest and symmetric improvements were identified in the motor/strength subscale suggesting that while motor impairment is present at baseline it may be beneath a function-impairing threshold.

4. Discussion

Our data indicate that photobiomodulation is an effective, low-toxicity treatment for CIPN. Nearly 90% of patients experience significant improvement in mTNS scores that begins within weeks of initiating treatment and persists for at least 10 weeks after the conclusion of therapy. The benefits appear to accrue similarly to patients with variable duration and intensity of neuropathy symptoms, as well as to patients with variable chemotherapy exposures.

Our results compare favorably with current pharmacologic therapies. For example, five weeks of daily duloxetine, the most successful drug to date, resulted in a 10% improvement in mean pain scores, with <25% of patients reporting a 50% reduction in pain [7]. Using recommendations from the Initiative on Methods, Measurements and

Please cite this article as: P.A. Argenta, et al., The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.013

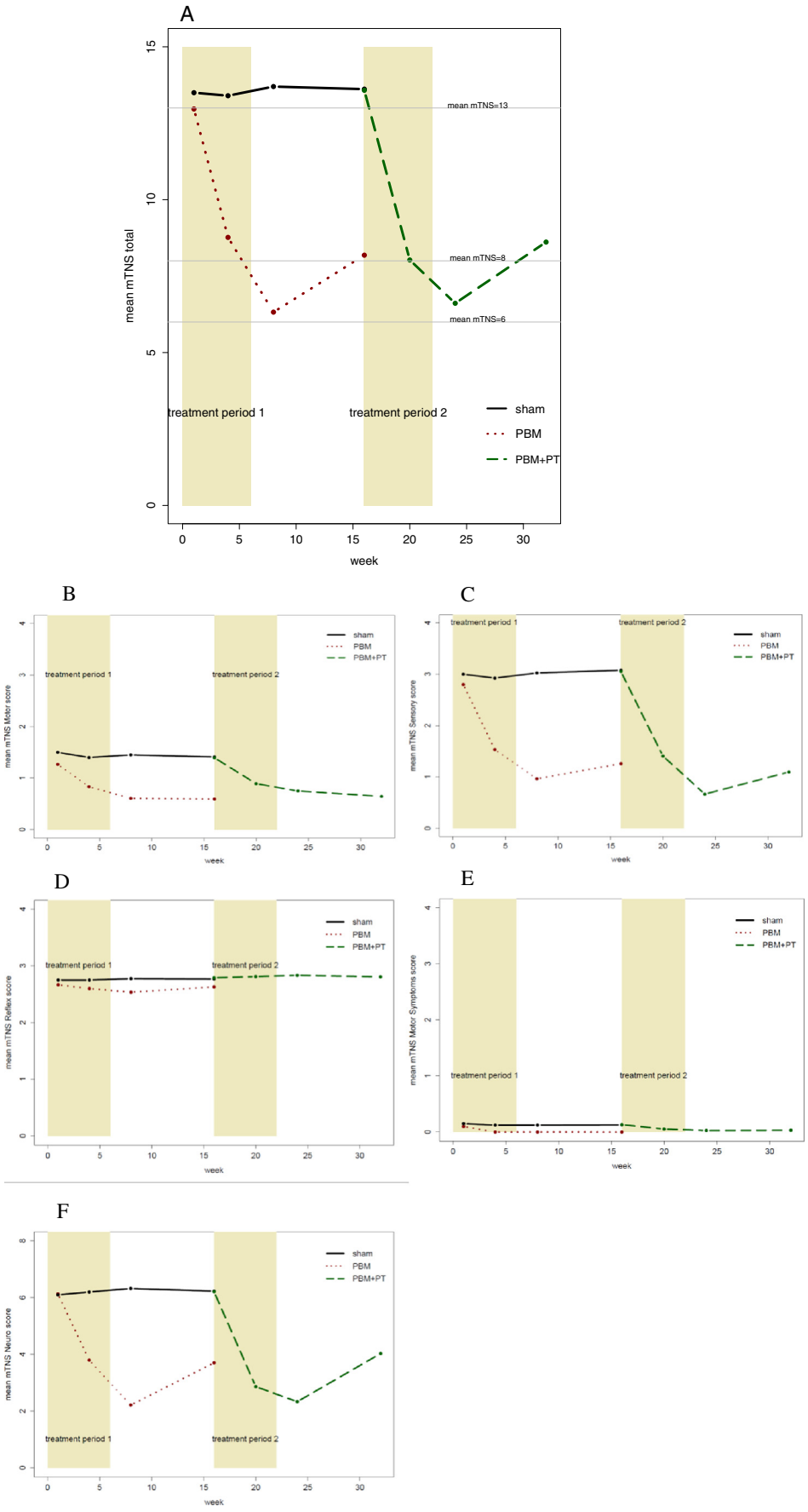


Fig. 3. Mean modified total neuropathy (mTNS) scores during and after treatment. a. Composite score for entire mTNS (scale 0–24). b. Mean score for mTNS-Motor/Strength subscale (scale 0–4). c. Means score for mTNS-Sensory symptoms subscale (scale 0–4). d. Mean score for mTNS-Reflex subscale (scale 0–4). e. Mean score for mTNS-Motor symptoms (scale 0–4). f. Mean score for mTNS-Neurologic subscale (combines vibratory and pinwheel scores, scale 0–8).

Please cite this article as: P.A. Argenta, et al., The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.013

Pain Assessment in Clinical Trials (IMMPACT) to assess magnitude of benefit, approximately one third of patients treated with duloxetine reported a ≥30% reduction in symptoms, corresponding to moderately important improvement compared to approximately 18% of patients on the placebo arm, yielding a number-needed-to-treat of approximately 6.7 [22]. By comparison, PBM-treated patients were more likely to experience a clinically meaningful response, with a number-needed-to-treat that approaches 1.

