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Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy

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Abstract

Purpose—Chemotherapy-induced peripheral neuropathy (CIPN), a common side effect of chemotherapy, needs better effective treatments. Preliminary data support the use of Scrambler therapy, a device which treats pain via noninvasive cutaneous electrostimulation, for the treatment

of CIPN. The current manuscript reports data from a pilot trial, performed to investigate the effect of Scrambler therapy for the treatment of established CIPN.

Methods—Eligible patients had CIPN symptoms of 1 month duration with tingling and/or pain 4/10 during the prior week. Patients were treated with Scrambler therapy to the affected area(s) for up to ten daily 30-min sessions. Symptoms were monitored using a neuropathy questionnaire consisting of numerical analog scales ranging from 0 to 10, daily before therapy as well as weekly for 10 weeks after therapy. Descriptive summary statistics formed the basis of data analysis.

Results—Thirty-seven patients were enrolled. Twenty-five patients were treated primarily on their lower extremities while 12 were treated primarily on their upper extremities. There was a 53 % reduction in pain score from baseline to day 10; a 44% reduction in tingling; and a 37% reduction in numbness. Benefit appeared to last throughout 10 weeks of follow-up. There were no substantial adverse events.

Conclusion—Preliminary data support that Scrambler therapy may be effective for the treatment of CIPN: a prospective placebo-controlled clinical trial should be performed.

Keywords

Scrambler therapy; Chemotherapy-induced peripheral neuropathy; Electroanalgesia

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN), a serious dose-limiting side effect of multiple chemotherapeutic agents, commonly occurs in 30–40 % of patients; it often presents with a sensory neuropathy, characterized by paresthesias and pain. Symptoms frequently start in fingers and toes and spread proximally in a “glove and stocking” distribution. CIPN may begin weeks to months after the initiation of chemotherapy and reach a peak at or after the end of treatment. Although symptoms may resolve after completion of therapy, they are often only partially reversible and can last for years [24].

Multiple agents have been investigated for the treatment of CIPN, many of which have failed to show benefit, including amitriptyline [11], nortriptyline [8], and lamotrigine [15]. Gabapentin, an anti-epileptic agent commonly used in the treatment of CIPN, also was found to be ineffective for the treatment of CIPN in a large, randomized, placebo-controlled trial [16]. Few agents have preliminary data supporting their use for the treatment of CIPN, including topical amitriptyline/ketamine/baclofen gel [1], venlafaxine [5], and pregabalin [19]. Recently, a large placebo-controlled, double-blinded clinical trial reported that duloxetine was effective in decreasing average pain when compared with placebo, albeit with a less than impressive pain reduction [20]. Further research is required to find more effective interventions for the treatment of CIPN.

Scrambler therapy is a novel device which provides non-invasive cutaneous electrostimulation, with a goal to substitute “nonpain” information for “pain” information. The device produces 16 different electrical currents that simulate normal nerve action potentials. These currents are organized into algorithms that take into account many factors, including previous outputs, frequency, duration, and amplitude of modulation [14]. The

impulses are transmitted via surface electrodes which are placed surrounding the area of pain. As the principal of therapy is to replace “pain” with “nonpain” signals, it is expected that the patient will experience immediate pain reduction if the electrodes are placed appropriately.

The electrical charge used in Scrambler therapy is low and has been approved as safe by the FDA. At the highest setting, “70” on the dial from 10 to 70, the amperage (A) is 3.50–5.50 mA, with a voltage range of 6.5–12.5 V. The maximum current density is 0.0002009 W/cm². The phase duration is 6.8–10.9 ms, and the pulse rate is 43–52 Hz. The average charge per phase is 38.8 µC, which is similar to conventional transcutaneous electrical nerve stimulation (TENS) device. In addition, since the frequency of the Scrambler device never exceeds 52 Hz, the mean energy delivered per second is less than most standard TENS [14, 21].

