Investigating Chemotherapy Induced Peripheral Neuropathy in Ovarian Cancer Patients

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I. Abstract

A woman's risk of developing ovarian cancer in her lifetime is 1 in 78. Ovarian cancer is characterized by rapid cell growth in or around the ovaries that can compromise healthy tissues. Its subtle early symptoms often delay diagnosis until advanced stages. Chemotherapy, combined with surgery, is a common treatment approach. However, it introduces chemotherapy-induced peripheral neuropathy (CIPN). This neuropathy arises from chemotherapy's impact on peripheral nerves, resulting in sensations like tingling, burning, and weakness. CIPN has profound physical and psychological effects, affecting patients' daily lives and diminishing their quality of life (QoL). This article provides an in-depth exploration of ovarian cancer, its treatments, CIPN's mechanisms, diagnosis, management, and its impact on QoL based on research studies. Two studies highlight CIPN's prevalence among ovarian cancer patients and its detrimental effects on their QoL. Future directions in CIPN management emphasize patient-centered care and further research to alleviate this treatment-induced challenge.

II. Keywords

Ovarian Cancer, Chemotherapy-induced peripheral neuropathy, Adult, Female, Middle Aged, Ovarian neoplasms / drug TB therapy, Quality of life, Chemotherapy drugs

III. Introduction to Ovarian Cancer and Chemotherapy Treatment

A. Background information on Ovarian Cancer

Ovarian cancer is a growth of cells that forms in the ovaries. The cells will multiple quickly and can destroy healthy body tissue. The female reproductive system contains two ovaries, both about the size of an almond. The ovaries produce eggs, estrogen, and progesterone. Symptoms are usually not noticeable early on. When they develop, signs and symptoms include weight loss, abdominal swelling, fatigue, back pain, and discomfort in the pelvic area. Ovarian cancer begins when cells in the ovaries develop mutations in their DNA. These mutations will lead to uncontrolled multiplication of cells, creating a mass of cancer cells. These cells can break off from the original tumor and metastasize or spread throughout the body (Mayo Clinic, 2023)

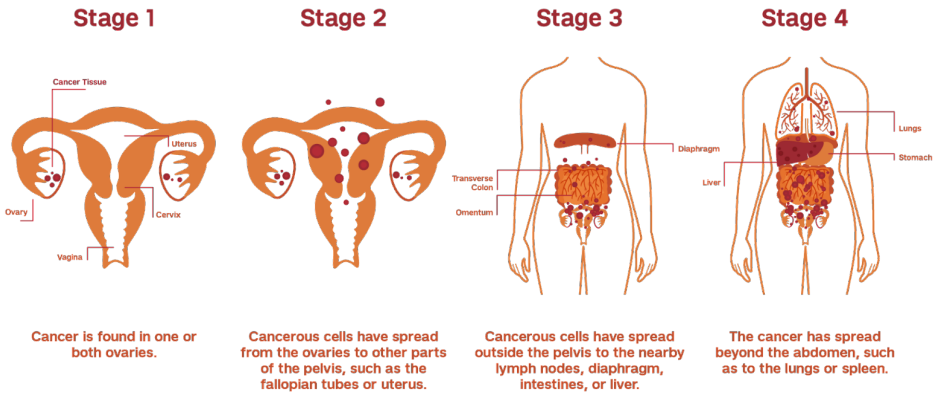

Figure 1: Ovarian Cancer Stages (Weill Cornell Medicine)

The type of ovarian cancer a patient has is determined by which type of cell the cancer began. The three types are epithelial ovarian cancer, stromal tumors, and germ cell tumors. Epithelial ovarian tumors start on the outer surface of the ovaries. They can be benign, borderline, or malignant. Cancerous epithelial tumors are called carcinogens. Of all malignant ovarian cancers, more than 85% are epithelial ovarian carcinomas. Based on how much the tumor cells look normal, each cancer is given a grade. Grade 3 carcinomas look less like normal tissue compared to grade 1. Ovarian germ cell tumors are less than 2% of all ovarian cancers. The most common germ cell tumors are teratomas and dysgerminomas. Ovarian stromal tumors only account for about 1% of ovarian cancers. These types of tumors usually cause vaginal bleeding.

