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Chemotherapy induced peripheral neuropathy: the modified total neuropathy score in clinical practice.

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Chemotherapy Induced Peripheral Neuropathy: The modified Total Neuropathy Score in clinical practice

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Abstract

Background: Chemotherapy induced peripheral neuropathy (CIPN) is a common, potentially reversible side-effect of some chemotherapeutic agents. CIPN is associated with decreased balance, function and quality of life (QoL). This association has to date been under-investigated.

Aims:

To profile patients presenting with CIPN using the modified Total Neuropathy Score (mTNS) in this cross-sectional study.

To examine the relationship between CIPN (measured by mTNS) and indices of balance, quality of life (QoL) and function

Methods: Patients receiving neurotoxic chemotherapy regimens were identified using hospital databases. Those who did not have a pre-existing neuropathy were invited to complete mTNS, berg balance scale (BBS), timed up and go (TUG), and FACT-G QoL questionnaire. mTNS scores were profiled and also correlated with BBS, TUG and FACT-G using Spearmans correlation coefficient.

Results: A total of 29 patients undergoing neurotoxic chemotherapy regimens were tested. The patients mTNS scores ranged between 1 and 12 (median = 5), indicating that all patients had clinical evidence of neuropathy on mTNS. No significant correlations were found between mTNS and BERG (r = -.29), TUG (r = .14), or FACT-G (r = 0.05).

Conclusions: This study found a high prevalence of CIPN in patients treated with neurotoxic chemotherapy regimens. The mTNS provided a clinically applicable, sensitive screening tool for CIPN which could prove useful in clinical practice. mTNS did not correlate with BBS, TUG or FACT-G in this sample, possibly due to relatively mild levels of CIPN and consequent subtle impairments which were not adequately captured by gross functional assessments.

Keywords: Peripheral Neuropathy, Neurotoxic, Physiotherapy, Chemotherapy, Function

Introduction

Peripheral neuropathy is a common, potentially reversible side-effect of some chemotherapeutic agents. Reversibility is dependant on early identification and modification of chemotherapy. Currently in clinical practice, general common toxicity scales are used to asses Chemotherapy Induced Peripheral Neuropathy (CIPN). However, these are heavily reliant on the patients subjective reports, and can be insensitive to change [1]. Studies suggest the incidence and sequalae of CIPN are poorly understood [2, 3] with more comprehensive investigation required [2, 4].

Peripheral neuropathy is associated with decreased balance, function and quality of life (QoL) [5]. Despite much research in the area of diabetic neuropathy and function, the association between CIPN and function has to date been under-investigated. Also, physiotherapy assessment and intervention in CIPN has not been extensively researched.

Aims:

1) To profile patients presenting with CIPN using the modified Total Neuropathy Score (mTNS) in this cross-sectional study [6].

2) To examine the relationship between CIPN (as measured by mTNS) and indices of balance, QoL and Function

Methods

Patient Recruitment

Included in the study were patients aged between 18 and 75 years of age who had completed ≥3 cycles of any of the following neurotoxic chemotherapy regimens: paclitaxel or docetaxel from the taxane class; vincristine or vinorelbine from the vinca alkaloid class; cisplatin, carboplatin or oxaliplatin from the platinum compounds class. Peripheral neuropathy can arise from metabolic, vascular, immunological or hereditary causes. For this reason any patients with previously diagnosed peripheral neuropathy were excluded from taking part in the study [7]. Other exclusion criteria

included any pre-existing neurological disorders, known diabetes, alcoholism, HIV, peripheral vascular disease, B12 deficiency, or inability to give informed consent.

Patients were identified using the Beaumont Hospital pharmacy chemotherapy order lists. Once patients on neurotoxic regimens had been identified from these lists, their medical charts were screened by the principal investigator (lead author) for inclusion/exclusion criteria. Information leaflets were posted to a total of 37 patients who met these criteria. On arrival to the Day Oncology Ward for their chemotherapy treatment, these patients were approached and invited to participate in the study. A total of 29 patients agreed to take part. The patients gave written informed consent and were tested while awaiting their chemotherapy treatment to arrive from the pharmacy department. Patient assessments ranged in length from 20 – 30 minutes and were completed within a seven week period between July and August 2011.

Ethical approval was sought from the Ethics Medical Research Committee at Beaumont Hospital and was granted on 24th June 2011.