Small trials have evaluated the Scrambler device in the treatment of multiple forms of neuropathic pain, with promising results [2, 3, 13, 14, 17, 18, 21, 22]. Three of these trials specifically investigated Scrambler therapy for the treatment of CIPN. The first study involved 16 patients, the majority of which had long-standing CIPN with symptom duration of >2 years. Each patient was treated with Scrambler therapy for ten 60-min sessions. Fifteen patients had a 20 % or greater reduction in pain score after 10 days of treatment. In addition, the mean pain score fell 59 % from baseline to after the last treatment. This study did not specifically investigate other CIPN symptoms such as tingling and numbness, but patients did report improvement in sensation and partial relief of numbness. Overall, treatment was well tolerated [21]. The second trial was a small randomized, double-blind study including 14 patients with neuropathic pain for >6 months. Seven patients were treated with Scrambler therapy, and seven patients were treated with a novel active sham device constructed to deliver a just perceptible electrical sensation. There was no difference between arms in pain score [2]. The third trial included 39 patients with neuropathic cancer pain, 33 of which had CIPN. Results for cancer pain as well as CIPN were reported together. The pain scores as measured using the pain numerical rating scale (0 is no pain and 10 is worst pain imaginable), reduced from 6.6 before treatment to 4.5 at 14 days and 4.6, 4.8, and 4.6 at 1, 2, and 3 months, respectively [3].

The current pilot trial was performed to further investigate the efficacy of Scrambler therapy in the treatment of CIPN.

Methods

Eligibility characteristics

The currently reported patients are part of an open access trial developed to investigate Scrambler therapy in the treatment of various pain syndromes (including CIPN, benign low back pain, or postherpetic neuralgia). Inclusion criteria included age ≥ 18 years, ECOG performance status ≤ 2, and life expectancy ≥ 3 months. Pain or symptoms of neuropathy had to be present for ≥ 1 month and tingling or pain had to be rated ≥ 4/10 (on a single numeric analog questionnaire) during the prior week. Participants also needed to have the ability to

complete questionnaires by themselves or with assistance and have the ability to provide informed written consent.

Patients were not eligible for the trial if they were pregnant or if they had an implantable drug delivery system, heart stents, or metal implants (pacemakers, automatic defibrillators, aneurysm clips, vena cava clips, and skull plates). In addition, they could not participate if they had a history of ischemic heart disease or myocardial infarction within the past 6 months or if they had symptomatic brain metastases. Patients were not eligible if they had a history of epilepsy, traumatic brain injury, use of anti-convulsants for seizure prevention, or were concurrently using ketamine. Patients could not have had skin conditions such as open sores that would prevent proper application of the electrodes. In addition, patients were not eligible if they were concurrently receiving neurotoxic chemotherapy and/or had other medical conditions that, in the opinion of the investigators, might compromise the objectives of the study. This protocol was approved by the Mayo Clinic Internal Review Board, and all patients signed consent forms.

The patients reported here are the first 37 patients that were treated with the diagnosis of CIPN.

Scrambler therapy

On the initial day of treatment, the most symptomatic area of CIPN was determined by patient report. Electrodes, similar to electrocardiogram patches, were placed outside and along the lines of pain and/or tingling. Once a pair of electrodes was positioned appropriately, the device was turned on and the electrode intensity was increased to the maximally tolerated intensity. If the patient did not have improvement in symptoms, the device was turned off and electrodes were removed and repositioned. Once proper initial electrode placement was achieved, resulting in a decrease in symptoms, additional electrode sets were placed to further encompass the symptomatic area. Up to five channels or sets of electrodes could be used during treatment. If the primary area of CIPN symptoms improved with less than five channels, remaining channels were used on other symptomatic areas (such as another leg or arm). Once all channels were used, or the patient had significant reduction of symptoms, the treatment session continued for 30 min. Each patient received daily sessions for up to ten consecutive days, Monday–Friday. Patients had the option to stop treatments for lack of significant benefit. Treatments were also stopped prior to 10 days if all the pain and tingling resolved.

Study endpoints

The primary measure of neuropathy symptoms was a peripheral neuropathy symptom questionnaire which included single numeric analog questions assessing the level of numbness, tingling, or pain in the patient's toes/feet or fingers/hands. Single-item visual analog scales have been demonstrated to be a valid and reliable measure of quality of life and symptoms in cancer patients [4, 9, 12]. Patients completed this questionnaire at baseline and before and after each treatment session. A similar numeric analog question asking about combined numbness, tingling, and pain was used daily prior to each treatment and then weekly after completion of treatment, for a total of 10 weeks. About half-way through this

study, patients were also asked to respond to single numeric analog questions assessing the level of numbness, tingling, or pain in the patient's toes/feet or fingers/hands, weekly after completion of treatment, for a total of 10 weeks. Finally, a global impression of change questionnaire was utilized, which is related to neuropathy symptoms, pain, and quality of life at baseline, daily during therapy, and weekly for 10 weeks. The global impression of change is a 7-point item in which the patient rates the change in overall status since beginning the study treatment. Global impression of change questionnaires that assess overall pain status and quality of life have established validity in a range of states characterized by chronic pain [6, 7].