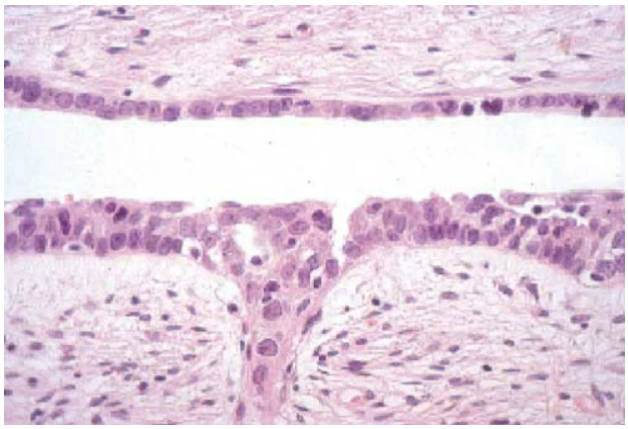

Figure 2: Ovarian carcinoma in situ. The epithelium is thickened by stratified cells showing loss of nuclear polarity and marked nuclear pleomorphism, hyperchromasia and chromatin clumping. (Bell 2005)

B. Overview of Chemotherapy as a Common Treatment for Ovarian Cancer

Treatment for ovarian cancer is usually a combination of surgery and chemotherapy. The surgery will remove the cancer tissue. Chemotherapy will use special medicines to kill the cancer. Chemotherapy can be performed through oral pills or intravenous medicines. Because ovarian cancer is a broad group of several types of cancer, treatment decisions are usually made based on the type of cancer, the stage, and any special conditions. Chemotherapy as a treatment is considered a systemic therapy because it can reach cancer cells throughout the body. Chemo is used to kill the remaining cells left in the body after surgery was performed ("What is Peripheral Neuropathy" 2019).

Chemotherapy for ovarian cancer will involve a combination of drugs. The combination includes a type of chemo drug called a platinum compound (usually cisplatin or carboplatin), and another type of chemo drug called a taxane, such as paclitaxel (Taxol®) or docetaxel (Taxotere®). The drugs are usually delivered via IV every 3-4 weeks. Depending on the type and stage of cancer, the chemotherapy will last between 3-6 cycles of treatment. Chemotherapy for germ cell tumors and stromal tumors can include different combinations of chemo medications.

IV. Understanding Chemotherapy-Induced Peripheral Neuropathy

A. Introduction to Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Cancer treatments and chemotherapy drugs can cause chemotherapy-induced peripheral neuropathy (CIPN). Peripheral neuropathy is defined as "a set of symptoms caused by damage to the nerves that are outside the brain and spinal cord" by the American Cancer Society. The nerves outside the brain and spinal cord are called the peripheral nerves and control the movement of our arms and legs. These nerves relay sensory and motor information. Peripheral neuropathy presents as several sensations in the hands and feets, including tingling, burning,

numbness, weakness, pain, cramps, and a decreased ability to feel hot and cold. CIPN is an adverse effect of anticancer agents. Patients will feel the sensations listed above that progress proximally in the arms and legs ("What is Peripheral Neuropathy" 2019).

B. Mechanisms of CIPN development

Patients that undergo treatment with taxanes, platinum drugs, vinca alkaloids, and immunomodulating drugs are most likely to develop CIPN. CIPN develops because of mitochondrial toxicity and oxidative stress, DNA damage, and more. "Platinum agents change the structure of DNA and appear to induce neural toxicity mainly through the dorsal root ganglion (DRG). They have been shown to reduce nucleolar size in the sensory DRG cells in which the degree of nucleolar size change correlated with the degree of neurotoxicity" (Desforges et al. 2022) Taxanes will hyper stabilize microtubules, which will impair axonal transport of cell products.

C. Importance of studying CIPN in Ovarian Cancer Patients

CIPN can severely decrease the quality of life of ovarian cancer patients. It has been seen that patients with severe CIPN experience decrease physical, emotional and social health. It will cause the patient more pain and fatigue. CIPN will affect a patient's ability to do simple tasks like button a shirt, write, and even walk. CIPN can affect a patient for months and years after their treatment was completed. If sensations get increasingly worse, serious problems like organ failure and paralysis can occur. CIPN can also become a financial burden on the patient, especially because the condition will interfere with their ability to work. In treating ovarian cancer patients, the chemotherapy drugs that are used are platinum compounds and taxanes. Some of the most common chemotherapy drugs that cause CIPN are platinum drugs like cisplatin and taxanes like paclitaxel and docetaxel. This puts ovarian cancer patients at high risk of developing CIPN short or long term. Because they are high risk, it is important to understand how often CIPN will develop and how it will affect a patient's quality of life. Additionally, the prevention and treatment of CIPN are challenging because it presents differently with each chemotherapy drug. The only way to assist patients with CIPN is regular patient assessment and patient awareness.

