JAMA Internal Medicine | Original Investigation

Preventive Effect of Neuromuscular Training on Chemotherapy-Induced Neuropathy
A Randomized Clinical Trial

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IMPORTANCE Chemotherapy-induced peripheral neuropathy (CIPN) is a highly prevalent and clinically relevant adverse effect of chemotherapy, negatively impacting patient quality of life. The lack of effective preventive or therapeutic options regarding CIPN often requires changes in cancer therapy, potentially resulting in reduced survival.

OBJECTIVE To determine whether sensorimotor training (SMT) and whole-body vibration (WBV) training reduce symptoms and decrease the onset of CIPN.

DESIGN, SETTING, AND PARTICIPANTS This prospective multicenter randomized clinical trial (STOP) followed up patients over 5 years at 4 centers in or near Cologne, Germany. Patients undergoing treatment with oxaliplatin or vinca alkaloids were recruited. Participants were recruited from May 2014 to November 2020. Data were last analyzed in June 2021.

INTERVENTIONS Participants in the intervention groups performed supervised SMT or WBV training sessions twice a week, each lasting approximately 15 to 30 minutes, concomitant to medical therapy.

MAIN OUTCOMES AND MEASURES The primary end point was the incidence of CIPN. Secondary end points included subjective neuropathy symptoms, balance control, physical activity levels, quality of life, and clinical outcome. For cross-stratum evaluations, the Mantel-Haenszel test (MH) was used, and within individual strata, Fisher exact test was used for analysis.

RESULTS A total of 1605 patients were screened, and 1196 patients did not meet all inclusion criteria, with 251 further excluded or declining participation. A total of 158 patients (mean [SD] age, 49.1 [18.0-82.0] years; 93 [58.9%] male) were randomized into 1 of 3 groups: 55 (34.8%) in SMT, 53 (33.5%) in WBV, and 50 (31.6%) in treatment as usual (TAU). The incidence of CIPN in participants was significantly lower in both intervention groups compared to the control group (TAU): (SMT, 12 of 40 [30.0%; 95% CI, 17.9%-42.1%] and WBV, 14 of 34 [41.2%; 95% CI, 27.9%-54.5%] vs TAU, 24 of 34 [70.6%; 95% CI, 58.0%-83.2%]; $P = .002$ for intention to treat–MH). Patients receiving vinca alkaloids and performing SMT benefited the most. Results were more pronounced in a per-protocol analysis (>75% participation in the intervention) (SMT, 8 of 28 [28.6%; 95% CI, 16.6%-40.5%] and WBV, 9 of 24 [37.5%; 95% CI, 24.4%-50.5%] vs TAU, 22 of 30 [73.3%; 95% CI, 61.6%-85.6%]). Improvements in favor of SMT compared to TAU were found for balance control bipedal with eyes open; bipedal with eyes closed; monopedal, vibration sensitivity, sense of touch, lower leg strength, pain reduction, burning sensation, chemotherapy dose reductions, and mortality.

CONCLUSION AND RELEVANCE This randomized clinical trial provides initial evidence that neuromuscular training decreases the onset of CIPN.

TRIAL REGISTRATION German Clinical Trials Register: DRKS00006088

Visual Abstract
Invited Commentary page 1053
Supplemental content

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JAMA Intern Med. 2024;184(9):1046-1053. doi:10.1001/jamainternmed.2024.2354
Published online July 1, 2024.

Chemotherapy-induced peripheral neuropathy (CIPN) is a highly prevalent and clinically relevant adverse effect (AE) of chemotherapy. In particular, oxaliplatin and vinca alkaloids induce acute CIPN with incidences of 70% to 90% and chronic CIPN with incidences of 50%.[1,2] CIPN includes loss of sensation, tingling, dysesthesia, reduced or absent Achilles tendon reflexes,[3] pain, and loss of balance leading to unstable gait and falling.[4] These symptoms diminish activities of daily living, reduce patients' quality of life, and compromise survival due to dose reduction, treatment delay, or discontinuation of therapy.[5] Pharmacological approaches lack a sound rationale and are limited to recommendations targeting neuropathic pain (duloxetine).[6] Recent systematic reviews revealed no conclusive evidence of efficacy for any medical treatments for CIPN.[1,7]

In contrast, positive results have been achieved with specific exercise interventions due to their wide range of prorege nerative effects, including expression of growth factors,[8,9] altered blood perfusion, and enhanced mechanoreceptor sensitivity.[10] Nine high-quality randomized clinical trials (RCTs) (Physiotherapy Evidence Database [PEDro] score, 6-8; ie, good clinical trial methodology rating) showed beneficial effects on postural control, neuropathic symptoms, and quality of life.[11] Neuromuscular stimulating interventions, such as sensorimotor training (SMT) or whole-body vibration (WBV) training, seem especially beneficial because they address both sensory and motor symptoms.[12] SMT is characterized by functional adaptations and regeneration of the neuromuscular system, resulting in fewer falls and injuries and increasing mobility.[13] WBV is thought to improve gait stability, isometric strength, postural sway, and neuropathic pain, and prevent falls.[12,14] Based on these findings, our a priori hypothesis was that SMT and WBV can reduce symptoms and decrease CIPN onset.