The Rydel-Seiffer graduated tuning fork is an instrument that can quantify the degree of vibration that can be detected by patients. It has been proposed to be used for patients with neuropathy related to diabetes mellitus and chemotherapy, among other neuropathy etiologies [10, 23]. It was used to record vibration sensation daily prior to treatment. For upper extremities, measurements were taken at the dorsum of the index finger distal interphalangeal joint and ulnar styloid process. For lower extremities, measurements were taken at the dorsum of the interphalangeal joint of the great toe and internal malleolus.

Statistical analysis

Descriptive summary statistics including means, standard deviations, and percentages formed the basis of analysis for the current study. Some *p* values were calculated, looking at changes from baseline. Supplemental graphical representations of CIPN symptom score changes were also included. Toxicities and self-reported side effects were also analyzed in a descriptive manner. For incomplete data in the first ten treatment days, the last observation was carried forward, unless otherwise indicated for certain data sets.

Results

A total of 37 consecutive CIPN patients were enrolled between 18 July 2011 and 6 May 2013. The average age was 58 (33–79); 12 were men and 25 were women. Patients had a history of a variety of cancer types (13 breast, 7 ovarian, 6 colon/rectal, 3 lymphoma, and 9 others). Thirteen patients were exposed to paclitaxel, eight to carboplatin/paclitaxel, nine to oxaliplatin, four to cisplatin-based regimens, and three to vincristine. Twenty-five patients were treated primarily on the lower extremities, while 12 patients were treated primarily on the upper extremities. Eighteen patients had symptoms of ≥ 2 years, eleven had symptoms of 1 year, and eight patients had symptoms of <1 year.

No patient was currently receiving TENS therapy, although some had previously. Many had previously undergone surgeries or analgesic injections, but none immediately prior to the Scrambler therapy. Patients were receiving a variety of analgesic medications at study entry.

Table 1 portrays data at baseline, at the end of the ten planned days of therapy, and the average percent drop in symptom score from baseline to the end of treatment, regarding patient-reported average and worst pain, tingling, and numbness over the preceding 24 h. At the end of 10 days of treatment, average pain decreased by 53 % ($p<0.0001$), while tingling decreased by 44 % ($p<0.0001$) and numbness decreased by 37 % ($p=0.0002$). This is also

demonstrated in Fig. 1a, utilizing patient-reported data, which shows that the numbness, tingling, and pain symptom scores improved daily during therapy. A similar image was seen when last value was carried forward for those patients who did not complete 10 days of treatment. Patients also experienced improvement in pain daily after each treatment as demonstrated in Fig. 1b.

Table 2 shows individual patient average pain reported over the past 24 h prior to treatment each day. Patients 23, 24, and 25 did not report any pain, as tingling and/or numbness was their primary symptom. Sixteen patients did not complete all 10 days of treatment. For these patients, last values are carried forward. Three patients (2, 27, and 34) stopped due to their conclusions that their symptoms had improved enough, even if they did not have full resolution. Eight patients stopped early due to lack of enough perceived benefit (16, 20, 21, 22, 24, 28, 33, and 35). Two patients had to travel back home as they lived far from the clinic (29 and 36), one patient became ill with stomach flu (37), one patient had cancer recur (25), and one developed hand/foot syndrome from capecitabine (3).

