Chemotherapy-induced neurotoxicity in the treatment of gynecological cancers: State of art and an innovative approach for prevention

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Author contributions: Oneda E wrote the paper; Abeni C, Zanina E and Bighè S collected data; Zanotti L analyzed the data; Zaniboni A revised the paper.

Conflict-of-interest statement: Authors have no conflict of interest.

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Manuscript source: Invited manuscript

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect that occurs in 20% of ovarian cancer patients treated with the combination of carboplatin/paclitaxel (CP). This toxicity is directly correlated with the dose of paclitaxel administered. Several studies have investigated whether different formulations of taxane can induce this side effect at a lower rate, but, unfortunately, no significant improvement was obtained. CIPN can be disabling in the daily lives of patients and can cause dose reduction or early termination of the treatment. Neuropathy can last for months and even years after its onset. Moreover, patients responsive to CP treatment are candidates for a reintroduction of the same drugs when disease relapse occurs, and residual neuropathy can affect the continuation of treatment. There are no approved drugs that mitigate or prevent the onset of CIPN. In this review, we summarize the evidence regarding the incidence of CIPN with different taxane formulations, regimen schedules and prevention systems. In particular, the Hilotherm® Chemo care device is a regional cooling system that lowers the temperature of the hands and feet to reduce the flow of chemotherapy into the capillaries. We used hilotherapy during chemotherapy infusion to prevent the onset of CIPN. Updated data from 44 ovarian cancer patients treated with 6 cycle of CP show that hilotherapy was well tolerated; only two patients (4.5%) stopped hilotherapy because of cold intolerance, and only one patient (2.2%) experienced grade ≥ 2 CIPN.

Key Words: Peripheral neuropathy; Ovarian cancer; Paclitaxel; Chemotherapy-induced peripheral neuropathy prevention; Hilotherapy

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INTRODUCTION

Carboplatin/paclitaxel (CP) is the chemotherapy of choice for ovarian cancer, in neo/adjuvant, first-line and in platinum-sensitive recurrence, and moreover, in advance stage a reintroduction of paclitaxel (PTX) monotherapy can be considered[1]. A significant proportion of recurring patients, with a platinum-free interval longer than 6-12 mo, are classified as platinum-sensitive and are candidates for retreatment with the same drugs used in first-line therapy[2]. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most life altering chemotherapy side effects[3,4] and it is frequently related to taxane treatment. The prevalence of CIPN ranges from 11% to over 87%[5]. In an online survey, 78% of 1360 women with ovarian cancer experienced CIPN 2.3 years after completing chemotherapy[6]. CIPN leads to peripheral nerve dysfunction or damage of varying intensity, duration and permanence. Symptoms range from acute transient paraesthesia or chronic pain to permanent peripheral nerve damage[4]. CIPN can occurs days after chemotherapy and gradually progresses to cumulative doses. Symptoms typically present as a “glove and stocking” neuropathy, with tingling, loss of dexterity in the fingers, hypoesthesia of the feet, and paraesthesia in the limbs. In addition, skin burns, electric shocks, as well as altered perception of pain to touch or heat may be felt[7-10]. In the worst case, sensory perception can be completely lost. CIPN can also manifest with motor symptoms with distal weakness, gait and balance disturbances, and impaired movements. Daily physical functioning can be impaired such as firmly grasping objects, unfastening jacket buttons, climbing steps or driving, it affects patient’s the quality of life (QoL)[11,12]. Health-related QoL can be impaired[6,11,13] with psychological consequences[14] such as major depression[15].

Due to this adverse event, treatment must unfortunately be interrupted or continued at a reduced dose, limiting the effectivity of chemotherapy. To date, none of the numerous drugs tested to prevent or relieve the symptoms of CIPN has obtained evidence of efficacy. Antidepressants (such as nortriptyline), duloxetine, gabapentin, baclofen-containing gel, amitriptyline, ketamine, lidocaine, tramadol, tapentadol, buprenorphine, and lithium were ineffective[16-25]. These agents have a record of efficacy for other common neuropathic pain conditions, but CIPN has a different pathological origin. The American Society of Clinical Oncology (ASCO) does not recommend any agent for the prevention of CIPN[16]. A number of nonpharmacologic interventions, such as acupuncture, limb hypothermia, surgical glove (SG) compression and electrocutaneous nerve stimulation, have also been investigated. However, the paucity of randomized controlled trial evidence prohibited the inclusion of those studies in this systematic review[16].