Key Points

Question Does neuromuscular training decrease the onset of chemotherapy-induced peripheral neuropathy (CIPN)?

Findings In this randomized clinical trial of 158 patients undergoing chemotherapy, neuromuscular training decreased the onset of CIPN by 50% to 70%, depending on the neurotoxic agent used. The prevention of neurological deficits enhances patient quality of life and may also impact clinical outcomes and overall survival by improving tolerability and adherence to oncological treatment.

Meaning These findings represent a substantial advancement in the management of CIPN and supportive care in oncology.

Methods

We conducted the prospective multicenter 3-arm preventive STOP RCT among patients with cancer receiving chemotherapy (oxaliplatin or vinca alkaloids). Patients were assigned to SMT, WBV, or treatment as usual (TAU) in a 1:1:1 ratio (**Figure 1**; see Supplement 1 for the trial protocol). The study was approved by the ethics committees of the University Hospital Cologne and the German Sport University Cologne. All patients gave written informed consent for treatment and prospective data collection in accordance with the Declaration of Helsinki.[15] We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Participants

Patients were recruited from 4 participating centers: University Hospital Cologne; Saint Antonius Hospital Eschweiler; Joint Practice for Oncology and Hematology, Sachsenring, Cologne; and Joint Practice for Internal Oncology and Haematology, Cologne. Patients were included if they were 18 years or older, had the mental and physical ability to provide signed informed consent, and were receiving first-line chemotherapy containing oxaliplatin or a vinca alkaloid. Exclusion criteria were preexisting neuropathy of other causes, previous therapies, contraindications for WBV (eg, unstable bone metastases, acute leg thrombosis, hip replacement), myocardial infarction, angina pectoris, or heart disease (New York Heart Association functional classification III or IV; ie, marked limitation or inability to complete physical activity) within the past 6 months. All patients received standard medical care. Intervention groups carried out the training intervention in addition to standard care.

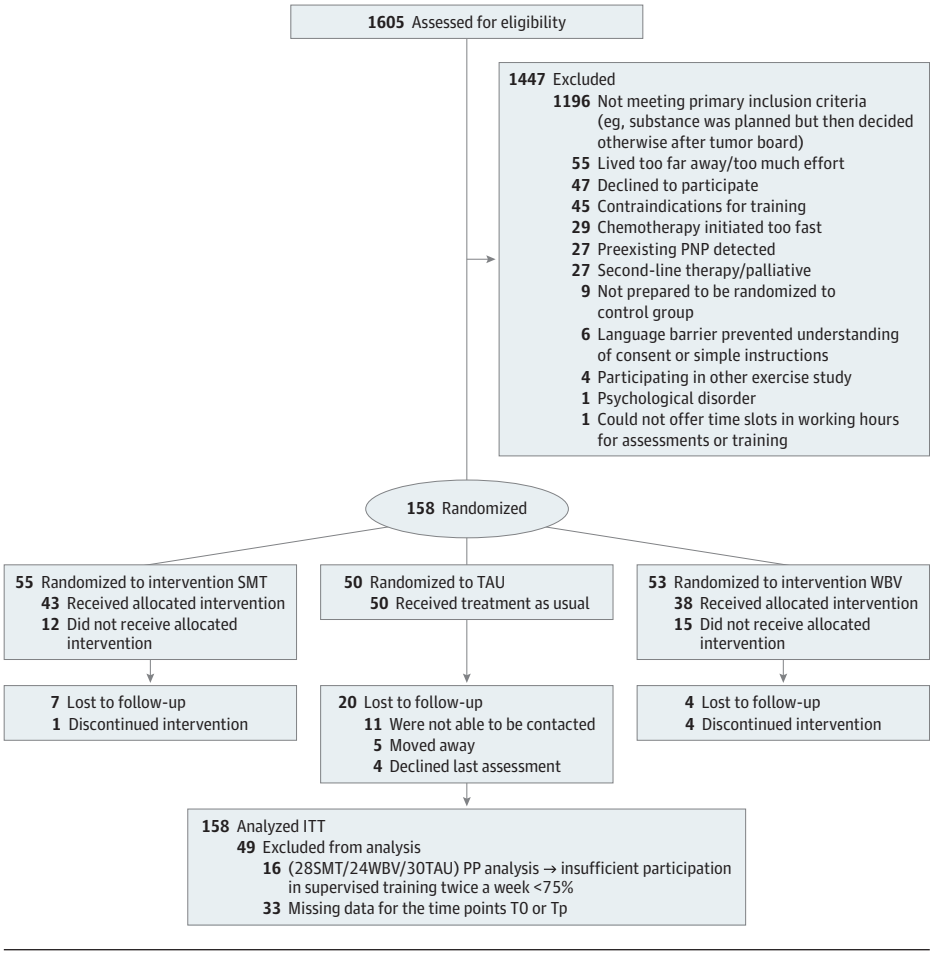
Study Design

Patients were randomized externally via the computer software RITA (Randomisation in Treatment Arms) in a 1:1:1 ratio, stratified according to chemotherapy (oxaliplatin or vinca alkaloid) and age. Intervention groups received a defined, standardized twice-weekly exercise program in addition to standard care. The control group received standard care and was given the opportunity to participate in an intervention of their choice after study completion. Data were assessed at 3 to 5 time points, depending on the length of chemotherapy (eFigure 1 in Supplement 2). All patients were assessed at baseline prior to initial chemotherapy and reassessed after 12 weeks. Longer therapy duration led to an interim analysis at week 12 and reassessment within 10 days after the last chemotherapy treatment period. A follow-up assessment was performed 12 weeks after completion of chemotherapy. Patients were asked to report any symptoms of CIPN immediately. Treating oncologists were asked to inquire about CIPN symptoms during regular visits. A short neurological test battery was performed every 6 weeks in all groups to assess for CIPN. On occurrence of CIPN symptoms, patients were referred to the leading neurologist for additional examination at the time of incidence.

