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REVIEW
ΑΝΑΣΚΟΠΗΣΗ

The effects of kinesiotherapy in cancer patients with chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a common treatment-related side effect experienced by cancer patients receiving antineoplastic agents. CIPN cannot be treated effectively with pharmaceutical intervention, and the management of its symptoms includes kinesiotherapy. This is a review of kinesiotherapy programs in cancer patients with CIPN. The programs proposed are usually a combination of aerobic exercises, muscle strengthening exercises, balance/sensorimotor training, or closed kinematic chain and core stability exercises. Overall, kinesiotherapy has been shown to reduce the clinical signs and symptoms caused by the side effects of CIPN, including neuropathic pain and altered sensation, improving the physical performance level, mobility, and balance control of the patients, and enhancing their quality of life. Further research is needed to clarify the underlying mechanisms of the exercise-induced reduction of CIPN symptoms.

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2023, 40(1):19–28

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Η επίδραση της κινησιοθεραπείας σε καρκινοπαθείς με χημειοθεραπευτικά-προκληθείσα περιφερική νευροπάθεια

Περίληψη στο τέλος του άρθρου

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1. INTRODUCTION

Cancer is the second leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. Lung, prostate, colorectal, stomach, and liver cancer are the most common types in men, and breast, colorectal, lung, cervical, and thyroid cancer in women. Current treatment of cancer requires specific regimens that include surgery, radiotherapy and chemotherapy.[1]

The antineoplastic agents used in chemotherapy, targeted at eliminating the rapidly dividing cancer cells, have proved to be highly effective in arresting cancer progression. Their untoward effects on normal cells, however, may result in various deleterious and sometimes even devastating side effects, including anemia, diarrhea, nausea and vomiting, infections, neurological impairment, including peripheral neuropathy, fatigue, hair loss, pain, and infertility. These adverse effects may require modification, or even interruption of chemotherapy, compromising the efficacy of the treatment.[2]

One serious adverse effect of antineoplastic agents is chemotherapy-induced peripheral neuropathy (CIPN), which is defined as damage and dysfunction of the peripheral nervous system, and is manifested by somatic and or autonomic signs or symptoms. The six main drug groups that can damage the peripheral sensory, motor, and autonomic neurons, and hence cause CIPN, are the following: platinum-based antineoplastic agents, vinca alkaloids, epothilones (ixabepilone), taxanes, proteasome inhibitors (bortezomib), and immunomodulatory drugs (thalidomide). Among these commonly used drugs, the most strongly neurotoxic are the platinum-based agents, taxanes, ixabepilone and thalidomide, while bortezomib and the vinca alkaloids show less neurotoxicity.[3]

CIPN is a common and persistent complication that can

affect both young and elderly patients, and is reported in an increasing number of cancer survivors. Its total prevalence has been estimated to exceed 32 million,[4] and it may cause persistent symptoms in as many as 40% of cancer survivors.[5] The prevalence of CIPN is agent-dependent, with reported rates varying from 19% to over 85%, and is highest in the case of platinum-based drugs (70–100%), taxanes (11–87%), thalidomide and its analogs (20–60%), and ixabepilone (60–65%).[6,7] Toxicity may occur either from a high single dose or after cumulative exposure. The observed symptoms vary in intensity and duration, and range from acute, transient thermal sensations to permanent changes in the peripheral nerves accompanied by chronic pain and irreversible nerve damage.[5]

Recent studies put the prevalence of CIPN at approximately 68.1% in the first month after chemotherapy, 60.0% at three months, and 30.0% after six months.[5] Several factors can affect its presentation, including as dosage, duration of treatment, the cumulative dose, co-administration of other neurotoxic chemotherapy agents, and pre-existing conditions associated with neurological damage, such as diabetes mellitus (DM) and alcohol abuse.[8]

Patients with CIPN generally suffer from altered sensations (numbness, burning, tingling, etc.), with dysesthesia and paresthesia, commonly located in the upper and lower extremities in a "glove-and-stocking" pattern.[9,10] They may also experience a variety of other symptoms, including pain, muscle weakness, compromised balance control, insecure gait, and reduced or absent reflexes.[9] These effects accumulate in a vicious cycle that leads to a reduction in physical activity, due to poor coordination, caused by both the cancer and the chemotherapy.[11,12]