PBM may improve neuropathy symptoms through a number of plausible mechanisms including prevention of neural apoptosis and enhancement of neurite outgrowth. Molecular level studies suggest that energy from low-level laser is absorbed by mitochondrial transmembrane proteins leading to: improved cellular respiration, and increased activation of oxidation-sensitive pathways including nuclear factor–KB and activator protein 1, which protect cells from apoptosis-promoting signals including tumor-necrosis factor-α, as well the JNK and lysosomal pathways [23–30]. Zhang and colleagues reported differential expression of 111 genes after exposing human fibroblasts to PBM with more than half involved in cellular proliferation or suppression of apoptosis [24]. In vitro study of human neural progenitor cells suggests laser light supports neurite outgrowth and whole animal studies of mice suggest significant improvement of functional recovery after nerve crush injury and platinum exposure using similar PBM strategies [12,13,31].

Our study benefits from multiple strengths. The prospective, randomized, and sham controlled design was essential for isolating the impact of the treatment and eliminating placebo effect. The balance of known risks factors suggests that the randomization was effective, and the relative stability of the mTNS scores in the Sham-group suggests the sham treatment did not have unanticipated benefits. The study patients were highly compliant with prescribed treatments, had a low drop-out rate, and a higher-than expected participation in the crossover improving the statistical validity of our findings. The crossover allowed us to use the Sham-group results both as an internal and external control, reducing the likelihood of spurious observations and allowing assessment of PT as an adjunct therapy.

There are, however, multiple weaknesses that must be considered in interpreting these data. With regard to inclusion, recruitment was through a single gynecologic oncology center, and though external referrals were allowed, only women were enrolled. The impact of this imbalance is unclear, as the incidence rates of CIPN are typically reported as similar between the sexes. There was also a relative paucity of racial minorities. Though we are unable to identify any reports suggesting that skin pigmentation adversely alters the efficacy (or toxicity) of PBM, there are few high-quality studies from which to draw inference.