Measurements

All clinical assessments were performed with the assessor blinded to group assignment and using reference-standard operating procedures. Electrophysiological studies were performed by a board-certified senior neurologist (M.B.) who was blinded to treatment group and under standard conditions. For exercise interventions, blinding to group assignment was not possible, and a sham procedure is not advisable. Thus, thera-

Figure 1. Trial Flow Diagram



This diagram shows the flow of 158 patients assigned to sensorimotor training (SMT), treatment as usual (TAU), or whole-body vibration (WBV) through the STOP randomized clinical trial. ITT, intention to treat; PNP, peripheral neuropathy; PP, per protocol; T0, baseline assessment; Tp, reassessment within 10 days after the last chemotherapy treatment period.

pists and patients were not allowed to communicate with assessors (eTable 1 in Supplement 2).

Primary End Point: Incidence of CIPN

The primary aim of the study was to reduce CIPN incidence by completion of chemotherapy detected by a comprehensive neurological assessment, containing objective and patient-reported outcomes, in accordance with international recommendations.[7,16,17] The following assessments were used to determine the incidence and severity of CIPN:

1. Clinical test battery containing vibration sensitivity, deep tendon reflexes (Achilles, patellar, biceps tendon), sense of the position of first and second toe, sense of touch of legs and feet, and lower leg strength according to Medical Research Council. CIPN was assumed if at least 2 of 3 clinical parameters (reflexes, vibration sensitivity, and sense of position) were pathological, further supported by additional assessments.[7,16,17]
2. Nerve conduction studies of motor and sensory nerves including tibial and sural nerves. The following values were regarded pathological: compound muscle action potential amplitude less than 5 mV, sensory nerve action potential amplitude less than 5 µV, and nerve conduction velocity of tibial or sural nerve less than 40 m/s.
3. Functional Assessment of Cancer Therapy/Gynaecology Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire for detection of subjective symptom severity[18] (score of 2 or higher indicates pathological symptom severity).

Secondary End Points

In addition to the primary end point, several secondary end points were established to provide a comprehensive assessment of the study's impact on various health and quality-of-life metrics. These secondary end points include a range of clinical and patient-reported outcomes. The following secondary end points were specified in this RCT:

1. Course of medical therapy: evaluated with therapy changes due to neuropathic symptoms, number of chemotherapy treatment periods, additional medication, in- and outpatient days, recurrent disease, and mortality.
2. Balance control: evaluated with changes in the center of pressure on a force plate (Leonardo Mechanograph [Novotec Medical GmbH]) during upright static and dynamic stance on a balance pad.
3. Subjective report of neuropathic symptoms: evaluated with a visual analog scale (VAS), 0 (not at all) to 10 (very strongly).

4. Physical activity levels: evaluated according to the Freiburger Physical Activity Questionnaire and metabolic equivalent of task scores.[19]
5. Quality of life: evaluated with the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-C30) questionnaire.
6. Neuropathic pain: evaluated with the Pain-DETECT questionnaire on a scale from 0 (not at all) to 10 (very strongly), resulting in a total score.
7. Safety analysis: evaluated through careful monitoring and documentation of AEs including serious AEs.

Training Intervention

Training sessions started 24 to 72 hours after randomization and were continued until completion of medical therapy, supervised and documented by sports therapists, practiced twice weekly on-site for approximately 15 to 30 minutes, focusing on maximum individual progression (eMethods in Supplement 2).

SMT consisted of balance exercises increasing in difficulty level on progressively unstable surfaces. Each patient performed 4 exercises per session following a standardized protocol. Each exercise was performed 3 times for 20 seconds, allowing a 40-second rest between each set and a 1-minute rest between each exercise to avoid neuronal fatigue.

Vibration training took place on a side-alternating vibration platform (Galileo [Novotec Medical GmbH]) with patients standing on their forefeet, performing 4 sets of 30- to 60-second vibration periods, vibration frequency ranging between 18 Hz and 35 Hz with a 2 mm to 4 mm amplitude followed by 1-minute rest.

Statistical Analysis

Sample size calculation was based on the primary outcome, incidence of CIPN, and carried out with G*Power 3.1.9.4 (Heinrich Heine Universität Düsseldorf). Power calculation was based on existing literature with an assumed incidence rate of CIPN of 90% for oxaliplatin and 70% for vinca alkaloids. A CIPN incidence reduction of 40% was defined as clinically meaningful. Using Fisher exact test (1-β = .80; 2-sided α = .05), we needed 60 evaluable patients for the oxaliplatin stratum (20 per group), and 72 evaluable patients for the vinca alkaloid stratum (24 per group). We anticipated a dropout rate of 20%, yielding a total of 158 patients to be recruited (53 per group).

