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The role of physical activity against chemotherapy-induced peripheral neuropathy: a narrative review

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Abstract

Several studies investigated the side effect of adjuvant cancer treatments, and different types of preventive techniques or treatments have been assessed. Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological side effect. Exercise training has been widely studied as an adjuvant therapy to prevent CIPN and improve post-chemotherapy functional outcome and quality of life (QoL). This narrative review aims to summarize the data obtained from the latest studies about physical activity (PA) for the prevention and treatment of CIPN and associated QoL measures. Literature research was conducted to obtain studies including PA interventions for patients with CIPN. Ten studies met inclusion criteria and were therefore summarized and discussed, focusing on exercise type and functional outcome. It seems clear that, regardless of the type of exercise, PA plays a positive role in the treatment of CIPN, providing a significant symptom improvement. There has been no standardization of type, quantity, and intensity of PA administered to the subjects in the various studies probably due to a physiological difference between samples, grade of neuropathy, and difference among therapies.

Keywords

Chemotherapy-induced peripheral neuropathy, cancer, physical activity, treatment, prevention

Introduction

In recent years, there have been many progress in neoplastic disease treatment, both in terms of diagnosis, through the development of increasingly sensitive analysis tests, and their treatment, through the use of new drugs. Suffice it to say that the number of cancer survivors is rising constantly: for example, in the United States more than 16.9 million Americans (8.1 million males and 8.8 million females) with a history

of cancer were alive on January 1st, 2019; this number is projected to reach more than 22.1 million by January 1st, 2030 [1].

With the rise in survivors of different kinds of tumors, there is more and more evidence of drug side effects. Indeed, survivors often develop physical limitations or pathological conditions caused by the chemotherapy treatment, and very often, these side effects are long-lasting, well beyond the end of the chemotherapy treatment [2, 3]. Although very effective for cancer treatment, antineoplastic drugs often determine side effects that can be very serious and could affect the quality of life (QoL). Chemotherapy-induced peripheral neuropathy (CIPN) is among the most relevant complication affecting the peripheral nervous system. Chemotherapy agents can cause a variety of neuropathies involving large and small fibers, with demyelinating and axonal features, determining sensory, motor, or autonomic dysfunction [4]. Prevalence of neuropathies is high (19–85%) especially if predisposing factors are present, including age, preexistent neuropathy, renal or hepatic function impairment, exposures to other neurotoxic agents, paraneoplastic antibodies, and independent cancer-associated neuropathy [5].

In the last few years, there has been an increase in the literature about the prevention and treatment of CIPN and the role of physical activity (PA) in managing the side effects of chemotherapy treatments.

PA for cancer survivors is recommended according to the international guidelines proposed by the sports medicine associations, such as the American College of Sports Medicine (ACSM), American Heart Association (AHA), American Cancer Society (ACS), and US Department of Health and Human Services (US DHHS) [6–8]. All these guidelines are similar, with minor variations.

In a concept paper published in 2017, a different approach has been proposed which takes into account the different characteristics of the European population compared to the American one, to provide a more suitable tool. These guidelines are not validated but adhere closely to the ACSM model [9].

Although it seems clear how the studies recognize the PA as an important role in terms of re-education to movement, countering negative effects, and QoL in cancer survivors, there are few references to the specific problem of CIPN.

This review aims to provide an overview of the role of PA as an adjunct preventative treatment for CIPN.

Methods

Pubmed and Scopus databases have been searched using various combinations of keywords related to CIPN and exercise and results were limited to manuscripts published in the last 20 years.

Studies had to include a PA intervention on cancer patient survivors who developed CIPN. Regardless of the design chosen by the authors, studies had to include a pre and post evaluation in order to assess the effect of the PA on patients at least as regards improvement of CIPN, balance, or QoL.

Further inclusion criteria were: English language, one or both genders from all races, all ages, and any diagnosis of cancer. Cross-sectional studies, case reports, published abstracts, dissertation materials, and conference presentations were not included.