D. Physical symptoms and manifestations of CIPN

Like mentioned above, CIPN will have sensory and motor effects on patients. Each patient will have a different presentation of symptoms, but general symptoms include numbness, weakness, pain, and tingling. Patients may also feel like needles are pricking their hands and feets. They may have difficulty with grasping objects. Ringing in the ears or loss of hearing and changes in vision are also common. Urination issues, muscle cramps, and a loss of balance are all physical presentations of CIPN.

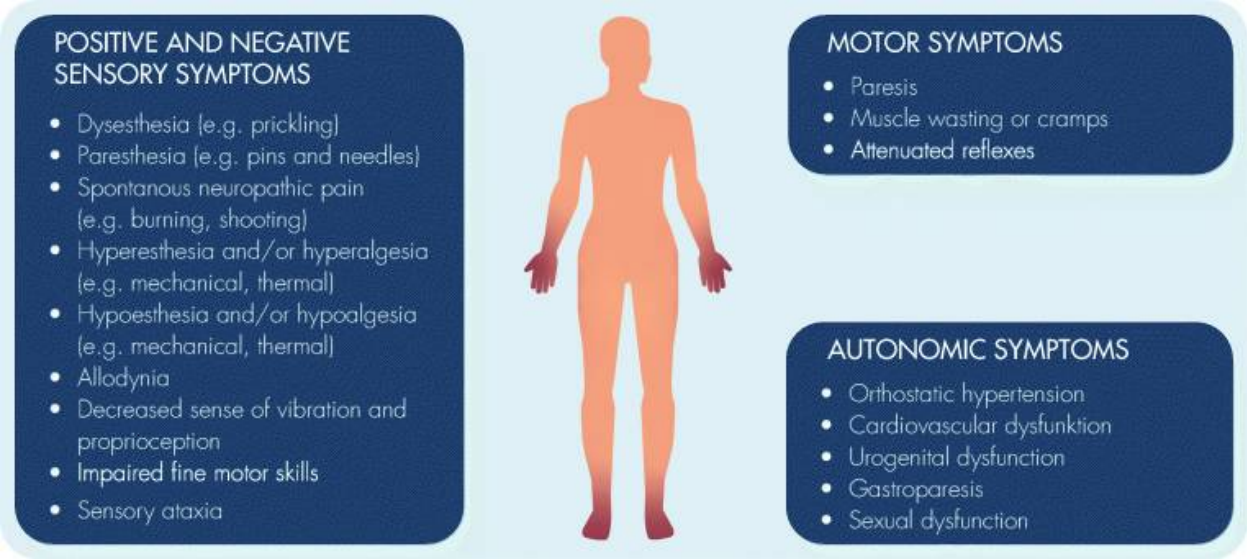

Figure 2: Symptoms of CIPN (Maihofner et al. 2021).

D. Psychological and emotional implications of CIPN

CIPN will affect patients ability to complete small tasks on their own if it is a moderate to severe case. They will not be able to button their shirt or tie their shoes. Patients will likely become dependent on a caregiver. The sudden lack of independence after the onset of CIPN will cause a patient's emotional health to decrease. They may become irritable, angry, or hopeless. These patients will also have a higher risk of becoming depressed. They may begin to refuse treatment because they don't see any improvement in their health.