Descriptive statistics for baseline characteristics were carried out with quantitative and qualitative variables, including mean, standard, absolute, and relative frequencies. The primary end point, incidence of CIPN, and all qualitative secondary end points were evaluated by Fisher exact test in each stratum separately, and by the Mantel-Haenszel test (MH) across strata, for comparing the 3 subgroups. We included time to incidence of CIPN using the log-rank test as an additional primary analysis. Consequently, both primary end points, incidence of CIPN and time to incidence of CIPN, were assessed with a significance threshold of 2.5% each. Quantitative secondary end points were evaluated by 2-way analyses of variance or multiple linear regression. All secondary end points were exploratory in nature. All statistical analyses were carried out for the intention-to-treat (ITT) and per-protocol (PP) populations using R version 4.0.3 (R Project for Statistical Computing). For the ITT analysis, data were collected from all patients until study termination or dropout, in which patient data from as many time points as possible were gathered. PP was defined as 75% successful attendance and missing data at baseline or completion of chemotherapy. Patients were stratified according to substance group and age within each center.

Study data were collected in pseudonymized form in a central database using the web-based REDCap version 6.4.6 (Vanderbilt University) electronic data capture system. Data quality was ensured through accompanying external monitoring in addition to the REDCap query system and plausibility checks after the data freeze. Approved data were exported in a CSV format for statistical analysis. Two-sided statistical testing with $P < .05$ was considered significant.

Results

Patient Characteristics

Between May 2014 and November 2020, 1605 patients were screened, and 1196 patients did not meet all inclusion criteria, with 251 further excluded or declining participation. A total of 158 patients (mean [SD] age, 49.1 [18.0-82.0] years; 93 [58.9%] male) were randomized into 1 of 3 groups: 55 in SMT, 53 in WBV, and 50 in TAU (Figure 1). Stratification within each center ensured homogenous groups. Neither significant baseline differences were found between groups, nor differences in the amount of neurotoxic substance received per group (**Table 1**). The mean (SD) compliance rates were 72.8% (3.5%) overall; 68.0% (6.6%) for TAU; 78.2% (5.6%) for SMT; and 71.7% (6.2%) for WBV. Patients in the intervention groups performed an average (range) of 18 (1-22) of 20 (12-30) training sessions.

Primary End Point: Incidence of CIPN

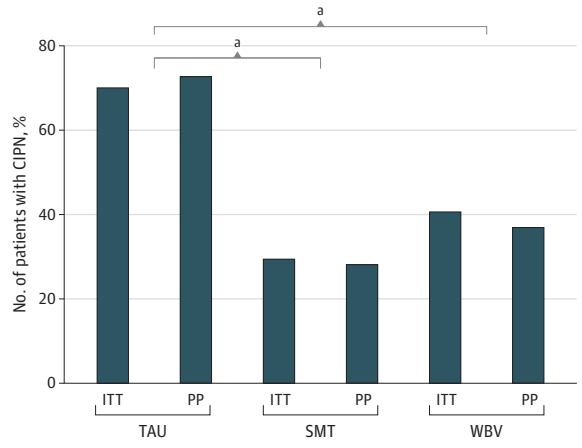
The incidence of CIPN was significantly different across groups in the ITT analysis, with rates of 24 of 34 (70.6%; 95% CI, 58.0%-83.2%) in the TAU group, 12 of 40 (30.0%; 95% CI, 17.9%-42.1%) in the SMT group, and 14 of 34 (41.2%; 95% CI, 27.9%-54.5%) in the WBV group ($P = .002$ for ITT-MH; **Figure 2**). These results were supported by the survival analysis, in which we also found a difference between the intervention groups and the TAU group in the ITT population, especially between SMT and TAU (eFigure 2 in Supplement 2). The significant difference in CIPN incidence, observed in the ITT analysis, was further corroborated by the PP analysis, which was conducted as a sensitivity analysis. In this analysis, CIPN incidence was found to be 22 of 30 (73.3%; 95% CI, 61.1%-85.6%) in the TAU group, 8 of 28 (28.6%; 95% CI, 16.6%-40.5%) in the SMT group, and 9 of 24 (37.5%; 95% CI, 24.4%-50.5%) in the WBV group ($P = .02$ for PP-MH). The most pronounced effect in a pairwise comparison was found in the SMT group (30.0%; 95% CI, 17.9%-54.5%), with less incidence of CIPN compared to the TAU group (70.6%; 95% CI, 58.0%-83.2%; $P = .001$ for ITT-MH) and 29.4% less CIPN in the WBV vs TAU group (41.2%; 95% CI, 27.9%-54.5%; $P = .03$ for ITT-MH; **Table 2**).