The studies considered most influential, have been inserted in a summary table (Table 1) where the types of PA administered, quantity, and the respective effects of the intervention have been underlined.

CIPN

From a clinical point of view, CIPN may appear with different symptoms, which are caused by the action of chemotherapeutic agents on nerves.

These symptoms often involve sensory aspects, such as numbness, widespread pain, hypersensitivity to mechanical and cold stimuli, paresthesia, and loss of proprioception. CIPN could affect the QoL and increase the risk of falling as well [10].

Sensory disturbances usually reflect the underlying length-dependent sensory neuropathy that progresses with a subacute course affecting distal limbs first and eventually progressing in a distal-proximal direction.

Table 1. Summary of the most relevant studies about CIPN and PA

Reference	Number subjects, age, median (range), sex, IG–CG	Diagnosis	Methods	Protocol	Outcome measurement	Results	Conclusions
Kneis et al. [11]	Pre-protocol subjects: *N* = 37 IG: 18, female: 14, male: 4, age median 70 (44–82) CG: 19, female: 12, male: 7, age median 60 (46–75)	Breast cancer, colorectal cancer, gynecological cancer, upper gastrointestinal cancer, NSCLC, non-Hodgkin's lymphoma, multiple myeloma	One-on-one IG: 12 weeks twice/weekly (endurance + balance training) CG: active control group (endurance training)	**Endurance training:** 30 min stable bike moderate intensity (under the IAT) **Balance training:** 3–8 exercises 3 repetitions each 20/30 s progressively increasing exercise difficulty (reducing the support surface, visual input, adding motor/cognitive tasks, and instability induction	Functional performance CIPN symptoms and QoL *Cardiorespiratory fitness*	Endurance training induced a reduction in sensory symptoms in both groups, while balance training additionally improved patients' functional status	Both exercises provide a clear and relevant benefit for patients with CIPN
Streckman et al. [12]	*N* = 61 IG: 30 CG: 31	Lymphoma	IG: 36 weeks, 2 times per week (sensorimotor-, endurance- and strength training) CG: usual care	**Endurance training:** Treadmill, bike-dynamometer 70–80% HRmax **Sensorimotor:** 4 postural stabilization tasks progressively increase task difficulty **Resistance training:** 4 exercises carried out at maximum force	QoL (EORTC QLQ-C30 questionnaire) Movement coordination, endurance, strength, and therapy-induced side-effects	Increase of balance in IG compared with CG. Static (P = 0.03), dynamic (P = 0.007), perturbed (P = 0.009), and bipedal (P = 0.006)	Exercise, especially sensorimotor training provide benefit to cancer patients, ↑ QoL (emotional function, pain, constipation, diarrhea), ↓ side-effects, ↑ balance control, ↑ mobility
Kleckner et al.[13]	*N* = 355, age: 56 ± 11, 93% female IG: 170 CG: 185	Different types of cancer (mostly breast cancer)	IG: 6 weeks, daily session (EXCAP©®) CG: usual care	**Endurance training:** Low-to-moderate walking: 60–85% of HRR **Strength training:** Bands: RPE of 3–5 (1–10 scale)	Effects of exercise on CIPN symptoms Factors that predict CIPN symptoms Factors that moderate effects of exercise on CIPN symptoms	Reduction symptoms (on 10-point scale) hot/cold in hand/feet (-0.46 point) P = 0.045; reduction numbness and tingling (-0.42 point) P = 0.061 More effect in older people (P = 0.086), male (P = 0.028), and breast cancer (0.076)	Exercise appears to reduce CIPN symptoms in patients receiving taxane-, platinum-, or vinca alkaloid-based chemotherapy

Table 1. Summary of the most relevant studies about CIPN and PA (*continued*)