V. Diagnosis and Assessment of Chemotherapy-Induced Peripheral Neuropathy

A. Clinical evaluation and assessment tools for CIPN

At the moment, there is no standard approach of diagnosing CIPN. One effective assessment that can be used is a neurophysiological examination. Nerve conduction studies are a useful tool in differentiating between pathologies as CIPN is mostly associated with axonopathy pathologies. Overall, nerve conduction studies assist in the evaluation of neuromuscular diseases by providing a physiologic assessment of the peripheral nerve, muscle, neuromuscular junction, dorsal root ganglion cell, and anterior horn cell. Other assessment techniques are using a 1-5 scale to grade peripheral neuropathy based on symptom severity. Some of these assessments are physician reported, whereas others are patient reported. Patient reported assessments showed more severe symptoms and decreased quality of life. Given the lack of knowledge on CIPN treatment and the limitation of objective and subjective assessments, evaluation is challenging. Composite studies have become more common. These studies combine a physician reported assessment and nerve conduction studies. Composite studies are usually more accurate, but they are time consuming and require busy technology (Jin et al. 2020).

B. Challenges in accurately diagnosing CIPN in ovarian cancer patients

It can become difficult to accurately diagnose CIPN in patients because symptoms are subjective. The first step in diagnosing CIPN is ruling out any pre-existing conditions, association with surgery, or other factors. Then, the assessment mentioned above can be used to diagnose. Again, these assessments are not highly accurate and are time-consuming. Additionally, a clinical assessment can only diagnose, it cannot prove the origin of the symptoms.

VI. Management Strategies for Chemotherapy-Induced Peripheral Neuropathy

A. Pharmacological interventions for managing CIPN symptoms

Several therapies have been explored for CIPN treatment. Nerve-protective therapy conducted by EPO (Erythropoietin) can enhance nerve regeneration and recovery after peripheral nerve injury. However, EPO cannot be used in treating CIPN. It is severely contraindicated because EPO has been associated with tumor cell growth. Anti-inflammatory therapies have also been suggested. Non steroidal anti-inflammatory drugs can reduce pain and inflammation. However, there is little research investigating the use of these drugs in the treatment of CIPN.

Venlafaxine and duloxetine are selective serotonin and norepinephrine reuptake inhibitors (SNRIs). These medications are used to treat depressive disorders and are the only-FDA approved drug for treating pain caused by diabetic peripheral neuropathy. One meta-analysis showed that SNRIs demonstrated therapeutic potential of both venlafaxine and duloxetine in CIPN. Other studies did not find any statistically significant reduction in acute or chronic CIPN symptoms. This is likely due to the dosages that the studies tested. These drug treatments appear to be promising, but are still in the early stage of testing (Desforges et al. 2022).

Glutamine is an amino acid that is naturally produced in the human body. Studies have supported the potential of oral glutamine therapy in helping CIPN symptoms. However, these studies had a small sample size and lacked a control group. There is no clear evidence of the efficacy of oral glutamine treating CIPN.

B. Non-pharmacological approaches to alleviate CIPN-related discomfort

Non-pharmacological approaches to treat CIPN have been studied. These studies have found that massages, acupuncture, and foot baths can reduce CIPN symptoms. Many studies have shown the effectiveness of acupuncture in treating pain and numbness caused by CIPN. Physical therapy is also a viable treatment option for neuropathic pain. A systematic review found that a group that performed physical activity had less pain and decreased pain compared to a group that did not perform any physical therapy (Desforges et al. 2022).

Neurofeedback (NF) targets brain activity to reduce the effects and severity of pain. A randomized controlled trial found that an EEG NF significantly reduced CIPN symptoms compared to control. NF may be a promising treatment option for CIPN patients.

VII. Research Studies and Findings

A. Review of Study 1: Chemotherapy-induced peripheral neuropathy among patients with ovarian cancer (Jin, Lin et al. 2020).

The objective of this study was to evaluate the course of chemotherapy-induced peripheral neuropathy (CIPN) among patients with ovarian cancer receiving taxanes.

A retrospective case-control study was conducted between January 1, 2016, and May 31, 2018, in Xiangya Hospital in Changsha, China. Women with ovarian cancer received taxane and platinum-complex combination therapy as their chemotherapy treatment. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Ovarian Cancer module questionnaire was used to assess the severity of neuropathy by telephone. (The EORTC QoL questionnaire is an integrated system for assessing the health related quality of life QoL of cancer patients participating in international clinical trials). Of the 88 women included in the study, 61 women reported CIPN symptoms. This is 69.3% of women in the study.