According to current documentation, CIPN cannot be treated effectively with pharmacological agents, and management of the symptoms includes kinesiotherapy.[13] Although therapeutic exercise is prescribed for cancer survivors, little is known about its effectiveness in reducing the symptoms of CIPN, while the appropriate kinesiotherapy parameters (type, frequency and duration) are yet to be determined.[14]

1.1. The clinical picture of chemotherapy-induced peripheral neuropathy

The symptoms of CIPN vary widely, depending on the chemotherapy regimen administered, the duration of exposure to the neurotoxic agent(s) and the dosage; they may be acute, mild or severe, transient or chronic. Apart from sensory disturbances, patients may also experience motor symptoms, including weakness, loss of balance, difficulty with fine motor skills, and diminished or absent deep tendon reflexes.[15] The muscle weakness caused by CIPN is sometimes not easy to recognize, as it may be obscured by other cancer-related factors, such as cancer-related fatigue, dietary deficiency, sleep disturbances, depression, various drugs of other categories (e.g., corticosteroids), or pre-existing neuropathy.[4] In addition to the symptoms of CIPN, the cumulative neurotoxic effects of chemotherapy may also result in a decrease of somatosensory feedback, resulting in impairment of smooth and stable ambulation. Somatosensory systems contribute to the modulation of spinal pattern generators and motor commands. They also affect the perception and control of movements dependant on information about mechanical stimuli, muscle activation, body and limb movement, position and velocity, temperature changes, and potential damage to the skin. Cutaneous sensory receptors monitor the body's spatial orientation, providing the data required for reflexive responses and assisting in the modulation of gait.[15]

Cancer patients with CIPN often report gait difficulties because they feel unsteady and have a reduced sense of balance,[10] concerns that are associated with an increased risk of falling, and which limit their ability to perform activities of daily living (ADL).[15] Cancer patients with CIPN display slower gait velocity (110.75 cm/s vs 147.79 cm/s in control subjects) and a shorter step length (mean 53.92 cm vs 77.15 cm in control subjects). In addition, they exhibit abnormalities in other gait parameters, such as cadence, swing, double support duration time, stride length variability, and swing time variability.[15]

A lower gait velocity has been found to be directly associated with a higher risk of falling.[16] Patients with CIPN are five times more likely to fall than others of similar age.[17] Falls are also experienced by younger patients undergoing chemotherapy because of impaired gait and balance, which are the main risk factors for falling.[15] To compound CIPN injury, the experience of one fall instils the fear of another, and fear of falling may prejudice the physical condition of patients who reduce their activity, thus increasing the likelihood of falling. Among patients with advanced cancer, during a 6-month study, 50% reported a fall, while 19% of those taking platinum-based agents or taxanes suffered at least one fall during chemotherapy.[18] Factors that exacerbate the risk of falling are advanced age, cancer-related fatigue, generalized weakness, muscle weakness or atrophy, anemia, poor physical condition, multiple cycles of chemotherapy, neuropathic symptoms, and loss of balance.[18]

1.2. Pathological mechanisms of chemotherapy-induced peripheral neuropathy

Many physicians view CIPN as an expected side-effect of life-saving, or at least life-prolonging treatment, and, accordingly, may consider it to be acceptable, or even inevitable.[3] Cancer patients are routinely treated by chemotherapy with antineoplastic drugs that may have neurotoxic effects on the peripheral nervous system that vary, depending on their class, their specific physicochemical properties, and single or cumulative dosage.[7]