Reference	Number subjects, age, median (range), sex, IG–CG	Diagnosis	Methods	Protocol	Outcome measurement	Results	Conclusions
Vollmers et al. [14]	*N* = 36 IG: 17, age: 48.56 ± 11.94 CG: 19, age: 52.39 ± 10.14	Breast cancer	IG: 2 times/week during chemotherapy and 6 weeks after the end (physical training and sensorimotor exercises) CG: received an instruction sheet with a PA program to do autonomously by the patients	Not reported	Balance, upper and lower strength, QoL (EORTC and MFI questionnaires)	No significant difference reported	↑ Postural stability in IG Moderate strength exercises proved to prevent a loss of upper extremity strength ↑ In the decreased intensity of CIPN or possibly faster remission
Zimmer et al. [15]	*N* = 30 IG: 17 CG:13	Colorectal cancer	IG: 8 weeks–two times/week (a combo of endurance and resistance training) CG: usual care (written standard recommendations to obtain physical fitness)	**Endurance training:** Walking, bicycle ergometer, or cross-trainer **Resistance training:** Circuit training of bench press, lat pulldown, leg press, seated row, and abdominal exercise	Trial outcome index (TOI) Balance	Neuropathic symptoms remained stable in the IG over time, while CIPN significantly worsened in CG of 7.14 points (P = 0.077) of the FACT/GOG-NTX questionnaire IG significantly Improved strength and balance function	↓ CIPN symptoms, ↑ balance, ↑ strength, ↑ QoL
Henke et al. [16]	*N* = 29 IG: 18 CG: 11	Lung cancer (NSCLC and SCLC)	IG: 5 times/week endurance training and breathing technique; 2 times/week strength training CG: usual care	**Endurance training:** Walking 55–70% of HRR **Strength training:** 50% of RM	Barthel index QoL (EORTC QLQ C-30/LC-13 questionnaire)	Barthel index was significantly worse after the intervention in CG (P = 0.041); functional capacity increased more in IG (6MWT); an increased single score of EORTC QLQ C-30/LC-13 questionnaire	↑ QoL (physical functioning, hemoptysis, pain in arms or shoulder, peripheral neuropathy, cognitive functioning) Training has a positive effect on the patient's endurance and strength capacity
Wonders et al. [17]	*N* = 6 (finished the intervention), female subjects	Breast cancer	IG: 10-week home-based program CG: not present	**Endurance training:** Moderate-intensity 55–65% of their self-estimated HRR Increase gradually from 20 min (1st week) to 150 min (10th week) of exercise per week **Resistance training:** Not reported	CIPN symptoms rate QoL (McGill QoL questionnaire)	Significantly lowered levels of both troublesome and pain symptoms	↓ CIPN symptoms ↑ QoL (level of troublesome symptoms related to peripheral neuropathy) Low adherence rate Difficulty getting subjects to complete the 10-week program

Table 1. Summary of the most relevant studies about CIPN and PA (*continued*)