The percentage of women suffering from sensory peripheral neuropathy (SPN) was higher than motor peripheral neuropathy (MPN) at any time during the study. Sensory peripheral neuropathy was associated with the use of docetaxel and paclitaxel. Additionally, the average weakness score in acute CIPN was lower than chronic CIPN (1.46 vs 2.00). The patients who were treated with vitamin B1 experienced better relief from CIPN.

The results of this study provided crucial information. 1. A significant proportion of ovarian cancer patients who receive taxanes suffer from residual neuropathy. 2. Docetaxel and paclitaxel have been associated with sensory peripheral neuropathy. 3. It is possible that Vitamin B1 or amifostine may improve the symptoms of CIPN.

B. Review of Study 2: The impact of peripheral neuropathy symptoms, self-care ability, and disturbances to daily life on quality of life among gynecological cancer patients undergoing chemotherapy: a cross-sectional survey (Mun, Sohee, and Hyojung Park 2022).

The study investigated the effects of peripheral neuropathy symptoms, self-care ability, and disturbances to daily life on QoL among gynecological cancer patients undergoing chemotherapy.

The study outlined the following four goals:

(1) Analyze the peripheral neuropathy symptoms, self-care ability, disturbances to daily life, and QoL of gynecological cancer patients
(2) Identify differences in the QoL of gynecological cancer patients according to their general characteristics and disease-related characteristics
(3) Identify the relationships between peripheral neuropathy symptoms, self-care ability, disturbances to daily life, and QoL in gynecological cancer patients
(4) Identify the factors that influence the QoL of gynecological cancer patients
This study was a correlational study investigating the relationship between peripheral neuropathy symptoms, self-care ability, disturbances to daily life, and QoL of gynecological

cancer patients undergoing chemotherapy. It was an observational study and data were collected using questionnaires that participants completed.

The study was a retrospective cohort study. This study analyzed data on 144 gynecological cancer patients undergoing chemotherapy at Asan Medical Center in Seoul, South Korea. There were multiple inclusion criteria for the participants of the study. The participants were required to be at least 19 years old, diagnosed with gynecological cancer (ovarian, endometrial, cervical, vaginal, or vulvar cancer), and have received four or more concurrent cycles of paclitaxel and platinum-based drugs.

Patient QoL was evaluated using the Korean version of the Functional Assessment Cancer Therapy-General developed by Cella et al. for measuring the QoL of cancer patients. The tool evaluates physical state, social/family status, emotional state, and functional state. Peripheral neuropathy symptoms were evaluated using an instrument developed by Tofthagen. Nine items on the occurrence of peripheral neuropathy symptoms, six items on the scope of occurrence, and nine items on the intensity of the symptoms were used in this study. For the intensity of the symptoms, nine items are evaluated on a 10-point scale (0 points, no symptoms; 10 points, very severe). Self-care ability was evaluated using an instrument developed by Geden and Taylor. It contains 32 items and uses a 6-point Likert scale (1 point, strongly disagree; 6 points, strongly agree). A higher score corresponds to a higher self-care ability, and possible scores range from 32 to 192 points. Disturbances to daily life were evaluated using an instrument developed by Tofthagen et al. Fourteen items that measured disturbances to daily life were used in this study and scored based on a scale ranging from 0 points (no effect at all) to 10 points (strong effect). A higher score corresponded to a higher degree of disturbances to daily life, and possible scores ranged from 0 to 140 points. General characteristics included six items on age, marital status, education level, economic status, living with family, and regular exercise, and disease-related characteristics, which included type of cancer, the first instance of chemotherapy-induced peripheral neuropathy (CIPN), and the duration of CIPN (3 items), were investigated using a structured questionnaire. Using electronic medical records, the number of types of chemotherapy cycles the patient had undergone, the number of chemotherapy treatments received, and the cumulative amount of anticancer agents administered were recorded.

The results of the study were as follows:

QoL showed significant differences according to age, education level, monthly family income, regular exercise, duration of CIPN experience, the number of types of chemotherapy, and the cumulative number of chemotherapy treatments.