The pathological mechanism by which antineoplastic drugs damage the components of the nervous system and causes CIPN is multifactorial.[3] In brief, platinum-based CIPN is initiated by the accumulation of platinum adducts in the dorsal root ganglion (DRG) and trigeminal ganglion (TG) neurons. The platinum-based antineoplastics target the microglia and astrocytes, causing activation of immune cells, altering DNA transcription, and damaging the mitochondria. This leads to increased production of reactive oxygen species (ROS), with oxidative stress, dysregulation of calcium homeostasis, and enzyme, protein, and lipid damage within the neurons. The activity of Na^+, K^+, and transient receptor potential (TRP) ion channels is also altered. By these mechanisms, the blood-brain barrier is damaged, and neuroinflammation develops, potentially altering the excitability of peripheral neurons.[3] Taxanes also activate the microglia and astrocytes, damage the mitochondria, and affect DNA transcription. In addition, they cause microtubule disruption, which impairs axonal transport and leads to Wallerian degeneration. Taxanes cause demyelination of peripheral nerves, alter the excitability of peripheral neurons, give rise to neuroinflammation and lead to nociceptor sensitization.[3] Epothilones (ixabepilone) cause mitochondrial damage, alter DNA transcription, trigger microtubule disruption, and attract and activate T-lymphocytes and monocytes. These mechanisms lead to the release of proinflammatory cytokines (interleukins and chemokines), which activate immune cells, change the excitability of the peripheral neurons, and cause neuroinflammation.[3] Thalidomide downregulates tumor necrosis factor-alpha (TNF-α) and inhibits nuclear factor kappa B (NF-κB), leading to dysregulation of neurotrophins and their receptors, and accelerating neuronal cell death. Thalidomide also has an antiangiogenic effect that causes secondary ischemia and hypoxia of nerve fibers, eventually resulting in irreversible damage to sensory neurons. Activation of the dihydroxy metabolite of thalidomide triggers extensive release and activation of ROS and activates DNA cleavage and axon degeneration.[3] Finally, vinca alkaloids affect large axons and DRG neurons in ways that lead to Wallerian degeneration, alteration in ion channel activity and peripheral neuron hyperexcitability. In addition, they inhibit polymerization in the microtubules and suppress axonal transport, which leads to distal axonopathy. Thus, the excitability of peripheral neurons is affected, while the attraction and activation of immune cells by vinca alkaloids also trigger the release of proinflammatory cytokines (interleukins and chemokines), resulting in neuroinflammation.[3]

Studies indicate that the possible mechanism underlying diabetic peripheral neuropathy and hereditary motor and sensory neuropathy may also apply to the cancer population. Several forms of chemotherapy, including docetaxel- and paclitaxel-based regimens, result in decreased mRNA expression of the transport proteins of the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase gene (SERCA2a), leading to impaired skeletal muscle relaxation.[19]

2. THE ROLE OF KINESIOTHERAPY IN NEUROPROTECTION

Several different theories have been promoted about the mechanisms underlying the role of kinesiotherapy in neuroprotection. One theory suggests that exercise increases endoneurial blood flow and nitric oxide (NO) synthesis and improves Na^+/K^+-ATPase activity.[20,21] Another theory is that kinesiotherapy may help mitigate pain by reducing the level of the proinflammatory cytokines TNF-α and interleukin-1-beta (IL1β), which play a role in the development of neuropathic pain in response to nerve injury,[22] and the level of heat shock protein-27 (HSP-27).[23]

Kinesiotherapy has also been shown to have a local effect on peripheral nerves, producing changes in both the vasculature and metabolic systems. In the short term, exercise stimulates endothelium-dependent vasodilatation and endoneurial blood flow, while in the long term, it increases blood flow, exposing blood vessels to shear stress and causing vasodilation, thus improving oxygen delivery.[24] In the CIPN population, kinesiotherapy may reduce the neuropathic pain associated with peripheral neuropathy,[19] by raising the pain threshold and pain tolerance level during and after exercise.[25]

3. EFFECTIVE KINESIOTHERAPY INTERVENTIONS

3.1. Selection of studies

This review was conducted to evaluate the efficacy of proposed kinesiotherapy programs as a means of reha-

bilitation for cancer patients with CIPN and to summarize their documented effects. The literature review was based on "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines.[26] The selection procedure is depicted in the flow diagram in figure 1.

PubMed, CINAHL, Scopus, and Google Scholar databases were searched for trials and meta-analyses that evaluated the effects of therapeutic exercise on CIPN, using the keywords: "Chemotherapy-induced peripheral neuropathy" associated with "cancer patients", "neuropathic pain", "muscle strengthening exercise", "aerobic training", "gait disorders", "balance training", "proprioception", "stability and falls". Articles were considered if they met all of the following inclusion criteria: Publication between 2010 and 2020 in the English language; single or two armed studies (research vs control); participants suffered from CIPN at baseline and had received or were receiving potentially neurotoxic chemotherapy; specific exercise interventions (kinesiotherapy) were tested; statistically significant results were demonstrated, pre- vs post-intervention observation was reported; sufficient details were provided to allow replication of the kinesiotherapy program in clinical practice. The literature review revealed eight studies[25,27–33] that fulfilled the study criteria.