During this study, treatment duration was standardized to prevent inadvertently revealing a patient's group assignment. Whether treatment outcomes would have been altered with planned optimization or use of the full Realief algorithm is unclear, however a recent meta-analysis demonstrated that PBM was effective at reducing pain across a spectrum of wavelengths, albeit not equally, with sizes ranging from Cohen's d-score of 0.6 to 2.44 (where a d score of 0.2, 0.5, and 0.8 indicate a small medium, and large effect of treatment respectively) suggesting that optimization is likely necessary to achieve the best results [9,32–34].

Lastly, we did not assess the impact of potential concurrent therapies such as acupuncture or other pharmacologic agents (such as selective serotonin re-uptake inhibitors). Patients did however consent to maintaining their pre-study neuropathy regimen during the period of treatment and follow-up. As such, and because known standard treatments was balance, it is hoped that the randomization process would balance the contributions of unmeasured effects.

In summary, six weeks of three times weekly PBM was well tolerated and significantly reduced the clinical manifestations of CIPN compared to sham therapy. Treatment effect lasts well beyond the period of active treatment but diminishes over time, suggesting that further optimization of the treatment algorithm should be explored. The addition of PT to PBM did not improve results over PBM alone.

Author contributions

Drs. Argenta and Ballman had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analyses.

Study concept and design: Argenta, Ballman.

Acquisition of data: Argenta, Carson, Ghebre, Geller, Mullany, Teoh, Winterhoff, Rivard, and Erickson.

Analysis and interpretation of the data: Argenta, Ballman, Geller, Rivard, Erickson.

Drafting of the manuscript: Argenta, Ballman, Geller, Rivard, Erickson.

Critical revision of the manuscript for important intellectual content: Carson, Ghebre, Mullany, Winterhoff.

Statistical analysis: Ballman, Argenta.

Obtained funding: Argenta.

Administrative, technical or material support: none.

Study supervision: Argenta, Ballman, Geller.

Conflict of interest disclosure

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Argenta reported receiving institutional support from the University of Minnesota. No other financial disclosures were made.

Funding/support

This study was supported by funding and technical support provided by Realief Neuropathy Centers.

Role of the sponsor

Realief Neuropathy Centers provided recommendations regarding standardization of the treatment intensity and duration. They further provided the lasers and technical support (laser technicians) and funding support for data acquisition and management. Realief Neuropathy Centers did not participate in the design of the study; collection, management, analysis or interpretation of the data; preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

Additional contributions

We thank the study participants and the research and support staff at both sites. Special thanks are extended to Matt Gerber (University of Minnesota) and to Dr. Timothy Kelm DCh (Realief Neuropathy Centers), for technical support.

References

[1] R. Soffietti, E. Trevisan, R. Ruda, Neurologic complications of chemotherapy and other newer and experimental approaches, in: Biller, Faro (Eds.), Handbook of Clinical Neurology, vol. 121, Elsevier, 2014.
[2] S. Quasthoff, H.P. Hartung, Chemotherapy-induced peripheral neuropathy, J. Neurol. 249 (1) (2002) 9–17.
[3] N.P. Ezendam, B. Pijlman, C. Bhugwandass, J.F. Pruijt, F. Mols, M.C. Vos, J.M. Pijnenborg, L.V. van de Poll-Franse, Chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer survivors: results from the population-based PROFILES registry, Gynecol. Oncol. 135 (3) (2014) 510–517.
[4] P. Alberti, E. Rossi, D.R. Cornblath, I.S. Merkies, T.J. Postma, et al., Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: two sides of the same coin, Ann. Oncol. 25 (1) (2014) 257–264.
[5] K. Shimozuma, Y. Ohashi, A. Takeuchi, T. Aranishi, S. Morita, et al., Taxane-induced peripheral neuropathy and health-related quality of life in postoperative breast