Variable	Categories	Mean±SD or n (%)	Quality of life	
			Mean±SD	t or F (*p*)
General characteristics				
Age (year)	Range, 32–76	56.38±8.59		
	<50[a]	30 (20.8)	68.57±16.52	12.64 (<.001)
	50–59[b]	59 (41.0)	65.98±19.27	a, b>c[‡]
	≥60[c]	55 (38.2)	51.07±18.52	
Marital status	Single	13 (9.0)	63.38±18.85	0.19 (.829)
	Married	123 (85.4)	60.74±20.04	
	Others	8 (5.6)	58.00±21.26	
Education level	≤Middle school[a]	16 (11.1)	50.31±20.71	6.15 (.003)
	High school[b]	81 (56.3)	58.74±19.46	a<c[‡]
	≥College[c]	47 (32.6)	68.00±18.24	
Monthly family income (KRW)	<1 milion[a]	49 (34.0)	53.92±19.77	6.60 (.002)
	1–3 milion[b]	50 (34.7)	60.88±20.85	a<c[‡]
	≥3 milion[c]	45 (31.3)	68.29±16.28	
Living with family	Yes	131 (91.0)	60.85±19.75	-.040 (.968)
	No	13 (9.0)	60.62±22.10	
Regular exercise	Yes	79 (54.9)	66.53±18.41	3.99 (<.001)
	No	65 (45.1)	53.89±19.55	
Disease-related characteristics				
Type of cancer	Ovarian	101 (70.1)	60.06±18.53	0.85 (.469)
	Endometrial	21 (14.6)	60.90±24.02	
	Cervical	20 (13.9)	64.05±22.77	
	Others (vaginal/vulvar)	2 (1.4)	82.00±18.39	
First incidence of CIPN	1–3	99 (68.8)	60.64±18.94	0.30 (.744)
	4–6	28 (19.4)	59.50±21.11	
	≥7	17 (11.8)	64.12±23.90	
Duration of CIPN (month)	<6 [a]	57 (39.6)	62.23±20.90	6.65(.002)
	6–23[b]	47 (32.6)	66.68±18.80	a, b>c[‡]
	≥24[c]	40 (27.8)	51.95±16.77	
Types of chemotherapy drugs	Range, 1–7	1.97±1.31		
	1[a]	73 (50.7)	66.10±19.41	6.10 (.003)
	2[b]	32 (22.2)	58.00±21.36	a, b>c[‡]

Table 1. Differences in quality of life according to participants' characteristics (N=144) (Mun et al, 2022).

The mean score for QoL was low at 60.83±19.89, with the functional state (14.82±5.98) showing the lowest mean score. The mean score for CIPN symptoms among the participants was 42.53±19.73. The mean score for self-care ability was 144.33±28.79, and physical skills showed a relatively lower score compared to the other categories. The mean score for disturbances to daily life was 56.24±34.09. The possible ranges and categories breakdowns are given below.

Variable	Categories	Mean±SD	Possible range	Data range
Quality of life		60.83±19.89	0–108	5–106
	Psychological state	14.89±4.82	0–24	0–24
	Physical state	15.91±7.34	0–28	0–28
	Social state	15.21±6.42	0–28	0–28
	Functional state	14.82±5.98	0–28	0–28
CIPN symptoms		42.53±19.73	0–90	2–90
	Sensory symptoms	30.93±13.93	0–60	2–58
	Motor symptoms	11.60±7.37	0–30	0–30
Self-care ability		144.33±28.79	32–192	46–190
	Perception of self-monitoring	5.20±0.96	1–6	2–6
	Attention to self-management	14.83±2.43	3–18	6–18
	Cognitive aspects of self-cares	50.48±10.27	6–66	11–66
	Judgment and decision-making process	18.33±4.07	4–24	4–24
	Information-seeking behaviors	17.10±3.50	4–24	5–24
	Physical skills		9–54	9–54
Disturbances to daily life		56.24±34.09	0–140	0–140
	General activities	44.58±25.27	0–100	0–100
	Manual dexterity	11.66±10.50	0–40	0–40

Table 2: Levels of quality of life, CIPN symptoms, self-care ability, and disturbances to daily life (N=144) (Mun et al, 2022).

The factors that affected quality of life of these patients were self-care ability, intensity of disturbances to daily life, duration of CIPN symptoms, and regular exercise. The factor with the greatest influence was self-care ability, followed by the intensity of disturbances to daily life, the duration of CIPN symptoms, and regular exercise. This makes it obvious that a lower QoL is correlated to a higher intensity of disturbances to daily life, a shorter duration of CIPN symptoms, a lack of regular exercise, and a low self-care ability. Other factors had little to no impact.