Figure 2 demonstrates the average CIPN score over the preceding 24 h, for pain, tingling, or numbness during therapy, as well as during the 10-week follow-up period. It also illustrates the data for patients who answered a question regarding the patient's symptoms over the preceding 24 h for a combination of numbness, tingling, and pain. Of note, questions regarding the individual symptoms, during the follow-up period, were added to the protocol after the first 23 patients, and therefore fewer patients (14) were asked to address these questions, during the follow-up period, while the combined question was there at protocol initiation. It was noted that the results for the combined question did not look as favorable as did the data for the individual item questions. From this observation, it was hypothesized that this might have been because the later patients might have done better than the earlier patients, as the study team became more experienced. Figure 3a evaluates this hypothesis by comparing the first 23 treated patients to the last 14 treated patients. This supports that the last 14 patients on study had a better response to treatment. This may have been because the treating providers learned how to more effectively place the electrodes and/or that the latter patients were more likely to complete all 10 days of therapy (13/14 later cohort patients completed 10 days as opposed to 7/23 earlier patients). Figure 3b explores this further and chronologically compares 4 quartiles of patients. Again the first quartile appeared to do worse than the later quartiles.

Global impression of change for daily and weekly neuropathy symptoms are demonstrated in Fig. 4. Patients also reported improvements in quality of life over treatment and during the 10 weeks of follow-up, with data that look similar to that seen in Fig. 4.

Vibration perception tended to improve with treatment as measured by the Rydel-Seiffer graduated tuning fork. There was a 0.53-point increase on average in the total study population (higher scores signify improvement), which trended toward significance ($p=0.06$). For the lower extremity cohort, there was a 0.65-point increase on average, while the upper extremity cohort demonstrated a 0.29-point increase on average.

Discussion

Results from this study support previous findings that suggest that Scrambler therapy is an effective treatment for CIPN [3, 21].

The first published trial of Scrambler therapy specifically for the treatment of CIPN reported a reduction in pain score of 59 % (5.81 ± 1.11 to 2.38 ± 1.82) by the end of 10 days of treatment [21], which is very similar to the current study results. In the study by Coyne et al., which included 33 patients with CIPN and 6 with other forms of cancer-related pain, there was a reduction in pain score of 35 % (6.5 vs 4.2, from baseline to 14-day follow-up. Although this percentage is lower than seen in the current study or that reported by Smith et al., the reduction from baseline was still statistically significant ($p=0.0005$). These results may have been affected by the combination with other cancer-related pain states.

The study by Smith et al. reported that most patients had their pain return to pretreatment levels 1 or 2 months after treatment ended [21]. Conversely, Coyne et al. found that the improvement in pain score seemed to last for 3 months of follow-up [3]. The current study results fall in between these extremes, as symptoms did tend to worsen after completion of therapy, however, remained improved, over pretreatment levels, at 10 weeks of follow-up. In trials involving Scrambler therapy for non-CIPN neuropathic pain syndromes, it has been reported that pain may return 2–3 months after treatment. However, retreatment and maintenance therapy have provided pain relief [14]. Of the patients included in the current study, eight patients, who reported good results with the first 10 days (patients 2, 4, 5, 6, 8, 11, 17, and 30 in Table 2) did receive a retreatment, on average 7 months from original treatment; most of these patients received just one to two treatments at this time and reported that the retreatments, again, helped them.

An important finding of the current study is the effect of Scrambler therapy on tingling and numbness, in addition to pain. Unlike the previous study by Smith et al., the inclusion criteria of this pilot trial was tingling or pain 4/10, while the previous trial only included patients with pain [21]. This is especially important because numbness and tingling appear to be more common and more highly reported to be bothersome, than pain, in patients with CIPN [25]. Although Smith et al. did not formally assess these symptoms, they did report that several participants did note benefit in numbness [21]. In addition, the study by Coyne et al. included patients with numbness that bothered the patients at least “a little bit” on the EORTC-CIPN 20 tool, and they noted an improvement in the sensory component of the EORTC-CIPN-20 which includes questions regarding numbness and tingling; however, they did not specifically report the effect on these symptoms individually [3].

In addition, in the current study, the Scrambler therapy was numerically associated with an improvement in quality of life as measured by the global impression of change scale, which lasted throughout 10 weeks of follow-up. Coyne et al. also noted improvements in general activity, mood, sleep, and enjoyment of life [3]. However, of note, Smith et al. reported that there was no change in the formal quality of life tool that they used [21].