3.2. Types and effects of kinesiotherapy programs

The studies[25,27–33] encompassed a range of broad-spectrum kinesiotherapy programs designed for cancer patients with CIPN, including a combination of aerobic exercises,

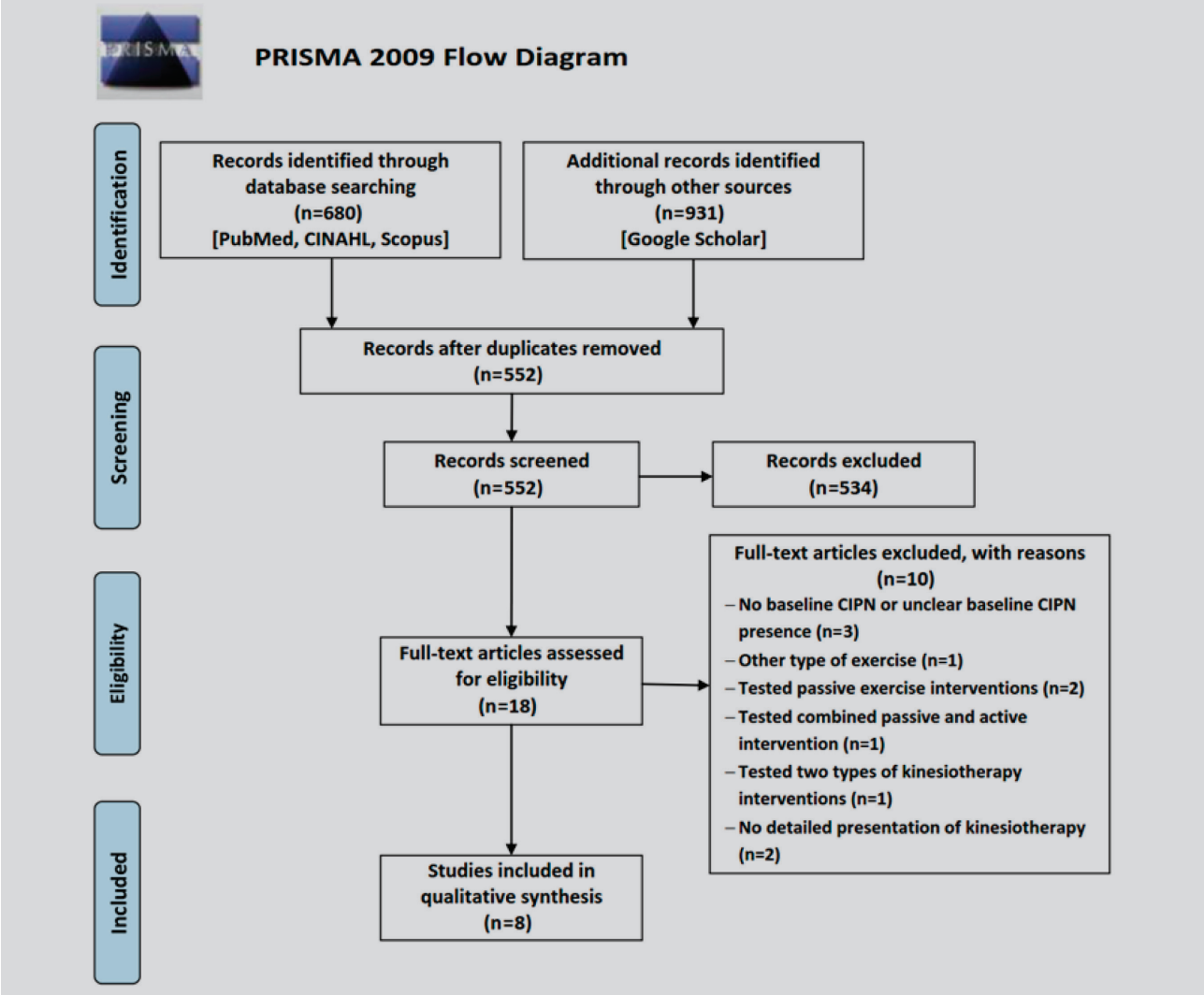

Figure 1. Kinesiotherapy (exercise-program) studies involving cancer patients with chemotherapy-induced peripheral neuropathy (published 2010–2020). Flow diagram of the selection of publications for the review.

muscle strengthening exercises, and balance/sensorimotor training or closed kinematic chain exercises, and core stability.