Patient Measurement

Instruments Employed

Modified Total Neuropathy Score (mTNS)

The Total Neuropathy Score (TNS) was first developed in 1994 [8]. Although it performed well in CIPN patients, it included nerve conduction studies, making it unsuitable for routine clinical use. Various authors have described versions of the TNS since then. In 2006 the mTNS, a version which did not include nerve conduction studies was first used [5]. This correlated well with the original TNS, indicating that nerve conduction studies did not add value to the test, and providing a clinically feasible alternative [5]. The mTNS is scored 0-24, with each neuropathy item being rated 0 to 4. A higher total score indicates a more severe neuropathy.

When the first version of the TNS was developed in 1994 (a 0-21 scoring system), results scores were divided into 3 levels: 0-7, 8-14, and 15-21 for mild, moderate, and

severe neuropathy [8]. Applying this same system to the modern mTNS, the 3 severity levels are: 0-8, 9-16, and 17-24.

As guidelines for using the grading tools for peripheral neuropathy are poorly described [7], standardised clinical testing [9] was used for the following items of the mTNS: vibration sense (using a 128Hz tuning fork), pin level test (using a neurotip™ - Owen Mumford Ltd), and reflexes.

Timed up and Go (TUG)

The TUG has been shown to have high levels of validity [10] and reliability [11]. The standard protocol was used in completing the TUG score. Following a practice trial, each patient was timed to get up from the chair, walk three metres at their usual pace, turn around and walk back to sit down in the chair again. A chair of standard height, 42", was used each time for the test.

Berg Balance Scale (BBS)

The standard instructions were used in completing the BBS. A step of standard height, 7", was used each time for item 12 of the scale. The BBS is marked out of a total of fifty-six marks. A lower score indicates worse balance, with low falls risk being classified as 41-56, medium falls risk 21-40, and high falls risk 0-20. The BBS was chosen for its ease of use and because it has been shown to be a valid and reliable measure of balance [12].

Functional Assessment of Cancer Therapy-General (FACT-G)

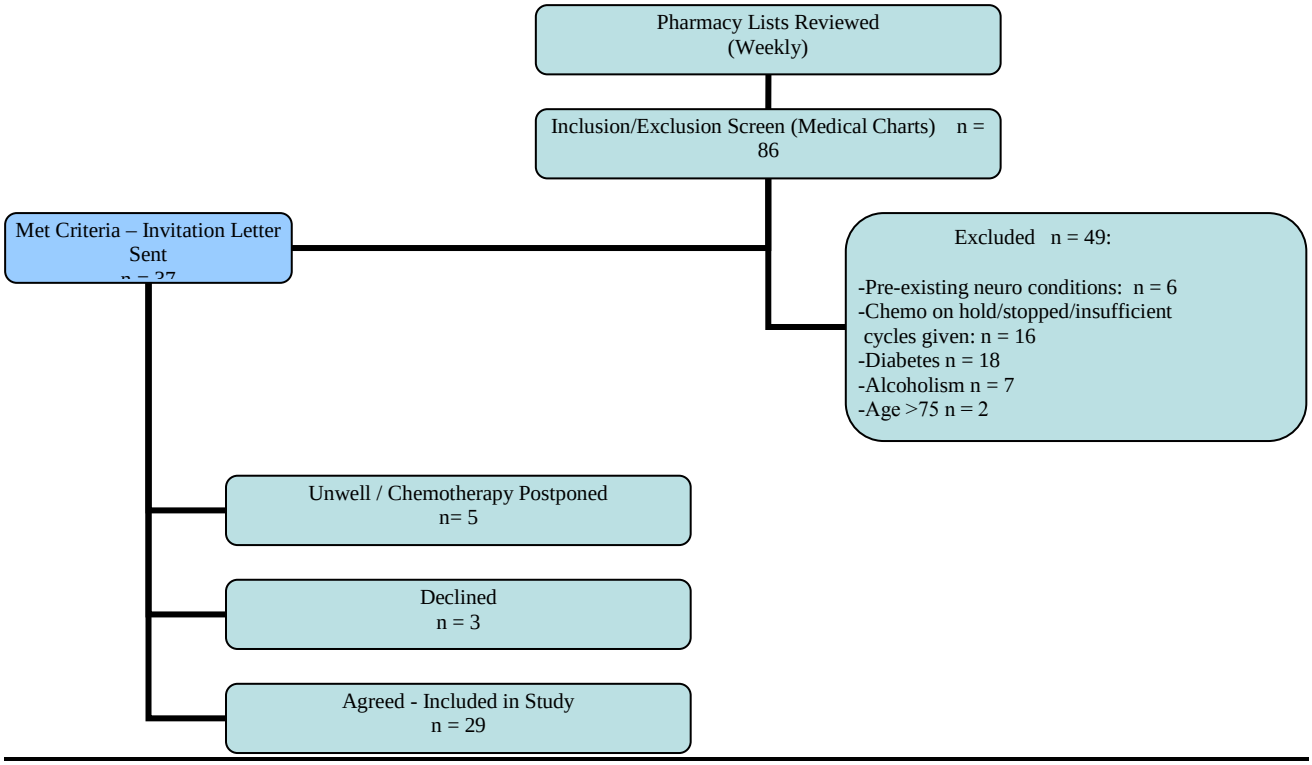
The FACT-G was originally developed exclusively for cancer patients but has now become widely used for many chronic illnesses [13]. It was chosen for this study due to its well-established reliability and validity [14]. It is a 27 item scale, with each item rated from 0 – 4, with 4 being "very much" and 0 being "not at all". Each section was scored according to FACIT criteria and a mark was given out of a total of 108.