Reference	Number subjects, age, median (range), sex, IG–CG	Diagnosis	Methods	Protocol	Outcome measurement	Results	Conclusions
Andersen Hammond et al. [18]	*N* = 48 IG: 22 mean age 56.3 ± 9.9 CG: 26 mean age 53.0 ± 10.3	Breast cancer	IG: 3 times daily home-based exercise program; 5/10 min every session CG: usual care	Nerve gliding exercise program	Effects of exercise on CIPN symptoms QoL (DASH questionnaire) Strength	Less pain for IG (P = 0.053) preservation of vibration (P = 0.001) and heat pain thresholds (left P = 0.021, right P = 0.039) Significant improvements in grip strength	↓ CIPN pain ↓ Pain pressure ↑ Grip dynamometry
Van Waart et al. [19]	*N* = 230 IG: 153; HBI = 77, HIP = 76 CG: 77	Breast or colon cancer	IG: divided into "**Onco-Move program**" and "**OnTrack program**" CG: usual care	**Onco-Move:** Home-based program, 30 min, 5 days/week, 12–14 Borg Scale, exercises not reported **OnTrack program:** Supervised 20 min, 2 days/week **Endurance training:** 30 minutes, 50% to 80% of the maximal workload, exercises not reported **Resistance training:** 2 series of 8 repetitions at 80% of the 1RM	Cardiorespiratory fitness, upper muscle strength, lower muscle strength, fatigue, QoL (EORTC QLQ-C30 questionnaire), functioning in daily life, quality of sleep, return to work, psychological distress, self-reported PA level, chemotherapy regimen, dose, and adverse effects of chemotherapy, compliance with exercise programs	IGs: less decline of cardiorespiratory fitness (P < 0.001), better physical functioning (P < 0.001), less pain (HBI P = 0.003, HIP P = 0.011)	Both IGs provide a benefit for patients, especially the HIP group
McCrary et al. [20]	A single group for pre and post *N* = 29 mean age 61.6 (32–79) Female 21, male 8	Breast cancer, colorectal cancer, ovarian cancer, endometrial cancer, appendix cancer, lymphoma, myeloma, urothelial, carcinoma	IG: 8 weeks, 3 times weekly (resistance training, balance training, and endurance training) CG: not present	Exercises performed at RPE of 13–15 (6–20 scale)	Objective CIPN, patient-reported CIPN, patient-reported disability, QoL (SF-36 questionnaire), mobility, dynamic balance/leg strength, standing balance, sensoryneurophysiology, motor neurophysiology	Dynamic balance, standing balance in eye-open conditions, mobility, and QoL were improved ($P \leq 0.05$) Ameliorating objective CIPN and patient reported CIPN	Significance increasing of: Objective CIPN, patient-reported CIPN, patient-reported disability, QoL, mobility Dynamic balance, stable surfacewith eyes open, unstable surface with eyes open

IG: intervention group; CG: control group; HRmax: maximum heart rate; HRR: heart rate reserve; RM: maximum repetitions; RPE: rated perceived exertion; IAT: individual anaerobic threshold; 1RM: one repetition maximum; NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer; ↑: increase; ↓: decrease; 6MWT: 6-minute walking test; HBI: home-based intervention; HIP: high intensity program

Symptoms could appear both while taking medication (e.g., typically using platinum-based drugs) [21], and even a long time after treatment, in a condition called "coasting" [22].

It is very common for patients to develop tingling and numbness in the hands and feet during the first year of chemotherapy treatment follow-up. Symptoms in the lower limbs typically last longer than those in the upper limbs [23].

The mechanisms of action and molecular target of these chemotherapeutic agents are diverse and include both DNA and microtubular targets to arrest cell division and induce cell death. The pathobiology of CIPN, irrespective of the causative agent, shares some important similarities. For example, sensory neurons are those most affected and longer axons are damaged first. Histopathological changes associated with CIPN commonly involve large, myelinated fibers and result in sensorimotor symptoms such as hypersensitivity to mechanical stimuli or distal weakness due to mechanisms that are not entirely understood [24, 25].

There are six main substance groups that may damage peripheral sensory and motor fibers: platinum-based antineoplastics (particularly oxaliplatin and cisplatin), vinca alkaloids (particularly vincristine and vinblastine), epothilones (ixabepilone), taxanes (paclitaxel, docetaxel), proteasome inhibitors (bortezomib) and immunomodulatory drugs (thalidomide) [24].

Antineoplastic drugs may induce CIPN with different timing and modalities. Platinum-based drugs have the highest incidence of neurotoxicity with a rate ranging from 70% to 100% of all treated patients [26]. Furthermore, oxaliplatin may induce neuropathy in the very early phase of the treatment [27]. The mechanism of action of platinum-based drugs develops damage to the nucleus inhibiting the DNA replication and mRNA transcription [24].

Vinca alkaloids, used mainly to treat lung, brain, and bladder testicular cancer, may determine CIPN in up to 20% of treated patients [26]. The cytotoxic action of vinca alkaloids is provoked by its ability to bond the β-subunit of tubulin and inhibits microtubule formation [24].