The aerobic training intensity was low to moderate; the maximum oxygen consumption (VO_{2max}) ranged between 40% and 60%,[25] while the maximum heart rate (HR_{max}) ranged between 55% and 70%,[31] or 70% and 80%.[27] Moderate intensity for strength training was suggested; the one-repetition maximum (1RM) ranged between 50% and 70%,[29] or 60% and 80%.[31] The weekly frequency of kinesiotherapy was a minimum of two days per week,[25,27,31] and a maximum of seven days per week;[32] the duration of a kinesiotherapy session of combined exercise programs was a minimum of 30 minutes and a maximum of 90 minutes per session.[33] The duration of the intervention programs ranged from a minimum of 3 weeks[32] to a maximum of 36 weeks.[29]

Post-intervention, the combined kinesiotherapy programs were found to have had a significant positive effect on the physical performance level of the patients,[25,27] and on muscle strength,[25,29,31] functional capacity,[28,33] fatigue,[29] balance control,[27,29–31] and CIPN-related symptoms (e.g., neuropathic pain and altered sensation).[25,27,30–33] In addition, the patients reported a better quality of life (QoL) after intervention.[25,27,29,32,33]

The types, frequency and duration of the kinesiotherapy, and the specific effects of the interventions in the studies reviewed are presented in detail in table 1.

4. KINESIOTHERAPY: BENEFITS AND CONCERNS

This review provides encouraging evidence that physiotherapy intervention using various different types of kinesiotherapy is a promising method for supporting cancer patients with CIPN. The essential benefit of kinesiotherapy is reduction of the neuropathic pain associated with CIPN. This neuropathic pain may become so severe that it undermines the QoL of the patient, and it has long been recognized as one of the more difficult types of pain to treat.[19] Aerobic exercise has been reported to decrease pain perception, and exercise-induced hypoalgesia (EIH) results in a rise in the pain threshold and pain tolerance level during and after exercise, while following exercise, pain intensity ratings appear to decrease.[25] It is still not clear what intensity of aerobic exercise is best for producing a hypoalgesic effect.[19]

Kinesiotherapy programs must be individualized to the patient, and should include appropriate warm-up and cool-down segments, and incorporate aerobic exercise, which is known to benefit cardiovascular performance and pain tolerance while reducing fatigue and depression.[22] Exercise has been shown to have a local effect on peripheral nerves, inducing changes in both the vasculature and metabolic systems.[34] It stimulates endothelium-dependent vasodilatation and endoneurial blood flow,[24] and has a positive effect on oxygen delivery, as increased blood flow exposes blood vessels to shear stress, which augments vasodilation.[35] EIH has been observed at aerobic exercise intensities between 60% and 75%,[36] and also during self-selected aerobic exercise intensities, where the patient was allowed to determine the level of exercise.[37] Clinical and experimental studies have also reported better Ca^{2+} handling and increased SERCA2a expression after long-term, moderate endurance training.[38,39] Although data regarding the effect of exercise training on $ErbB_2$-inhibitors in patients with peripheral neuropathy were not available, one animal study showed that 10 weeks of exercise training in rats improved cardiac dysfunction by reducing oxidative stress,[40] which is thought to be an underlying cause of the neuronal damage observed in many forms of peripheral neuropathies, including CIPN.[41]

Improvement of muscle strength and power promotes dynamic balance control. It is recommended that appropriate intervention be applied in cancer patients, even those in the metastatic stage, given the expected analgesic effects.[25] Cancer patients have benefited from resistance training; just one day per week was associated with 33% lower all-cause mortality.[42] Although reports are limited, EIH has been observed following a 45-min session of resistance training, performed at 75% of the individual's 1RM.[43]

Patients who participate in kinesiotherapy programs show a better chemotherapy completion rate, with no significant additional adverse events, and they also report higher levels of physical activity and less severe CIPN.[3] CIPN has been reported to be a fundamental reason (in 31% of cases) for dose reduction or interruption of chemotherapy.[3] In these patients, moderate to high-intensity aerobic training during chemotherapy showed the best results, preventing a drop in cardiorespiratory capacity or reducing it to a minimum. Aerobic exercise prevented the decrease of muscular strength, and lessened cancer-related fatigue and symptom severity, while no reduction in the dosage of chemotherapy was required.[3,9]

Medical monitoring may be necessary during the performance of exercise, especially in patients who suffer cancer-related fatigue.[44,45] Signs of aerobic training fatigue include severe muscle cramps, a feeling of heaviness in the lower extremities, and prolonged shallow breathing.[43]

Table 1. Kinesiotherapy (exercise-program) studies involving cancer patients with chemotherapy-induced peripheral neuropathy (published 2010–2020).