cancer patients undergoing adjuvant chemotherapy: N-SAS BC 02, a randomized clinical trial, Support Care Cancer 20 (12) (2012) 3355–3364.
[6] C. Tofthagen, Surviving chemotherapy for colon cancer and living with the consequences, J. Palliat. Med. 13 (11) (2010) 1389–1391.
[7] R.D. Rao, J.C. Michalak, J.A. Sloan, C.L. Loprinzi, G.S. Soori, et al., Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3), Cancer 110 (9) (2007) 2110–2118.
[8] M.D. Stubblefield, H.J. Burstein, A.W. Burton, C.M. Custodio, G.E. Deng, et al., NCCN task force report: management of neuropathy in cancer, J. Natl. Compr. Cancer Netw. 7 (Suppl. 5) (2009) S1–S26.
[9] E.M. Lavoie Smith, H. Pang, C. Cirrincione, S. Fleishman, E.D. Paskett, et al., Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial, JAMA 309 (13) (2013) 1359–1367.
[10] D.R. Pachman, B.L. Weisbrod, D.K. Seisler, D.L. Barton, K.C. Fee-Schroeder, et al., Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy, Support Care Cancer 23 (4) (2015) 943–951.
[11] J.H. Kim, E.J. Kim, B.K. Seo, S. Lee, S. Lee, et al., Electroacupuncture for chemotherapy-induced peripheral neuropathy: study protocol for a pilot multicentre randomized, patient-assessor-blinded, controlled trial, Trials 14 (2013) 254.
[12] C.Z. Wang, Y.J. Chen, Y.H. Wang, M.L. Yeh, M.H. Huang, et al., Low-level laser irradiation improves functional recovery and nerve regeneration in sciatic nerve crush rat injury model, PLoS One 9 (8) (2014), e103348.
[13] Y.L. Hsieh, Y.C. Fan, C.C. Yang, Low-level laser therapy alleviates mechanical and cold allodynia induced by oxaliplatin administration in rats, Support Care Cancer 24 (1) (2016) 233–242.
[14] L.H. Zinman, M. Ngo, E.T. Ng, K.T. Nwe, S. Gogov, V. Bril, Low-intensity laser therapy for painful symptoms of diabetic sensorimotor polyneuropathy: a controlled trial, Diabetes Care 27 (4) (2004) 921–924.
[15] S.M. Shooshtari, V. Badiee, S.H. Taghizadeh, A.H. Nematollahi, A.H. Amanollahi, M.T. Grami, The effects of low level laser in clinical outcome and neurophysiological results of carpal tunnel syndrome, Electromyogr. Clin. Neurophysiol. 48 (5) (2008) 229–231.
[16] G. Taveggia, J.H. Villafañe, F. Vavassori, C. Lecchi, A. Borboni, S. Negrini, Multimodal treatment of distal sensorimotor polyneuropathy in diabetic patients: a randomized clinical trial, J. Manip. Physiol. Ther. 37 (4) (2014) 242–252.
[17] U. Chatchawan, W. Eungpinichpong, P. Plandee, J. Yamauchi, Effects of thai foot massage on balance performance in diabetic patients with peripheral neuropathy: a randomized parallel-controlled trial, Med. Sci. Monit. Basic Res. 20 (2015) 68–75.
[18] C. Brami, T. Bao, G. Deng, Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: a systematic review, Crit. Rev. Oncol. Hematol. 998 (2016) 325–334.
[19] E.M. Lavoie Smith, J.A. Cohen, M.A. Pett, S.L. Beck, The reliability and validity of a modified total neuropathy score-reduced and neuropathic pain severity items when used to measure chemotherapy-induced peripheral neuropathy in patients receiving taxanes and platinums, Cancer Nurs. 33 (3) (2010) 173–183.