The ixabepilone is an analog of epothilone B used in breast cancer patients and belongs to a relatively new class of anti-cancer drugs that act as tubulin destabilizers effectively preventing divisions of cancer cells. Evidence from clinical trials showed that 65% of patients treated with ixabepilone demonstrated symptoms of neuropathy, therefore reflecting a high incidence of CIPN [26]. Taxanes are drugs used for different types of cancer: breast, ovarian, lung, pancreatic, and prostate cancer. In relation to the type of taxanes used, there is a variety in the incidence of CIPN ranging from 11% to 87% [26]. Proteasome inhibitors are drugs used against multiple myeloma and achieve their anticancer effects by inhibiting the activity of the proteasome of cancer cells. This leads to an accumulation of aberrant proteins, hence the arrest of the cell cycle and finally to apoptosis. These drugs determine a moderate (20–30%) incidence of CIPN [26].

Immunomodulatory drugs such as thalidomide cause lower limb neuropathies estimated to affect 20% to 60% of all cancer patients treated with this drug [26].

Long-term effects of CIPN consist of depression, insomnia, and worse QoL. Although some risk factors have been identified such as age, pre-existing neuropathy, nutrient deficiency, and concomitant drugs facilitating neurotoxicity, these are difficult to overcome and CIPN incidence is still very high [28].

Literature on long-term effects is still very sparse, especially regarding the effects of thalidomide and bortezomib. In addition, there is ample literature regarding the effects of chemotherapy drugs but, only recently some studies have been considered the QoL of cancer patients with CIPN.

Prevention and therapy

Pharmacological intervention

To date, drug therapies aimed at preventing CIPN have not produced encouraging results. Indeed, studies evaluating the effects of some drugs, including chemoprotective, anticonvulsants, antidepressants, and dietary supplements, did not yield any significant data [29].

This is also confirmed by a more recent review, which assessed the effect of many drugs to prevent CIPN (carbamazepine, minocycline, nimodipine) and supplements (acetyl-*L*-carnitine, acetylcysteine,

α-lipoic acid, amifostine, calcium, magnesium, diethyldithiocarbamate, glutathione, gosha-jinki-gan, omega-3 fatty acids, vitamins B and E) without demonstrating any positive results [30].

Limitations in studies of these substances include small sample sizes, lack of placebo control groups, and in some cases, the study design was not blinded [31].

In another recent review, Hu et al. [32] highlighted the effects of some preventive treatments aimed at blocking CIPN onset. To do this, they examined the mechanisms by which antineoplastic drugs cause a degeneration of the nervous system. Unlike the previous study, this review showed that glutathione and its precursor, *N*-acetylcysteine, could have positive effects to prevent neurotoxicity induced by platinum-based drugs.

Non-pharmacological intervention

There are studies supporting the hypothesis that the cryotherapy technique may have a decisive role in the prevention of CIPN. In a recent study, encouraging results were obtained about neuropathies induced by taxanes drugs (paclitaxel) [33]. A recently published review highlighted how there is a positive effect on the prevention of CIPN through the use of cryotherapy without finding any type of side effect [34]. However, many studies are still needed to confirm the efficacy of cryotherapy in the prevention of CIPN. Cryotherapy associated with taxane-based chemotherapy determined better sensory and motor scores on the Patient Neurotoxicity Questionnaire [35].

Another non-pharmacological strategy derives from the use of surgical gloves which reduce blood flow in the most distal part of the fingers due to compression. The glove is worn before, during, and after chemotherapy treatment. This technique appeared effective in some studies related to taxane-induced CIPN [36]. Another recent double-blind study, however, seems to refute this hypothesis as there would be no significant differences in the incidence of CIPN between the hand compressed by the glove and the free hand [37].

Another approach to treat CIPN-related pain is the "Scrambler therapy", which involves a device providing non-invasive cutaneous electrical stimulation. The impulses are transmitted via surface electrodes placed above the pain region. Exploiting the spinal gating mechanisms, this therapy aims to replace "painful" with "non-painful" signals, with immediate pain reduction [38].

Scrambler therapy proved more effective than transcutaneous electrical nerve stimulation (TENS) in CIPN patients [39]. However, further studies with placebo and double-blind groups still need to be conducted in order to confirm their efficacy [40].