Data Analysis

Statistical Package for the Social Sciences (IBM) was used to calculate Spearman's correlation in order to compare mTNS scores with scores for BBS, TUG, and FACT-G. Descriptive statistics and graphs used to profile mTNS were completed in Microsoft Excel and Graphpad Prism.

Results

Figure 1 below represents the recruitment process for this study.



A total of 29 patients completed testing. Patients ranged in age from 31 to 74, with a median age of 62 years. The median number of chemotherapy cycles completed was 4 (range 3-6).

Four patients had previously received lines of neurotoxic chemotherapy. However these were all completed at least two years prior to commencement of their current regimen.

Table 1 Patient characteristics and chemotherapy type

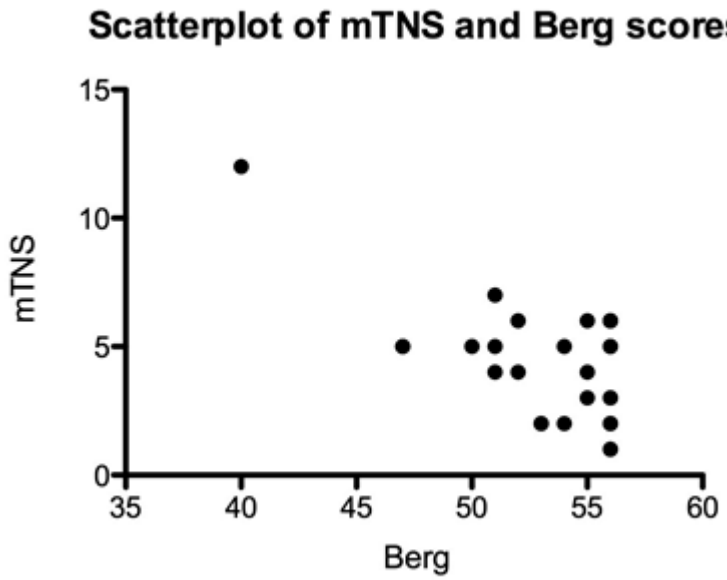
Chemotherapy Class	**Taxanes (n=9)**	**Platinums (n=13)**	**Taxane & Platinum (n=4)**	**Vinca-Alkaloid (n=3)**
Median Age	47 (range 31-63)	65 (range 44-74)	65.5 (range 47-72)	74 (range 47-74)
Male: Female	1:8	8:5	0:4	0:3
Type of Cancer	7 Primary Breast 1 Metastatic Breast 1 Metastatic Testicular	3 Primary Colorectal 2 Metastatic Colorectal 4 Primary Lung 2 Primary Oesophogeal 1 Metastatic Breast 1 Primary Gastric	4 Primary Ovarian	2 Non-Hodgkins lymphoma 1 Metastatic Breast
Median no. of cycles	3 (range 3-6)	4 (range3-6)	3.5 (range 3-5)	3 (range 3-3)
Median mTNS score	5 (range 1-6)	4 (range 1-6)	5.5 (range 4-7)	5 (range 2-12)

Median mTNS score was 5, with a range of 1-12. Using severity levels described above, 28 patients would be classified as having a mild neuropathy, and 1 as moderate. Notably no patient had an mTNS score of zero.