Reducing the penetration of chemotherapeutic agents into the capillaries of hands and feet and lowering the temperature of the patient’s extremities can be a way to slow blood circulation and cell metabolism in order to prevent the onset of CIPN. In fact, the tissue metabolic rate can be reduced by 50% dropping the tissue temperature by up to 10 °C. Hilotherapy is an effective method to constantly cool the temperature of the hands and feet during treatment and prevents the development of CIPN and polyneuropathy, giving patients a better QoL. In this review, we will discuss the
TAXANE-RELATED CIPN

Taxane-induced CIPN is predominantly sensory (SPN) and rarely presents with motor and autonomic changes[4]. Symptoms may arise early and even after the first administration, they are dose dependent, but tend to improve after discontinuation of treatment. However, the onset and severity are highly variable from individual to individual; no anticipatory signal can suggest a dose reduction, and there are no indications of a de-escalation of therapy to mitigate the symptoms once they arise. Furthermore, CIPN even after the end of chemotherapy can persist for months or years afterwards and in rare cases be permanent[9]. The only certain risk factor is the dose administered, with increases in risk proportional to the cumulative dose[4]. Pignata et al[26] found that approximately three fourths of patients treated with CP experienced peripheral neuropathy, and 7% had ≥ grade 3 CIPN. Residual neurotoxicity occurs frequently in patients after completion of CP, with a long-lasting pattern of recovery and 14% of patients still suffer residual neuropathy 1 year after treatment[27]. Such toxicity still persists in a significant proportion of patients who experience relapse and therefore, affects second-line treatment choice.

The Gynecologic Oncology Group (GOG) reported that approximately 20% of ovarian cancer, patients treated with the combination of carboplatin and PTX at 175 mg/mq every 3 wk in first-line therapy experienced grade 2 or higher neuropathy, and this percentage was increased among older patients[4]. Considering a similar total dose, the MITO-7 study showed that in patients with advanced ovarian cancer the regimen with carboplatin area under the curve (AUC) 2 mg/mL per min plus weekly PTX at 60 mg/mq was less neurotoxic than carboplatin AUC 6 mg/mL per min plus PTX at 175 mg/mq every 3 wk (grade 2 or higher neuropathy of 6% vs 17%, respectively). However, despite the better toxicity profile and the incremented QoL, the weekly regimen did not prolong progression free-survival (PFS)[28]. The Japanese Gynecologic Oncology Group (JGOG) randomized patients to receive carboplatin AUC 6 mg/mL per min every 3 wk plus dose dense PTX at 80 mg/mq (on days 1, 8, 15) or plus PTX at 180 mg/mq every 3 wk. The study showed that the 7% of patients treated with the dose-dense scheme had grade 3 or higher SPN and 5% had grade 3 or higher motor peripheral neuropathy (MPN), while 6% of patients treated with the standard regimen reported grade 3 or higher SPN and 4% grade 3 or higher MPN[29]. Despite a better median PFS benefit of 28.0 mo vs 17.2 mo and an overall survival benefit at 3 years of 72.1% vs 65.1% in the dose-dense treatment group compared to the conventional treatment group, more patients in the dose-dense group discontinued the treatment due to hematologic toxicity[29]. In contrast, in the JGOG-3016[30] and GOG-0262[31] studies, patients in groups 2 and 3 of ICON8[32] received up to 80 mg/mq of PTX per week and showed worse SPN in the weekly treatment group than in the every 3-wk treatment group. These findings suggest that SNP could be caused by cumulative PTX exposure rather than its dosing intensity[32]. The Scottish Ginecological Cancer Trials Group suggested that docetaxel could be less neurotoxic than PTX, and they reported a rate of 11% grade 2 or higher SPN with carboplatin AUC 5 mg/mL per min plus docetaxel 75 mg/mq vs a rate of 30% with carboplatin AUC 5 mg/mL plus PTX 175 mg/mq every three weeks in first-line ovarian cancer; however, this research did not demonstrate any survival benefit[33]. Unfortunately, platinum-sensitive patients who relapse are candidates for retreatment with CP, so residual peripheral neuropathy can be a limiting factor. However, studies that have evaluated the incidence of neuropathy in this setting report a 20% incidence of CIPN > 2 grade[2,34]. This proportion is lower than expected, which is a bias that is due to poor recruitment of patients with residual CIPN[2].

