A Randomised Phase II Clinical Trial of Acupuncture Plus Standard Care Versus Standard Care Alone for Chemotherapy- Induced Peripheral Neuropathy (CIPN)

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose limiting toxicity that poses a major clinical challenge when managing patients receiving specific chemotherapy regimens (e.g. taxanes and Bortezomib). There is a growing body of literature that suggests acupuncture can lead to improvements in CIPN symptoms.

Objective: To evaluate the effectiveness of acupuncture as a management tool for CIPN by comparing use of acupuncture with standard care (Acupuncture) against standard care alone (Control), to reduce symptoms of CIPN.

Methods: This two-site clinical trial used a phase II, randomised, parallel group design to investigate the effectiveness of a 10-week course of acupuncture. Patients experiencing CIPN of ≥ Grade II (CTCAE v4.03), recording a 'Most Troublesome' CIPN symptom score of ≥ 3 using the "Measure Yourself Medical Outcome Profile" (MYMOP 2), were randomised (1:1) to 'Acupuncture' or 'Control' (note: Patients in Control were offered acupuncture off trial at the end of their study period). Primary endpoint was a ≥ 2-point improvement (success) in MYMOP2 score at week 10. 100 participants (120 randomised to allow for attrition) were required (90% power; 10% one-sided alpha) for a hypothesised improvement in success proportions from 30% to 55% using a primary analysis model with logistic regression adjusted for stratification factors and baseline MYMOP2 scores.

Results: Primary MYMOP2 outcome data at week 10 was available for 108 of 120 randomised participants. There were 36/53 (68%) successes in 'Acupuncture' compared to 18/55 (33%) in 'Control'. The adjusted success odds ratio was 4.3 (95% CI 1.9 to 9.6; 2p < 0.001; Acupuncture vs Control). Beneficial effects were also seen in the secondary outcome data, including clinicians' grading of neuropathy, EORTC QLQ-CIPN20, QLQ-C30 summary scores and patient reported pain scores.

Conclusion: A 10-week course of acupuncture resulted in measureable improvement in participants symptoms of CIPN. The results warrant further investigation within a phase III trial.

Trial Registration: Trial No. NCT02275403 on Clinicaltrials.gov, registered on 22nd October 2014.

Background

Chemotherapy induced peripheral neuropathy (CIPN) is an extremely debilitating side-effect for patients undergoing a variety of chemotherapy regimens. Symptoms include: pain, paraesthesia and loss of proprioception. All of which can have a detrimental effect on patients' quality of life by affecting gait, mobility and by limiting the ability to perform simple acts of dexterity such as buttoning a shirt or tying a shoelace. CIPN is a dose-limiting factor for efficacious chemotherapies such as taxanes, thalidomide and bortezomib, with instances of CIPN of CTCAE grade II and above [[i]] having associated risks of compromising the patient's ability to function normally and the possible reduction or even withdrawal of chemotherapy. Patients with tumours that are responding to chemotherapy may fail to report symptoms for fear of dose reduction, a break in treatment and /or the risk of recurrence. Oral pharmacological treatments for CIPN include tricyclic antidepressants, antiepileptics and opioids. These medications tend to target only the painful symptoms of CIPN, have limited efficacy and potential side-effects such as drowsiness and constipation [[ii], [iii]]. Gewandter et al investigated the efficacy of ketamine and amitriptyline cream for reducing CIPN symptoms following treatment with taxanes (n=462) [[iv]] and the results after 6 weeks showed no significant effects on CIPN scores.

Given that standard medication for CIPN is not consistently effective [[v], [vi]], it is necessary to investigate interventions that would allow patients to continue on chemotherapy regimens at appropriate doses as well as alleviate CIPN symptoms once the course of chemotherapy has concluded. Acupuncture is a non-pharmacological treatment, which has attracted attention as a clinical management tool for complex symptoms such as neuropathy. There is an increasing field of

literature illustrating the benefits of acupuncture in pain related conditions including neck pain [[vii], [viii], [ix]], tension-type headaches [[x], [xi]] and lower back pain [[xii], [xiii]].