The results of the current study are not consistent with a small randomized, double-blind study of Scrambler therapy vs a sham treatment for CIPN, which showed no difference in

change in numerical rating scale (NRS) score between groups. However, the change in NRS by day 10 in the seven patients treated with Scrambler was -0.10 , which is a much smaller reduction than was seen in the current study or the previous existing studies. The reduction in the sham group pain score was -0.4 by the end of treatment, which is also less than the reduction seen in the current study. This smaller reduction of pain might have been because this investigative group had not conducted pilot studies and thus had less experience with the use of Scrambler therapy. Nonetheless, this small study, which, to date, has only been published as an abstract, did show the feasibility of the sham control which may be important in the conduction of a larger controlled clinical trial [2].

Another important observation from the current study was that patients who were treated later in the study had a better response to treatment. This may be due to the development of expertise of the treating providers, supporting that Scrambler therapy may be more effective when provided by an experienced treatment team. This variability between users can be considered a potential limitation of Scrambler therapy.

One of the strengths of this current study is that the Scrambler treatment was performed by a research team that was trained directly by an inventor of the device. Limitations of this study include the small sample size, the relatively short period of follow-up, and that all patients did not complete the planned therapy. In addition, as a pilot study, the trial was not controlled for a possible placebo effect. However, the pain reduction of 53 % is greater than that seen in previous placebo-controlled trials of CIPN treatment [1, 16].

Thus, Scrambler therapy is a novel device, which, based on preliminary data, appears to have benefit in the treatment of CIPN. This current trial supports previous reports of the efficacy of Scrambler therapy for the treatment of chronic neuropathic pain. In addition to providing this confirmatory information from another treatment group, it supports that Scrambler therapy may be beneficial for the treatment of chemotherapy-induced tingling and numbness. Also, it suggests that there is a learning curve with this new treatment, with improved results over time. Further larger placebo-controlled trials are needed to better assess the efficacy of Scrambler therapy in the treatment of CIPN and other chronic neuropathic pain syndromes and to define which patients and symptoms are most responsive to therapy. In addition, research is needed to further investigate the mechanism of action of the device, which may provide further data on the pathophysiology of CIPN.

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References

1. Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD 3rd, Kugler JW, Hoff KL, Reddy PS, Rowland KM Jr, Riepl M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. 2011; 19:833–841. [PubMed: 20496177]

2. Campbell TC, Nimunkar AJ, Retseck J, Eickhoff JC, Backonja M, Cleary JF, Kwekkeboom KL, Yen TY. A randomized, double-blind study of "Scrambler" therapy versus sham for painful chemotherapy-induced peripheral neuropathy (CIPN). *J Clin Oncol*. 2013; 31(suppl) abstr 9635.
3. Coyne PJ, Wan W, Dodson P, Swainey C, Smith TJ. A trial of scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *J Pain Palliat Care Pharmacother*. 2013; 27:359–364. [PubMed: 24143893]
4. de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC, Sprangers MA. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res*. 2004; 13:311–320. [PubMed: 15085903]
5. Durand JP, Deplanque G, Montheil V, Gornet JM, Scotte F, Mir O, Cessot A, Coriat R, Raymond E, Mitry E, Herait P, Yataghene Y, Goldwasser F. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. *Ann Oncol*. 2011; 1:200–205. [PubMed: 21427067]
6. Eurich DT, Johnson JA, Reid KJ, Spertus JA. Assessing responsiveness of generic and specific health related quality of life measures in heart failure. *Health Qual Life Outcomes*. 2006; 4:89. [PubMed: 17125512]
7. Fitzpatrick R, Ziehlend S, Jenkinson C, Mowat A. Transition questions to assess outcomes in rheumatoid arthritis. *Br J Rheumatol*. 1993; 32:807–811. [PubMed: 8369891]
8. Hammack JE, Michalak JC, Loprinzi CL, Sloan JA, Novotny PJ, Soori GS, Tirona MT, Rowland KM Jr, Stella PJ, Johnson JA. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain*. 2002; 98:195–203. [PubMed: 12098632]
9. Hauser K, Walsh D. Visual analogue scales and assessment of quality of life in cancer. *J Support Oncol*. 2008; 6:277–282. [PubMed: 18724538]
10. Kastenbauer T, Sauseng S, Brath H, Abrahamian H, Irsigler K. The value of the Rydel-Seiffer tuning fork as a predictor of diabetic polyneuropathy compared with a neurothesiometer. *Diabetic Med: J B Diabetic Assoc*. 2004; 21:563–567.
11. Kautio AL, Haanpaa M, Saarto T, Kalso E. Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. *J Pain Symptom Manag*. 2008; 35:31–39.
12. Locke DE, Decker PA, Sloan JA, Brown PD, Malec JF, Clark MM, Rummans TA, Ballman KV, Schaefer PL, Buckner JC. Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *J Pain Symptom Manag*. 2007; 34:628–638.
13. Marineo G. Untreatable pain resulting from abdominal cancer: new hope from biophysics? *JOP*. 2003; 4:1–10. [PubMed: 12555009]
14. Marineo G, Iorno V, Gandini C, Moschini V, Smith TJ. Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: results of a pilot, randomized. *Controll Trial J Pain Symptom Manag*. 2011; 43(1):87–95.
15. Rao RD, Flynn PJ, Sloan JA, Wong GY, Novotny P, Johnson DB, Gross HM, Renno SI, Nashawaty M, Loprinzi CL. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. *Cancer*. 2008; 112:2802–2808. [PubMed: 18428211]
16. Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikceovich DA, Warner DO, Novotny P, Kutteh LA, Wong GY. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer*. 2007; 110:2110–2118. [PubMed: 17853395]
17. Ricci M, Pirotti S, Scarpi E, Burgio M, Maltoni M, Sansoni E, Amadori D. Managing chronic pain: results from an open-label study using MC5-A Calmare(R) device. *Support Care Cancer*. 2011; (2):405–412. [PubMed: 21394458]
18. Sabato AF, Marineo G, Gatti A. Scrambler therapy. *Minerva Anestesiol*. 2005; 71:479–482. [PubMed: 16012423]
19. Saif MW, Syrigos K, Kaley K, Isufi I. Role of pregabalin in treatment of oxaliplatin-induced sensory neuropathy. *Anticancer Res*. 2010; 30:2927–2933. [PubMed: 20683034]
20. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL. Effect of duloxetine on pain, function, and

quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *Jama*. 2013; 309:1359–1367. [PubMed: 23549581]

21. Smith TJ, Coyne PJ, Parker GL, Dodson P, Ramakrishnan V. Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare(R)) for chemotherapy-induced peripheral neuropathy. *J Pain Symptom Manag*. 2010; 40:883–891.
22. Sparadeo F, Kaufman C, D'Amato S. Scrambler therapy: an innovative and effective treatment for chronic neuropathic pain. *J Life Care Plan*. 2012; 11:3–15.
23. Whitton TL, Johnson RW, Lovell AT. Use of the Rydel-Seiffer graduated tuning fork in the assessment of vibration threshold in postherpetic neuralgia patients and healthy controls. *Eur J Pain*. 2005; 9:167–171. [PubMed: 15737809]
24. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst*. 2008; 13:27–46. [PubMed: 18346229]
25. Wolf SL, Barton DL, Qin R, Wos EJ, Sloan JA, Liu H, Aaronson NK, Satele DV, Mattar BI, Green NB, Loprinzi CL. The relationship between numbness, tingling, and shooting/burning pain in patients with chemotherapy-induced peripheral neuropathy (CIPN) as measured by the EORTC QLQ-CIPN20 instrument, N06CA. *Support Care Cancer*. 2011; 20(3):625–632. [PubMed: 21479990]

Fig. 1. Daily CIPN scores (numbness, tingling, and pain) over 10 days of treatment. Reported scores refer to the average pain over the previous 24 h (1a). In Fig. 1b, current pain scores are illustrated just prior to and just after each daily treatment

Fig. 2. CIPN scores daily during treatment as well as during 10-week follow-up. The numbness, tingling, or pain combined group includes the total study population. Individual determinations of pain, numbness, or tingling involved the total study population during the daily treatments, but, during the follow-up weeks, only involved the last 14 patients, when a protocol modification was made to include these measures

Fig. 3. CIPN scores (for the combination of numbness, tingling, or pain) daily during treatment as well as during 10 week follow-up separated by earlier and later cohorts, defined by the time that the individual symptom questions were added to the protocol (**a**) and then further separated chronologically into four quartile groups (**b**)

Fig. 4.
Global impression of change score for neuropathy symptoms daily during treatment as well as during the 10 week follow-up