Table 1. Patient Characteristics

Characteristic	No. (%)				
	Total (N = 158)	Treatment as usual (n= 50)	Sensorimotor training (n = 55)	Vibration training (n = 53)	*P* value
Study center					
University Hospital of Cologne	89 (56.3)	30	30	29	NA
Sachsenring	35 (22.2)	10	12	13	NA
Eschweiler	30 (19.0)	9	11	10	NA
PIOH	4 (2.5)	1	2	1	NA
Sex					
Female	65 (41.1)	22 (44)	25 (45.5)	18 (34)	.43
Male	93 (58.9)	28 (56)	30 (54.5)	35 (66)	
Age, mean (range), y	49.1 (18.0-82.0)	51.2 (20.0-82.0)	46.5 (18.0-79.0)	49.8 (20.0-81.0)	.70
Neurotoxic substance					
Oxaliplatin	66 (41.8)	20 (40)	23 (41.8)	23 (43.4)	.98
Vinca alkaloid	92 (58.2)	30 (60)	32 (58.2)	30 (56.6)	
Cumulative dose, mean (SD), mg/m^2					
Oxaliplatin	NA	1114.7 (420.6)	1328.9 (404.3)	1231 (613.3)	.08
Vincristine	NA	8.7 (3.4)	8.9 (3.5)	8.9 (3.5)	.95
Vinblastine	NA	36.5 (21.1)	31.7 (10.5)	29.7 (10.4)	.06
Diagnosis					
Lymphoma	92 (58.2)	30 (60.0)	32 (58.2)	30 (56.6)	.98
Stage I, II, III, IV	15, 23, 19, 21	3, 8, 6, 7	5, 5, 8, 10	7, 10, 5, 4	.41
Colorectal	59 (37.3)	19 (38.0)	19 (34.5)	21 (39.6)	.88
Stage T1, T2, T3, T4	1, 5, 28, 10	0, 1, 10, 4	1, 1, 10, 3	0, 3, 8, 3	.81
Other	7 (4.4)	1 (2.0)	4 (7.3)	2 (3.8)	.51
Dropped out	43 (27.2)	16 (32.0)	12 (21.8)	15 (28.3)	.49

Abbreviations: NA, not assessed; PIOH, Praxis Internistischer Onkologie und Hämatologie.

Figure 2. Incidence of Chemotherapy-Induced Peripheral Neuropathy (CIPN) Between Groups



This figure shows CIPN incidence among patients randomized to sensorimotor training (SMT), treatment as usual (TAU), or whole-body vibration (WBV) groups, stratified by intention to treat (ITT) and per protocol (PP).

Secondary End Points

The clinical test battery suggested an additional benefit in favor of the intervention groups. Overall, the SMT group benefited most in these areas in terms of CIPN indication: Achilles tendon reflex (26 of 55 [47.3%]), vibration sensitivity (18 of 55 [32.7%]; *P* = .02 for MH), sense of touch (0 of 55; *P* = .04 for MH), and lower leg strength (1 of 55 [1.8%]; *P* = .04 for MH), in comparison to the TAU group (28 of 50 [56.0%], 25 of 50 [50.0%], 4 of 50 [8.0%], 6 of 50 [12.0%], respectively) and the WBV group (26 of 53 [49.1%], 18 of 53 [34.0%], 5 of 53 [9.4%], 1 of 53 [1.9%], respectively; eTable 2 in Supplement 2). The FACT/GOG-Ntx questionnaire revealed no significant group differences.

Differences further occurred for the substance groups in the ITT and PP analysis. Patients receiving vinca alkaloids benefited most from SMT and WBV interventions, showing the lowest incidence of CIPN compared to TAU for both the ITT cohort (SMT and WBV vs TAU: 7 of 25 [28.0%]; *P* = .004 for ITT-Fisher and 9 of 21 [42.9%]; *P* = .08 for ITT-Fisher vs 17 of 24 [70.8%], respectively) and the PP cohort (SMT and WBV vs TAU: 4 of 17 [23.5%]; *P* = .01 for PP-Fisher and 5 of 15 [33.3%]; *P* = .04 for PP-Fisher vs 15 of 21 [71.4%], respectively; eTable 3 in Supplement 2). Combined with SMT, these patients also showed the fewest problems with reduced vibration sensitivity compared to TAU (ITT: 10 [31.3%; 95% CI, 15.2%-47.4%] vs 17 [56.7%; 95% CI, 39.0%-74.4%]; *P* = .045; PP: 5 [29.4%; 95% CI, 7.7%-51.1%] vs 15 [71.4%; 95% CI, 52.1%-90.7%]; *P* = .02). No differences were found between colon and rectal carcinoma or between Hodgkin and non-Hodgkin lymphomas.

The secondary end points included (1) medical therapy and clinical outcome, (2) balance control, (3) neuropathy symptoms (VAS), (4) physical activity levels, and (5) quality of life. This analysis revealed significant intergroup differences in medical therapy and clinical outcome as well as balance control.