Symptom improvement or resolution after 3-6 mo at the end of standard treatment can be achieved by most of patient; however, in some cases, symptoms can last years, with a probability of 15% of patients still having neuropathy 6 mo after completion of chemotherapy and an 11% probability of still experiencing neuropathy at 2 years after completion of chemotherapy[4]. In the secondary analyses of the ROGY care trial among ovarian cancer patients, the course of SPN among chemotherapy-treated patients remained stable over the course of 2 years, while MPN symptoms declined at 12 mo. Furthermore, at 2 years, 13% still reported high levels of SPN[3]. Similar findings were seen in the previous PROFILE study with a prevalence of 6%-9% of SPN and 14% of MPN at 2-12 years after treatment, and a decreased in CIPN symptoms
three years after the end of treatment[6] (Table 1).

**MECHANICAL SYSTEMS OF CIPN PREVENTION**

Many studies have investigated the potential use of non-invasive approaches to prevent CIPN. The different mechanical systems tested include: acupuncture, scrambler therapy, hypothermia and compression therapy which aim to reduce damage to the peripheral nerves of the extremities. Acupuncture technique showed grade 3 symptom regression or stability in patients experiencing grade > 2 CIPN with weekly PTX for breast cancer[35]. Transcutaneous electrical nerve stimulation (scrambler therapy) was observed to relieve CIPN symptoms in several trials[36-41] (53% reduction in pain, 44% reduction in tingling and 37% reduction in numbness [37]), and these effects were maintained for 3 mo of follow-up[40]. The use of SG compression therapy was investigated by Tsuyuki et al[42] the reduction of microvascular flow to the hands during PTX administration allows to reduce the incidence of grade 2 or higher CIPN. The incidence of grade 2 or higher sensory CIPN, according to Common Terminology Criteria for Adverse Events (CTCAE), with SG compression therapy was low at 13.8% vs the incidence in the historical control group (44.1%)[42].

Cold temperature is known to reduce tissue microvascular perfusion, “therapeutic regional hypothermia” or “cryotherapy” using different limb cooling modalities (e.g., direct application of ice or frozen gloves) and has been used in attempt to prevent chemotherapy-induced nail and skin toxicity, but the mechanism of the large cooling gradients of these modalities permits only intermittent coolant application and are limited by substantial intolerance and sometimes frostbite[43,44]. Rosenbaek et al[45] demonstrated that cryotherapy associated with PTX treatment in the adjuvant treatment of breast cancer reduces the risk of dose-limiting CIPN, and increases the number of patients receiving the full chemotherapy dose (77% of patients). However, the comparison study between cryotherapy and preventive compression therapy during treatment with nab-PTX showed no benefit for either system[46]. A recent randomized controlled trial that investigated the effect of cryotherapy administered on all four limbs during PTX treatment among early and locally advanced breast cancer patients did not decrease the incidence and severity of sensory symptoms[47]. This study was unable to conclude that cryotherapy prevents sensory neuropathy probably because of the high rates of cryotherapy interruption[47].

**HILOThERAPY A NEW PREVENTIVE APPROACH**

The Hilotherm® Chemo care device is a regional cooling system that uses cuffs and piping for the hands and feet through which the coolant flows at a temperature of 10 °C. The insulators were fitted on both the hands and feet for 30 min before the start to 60 min after chemotherapy administration. A recent study in Germany evaluated the use of this device in 20 cancer patients treated with taxane-based chemotherapy as a preventative method. No patients developed grade 2 or 3 symptoms of CIPN. Four weeks after their chemotherapy ended, 70% of patients who used hilotherapy had no symptoms at all. The other 30% of patients were found to have grade 1 symptoms. Although cooling from the start of treatment achieved the best outcome, the group of patients (n = 36) who started hilotherapy when CIPN symptoms occurred showed a reduction in severe symptoms of CIPN. The use of hilotherapy was found to be comfortable and safe[48].