Study	Participants	Type of intervention duration and frequency	Post-intervention results* (outcome measures)
Wonders[25]	n=38 (men: 14; women: 24) Age: 60±3.4 years	Each exercise session included mild stretching An aerobic component of approximately 20–30 min in length at 40–60% VO_{2max}, and Strength-training that involved a full-body workout focused on muscular endurance improvements. Subjects completed 2–3 sets of 10–12 reps of exercises targeting major muscle groups 12 weeks, 2 days/week	Improvements in both VO_{2max} and muscular endurance Decrease of CIPN-related symptoms (Leeds Assessment of Neuropathic Symptoms and Signs, LANSS) Improvement in quality of life (McGill QOL questionnaire)
Streckmann et al[27]	n=56 (men: 42; women: 14) Intervention group (n=28) Age: 44 years	The intervention group trained with the supervision of a certified trainer (one-on-one) Aerobic endurance training: warm-up on a bicycle dynamometer (60–70% HR_{max}), 10–30 min on a treadmill or bicycle dynamometer (70–80% HR_{max}) at the end of the session Sensorimotor training: Four postural stabilization tasks, of progressively increasing difficulty, as well as surface instability (20 s exercise+20 s rest for 3 sets, 1 min rest between different exercises) Strength training: Four different resistance exercises performed with Thera-Band, at maximum force 36 weeks, 2 days/week, 1 hour	Reduced peripheral deep sensitivity Higher activity level (2.5 MET/week) Improvement in balance control Improvement in failed attempts Improved time to regain balance Improvement in quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, EORTC QLQ-C30)
Henke et al[28]	n=29 Intervention group (n=18) (sex and age not reported)	Aerobic – moderate intensity (55–70% HR reserve). Participants had to walk 6 min in the hallway Strength – 4 tasks: A bridging exercise, an abdominal exercise, a biceps curl exercise, and a triceps extension exercise were included. The upper limb's exercises were performed with the help of an elastic band of medium resistance (4.6 lbs resistance at 100% elongation). Patient trained at 50% of their maximal amount of repetitions possible (3 sets of 10 reps) 4 weeks, 5 days/week, 40 min/week (8 min/day)	Decrease of CIPN-related symptoms, pain and improvement in quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, EORTC QLQ-C30/LC13) Improvement in activities of daily living (Barthel index) Improvement in functional capacity (6-minute walking test, staircase walking, Modified Borg Scale, muscle strength)
Mizrahi et al[29]	n=30 (women) Age: 58.6±10.9 years	Participants were prescribed home-based, individualized, and low-to-moderate intensity exercise, for 90 min per week Aerobic exercise: walking, cycling or swimming (55–70% HR_{max}) Strength training: Resistance bands and body weight exercises (3 sets/10 reps, 50–70% 1RM) Core stability: Floor and stability ball exercises; 11–14 RPE. 12 weeks, 3–4 days/week, 90 min/week (10–30 min/day)	Decrease of CIPN-related symptoms (functional assessment of cancer therapies, FACT), Gynecologic Oncology Group Neurotoxicity Scale, GOG-Ntx) Improvement in physical activity (30 seconds sit-to-stand test, International Physical Activity Questionnaire (IPAQ) Improvement in fatigue (Somatic and Psychological Health Report, SPHERE) Improvement in quality of life (functional assessment of cancer therapies-ovarian module, FACT-O)
Fernandes & Kumar[30]	n=25 (men: 12; women 13) Intervention group (n=25) Age: 47±12 years	Closed kinematic chain exercises were performed on a firm surface, (a) Open chain active ankle range of motion, (b) bipedal toe raises and heel raises, (c) bipedal inversion and eversion, (d) unipedal toe raises and heel raises, (e) unipedal inversion and eversion, (f) wall slides, (g) unipedal balance for time, with eyes open. Initially, patients started with one set of 5/10 repetitions, and increased gradually to a total of three sets for each exercise. 3 weeks, 5 days/week, 12 min for a total of 7 exercises	Decrease of CIPN-related symptoms (Modified Total Neuropathy Score, mTNS) Improvement in balance (Berg Balance Scale, BBS)

*$p<0.05$

Min: Minutes, s: Seconds, reps: Repetitions, HR_{max}: Maximum heart rate, HR reserve: Heart rate reserve, RPE: Rate perceived exertion, VO_{2max}: Maximum rate of oxygen consumption, 1RM: One-repetition maximum

Table 1. (continued) Kinesiotherapy (exercise-program) studies involving cancer patients with chemotherapy-induced peripheral neuropathy (published 2010–2020).