Table 2. Results of the Primary End Point Chemotherapy-Induced Peripheral Neuropathy (CIPN) Between Treatment Groups

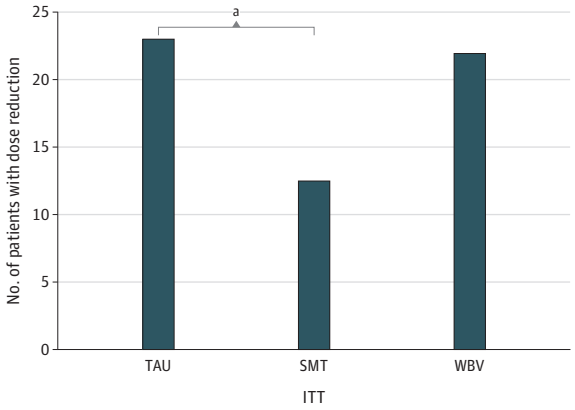
Analysis	Control (TAU)	SMT	WBV	Pairwise comparison (Mantel-Haenszel test)	
				P value (TAU vs SMT)	*P* value (TAU vs WBV)
Total No.	34	40	34	NA	NA
CIPN incidence for ITT (95% CI), %[a]	70.6 (58.0-83.2)	30.0 (17.9-42.1)	41.2 (27.9-54.5)	.001	.03
Total No.	30	28	24	NA	NA
CIPN incidence for PP (95% CI), %[a]	73.3 (61.1-85.6)	28.6 (16.6-40.5)	37.5 (24.4-50.5)	.002	.01

Abbreviations: ITT, intention to treat; NA, not applicable; PP, per protocol; SMT, sensorimotor training; TAU, treatment as usual; WBV, whole-body vibration.
[a] 95% CIs represent relative frequencies.

In the SMT group, fewer dose reductions compared to the TAU and WBV group were observed (12 of 38 [31.6%] vs 22 of 39 [56.4%] and 21 of 39 [53.8%], respectively; $P = .04$; **Figure 3** and eTable 2 in Supplement 2). Furthermore, lower mortality in the SMT group reached statistical significance compared to the TAU group (1 of 52 [1.9%; 95% CI, 0.0%-5.7%] vs 7 of 41 [17.1%; 95% CI, 5.6%-28.6%]; $P = .04$; eTable 2 in Supplement 2). No differences were found for inpatient or outpatient days or the likelihood of relapse. Patients in the SMT group reported significantly less pain and burning sensation (VAS) than in the WBV or TAU groups (eTable 2 in Supplement 2).

Intervention groups were able to improve balance control in bipedal stance. Patients in the SMT group, however, were additionally able to improve bipedal stance with eyes closed and monopedal stance. Both intervention groups were also able to maintain the advantage in the bipedal stance with eyes closed for at least 3 months after completion of therapy (follow-up). Physical activity levels and health-related quality of life were higher in the intervention groups, but they did not reach statistical significance (eTable 2 in Supplement 2).

Figure 3. Number of Patients With Necessary Dose Reductions Due to Chemotherapy-Induced Peripheral Neuropathy



This figure shows the necessary dose reductions in the sensorimotor training (SMT), treatment as usual (TAU), or whole-body vibration (WBV) groups. All patients were in the intention-to-treat (ITT) analysis.

Safety Analysis

Seven AEs (eTable 4 in Supplement 2), including 1 serious AE, were reported. After thorough examination, no correlation with the interventions could be found. Consequently, the interventions can be regarded as safe.

Discussion

Considering the results of this RCT and previous studies,[12] specific exercises have significant potential to counter chemotherapy-related AEs. We were able to show that SMT can decrease CIPN, as well as maintain and improve subjective and objective outcomes, such as vibration sensitivity, sense of touch, lower leg strength, pain, burning sensation, and balance control. Furthermore, patients needed fewer dose reductions and had less mortality, better quality of life, and higher physical activity levels. WBV showed a reduced incidence of CIPN and improved balance in a bipedal stance. SMT and WBV ensure independence in gait and balance and can lead to higher levels of physical activity, enhancing physical and psychological well-being.

Although medical therapy is constantly improving,[20] clinical reports conclude that these new agents also provoke neuropathy. Polypharmacy, higher need for assistance, sleep disturbances, and high health care costs ($17 300 per patient with CIPN)[21] are notable consequences. The need to treat, or ideally prevent CIPN, remains of the utmost interest.

In this RCT, we focused on oxaliplatin and vinca alkaloids, which rank among the most frequently used substances in cancer treatment, with high CIPN incidence (70%-90%).[1,2] This design allowed for a homogeneous study population with a manageable study size. Analyzing differences according to substance groups, patients receiving vinca alkaloids benefited the most from the training in comparison to oxaliplatin. This may be explained by different pathomechanisms of neuropathy induction of the 2 substances. Vinca alkaloids damage myelin sheaths and axonal microtubules, whereas oxaliplatin can also cause damage to dorsal root ganglia by altering chemokine expression, which induces more pronounced sensory neuropathy.

The findings of this RCT support the idea that SMT has high neuro-modulating potential and can stimulate regenerative and adaptive mechanisms of muscle spindles and sensory afferent nerves (Ia, Ib), leading to neural plasticity. WBV appears to target more superficial nerves.[12] Our observations indicate that the human neuromuscular system, if exposed to regular use and trained at maximum progression, seems to be able to maintain relevant neural functions even throughout chemotherapy, as preclinical models have demonstrated.[22] Periph-

eral nerve regeneration is possible, and exercise plays a decisive role in maintaining and restoring neuromuscular function.