There were no significant correlations found between mTNS and BERG ($r = -.29$, $p = .13$), TUG ($r = .14$, $p = .48$), or FACT-G ($r = 0.05$, $p = .8$). Figures 2 to 4 below show the relationship between mTNS and BERG, TUG and FACT –G scores respectively

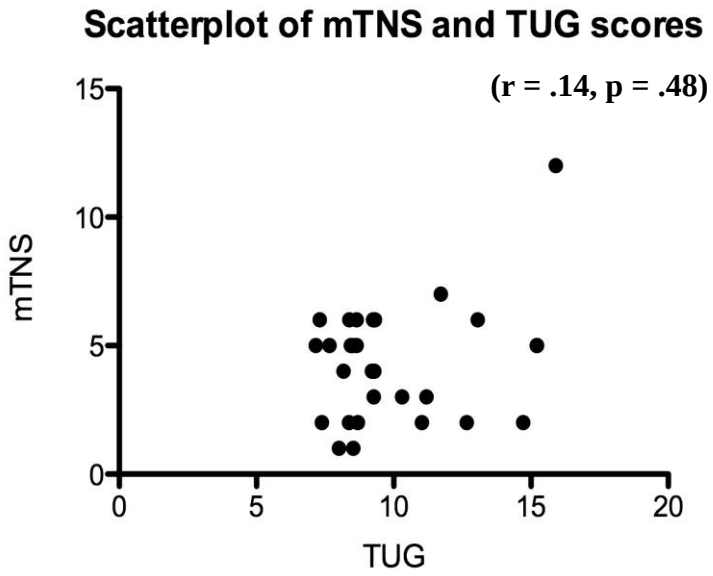
A BBS score below 35 is accepted as indicating a 100% risk of falls, while a score of <45 indicates balance impairment, and a score of <40 indicates a need for a balance retraining program [15]. In the current sample, the median BBS score was 55 (range 40-56). No patient scored below 40, and only one patient scored below 45, indicating that only one patient in this sample showed signs of balance impairment. This patient also had the highest mTNS score (12) and TUG score (15.91).

Fig. 2 Scatter plot illustrating association between mTNS and BBS scores



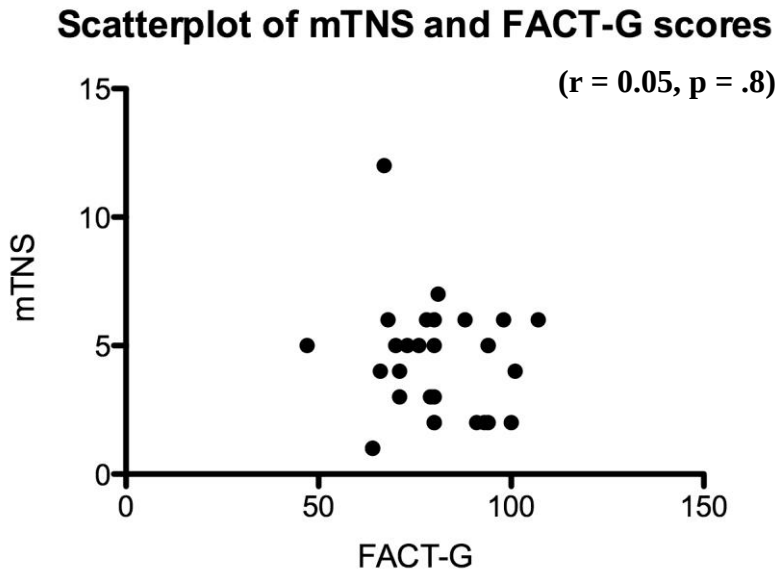
There are established normal values for TUG: 0-10 seconds: independent/normal, 10-20 seconds: independent with basic mobility, transfers and stairs, 20-29 seconds: variance in gait speed, balance and functional capacity, and ≥30 seconds: need help with mobility, transfers & stairs, further assessment warranted [16]. According to our data, 19 patients had scores <10 seconds, and 10 patients had scores between 10-20 seconds, indicating that function in this cohort was not severely impaired.

Fig. 3 Scatterplot illustrating association between mTNS and TUG scores



Normative data exists for the USA for FACT-G. The mean normal total score for the FACT-G amongst a sample of 1075 men and women was 80.1 [14]. The mean in the current sample was 80.5, only slightly higher than that of a normal sample. Median score was 80, with a range of 41-107.

Fig. 4 Scatterplot illustrating association between mTNS and FACT-G scores



Discussion

This study has provided a profile of CIPN in a cohort of patients treated with neurotoxic chemotherapy regimens. It is of interest that all patients had clinical evidence of CIPN on mTNS, with a majority having mild levels of neuropathy.