Study	Participants	Type of intervention duration and frequency	Post-intervention results* (outcome measures)
Zimmer et al[31]	n=30 (men: 5; women: 12) Intervention group (n=17) Age: 68.53 years	Aerobic – bicycle ergometer or walking 20 min/week (10 min/day); moderate intensity (60–70% HR_{max}) Strength – 5 tasks: Bench press, lat pulldown, leg press, seated row, abdominal exercise, 2 sets of 8–12 reps (20 min/day); moderate intensity (60–80% 1RM) Balance – 4 tasks: Balance pads (standing on a stable, or an unstable surface), balancing on lines, etc. (15 min/day) 8 weeks, 2 days/week	Decrease of CIPN-related symptoms, pain and improvement in quality of life (functional assessment of cancer therapy/ Gynecologic Oncology Group Neurotoxicity questionnaire, FACT/GOG-NTX) Improvement in balance (Gleichgewichtstest) Improvement in strength and functional capacity (1 repetition max (1RM) and 6-minute walking test)
Dhawan et al[32]	n=46 (men: 7; women: 38) Intervention group (n=22) Age: 50.5±7.9 years	Strength, light intensity (body weight only) – 8 tasks (lying down position) ankle motion, hip abduction, straight leg raise (sitting position), digit abduction/adduction, wrist motion, elbow flexion/extension, knee flexion/extension, toe tapping (20 min) Balance – 4 tasks: One legged stand, toe stand, hip extension, tandem forward walking (10 min) 10 weeks, 7 days/week	Decrease of CIPN-related symptoms (Chemotherapy-induced Peripheral Neuropathy Assessment Tool, CIPNAT) Decrease of pain (Leeds Assessment of Neuropathic Symptoms and Signs, LANSS) Improvement in quality of life (QLQ-C30)
McCrary et al[33]	n=29 (men: 8; women: 21) Age: 61.6±11.8 years	Aerobic – 60 min/week (20 min/day); moderate intensity (RPE): 13–15 Strength – 4 tasks (2 sets/task (20 min/day) 1–4 week period: (a) Upper body horizontal press (dumbbell/Theraband chest press), (b) upper body horizontal pull (dumbbell/Theraband row), (c) lower body single leg press (1-leg sit-to-stand), (d) lower body double leg pull (Romanian deadlift) 5–8 week period: (a) Upper body vertical press (dumbbell/ Theraband shoulder press), (b) upper body vertical pull (machine/Theraband lat pulldown), (c) lower body double leg press (squat), (d) lower body single leg pull (1-leg Romanian deadlift) Balance – 4 tasks, 2 sets of 15–30 s or 8 reps/task (20 min/day) 1–4 week period: (a) Two-leg exercise (tandem standing for 30 seconds, eyes open), (b) two-leg exercise (tandem walk), (c) single-leg exercise (single-leg stance for 15 seconds), (d) single-leg exercise (single-leg stance with arm extension; eight reps each leg) 5–8 week period: (a) Two-leg exercise (tandem standing for 15 seconds, eyes closed), (b) two-leg exercise (tandem walk with torso rotation), (c) single-leg exercise (single-leg stance with torso rotation, (d) single leg exercise (single-leg stance, eyes closed-hands progressively moved off wall) 8 weeks, 3 days/week	Decrease of CIPN-related symptoms and improvement in quality of life (Total Neuropathy Score-clinical version, TNSc), EORTC QLQ CIPN20, and *36*-Item Short Form Survey (SF-36) Improvement in physical function [6-minute walking test, 5-time sit-to-stand test, and CIPN Rasch Built Overall Disability Score (CIPN-R-ODS)] Improvement in balance (Swaymeter)

*$p<0.05$

Min: Minutes, s: Seconds, reps: Repetitions, HR_{max}: Maximum heart rate, HR reserve: Heart rate reserve, RPE: Rate perceived exertion, VO_{2max}: Maximum rate of oxygen consumption, 1RM: One-repetition maximum