Strengths and Limitations

This study is the first RCT, to our knowledge, investigating the preventive effects of specific exercises on CIPN. Its strength lies in the detailed and objective workup of the influence of exercise therapy on neural function by clinical and electrophysiological assessments and the excellent potential for translation into clinical practice and patients' daily lives. The exercises presented are standardized and feasible, with low intensity and high impact, making them ideal for patients in all phases of oncologic care, including posttherapy at-home care. SMT is low cost, with no contraindications or AEs. WBV is especially beneficial when patients are immobile. A further strength is that the impact of specific exercise therapy has not previously been correlated with the course of medical therapy and clinical outcome measures.

This clinical trial was affected by COVID-19, which caused a delay in testing and training, a higher dropout rate, and some missing data for the last 5 patients. Additionally, the validity of the questionnaires was limited in this study. The PainDETECT was often filled out incorrectly (other causes of pain included headaches or arthritis). EORTC-QLQ-C-30 was not specific because many questions refer to overall health status or financial problems, which may not be related to an exercise intervention. Because CIPN represents a systemic neuropathy, we used the FACT/GOG-Ntx questionnaire, which contained not only questions regarding the anatomic regions in question, the feet, but also the hands and hearing. The training specifically addresses the sensorimotor system of the legs, and the questionnaire is not sensitive enough to detect subtle changes throughout the clinical trial. Yet, patients reported improvements in specific symptoms related to feet/legs in the VAS and the short test battery reflecting therapy effects.

Conclusions

Consistent with our a priori hypothesis, this RCT provides initial evidence that specific, neuromuscular stimulating training (SMT and WBV) reduces the onset of CIPN by 50% to 70%. Further explorative analysis showed additional benefits for the intervention groups. The SMT group benefited most, improving their vibration sensitivity, balance control, pain, burning sensation, and lower leg strength. Additionally, the SMT group needed fewer dose reductions and had less mortality, better quality of life, and higher physical activity levels. The WBV group improves bipedal stance. Overall, patients receiving vinca alkaloids were more sensitive to the interventions than patients receiving oxaliplatin, especially when combined with SMT.

Based on our results as well as the current literature, this specific exercise regimen not only presents potentially the best current treatment option for CIPN but also has the potential to prevent CIPN, improve quality of life, and have a positive impact on the course of oncological treatment. Although more studies are necessary to verify these results, the present results are of high clinical relevance and present a milestone for the management of CIPN and supportive care in oncology.

ARTICLE INFORMATION

Accepted for Publication: March 4, 2024.

Published Online: July 1, 2024. doi:10.1001/jamainternmed.2024.2354

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Obtained funding: Streckmann, Bloch.
Administrative, technical, or material support: Elter, Lehmann, Oschwald, Koliamitra, Otten, Steinmetz, Hallek, Bloch, Balke.
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Conflict of Interest Disclosures: Dr Draube reported speaker fees from BMS outside the submitted work. Dr Balke reported speaker fees from AbbVie/Allergan outside the submitted work. No other disclosures were reported.

Funding/Support: The study was funded by the German Cancer Aid (DHK).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We express our gratitude to Freerk Baumann, PD, University Hospital Cologne, for his advisory support during the study design. The students who supported the study during their thesis work with great dedication and commitment: Robin Ackfeld, Katharina Brilling, Melissa Camara-Romero, Sarah Gabriel, Franziska Glasenapp, Paul Haneke, Berit Hollerbach, Jule Möller, Leon Rauprich, Kim Strohmann, Lara Feder, Tamara Gehlen, and Heike Gier. Neil Aaronson, PD, Netherlands Cancer Institute, for his advisory support regarding the questionnaires. The study coordinators Melanie Heinz, Karin Lanzerath, Pantea Pape, MD, Helma Lau, Elisabeth von Kruechten, NTC and Saint Mary Hospital Cologne, for their support in neurological laboratory coordination and assessments. Margarethe Platz, Rainer Rawer, Novotec, for their support in preparing the raw data of the balance tests. Dr Alexander Schenk, PhD, TU Dortmund, for randomization. Eckhard Schoenau, and Baerbel Tutlewski, Uni Reha Cologne, for their support with the assessments. Philipp Zimmer, PD, TU Dortmund, for his advisory support during study planning. Eva Zopf, MD, ACU Australia, for her advisory support during study conception, as well

as all physicians who helped us to recruit patients and the patients for their participation in the study. No additional compensation was received by any parties.

REFERENCES

1. Cavaletti G, Marmiroli P. Management of oxaliplatin-induced peripheral sensory neuropathy. *Cancers (Basel)*. 2020;12(6):12. doi:10.3390/cancers12061370

2. Laforgia M, Laface C, Calabrò C, et al. Peripheral neuropathy under oncologic therapies: a literature review on pathogenetic mechanisms. *Int J Mol Sci*. 2021;22(4):22. doi:10.3390/ijms22041980

3. Pietrangeli A, Leandri M, Terzoli E, Jandolo B, Garufi C. Persistence of high-dose oxaliplatin-induced neuropathy at long-term follow-up. *Eur Neurol*. 2006;56(1):13-16. doi:10.1159/000094376

4. Richardson JK, Ashton-Miller JA. Peripheral neuropathy: an often-overlooked cause of falls in the elderly. *Postgrad Med*. 1996;99(6):161-172. doi:10.1080/00325481.1996.11946142