[20] M.A. Wampler, C. Miasskowski, K. Hamel, N. Byl, H. Rugo, K.S. Topp, The modified total neuropathy score: a clinically feasible and valid measure of taxane-induced peripheral neuropathy in women with breast cancer, J. Support. Oncol. 4 (8) (2006) w9–w16.
[21] D.R. Cornblath, V. Chaudhry, K. Carter, D. Lee, M. Seysedadr, et al., Total neuropathy score: validation and reliability study, Neurology 53 (8) (1999) 1660–1664.
[22] R.H. Dworkin, D.C. Turk, M.P. McDermott, S. Peirce-Sandner, L.B. Burke, et al., Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations, Pain 146 (3) (2009) 238–244.
[23] J.T. Hashmi, Y.Y. Huang, B.Z. Osmani, S.K. Sharma, M.A. Naeser, M.R. Hamblin, Role of low-level laser therapy in neurorehabilitation, PM R 12 (Suppl. 2) (2010) S292–S305.
[24] Y. Zhang, S. Song, C.C. Fong, C.H. Tsang, Z. Yang, M. Yang, cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light, J. Invest. Dermatol. 120 (5) (2003) 849–857.
[25] M.T. Wong-Riley, H.L. Liang, J.T. Eells, B. Chance, M.M. Henry, E. Buchmann, M. Kane, H.T. Whelan, Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome *c* oxidase, J. Biol. Chem. 280 (6) (2005) 4761–4771.
[26] T. Karu, L. Pyatibrat, G. Kalendo, Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro, J. Photochem. Photobiol. B 27 (3) (1995) 219–223.
[27] D. Pastore, M. Greco, V.A. Petragallo, S. Passarella, Increase in $\leftarrow H+/e-$ ratio of the cytochrome *c* oxidase reaction in mitochondria irradiated with helium-neon laser, Biochem. Mol. Biol. Int. 34 (4) (1994 Oct) 817–826.
[28] C.G. Pham, C. Bubici, F. Zazzeroni, S. Papa, J. Jones, K. Alvarez, S. Jayawardena, E. De Smaele, R. Cong, C. Beaumont, F.M. Torti, S.V. Torti, G. Franzoso, Ferritin heavy chain upregulation by NF-kappaB inhibits TNFalpha-induced apoptosis by suppressing reactive oxygen species, Cell 119 (4) (2004) 529–542.
[29] E. De Smaele, F. Zazzeroni, S. Papa, D.U. Nguyen, R. Jin, J. Jones, R. Cong, G. Franzoso, Induction of gadd45beta by NF-kappaB downregulates pro-apoptotic JNK signaling, Nature 414 (6861) (2001) 308–313.
[30] N. Liu, S.M. Raja, F. Zazzeroni, S.S. Metkar, R. Shah, M. Zhang, Y. Wang, D. Brömme, W.A. Russin, J.C. Lee, M.E. Peter, C.J. Froelich, G. Franzoso, P.G. Ashton-Rickardt, NF-kappaB protects from the lysosomal pathway of cell death, EMBO J. 22 (19) (2003) 5313–5322.
[31] J.A. Anders, T.B. Romanczyk, I.K. Ilev, H. Moges, L. Longo, X. Wu, R.W. Waynant, Light supports neurite outgrowth of human neural progenitor cells in vitro: the role of P2Y receptors, J. Sel. Top. Quantum Electron. 14 (1) (2008) 118–125.
[32] J.J. Anders, H. Moges, X. Wu, I.D. Erbele, S.L. Alberico, E.K. Saidu, J.T. Smith, B.A. Pryor, In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves, Lasers Surg. Med. 46 (1) (2014) 34–45.
[33] C.S.L. Enwemeka, J.C. Parker, D.S. Dowdy, E.E. Harkness, L.E. Sanford, L.D. Woodruff, The efficacy of low-power lasers in tissue repair and pain control: a meta-analysis study, Photomed. Laser Surg. 22 (4) (Aug. 2004) 323–329.
[34] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, second ed. Lawrence Earlbaum, Hillsdale, NJ, 1988.

Please cite this article as: P.A. Argenta, et al., The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.013