**OUR PERSONAL EXPERIENCE**

In the published small retrospective trial from our center we enrolled 64 patients with breast, gynecologic and pancreatic cancer to wear Hilotherm cuffs and piping on their hands and feet. Fifty-four (84%) of these patients completed all cooling cycles during their taxane-based chemotherapy. Continuous cooling was well tolerated by all patients. No patients had grade > 2 CIPN or had serious or lasting side effects as a result of hilotherapy. The median time to CIPN onset was 77 d for the entire population[49].

The updated data in the subgroup of patients with gynecological cancer treated with the combination of carboplatin AUC 5 mg/mL per min plus PTX at 175 mg/mq
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| Trail | Indication | No. of patients | Treatment | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) |
|-------|------------|----------------|-----------|-------------|-------------|-------------|
| AGO OVAR 3 [35] | FIGO II-IV fist line | 388 | CP | 39 | 28 | 6.7 |
| AGO OVAR 3 [35] | FIGO II-IV fist line | 384 | PP | 33 | 36 | 12.5 |
| JGOG [29] | FIGO II-IV fist line | 319 | CP | | | 20 (6) |
| JGOG [29] | FIGO II-IV fist line | 312 | C-P | | | 21 (7) |
| MITO 4 [27] | FIGO IC-IV fist line | 120 | CP | 51 (42) | 13 (11) | 1 (1) |
| MITO 2 [26] | FIGO IC-IV fist line | 407 | CP | 115 (28) | 64 (16) | 12 (3) |
| MITO 7 [28] | FIGO IC-IV fist line | 396 | C-PLD | 47 (12) | 11 (3) | 1 (< 1) |
| ICON 4 [21] | Platinum-sensitive relapse > 6 mo | 410 | P-based | 98 (25) | 4 (1) | |
| ICON 4 [21] | Platinum-sensitive relapse > 6 mo | 392 | CP/PP | 76 (20) | | |

CP: Carboplatin area under the curve (AUC) 5/6 mg/mL per min plus paclitaxel 175-185 mg/m^2 every 3 wk; CP weekly: Carboplatin AUC 2 mg/mL per min plus paclitaxel 80 mg/m^2 on days 1, 8, 15, and every 21 d; C-P: Carboplatin AUC 6 mg/mL per min every 3 wk plus paclitaxel 80 mg/m^2 on days 1, 8, 15, and every 21 d; C-PLD: Carboplatin AUC 5 mg/mL per minute plus pegylated liposomal doxorubicin 30 mg/m^2 every 3 wk; P-based: Cisplatin (50 mg/m^2 in combination with other drugs or 75 mg/m^2 as a single agent)/carboplatin AUC 5/6 mg/mL every 3 wk; PP: Cisplatin 75 mg/m^2 plus paclitaxel 175 mg/m^2 every 3 wk.

every 3 wk show that 35 of 44 patients (79.5%) completed all the planned cycles of chemotherapy with the cooling system. The severity of PN was evaluated by a nurse using the CTCAE (2017). Statistical analyses were performed using STATA 13.0 (StataCorp LP, Collage Station, TX, United States). Only 1 patient (2.2%) had grade ≥ 2 CIPN after 4 cycles of CP and completed the last cycle with carboplatin monotherapy; 2 patients (4.5%) stopped treatment due to excessive coldness; 3 patients (6.8%) stopped treatment due to disease progression and 2 patients (4.5%) stopped the treatment due to PTX allergic reaction; 3 patients (6.8%) had PTX reduction/interuption that was due to PTX hematologic toxicity and completed the cycles with carboplatin monotherapy and 3 patients (6.8%) concluded the treatment after 3/4 cycles due to hospitalization for planned surgery. Follow-up data are premature at the time of writing this review. Tables 2-4 show patient characteristics and results.