5. Stubblefield MD, Burstein HJ, Burton AW, et al. NCCN task force report: management of neuropathy in cancer. *J Natl Compr Canc Netw*. 2009;7(suppl 5):S1-S26. doi:10.6004/jnccn.2009.0078

6. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *J Clin Oncol*. 2020;38(28):3325-3348. doi:10.1200/JCO.20.01399

7. Gewandter JS, Brell J, Cavaletti G, et al. Trial designs for chemotherapy-induced peripheral neuropathy prevention: ACTTION recommendations. *Neurology*. 2018;91(9):403-413. doi:10.1212/WNL.0000000000006083

8. Gómez-Pinilla F, Ying Z, Roy RR, Molteni R, Edgerton VR. Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *J Neurophysiol*. 2002;88(5):2187-2195. doi:10.1152/jn.00152.2002

9. Molteni R, Zheng JQ, Ying Z, Gómez-Pinilla F, Twiss JL. Voluntary exercise increases axonal regeneration from sensory neurons. *Proc Natl Acad Sci U S A*. 2004;101(22):8473-8478. doi:10.1073/pnas.0401443101

10. Sonza A, Maurer C, Achaval M, Zaro MA, Nigg BM. Human cutaneous sensors on the sole of the foot: altered sensitivity and recovery time after whole body vibration. *Neurosci Lett*. 2013;533:81-85. doi:10.1016/j.neulet.2012.11.036

11. Streckmann F, et al. Exercise and neuropathy: systematic review with meta-analysis. *Sports Med*. 2021.

12. Streckmann F, Lehmann HC, Balke M, et al. Sensorimotor training and whole-body vibration training have the potential to reduce motor and sensory symptoms of chemotherapy-induced peripheral neuropathy-a randomized controlled pilot trial. *Support Care Cancer*. 2019;27(7):2471-2478. doi:10.1007/s00520-018-4531-4

13. Taube W, Gruber M, Gollhofer A. Spinal and supraspinal adaptations associated with balance training and their functional relevance. *Acta Physiol (Oxf)*. 2008;193(2):101-116. doi:10.1111/j.1748-1716.2008.01850.x

14. Cochrane DJ. Vibration exercise: the potential benefits. *Int J Sports Med*. 2011;32(2):75-99. doi:10.1055/s-0030-1268010

15. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

16. Gewandter JS, Freeman R, Kitt RA, et al. Chemotherapy-induced peripheral neuropathy clinical trials: Review and recommendations. *Neurology*. 2017;89(8):859-869. doi:10.1212/WNL.0000000000004272

17. Cavaletti G, Cornblath DR, Merkies ISJ, et al; CI-PeriNomS Group. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Ann Oncol*. 2013;24(2):454-462. doi:10.1093/annonc/mds329

18. Hayes S, Newman B. Exercise in cancer recovery: An overview of the evidence. *Cancer Forum*. 2006;30.

19. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575-1581. doi:10.1249/MSS.0b013e31821ece12

20. Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. *J Clin Invest*. 2015;125(9):3335-3337. doi:10.1172/JCI83871

21. Pike CT, Birnbaum HG, Muehlenbein CE, Pohl GM, Natale RB. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and non–small cell lung cancer. *Chemother Res Pract*. 2012;2012:913848.

22. Park JS, Höke A. Treadmill exercise induced functional recovery after peripheral nerve repair is associated with increased levels of neurotrophic factors. *PLoS One*. 2014;9(3):e90245. doi:10.1371/journal.pone.0090245

Invited Commentary

Exercise and Physical Medicine Interventions for Managing Chemotherapy-Induced Peripheral Neuropathy

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Chemotherapy-induced peripheral neuropathy (CIPN) is a frustrating and distressing complication of many chemotherapy drugs. In addition to bothersome symptoms, such as numbness and tingling, CIPN can affect daily living and socio-occupational function, cause balance disequilibrium and falls, and limit the amount of chemotherapy that can be administered, contributing to worse oncological outcomes. Current evidence-based approaches for treatment of established CIPN are limited[1]; duloxetine has shown modest efficacy in improving painful neuropathy (average improvement in pain of 1 point vs 0.3 points for placebo on a 10-point scale). Given the lack of effective treatment, there is growing recognition of the importance of primary prevention of CIPN in the oncology community. The association of obesity and lower physical activity with CIPN and recognition of exercise-based interventions in improving general health, inflammation, and neuromodulation have been followed by increasing interest in evaluating exercise-based interventions (exercise oncology) in managing CIPN.[2]

Related article page 1046

In this issue of *JAMA Internal Medicine*, Streckmann et al[3] present the results of the STOP trial, a rigorous, multisite trial that assessed in person supervised, movement-based interventions for preventing CIPN. The authors randomized 158 adults (mean age of 49 years, most with lymphoma or colorectal cancer, initiating vinca or oxaliplatin-based chemotherapy) to 1 of 3 arms: sensorimotor training, vibration training, or usual care. Participants in the intervention arms underwent twice-weekly 15- to 30-minute sessions with trained sports therapists (sensorimotor training largely involved postural control on an unstable surface, and vibration training involved participants standing on a vibration platform), with a focus on individual progression over the course of the sessions. The primary end point was the incidence of CIPN during chemotherapy as assessed by physical examination; addition-