Effect of PA in subjects with CIPN

The positive effects of PA in patients with CIPN have now been demonstrated by several studies. Indeed, it now seems well known how a resistance or endurance exercise program can significantly reduce the side effects of adjuvant therapies involving peripheral neuropathies [41].

A study conducted on mice has shown that PA carried out beforehand at the beginning of adjuvant therapy with paclitaxel, could have a preventive effect on the onset of thermal hypoalgesia and prevent the reduction of the number of unmyelinated axons [42]. Furthermore, although the data were not significant, a reduction in the diameter of the axons was noted in the group that did not perform exercise.

Apart from sensory deficits, antineoplastic drug cumulative dose, and cycle number, the risk of falls in persons with CIPN includes the severity of muscle weakness and performance status [43]. A recent review highlighted that PA always produces a positive effect on subjects, regardless of the type of exercise, dosage, and setting [44]. It was also pointed out that studies show a moderate/high risk of bias in addition to considering only an adult population. The same review also argues that, although endurance exercise appears to be very effective in counteracting the limiting effects of CIPN, no studies tested aerobic exercise alone to ameliorate CIPN.

In fact, a randomized controlled trial study by Kneis et al. [11] developed a protocol in which the control group performed only aerobic activity, and it was then compared to the intervention group where

balance exercises were added. In this study, both groups benefited from their respective PA program in terms of neuropathy-related symptoms, suggesting that even endurance exercises alone can be effective in counteracting CIPN [11].

Due to the physiological diversity of the subject's conditions, antineoplastic drug type and dose, and the difficulty of quantifying the degree of CIPN, the studies that have dealt with this topic show many differences both in type and quantity of exercises carried out. Although the benefit of a PA intervention is well established, it is not easy to find a standardization of the exercises to propose.

In a randomized study, Courneya et al. [45] showed how a higher intensity activity can be more effective than moderate activity for younger, normal weight, and more fit subjects [45]. This implies that individuals require different doses of PA depending on their baseline conditions.

Vollmers et al. [14] structured an intervention where subjects exercised twice a week during the course of chemotherapy and for six weeks thereafter. Although there are no details on the sensorimotor exercises performed, an increase in postural stability was detected in the intervention group [14].

Some authors have chosen an activity throughout the week, even every day [13, 14] while others have administered PA two or three times per week [14, 15]. However, all authors obtained encouraging results from their respective training protocols.

The methodology for carrying out the protocol is also at the discretion of the authors. Some prescribe exercises in a gym or in a specialized clinic, instead, other authors have the subjects carry out the training program independently at home [13, 17, 18]. Subjects are instructed about how to perform the exercises and, in some cases, also about effort perception in order to remain within predefined parameters avoiding excessive or insufficient training.

A mixed methodology was also used one group carried out the activity in the gym at a higher intensity (OnTrack: a moderate- to high-intensity, combined supervised resistance and aerobic exercise program), while another group carried out a more moderate home training program called "Onco-Move": a low-intensity, home-based PA program. Although both programs produced positive outcomes, the group that performed higher intensity training reached better results [19].

Another mixed methodology was developed by McCrary et al. [20] in which a single group alternated exercises in a gym, assisted by an operator, and exercises carried out independently at their own home. Also, in this case, there was an improvement in the symptoms of CIPN as well as static and dynamic balance [20]. The Table 1 shows a summary of the studies assessing the effects of PA in relation to the type of exercise carried out.

It seems clear that there is no standardized methodology to evaluate the effects of PA in terms of methods of administering the exercises: type of activity, duration, and intensity.

However, it seems clear that, regardless of the method and exercises are chosen, the effects are always ameliorative compared to the control groups that do not carry out any type of activity. Notably, it would be useful to further investigate the effects of aerobic exercise alone as already proposed by Kanzawa-Lee et al. [44].

Effect of PA in individuals with CIPN on QoL

Paralleling evidence of a positive role of PA on the physical condition (e.g., strength or balance) of subjects with CIPN, there is much literature that deals with how an exercise program can improve the QoL of individuals during and after chemotherapy treatment.