DISCUSSION

Neuropathy is an important, dose-limiting, painful, and often irreversible toxicity associated with taxane therapy. Approximately 20% of women treated for ovarian cancer show CIPN, and this toxicity impairs their QoL and can persist for months or even years after the end of treatment. Instead, for recurrent disease the established treatment is a reintroduction of the first-line scheme in sensitive patients, with a with a higher probability of developing toxicity or worsening of pre-existing toxicity with a consequent limitation of the duration of treatment. The only prophylactic therapy for CIPN suggested by the guidelines of the ASCO 2014 [16] is duloxetine, but it has limited efficacy in chemotherapy-induced neuropathic pain and has no benefit on paraesthesia and functional disability. Recently, ganglioside monosialic acid has shown promising effects on the prevention of neuropathic symptoms with a lower incidence of grade ≥ 1 on the CTCAE v4.0 scale (14.3% vs 100.0%, *P* < 0.001) both sensory (26.4% vs 97.8%, *P* < 0.001) and motor (20.9% vs 81.5%, *P* < 0.001) in patients with breast cancer treated with PTX [30]. Previous studies suggested positive effects of physical activity on CIPN with a higher CIPN in patients who do not meet recommended activity levels [51,52]. Moderate to vigorous activity was associated with lower CIPN in taxane-treated patients [53]. Patients who followed physical activity guidelines reported a longer time to the onset of CIPN since completing chemotherapy, potentially suggesting adaptation to neuropathic symptoms over time, enabling the return to physical activity [53]. Conveying PTX using lipid-based nanoformulations represents a potential strategy to overcome PTX side effects. In a recent
Table 2 Patient characteristics

| Characteristics                  | n (%)          |
|----------------------------------|----------------|
| Age, mean (range)                | 61 (35-74)     |
| Gynecologic cancer               | 44             |
| Risk factors                     |                |
| None                             | 38 (86.3)      |
| Diabetes                         | 3 (6.8)        |
| Arthritis and diabetes           | 1 (2.3)        |
| Hypothyroidism                   | 2 (4.6)        |

Table 3 Chemotherapy-induced peripheral neuropathy per cycle, according to Common Terminology Criteria for Adverse Events (version 4.0)

| Chemotherapy | Number of patients | Reported CIPN, n (%) |
|--------------|--------------------|----------------------|
|              |                    | Grade 0 | Grade 1 | Grade ≥ 2 |
| Cycle 1      | 44                 | 44 (100) | 0 (0)   | 0 (0)     |
| Cycle 2      | 44                 | 43 (97.7) | 0 (0)   | 0 (0)     |
| Cycle 3      | 43                 | 40 (93.0) | 1 (2.3) | 0 (0)     |
| Cycle 4      | 41                 | 33 (80.5) | 1 (2.4) | 0 (0)     |
| Cycle 5      | 34                 | 22 (64.7) | 1 (2.9) | 1 (2.9)   |
| Cycle 6      | 24                 | 20 (83.3) | 2 (8.3) | 1 (4.2)   |

Table 4 Chemotherapy (paclitaxel) dose changes during halotherapy treatment

| Patients, n (%)                          |
|------------------------------------------|
| Completed scheduled CP cycle¹            | 37 (84.1) |
| Paclitaxel dose reduction/discontinuation| 9 (20)    |
| Reason for Paclitaxel reduction/discontinuation | 3 (6.8) hematological toxicity; 3 (6.8) disease progression; 2 (4.5) paclitaxel allergic reaction; 1 (2.2) CIPN ≥ 2 |

¹Carboplatin area under the curve 5 mg/mL per min plus paclitaxel at 175 mg/m² every 3 wk.
CP: Carboplatin/paclitaxel; CIPN: Chemotherapy-induced peripheral neuropathy.

CIPN: Chemotherapy-induced peripheral neuropathy.

study, this formulation was tested on lung tumor cells and in vivo and showed a very low concentration in the dorsal root ganglia, where PTX accumulates and causes damage to the somas of peripheral sensory neurons[54]. This approach could lead to a reduction in the incidence of peripheral neuropathy and be the subject of study in gynecological cancers.

Different mechanical system of CIPN prevention were tested and founded that vasoconstriction and cold reduce drug exposure during chemotherapy infusion[55], but the limits of cooling systems are primarily the cold intolerance and cold-related injuries. The small single-arm trial from our center that investigated the effects of halotherapy cooling system demonstrate to prevent CIPN[49]. The advantages of continuous cooling are a more tolerable and controlled temperature reduction for the duration of chemotherapy instead of ice or frozen gloves. Continuous cooling whit a coolant temperature of 10 °C continued for the duration of chemotherapy and was well tolerated. In the ovarian cancer subgroup only one patient showed CIPN ≥ 2, and only two patients (4.5%) stopped halotherapy for cold intolerance. Published data showed that no patients reported the appearance of CIPN symptom at a follow-up time of 6 mo[49]. We expect to maintain these follow-up results also from the new
enrolled patients.