Variable	B	SE	β	t (*p*)
(Constant)	35.22	12.91		3.37 (.001)
Regular exercise‡	−5.00	2.36	−.13	−2.12 (.036)
Number of types of chemotherapy	−2.67	1.67	−.18	−1.60 (.113)
Monthly family income (KRW)‡				
1–3 million	2.87	2.98	.07	0.97 (.336)
>3 million	1.08	3.13	.04	0.58 (.556)
Number of chemotherapy treatments	0.08	0.18	.05	0.45 (.655)
Education level‡				
≤Middle school	0.64	3.86	.01	0.17 (.868)
≥College	1.28	2.69	.03	0.48 (.635)
Age (year)	0.07	0.16	.03	0.44 (.662)
Self-care ability	0.27	0.05	.39	5.65 (<.001)
Disturbances to daily life	−0.22	0.05	−.38	−4.51 (<.001)
Duration of peripheral neuropathy symptoms‡ (month)				
6–23	6.04	2.82	.14	2.14 (.034)
≥24	2.14	4.2	.05	0.51 (.611)
CIPN symptoms	−0.06	0.08	−.06	−0.85 (.400)
R^2=60.6, adjusted R^2=56.7, F(*p*)=15.38(<.001)				

Table 3: Factors influencing quality of life (N=144) (Mun et al, 2022).

This study provided the scientific community with a substantial amount of usable data. It focused on understanding the physical restriction on the QoL of patients. It can be understood from this study that more exercise in a patient's life can help their self-care ability, increasing their quality of life. The study informs the scientific community that physical skills become the weakest and have the most effect on a patient's quality of life. Physicians can use this information to design treatment plans for their patients. They can use physical therapy or incorporate exercise into their patient's routine.

C. Key takeaways from both studies

Chemotherapy-induced peripheral neuropathy is significantly present in ovarian cancer patients. It negatively affects a patient's QoL. In addition, both studies point towards SPN being worse than MPN at any given time.

In order to improve the QoL of ovarian cancer patients, periodic patient education and assessments should be undertaken for the early identification of peripheral neuropathy. In

addition, programs to improve self-care ability and alleviate patients' daily limitations may help improve their QoL.

More research needs to be done on the medications that can help reduce a patient's CIPN symptoms. Vitamin B1 and amifostine can be explored as options for treatment.

VIII. Future of CIPN Management

A. Advances in CIPN research and potential future directions

Research for CIPN treatments should continue because as seen in the studies, CIPN causes serious effects on the quality of life of patients. Treatments including Venlafaxine and Duloxetine, Glutamine, and more should be further investigated. The proper doses for treatment should be identified and tested (Maihöfner et al. 2021). For ovarian cancer specifically, physicians should create new assessment types or focus on composite studies. This will allow them to understand the true condition of the patient. Additionally, if a patient is undergoing chemotherapy drugs, they should be constantly monitored and made aware of any signs or symptoms of CIPN. This continuous monitoring alongside chemotherapy cycles will ensure the onset of the CIPN is pinpointed and helpful measures like physical therapy or acupuncture can be started.

B. Importance of patient-centered care and tailored interventions

It is crucial that cancer care, including CIPN care, is focused solely on the patients needs. Patients are in a critical situation because of their health, and physicians should be supporting them medically and emotionally. Medicine should be personal to each patient. Depending on their symptoms, complaints, and presentation, the correct interventions should be selected. Patients should be cared for in a manner where they feel validated and understood. This will occur when physicians take patient assessment reports into consideration. Overall, patient-centered care is the goal of healthcare and each physician should focus on making their patient safe and comfortable during their treatment.

IX. Conclusion

While chemotherapy offers promise in combating cancer cells, CIPN complicates a patient's recovery journey. This comprehensive analysis explores CIPN's pervasive impact on ovarian cancer patients, affecting physical health and emotional well-being. The studies analyzed underline the need for early assessment, more research and patient-centered care. As medical science advances, future endeavors should strive to minimize CIPN's toll, enabling patients to undergo treatment with enhanced comfort and improved QoL. Ultimately, rigorous research, compassionate care, and targeted therapies will make the recovery of ovarian cancer patients an easier process.

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