Resistance training should be limited to a level that does not result in the muscles being overworked or becoming exhausted. Symptoms indicative of muscle exhaustion include, but are not limited to, muscle weakness within half an hour after exercise and excessive muscle soreness between 24 h and 48 h later.[46]

The findings presented in this review allow us to hypothesize that kinesiotherapy could be beneficial for patients

with CIPN. For cancer patients who are able to tolerate a regular physical activity program, exercise rehabilitation should be recommended as a lifestyle modification that could mitigate peripheral nerve damage caused by chemotherapy. Further studies are needed to add to the current limited knowledge and determine the optimal future standards for exercise prescription.[19]

The survival rate and lifespan of cancer patients are expected to continue to increase in the coming years, as a result of earlier diagnosis and improved treatment. Recognition of the various factors that increase QoL and reduce the mortality of the survivors is an important task and a challenge. Chemotherapy and neurotoxicity represent an important area of research that has attracted a great deal of interest in recent years, and it is apparent that the symptoms caused by CIPN are not adequately treated by medication and significantly affect the QoL of patients. Kinesiotherapy is associated with higher levels of physical activity and less severe CIPN, and it improves the chemotherapy completion rate without causing significant adverse events.

5. CONCLUSIONS

This review showed that various different exercise protocols for cancer patients with CIPN symptoms are feasible and effective. Kinesiotherapy may be the most basic physiotherapeutic intervention for the cancer patient, improving cardiovascular endurance and aerobic capacity, muscle activation and strength, balance control, functional capacity, mood, emotional distress, and quality of sleep, while decreasing neuropathic pain and cancer-related fatigue. Exercise can also maintain and or improve the function of the nervous system in patients who are or were undergoing chemotherapy.

Management of the cancer patient should be further developed and should always be individualized, aiming at a high level of QoL and the best possible positive result. Kinesiotherapy should be used as an effective strategy to minimize CIPN-induced detriments to QoL, and further research is necessary to clarify the specific mechanisms and the clinical short- and long-term impact of exercise-induced improvement.

ΠΕΡΙΛΗΨΗ

Η επίδραση της κινησιοθεραπείας σε καρκινοπαθείς με χημειοθεραπευτικά-προκληθείσα περιφερική νευροπάθεια

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Η χημειοθεραπευτικά-προκληθείσα περιφερική νευροπάθεια (ΧΠΠΝ) αποτελεί συνήθη ανεπιθύμητη ενέργεια των αντινεοπλασματικών παραγόντων που χρησιμοποιούνται σε θεραπευτικά σχήματα καρκινοπαθών ασθενών. Η ΧΠΠΝ δεν αντιμετωπίζεται αποτελεσματικά με φαρμακευτική αγωγή και για τον έλεγχο των συμπτωμάτων της συχνά χρησιμοποιείται κινησιοθεραπεία. Στην παρούσα ανασκόπηση παρουσιάζονται προγράμματα κινησιοθεραπείας τα οποία έχουν επιτυχώς εφαρμοστεί σε καρκινοπαθείς με ΧΠΠΝ. Τα προτεινόμενα προγράμματα κινησιοθεραπείας είναι σύνθετα και περιλαμβάνουν συνδυασμούς αεροβικών ασκήσεων, μυϊκής ενδυνάμωσης και ισορροπίας/αισθητοκινητικής εξάσκησης, ή συνδυασμούς ασκήσεων κλειστής κινητικής αλυσίδας και σταθερότητας κορμού. Η κινησιοθεραπεία μειώνει τα συμπτώματα της ΧΠΠΝ, όπως τον νευροπαθητικό πόνο και την αλλοιωμένη αισθητικότητα, ενώ βελτιώνει το επίπεδο της φυσικής κατάστασης, της κινητικότητας και τον έλεγχο της ισορροπίας του ασθενούς. Ωστόσο, απαιτείται περαιτέρω έρευνα για να αποσαφηνιστούν οι μηχανισμοί επίδρασης της άσκησης στη βελτίωση των συμπτωμάτων της ΧΠΠΝ.

Λέξεις ευρετηρίου: Αισθητικοκινητικές διαταραχές βάδισης, Νευροπαθητικός πόνος, Ποιότητα ζωής, Φυσικοθεραπεία, Χημειοθεραπεία

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