Table 1

Effect of Scrambler therapy on CIPN scores

Symptom	Mean baseline score		Mean final score		Average percent drop in symptom score		p values (Wilcoxon test)	
	Average ^a	Worst ^b	Average ^a	Worst ^b	Average ^a (%)	Worst ^b (%)	Average	Worst
Pain	5.7	6.4	2.6	3.2	53	51	<0.0001	<0.0001
Tingling	6.0	6.5	3.3	3.7	44	40	0.0001	<0.0001
Numbness	6.3	6.8	4.0	4.0	37	41	0.0002	<0.0001

^a Average symptom score over past 24 h

^b Worst symptom score over past 24 h

Table 2
Table of individual patient scores over treatment days (average pain in the past 24 h)

Study ID	Treatment day										Percent change
	1	2	3	4	5	6	7	8	9	10	
Lower extremities											
1	5	7	2	2	0	0	0	0	0	0	-100
2	4	4	6	2	1	0	0 ^a	0 ^a	0 ^a	0 ^a	-100
3	9	8	7	0	0 ^a	0 ^a	0 ^a	0 ^a	0 ^a	0 ^a	-100
4	5	4	3	0	0	1	0	0	0	0	-100
5	8	8	0	3	3	2	1	1	0	0	-100
6	5	5	5	5	4	3	3	2	0	0	-100
7	5	5	5	4	3	3	2	2	1	0	-100
8	6	4	2	2	2	3	2	1	1	1	-83.3
9	6	5	4	4	3	5	3	2	2	1	-83.3
10	8	7	7	5	5	5	4	3	2	2	-75.0
11	5	5	7	5	6	5	2	2	4	2	-60.0
12	6	6	5	5	5	4	4	4	4	3	-50.0
13	5	5	5	5	5	5	3	3	4	3	-40.0
14	8	8	7	6	6	6	6	5	5	5	-37.5
15	8	5	6	6	5	6	5	5	5	5	-37.5
16	8	8	7	5	5 ^a	5 ^a	5 ^a	5 ^a	5 ^a	5 ^a	-37.5
17	8	7	7	6	6	6	6	5	5	5	-37.5
18	3	3	3	3	2	2	2	1	2	2	-33.3
19	8	8	10	9	7	7	5	6	5	6	-25.0
20	5	5	5	4	4 ^a	4 ^a	4 ^a	4 ^a	4 ^a	4 ^a	-20.0
21	6	5	6	5	5	5	5	5	5 ^a	5 ^a	-16.7
22	3	6	5	5	5 ^a	5 ^a	5 ^a	5 ^a	5 ^a	5 ^a	+66.7
23	0	0	0	0	0	0	0	0	0	0	
24	0	0	0	0	0	0 ^a	0 ^a	0 ^a	0 ^a	0 ^a	
25	0	0	0	0	0	0	0	0	0	0 ^a	

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Study ID	Treatment day										Percent change
	1	2	3	4	5	6	7	8	9	10	
Upper extremities											
26	2	2	1	0	0	3	0	0	0	0	-100
27	9	6	5	2	1	0	1	1 ^a	1 ^a	1 ^a	-88.9
28	8	1	0	1	1	1 ^a	1 ^a	1 ^a	1 ^a	1 ^a	-87.5
29	5	6	4	2	2 ^a	2 ^a	2 ^a	2 ^a	2 ^a	2 ^a	-60.0
30	8	6	6	5	5	5	5	5	4	4	-50.0
31	9	6	5	6	5	7	5	5	5	5	-44.4
32	3	3	3	3	3	2	3	2	2	2	-33.3
33	9	10	7	7	6	6 ^a	6 ^a	6 ^a	6 ^a	6 ^a	-33.3
34	3	3	2	2 ^a	2 ^a	2 ^a	2 ^a	2 ^a	2 ^a	2 ^a	-33.3
35	6	6	3	5	4	4 ^a	4 ^a	4 ^a	4 ^a	4 ^a	-33.3
36	9	9	8	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	-11.1
37	8	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	8 ^a	0.0
Average pain	5.7	5.2	4.5	3.8	3.4	3.5	3.0	2.8	2.8	2.6	-53.8
(SD)	2.6	2.5	2.6	2.5	2.4	2.4	2.4	2.4	2.4	2.4	(7.4)

^a Last value carried forward