The exact mechanism of acupuncture analgesia remains unclear with multiple studies offering possible explanations. Experimental data from functional magnetic resonance imaging (fMRI) studies have confirmed that areas of the limbic system, such as the nucleus raphe magnus, locus ceruleus and periaqueductal gray, become deactivated during acupuncture stimulation whilst regions within sensorimotor structures become activated [[xiv], [xv]]. This may be why acupuncture can reduce perception of pain and increase sensation – two problematic manifestations of peripheral neuropathy. Further research has pointed to the involvement of a variety of endogenous ligands as possible biochemical mediators in the acupuncture response including opioids (e.g. β-endorphin), neurotransmitters (e.g. GABA, glutamate), neuropeptides (e.g. oxytocin) and neurotrophins (e.g. nerve growth factor) [[xvi], [xvii]], suggesting acupuncture may cause the release of biochemicals that work directly on the nervous system. The findings from these research studies provide a possible theoretical framework to explain how and why acupuncture might work in the management of CIPN symptoms.

A service evaluation at the study site (n=18), utilising an established acupuncture protocol reported improvements in CIPN symptoms for 14 participants whose symptoms were refractory to standard management practice [[xviii]]. Additional benefits included reduction in use of analgesia and improved sleep. The current trial was designed to build on the clinical experience of an acupuncture service that has been continuous in its provision for CIPN since 2009. The primary research question being: "Does the addition of acupuncture to standard treatment reduce the level of CIPN experienced by patients during or following treatment with neurotoxic chemotherapy?"

Methods

The primary aim of the study was to investigate the efficacy of a 10-week course of acupuncture in the management of patients' most troublesome symptoms relating to CIPN measured by a self-reported outcome scale. Secondary aims included use of clinicians' functional assessments of neuropathy (graded in accordance with CTCAEv4.03) to evaluate effectiveness of acupuncture, in addition to patient reported pain related scores and quality of life assessments.

The study was set over two sites, which form part of a large tertiary cancer centre in North West of England.

Participants

Patients with breast cancer and multiple myeloma were initially eligible for randomisation if their neuropathy was of grade II or above (CTCAE v4.03). To increase recruitment the protocol was amended to widen patient eligibility to include gastrointestinal and gynaecological cancer diagnoses. The rationale for using patients from these four cancer disease groups was to allow for comparison of effect across pathologies/different drug regimens, without making the trial design too complex. Additional key inclusion criteria included a platelet count of $\geq 30 \times 10^9$/L, a neutrophil count of $\geq 0.5 \times 10^9$/L and a MYMOP2 score of their most troubling CIPN symptom of ≥ 3. The blood counts stipulated for entry to the study are lower than would be recommended in standard clinical practice. Study processes monitored the safety of these amended parameters, although this was not a documented aim of the trial.

Design

This study (Trial No. NCT02275403) was designed as a parallel group, open label, randomised phase II clinical trial. Acupuncture was added to standard care for CIPN, in patients randomised to the intervention (Acupuncture) arm. Patients received medication to manage symptoms of CIPN in accordance with local trust policy in addition to 10 weekly sessions of acupuncture from a trained acupuncturist. Patients randomised to the control Arm (Control) received only medication to manage symptoms of CIPN in accordance with local trust policy.

Eligible patients were randomised in a 1:1 ratio to either Acupuncture or Control. A stratified permuted block (size 6-10) allocation scheme was implemented by the study statistician using a bespoke computer system which had username/password control and a full audit trail. Researchers telephoned a central number whereupon trained CTU staff recorded the participant's details in the system and the allocated trial ID and arm were only revealed after commitment of these details ensuring "allocation concealment" from both researchers and CTU staff. The system also sent an automatic confirmatory e-mail to site. The following two factors were controlled for in the algorithm:

1. Cancer diagnosis (Breast Cancer vs. multiple myeloma vs. gastrointestinal cancer vs. gynaecological cancer)
2. Treatment intention (one of the below):

- Patient was currently on chemotherapy or any other cancer treatment (to end during the 10-week study or beyond)
- Patient was on chemotherapy, but this had been suspended due to neuropathy or continued but the neurotoxic agent omitted (but could restart in the 10-week study period)
- Patient was due to start their next line of chemotherapy during the 10-week study period
- Patient had finished treatment for their cancer and no further treatment is planned to start within the 10-week study period

Recruitment for the study began in April 2015 and ended in November 2018. Participants remained on the study for 10 weeks, with those allocated to Acupuncture attending the hospital for acupuncture every week. In addition, they were followed up one week after the final acupuncture session to document any adverse events. Patients in Control were only required to attend for the compulsory assessment visits at baseline, 6 and 10 weeks. Whilst not a documented aim of the study, participants were assessed at week 6 and 10 to provide some explorative data on whether a 10-week course of acupuncture is required to provide a significant level of benefit or whether 6 weeks might be sufficient (Appendix 2).