This sample included patients up to 74 years of age. Although advanced age is a risk factor for neuropathy, these patients were screened for such underlying neuropathy. It has previously been shown that advanced age is not associated with greater risk of developing neuropathy as a result of neurotoxic agents, or with more severe CIPN should it develop [17]

There were no correlations between mTNS scores and BERG, TUG, or FACT-G. This was in contrast with the findings of a study in 2006, which found that the mTNS correlated moderately with measures of balance, function, and QoL, including the TUG [5]. This study was exclusive to breast cancer patients on taxanes. There were 9 patients on the current study on taxane regimens, 8 of whom had breast cancer. Their mTNS scores did not correlate with the TUG (r = -.28, p = .46), BERG (r=.09, p = .83) or FACT-G (r = .04, p = .91).

Although this study was sufficiently powered, it would be interesting to look at these relationships in a larger sample in order to facilitate statistical analysis of subgroups by chemotherapy regimen. Notably however, the abovementioned study [5] had a sample size of only 20. It may be the case that because both mTNS scores and functional measures showed only mild impairment, this level of impairment was not sufficient enough to correlate. It would be interesting to look at the changes in mTNS levels and functional outcome measures over the course of chemotherapy and beyond. Notably, most of these patients were reviewed in the early stages of their chemotherapy treatment.

The functional measures used were chosen because of validity, frequent use in the clinical setting, and ease of use. However, it may be that these global tests of balance and function may not be specific enough to detect the functional changes associated with CIPN. These measures are used widely in ageing populations, and thus may not be sensitive enough to detect small changes in function in an otherwise healthy and relatively young CIPN population. It is likely that such a cohort may compensate well for a sensory deficit, and thus it will not be picked up by global functional measures. Future studies could look at measures such as postural sway patterns on a force plate or gait variability in a movement laboratory. This would provide more sensitive objective detection of smaller changes in gait and balance and capture changes before they would be detected by functional outcome measures such as BBS and TUG.

The mTNS proved a sensitive CIPN screening tool, in that it detected even mild levels of CIPN, and displayed no floor effect. Although clearly a more objective and sensitive tool than global screening tools such as the National Cancer Institute Common Toxicity Criteria (NCI-CTC), it is unlikely that the mTNS will be used routinely as an alternative to these tools in the clinical setting in light of time and training issues. It is however a useful tool for research in this area, and for physiotherapy assessment, and could be recommended for clinical use in these two areas.

Due to a lack of prospective follow-up studies in this area, there are currently no data available as to what score on the mTNS can be considered clinically significant, or what increase in mTNS scores would be considered a minimal detectable change in

scores over time from baseline to various time points during and after chemotherapy treatment. Prospective follow-up studies with multiple time points would give information on the natural history of CIPN and inform the interpretation of mTNS scores with respect to sensitivity, specificity, and minimal detectable change. This information would make the mTNS more clinically relevant, and could aid in the decision for dose reduction or treatment cessation. A study in 2007 which looked at patients experience of CIPN, found that half of the participants in their study (n=28) had not been informed of the possibility of developing CIPN as a side-effect of treatment and therefore many of the patients were unaware that they had a neuropathy [18]. Currently screening for CIPN relies heavily on subjective descriptions by the patient. Patients can be hesitant in reporting any symptoms in fear that their chemotherapy dose will be reduced, compromising their treatment [19]. In light of this, it may be that neuropathy is currently under-reported and therefore under-investigated in the clinical setting.

There is a dearth of research into CIPN itself, the use of comprehensive and clinically relevant screening tools such as the mTNS, and the relationships between CIPN and function. This study has added to the research in these areas. Future research is needed specifically to comprehensively validate the mTNS in this population, and to examine longitudinally the relationships between CIPN and function and quality of life. There is also work to be done in establishing normal values and minimally detectable change for the mTNS.

Conclusions

This study provided a profile of CIPN in patients being treated with neurotoxic chemotherapy. All patients had clinical evidence of neuropathy on mTNS, indicating a high prevalence of CIPN in patients with no other risk factors for peripheral neuropathy, who are treated with a neurotoxic chemotherapy regimen. The mTNS provided a clinically applicable, sensitive screening tool for CIPN. mTNS did not correlate with BERG, TUG or FACT-G in this sample. This may have been due to relatively mild levels of CIPN and functional impairments. Future studies should validate the mTNS, and prospective follow-up studies with multiple time points are warranted to investigate the natural history of CIPN and inform the interpretation of

mTNS scores with respect to sensitivity, specificity, and minimal detectable change. Studies examining the relationships between CIPN and function should use more sensitive measures to detect subtle changes in balance and gait over the course of chemotherapy treatment.

Conflict of Interest: None

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