Regarding the assessment of the degree of the CIPN, it is not always easy to have objective data as it is necessary to rely on very different assessment tools.

In a recent review, Park et al. [46] identified 41 assessment tools and, among other results, underlined that most of them (41.5%) are based on patient-reported outcomes (PROs) questionnaires highlighting how there is increasing attention to the subjective evaluation of symptoms.

However, there is always a discrepancy when using clinical assessment tools and PRO, especially in the intermediate grades of CIPN. It would be advisable to consider the results of clinical tests together with PRO in order to improve the quality of the evaluation of CIPN [47].

Among subjects diagnosed with cancer undergoing chemotherapy, there are common aspects that can affect their QoL such as depression, anxiety, and lower self-esteem. Physical issues, on the other hand, include fatigue, reduced cardiovascular and respiratory efficiency, muscle weakness and atrophy, pain, difficulty sleeping, and nausea [48].

In a recent review, it was reported how PA improved QoL in 4 out of 8 studies that considered the topic [44]. Furthermore, Mols et al. [49] indirectly demonstrated that neuropathies induced by chemotherapy drugs are inversely proportional to the PA performed weekly: they showed that statistically significant and clinically relevant worse scores on almost all EORTC QLQ-C30 [50] subscales were reported by those not meeting the PA guideline compared to those who did meet the guideline, regardless of CIPN symptoms.

Streckmann et al. [12] developed a training protocol for patients with lymphoma, assessing the effects of QoL as the first endpoint. They found a significant improvement in the comparison of the intervention group. In this case, the activity was carried out twice a week for 36 weeks and training sessions lasted about an hour [12].

Some aspects of QoL such as global health status, social functioning, physical functioning, role functioning, and fatigue, significantly improved in the intervention groups with resistance training and sensorimotor exercise training protocols compared to the usual care. In addition, there was an increase in fear of falling in the usual care group, but not in the resistance training and sensorimotor exercise groups [51].

These data have been also confirmed by a review that investigated the effects of physical exercise on fatigue (using the multidimensional fatigue inventory), highlighting how subjects benefited from a physical exercise program as regards general fatigue, physical fatigue, reduced activity, and reduced motivation [52].

Conclusions

We could not find standardized protocols indicating which type of PA is better for subjects with CIPN, and no uniformity in the modality, quantity, or intensity of the exercises.

Perhaps this is because samples are always different and not homogeneous as regards age, medical therapy, and entry physical condition.

More randomized controlled trials are needed to assess the efficacy of specific exercise interventions in order to confirm the efficacy of a single type of PA and provide information to the clinicians about which kind of exercise is preferred to manage CIPN symptoms.

It seems that aerobic PA plays a decisive role against CIPN symptoms since aerobic exercise-containing interventions led to significant CIPN benefits [44].

Since endurance PA determined encouraging results in all studies, it is reasonable to think that this type of PA is to be preferred in the management of neuropathies. Walking may also be useful to improve dynamic balance.

As already suggested by Kanzawa-Lee et al. [44], it would be advisable to develop more protocols that use this training modality to better understand its value.

However, it seems clear that PA plays a decisive role in significantly reducing the side effects of chemotherapy compared to physical inactivity or usual care. The improvement effect of PA and a better QoL is a consequence of the improvement of specific training aspects (strength, balance, endurance). Exercise seems the best, non-invasive, and side-effect-free practice as an adjuvant treatment of CIPN.

Furthermore, in most of the studies, PA at home or supported by an operator in specialized structures (labs or gym) is the preferred modality. Future studies could consider PA performed in groups rather than individually in order to evaluate the positive effects on mood and motivation.

Abbreviations

CIPN: chemotherapy-induced peripheral neuropathy

PA: physical activity

PROs: patient-reported outcomes

QoL: quality of life

Declarations

Author contributions

DD designed the study and wrote the first draft of the manuscript; ES and CC contributed to the study conception and design; L Marinelli, LP, L Mori and CT revised the manuscript. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

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