Intervention - Acupuncture

The needles used in this study were for single use, size 32 gauge (0.25mm) and 15-30mm in length. The points were punctured perpendicularly to a depth of approximately 1.0cm (0.5 inch), dependent on the patients' size, sensitivity, state of health and the particular point. The intervention was documented based on the STRICTA recommendations for reporting acupuncture trials by [[i]]. Patients received a standardised 40-minute, weekly acupuncture session. Eight core points were needled bilaterally (LV3, SP6, ST36, EXLE (x4) and BL60) for lower limb CIPN, as utilised by Abuaisha et al, Zhang et al and Schroeder et al [[ii], [iii], [iv]]. Five bilateral core points (EXUE (BAXI) (x4) and LI4) were needled for upper limb CIPN as previously employed by Bao et al [[v]] and Rajan [[vi]] who used LI4 as the distal and analgesic point. If a patient was experiencing both lower and upper limb CIPN, all points were needled giving a maximum of 26 core points. There was flexibility in cases of lymphoedema for example, for the selection of alternative points to maintain an equal dose of treatment. Acupuncturists had flexibility to add and record points for related symptoms, reflecting naturalistic current acupuncture practice within this NHS setting (see Table I).

Conversation between therapist and patient was limited to facilitation of treatment only. Although appropriate care was shown to the patient, any conversation about the effects of acupuncture was kept to the minimum and in response to questions the patients raised.

Participants randomised to Control were able to access the site's existing acupuncture service provision after the 10 week study period was over.

Outcome Measures

All outcome data was collected at baseline, 6 and 10 weeks. The primary outcome measure chosen for the study was the Patient Reported Outcome Measure (PROM): "Measure Yourself Medical Outcome Profile" (MYMOP2), see appendix 1

[[vii]]. With this validated scale, patients identified and graded their own worst symptom, thus data capture was flexible enough to address the complexity of CIPN. MYMOP2 is scored on an integer 0-6 scale with higher scores denoting greater issues. The eligibility criteria for the study required a 'Most Troublesome' CIPN symptom score of ≥ 3 at baseline, with the primary end-point being a subjective ≥2 point improvement (success). The necessary sample size required to appropriately power the study for a hypothesised improvement in success proportions from 30% to 55%, was calculated at 100 patients with a plan to randomise 120 to allow for attrition (90% power; relaxed 10% one-sided alpha).

MYMOP2 data was triangulated with assessment of functionality, which was completed by a clinician at the set time points. The clinicians used standardised questions and visual assessments of function, in accordance with CTCAE v4.03. The key secondary endpoint was functional improvement set at reduction of CIPN to grade ≤ I (CTCAE v4.03). Additionally, a broader measurement of change in symptom burden and quality of life was assessed through completion of the EORTC QLQ-C30 and associated CIPN20 module.

Patients were also asked to complete weekly diaries throughout the study period to capture daily pain scores and CIPN medication usage. These supplementary measures allowed for evaluation of the following secondary endpoints:

- Change in quality of life and symptom burden (EORTC QLQ-C30 + CIPN20 module)
- Alteration in pain related scores

Data Analyses

Both of the randomisation stratification factors were collapsed to binary factors in the analysis as some levels had low frequencies. Approximately 50% of patients in both arms had a diagnosis of breast cancer, (see Table 1 below) therefore a decision was made to stratify diagnosis as Breast cancer (yes/no). Equally approximately 40% of participants had completed treatment on study entry therefore adjustment was made for treatment complete status (no/yes) (see Table 1 below). All analyses were carried out on an intention to treat basis i.e. as randomised.

Primary Outcome (Week 10)

The analysis of the primary outcome was undertaken with a logistic regression, the focus being on the trial arm effect after adjustment for diagnosis, treatment status and the baseline MYMOP2 score. In addition, a worst-best case sensitivity analysis was conducted in which any missing outcomes in 'Acupuncture' were imputed as "failures" and those in 'Control' as "successes".

Secondary outcomes (week 10)

Physician assessed CTCAE CIPN grade ≤ 1: analogous analyses to those for the primary outcome were conducted for this binary outcome variable i.e. logistic regression with adjustment for diagnosis, treatment status and baseline grade. Again a worst-best case sensitivity analysis was conducted in which missing outcomes in 'Acupuncture' were imputed as "failures" and those in 'Control' as "successes".

EORTC QLQ-CIPN20: During the data collection period of the study, we sought and received advice from the EORTC that previously proposed subscales for this PROM (sensory, motor and autonomic), had been found unreliable and their current recommendation is to use an overall score based on the first 18 of the 20 items in the questionnaire. This maps to a 0-100 scale with lower scores being better. An analysis of covariance (ANCOVA) model was used with adjustment for baseline score, diagnosis and treatment status.

EORTC QLQ-C30 Summary Score: The Summary Score was calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale were not included). Prior to calculating the mean, symptom scales are reversed to obtain a uniform direction of all scales. The summary score was only calculated if all of the required

13 scale scores were available (using scale scores based on the completed items, provided that at least 50% of the items in that scale have been completed). This results in a 0-100 scale in which higher scores represents better overall quality of life. An analysis of covariance (ANCOVA) model was used with adjustment for baseline score, diagnosis and treatment status.

Patient reported pain scores: Participants were asked to complete diaries in which they recorded their worst pain daily on an integer 0-10 scale with landmarks (0= “no pain at all”, 10= “the most intense pain I can imagine”). Within patient weekly mean scores were calculated and the week 1 means were taken as baseline as there was no true baseline i.e. no pre-randomisation diary. An analysis of covariance (ANCOVA) model was used with adjustment for baseline score, diagnosis and treatment status.

Longitudinal models: Outcome data were also recorded at week 6 and longitudinal models with both week 6 and week 10 outcomes were fitted in further exploratory analyses. These models again adjusted for baseline value, diagnosis and treatment status. In addition, they included the week effect and the full interaction of week with each of the other model terms. With this approach we were able to assess differences in the trial arm effect between weeks 6 and 10.

Results

120 patients were randomised with 61 allocated to Acupuncture and 59 allocated to Control. Diagnostic groups of the participants are as follows: breast 61 (51%), multiple myeloma 9 (8%), GI 48 (40%), gynaecological 2 (2%). MYMOP2 score for most troubling CIPN symptom at baseline: 3-4 33 (28%), 5-6 87 (73%). CTCAE CIPN at baseline; grade II 103 (86%), grade III 17 (14%). Baseline characteristics were balanced between arms.

Descriptors used for ‘Most Troublesome Symptom’ on baseline MYMOP2: As anticipated, symptom burden and impact of CIPN was expressed in a variety of different ways. The descriptors used by participants are laid out in Table II below:

Primary Outcome (Week 10)

Data was available for 108 of 120 randomised participants with 36/53 (68%) successes in Acupuncture compared to 18/55 (33%) in Control. The adjusted success odds ratio from the logistic regression model was 4.3 (95% CI 1.9 to 9.6; 2p < 0.001; A vs C) after adjustment. The worst-best case sensitivity analysis, using the pessimistic assumptions described above, showed 36/61 (59%) successes in Acupuncture compared to 22/59 (37%) in Control and the adjusted success odds ratio was 2.4 (95% CI 1.1 to 5.0; 2p = 0.02; A vs C). Therefore, the substantive finding of benefit of the intervention for the primary outcome is unaffected by missing data.

Secondary outcomes (week 10)

Physician assessed CTCAE CIPN grade $\leq$ 1: Data was available for 109 participants with 27/53 (51%) successes in Acupuncture compared to 4/56 (7%) in Control. The adjusted success odds ratio from a logistic regression model was 13.1 (95% CI 4.1 to 42; 2p < 0.001; A vs B). Using the worst-best case sensitivity analysis, the 7 missing outcomes in Acupuncture were imputed as "failures" and the 3 in Control as "successes". With these pessimistic assumptions there were 27/61 (44%) successes in Acupuncture compared to 7/59 (12%) in Control and the adjusted success odds ratio was 5.9 (95% CI 2.3 to 15; 2p < 0.001; A vs C). The substantive finding of benefit of the intervention for this secondary outcome is therefore unaffected by missing data.

EORTC QLQ-CIPN20: Data was available for 107 participants; (A =53 vs B =54). In an analysis of covariance (ANCOVA) model the adjusted mean difference in week 10 outcome values using overall score from the first 18 questions was estimated to be -11.7 (95% CI -17.3 to -6.1; 2p < 0.001; A vs C).

EORTC QLQ-C30 Summary Score: Data was available for 103 participants and in an analysis of covariance (ANCOVA) model the adjusted mean difference in week 10 outcome values was estimated to be 9.5 (95% CI 5.0 to 14.0; 2p < 0.001; A vs C).

Patient reported pain scores: Data was available for 97 participants and the adjusted mean difference in week 10 outcome values was estimated to be -1.45 (95% CI -2.25 to -0.65; 2p = 0.001; A vs C).

Longitudinal models: Week 6 trial arm effects were also statistically significant but tended to be somewhat smaller in magnitude than the week 10 effects though not statistically significantly so.

Safety Data

Blood parameters for eligibility into the study were reduced compared to standard clinical practice for both platelets and neutrophils. However, no serious adverse events and only 16 acupuncture related adverse events (11 pts), were documented (tingling, ache/pain, bruising & 'spotting' of blood). Of these 16, none required action and 12 (75%) were reported as mild.

Discussion

In recent years, acupuncture has been identified as a possible management tool for CIPN [[i], [ii]]. Whilst data so far would suggest acupuncture may be beneficial, because of the complexity of symptom load it is a challenge to validate efficacy in all presentations (e.g. numbness and pain). In order to provide preliminary data encompassing all presentation of symptoms, the primary outcome data from this study was from the patient reported measure; MYMOP2. Patients identified their own symptoms, described each symptom in a way that was meaningful to them and scored the symptom. 'Success' was set as a $\geq$ 2 point improvement in symptom score, with this being accepted as a clinically significant reduction in symptom burden. The results showed a highly significant level of benefit, with double the number of patients in Acupuncture showing a 'success' at week 10 compared to Control. Secondary outcome data in the form of clinician assessment was collected to triangulate with the patient reported primary outcome measure. As with the primary outcome data, the results showed a significantly higher level of benefit for participants in the Acupuncture arm than in the Control. Consequently, the results from the clinician rated outcome, go some way to validating the clinical significance of a 2 point reduction in MYMOP2 scores. Additional secondary outcome data from the EORTC-QLQ-C30 and associated CIPN-20 was collected in order to further triangulate the data, as it is recognised that the impact of CIPN is notoriously difficult to capture in one measure [1]. These measures also indicated a high level of benefit from adding acupuncture into routine care for patients with CIPN, thus strongly suggesting that acupuncture improved quality of life and reduced the level of reported pain in this patient cohort.

In order to clarify the length of treatment required to ensure benefit from acupuncture, longitudinal models were used to compare effects of the acupuncture at week six and ten. Whilst significant benefit was seen at both time points, the magnitude was less at week six. It will therefore be appropriate to undertake further exploratory analyses to better understand whether there are certain sub-sets of patients, who will gain the same level of benefit with a shorter course of acupuncture, such as those on certain chemotherapy protocols, or with a specific symptom burden, for example: numbness vs pain.

Limitations

The patient reported primary outcome measure was key to the study design as it ensured that the data captured by the study was patient specific for all participants However, MYMOP2 has a limitation as an outcome measure as it is subjective rather than objective. Reported benefit to participants was part-validated within the study by the clinician's grading of motor skills but, due to funding limitations, no completely objective outcome measure was included within the

study design. For any future study, it is recommended that data be triangulated with an objective outcome such as nerve conduction studies.

A related issue concerns the decision not to incorporate sham acupuncture as a control within the study design. This decision was based an ethical rationale. A proportion of the study participants were still undergoing chemotherapy for their underlying cancer diagnosis. It was therefore decided that it would be unethical to provide sham acupuncture to patients who were potentially at higher risk of bleeding and infection due to low blood counts only to provide a higher degree of control to the study design. It is recommended that this decision would require review in any future study design.

Clinical Implications and Future Work

Data from this study can be used to inform the treatment options available to patients with debilitating and painful symptoms of CIPN. The results clearly suggest clinical benefits from acupuncture and will add to the growing evidence base of this non-pharmacological treatment as a clinical management tool. The hope is that this study will help increase patients' and clinicians' confidence to actively consider acupuncture as a means of reducing the symptom burden associated with CIPN. The study goal was to maintain physical functioning / mobility, reduce symptoms relating to sensation (including pain and dexterity), enhance wellbeing and when appropriate, facilitate ongoing treatment with drugs designed to improve mortality from cancer.

The data from this study has provided evidence, which healthcare professionals can use to inform the advice offered in primary, secondary and tertiary care to this cohort of patients regarding the possible use of acupuncture. However, the design of the study was such that only short-term benefit (10 weeks) was evidenced. For assessment of longer-term value, a defined follow-up period would be required.

To address some of the issues highlighted by this study, it is proposed that a larger multicentre study be undertaken. It is suggested that the design incorporates maintenance protocols to monitor continuation of effect and identification of factors, which would provide clarity regarding whether patients require a 6 or a 10 week protocol. A full cost-benefit analysis is also proposed to strengthen the case for the adoption of acupuncture as a patient care pathway within the NHS.

Conclusion

In summary, the immediate impact of the study was the corroboration of results from a previous service evaluation confirming that this cohort of patients benefited from the acupuncture they received. However, sustainability of any improvements in symptoms requires further investigation.

Long-term, this study is the initial phase of a larger programme of work in which the data collected will be used to inform the design of a large multicentre trial.

List Of Abbreviations

ANCOVA – Analysis of Co-Variance

CIPN – Chemotherapy Induced Peripheral Neuropathy

CTCAE – Common Terminology Criteria for Adverse Events

EORTC QLQ C30 – European Organisation for Research & Treatment of Cancer Quality of Life Questionnaire

fMRI – functional Magnetic Resonance Imaging

MYMOP – Measure Yourself Medical Outcome Profile

PROM – Patient Reported Outcome Measure

STRICTA – Standards for Reporting Interventions in Clinical Trials of Acupuncture

Declarations

***Ethics approval and consent to participate*:**

Ethical approval was received from the National Research Ethics Service Committee North West, Greater Manchester East on 19th February 2015 (Reference: 14/NW/1492).

Written consent was obtained from all participants.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions

JS - Design, Principal Investigator, significant contribution to drafting manuscript

MAS – Study co-ordinator, contribution to manuscript

PM - Design, providing interventions, contribution to manuscript

WDR - Design, data analysis, contribution to manuscript

VM – Principal investigator, manuscript review

AMW – Chief investigator, manuscript over-sight

All authors read and approved the manuscript

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Tables

Table I: Core acupuncture points

	Point Location	Location/description
CIPN Feet	LV 3	On the dorsum of the foot between the 1st and 2nd metatarsals
	SP6	Above the tip of the medial malleolus and posterior to the medial boarder of the tibia
	ST36	Below the knee in the anterior boarder of the tibia
	EXLE (x4)	In the webs between the bases of the toes
	BL60	Posterior to the tip of the lateral malleolus, mid-way between this and the Achilles tendon
CIPN Hands	EXUE (BAXI) (x4)	In the webs between the bases of fingers
	LI4	On the dorsum of the hand between the first and second metacarpal bones
Extras	Additional points to core points are allowed as appropriate to address additional symptoms (e.g. fatigue, anxiety or sexual dysfunction). These must be documented.	

Table II: Baseline Characteristics

Baseline characteristics		**Control (n = 59)**	**Acupuncture (n = 61)**
Age*		60 (29 to 79)	61 (37 to 76)
MYMOP2. Symptom 1 (S1)	3 or 4**5 or 6**	19 (32%)**40 (68%)**	14 (23%)**47 (77%)**
CTCAE-CIPN grade	23	48 (81%)11 (19%)	55 (90%)6 (10%)
EORTC-CIPN20*		**41.2 (9.3 to 90.7)**	**50.0 (14.8 to 88.9)**
Diagnosis	BreastMultiple MyelomaGastrointestinalGynaecological	29 (49%)3 (5%)25 (42%)2 (3%)	32 (52%)6 (10%)23 (38%)0 (0%)
Cancer treatment^	On treatmentSuspendedDue to startComplete	34 (58%)2 (3%)0 (0%)23 (39%)	33 (54%)0 (0%)3 (5%)25 (41%)

* Median (range)

^ See methods for a fuller description of the treatment categories

Table III: 'Most Troublesome Symptom' on baseline MYMOP2

Descriptor	Number	Comments
Numbness (+cold)	**36 (+2)**	Feet, toes, fingers, face
Pain (+burning)	**27 (+3)**	Feet, hands, fingers, thumbs
Tingling /pins & needles	**22**	Fingers, numb, feet, hands, toes, heat
Mobility	**14**	Lumpy, unsteady, 'gravel', numb
Dexterity (+weakness)	**5 (+5)**	Buttons, jars, gripping
Cramps	**2**	Feet
Body Parts	**4**	Feet, fingers, hands
NOTE: Often multiple issues 'packed' into one symptom		

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- APPENDICES.docx
- CONSORT2010Checklist150920.doc