CONCLUSION

The prevalence of CIPN was approximately 68% within the first month following the end of taxane chemotherapy treatment and 30% after 6 mo or more[4]. In a survey of ovarian cancer patients, CIPN symptoms were associated with lower functioning and greater health-related worry[5]. Additionally, a survey covering various cancer types found that patients reporting neurotoxicity had higher symptom burden and stress, and poorer QoL[56]. Reducing the incidence of neuropathy to improve the patient’s QoL and avoiding discontinuation or dose reduction of anticancer treatment is of primary importance. Unfortunately, comprehensive knowledge of the mechanisms leading to CIPN is still lacking and no drug has been approved to prevent or cure it. Hiloterapy has proven to be a safe, well tolerated and effective method of preventing and treating CIPN. To validate the use of hiloterapy as a preventive method a large-scale trial and a longer follow up are necessary.

REFERENCES

1. McGuire WP. Taxol: a new drug with significant activity as a salvage therapy in advanced epithelial ovarian carcinoma. Gynecol Oncol 1993; 51: 78-85 [PMID: 7902314 DOI: 10.1016/0090-8258(93)90169-7]
2. Parmar MK, Ledermann JA, Colombo N, du Bois A, Deleloye JB, Kristensen GB, Wheeler S, Swart AM, Qian W, Torri V, Floriani I, Jayson G, Lamont A, Tropé C; ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy vs conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003; 361: 2099-2106 [PMID: 12826431 DOI: 10.1016/S0140-6736(03)1718-x]
3. Bonhof CS, Mols F, Vos MC, Pijnenborg JMA, Boll D, Vreugdenhil G, Ezendam NPM, van de Poll-Franse LV. Course of chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer patients: A longitudinal study. Gynecol Oncol 2018; 149: 455-463 [PMID: 29605500 DOI: 10.1016/j.ygyno.2018.03.052]
4. Brewer JR, Morrison G, Dolan ME, Fleming GF. Chemotherapy-induced peripheral neuropathy: Current status and progress. Gynecol Oncol 2016; 140: 176-183 [PMID: 26556766 DOI: 10.1016/j.ygyno.2015.11.011]
5. Glare PA, Davies PS, Finlay E, Gulati A, Lemanne D, Moryl N, Oeffinger KC, Paice JA, Stubblefield MD, Syrjala KL. Pain in cancer survivors. J Clin Oncol 2014; 32: 1739-1747 [PMID: 24799477 DOI: 10.1200/JCO.2013.52.4629]
6. Ezendam NP, Pijlman B, Bhugwandass C, Pruijt JF, Mols F, Vos MC, Pijnenborg JGM, van de Poll-Franse LV. Chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer survivors: results from the population-based PROFILES registry. Gynecol Oncol 2014; 135: 510-517 [PMID: 25281491 DOI: 10.1016/j.ygyno.2014.09.015]
7. Banach M, Juraneck JK, Zyguilska AL. Chemotherapy-induced neuropathies—a growing problem for patients and health care providers. Brain Behav 2017; 7: e00558 [PMID: 28127506 DOI: 10.1002/bbr3.558]
8. Bernhardson BM, Tishelman C, Rutqvist LE. Chemosensory changes experienced by patients undergoing cancer chemotherapy: a qualitative interview study. J Pain Symptom Manage 2007; 34: 403-412 [PMID: 17616338 DOI: 10.1016/j.jpainsymman.2006.12.010]
9. Scripture CD, Figg WD, Sparreboom A. Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives. Curr Neuropsychopharmacol 2006; 4: 165-172 [PMID: 18615126 DOI: 10.2174/157015906776359568]
10. De Iuliiis F, Tagliari L, Salerno G, Lanza R, Scarpa S. Taxane induced neuropathy in patients affected by breast cancer: Literature review. Crit Rev Oncol Hematol 2015; 96: 34-45 [PMID: 26004917 DOI: 10.1016/j.critrevonc.2015.04.011]
11. Bakitas MA. Background noise: the experience of chemotherapy-induced peripheral neuropathy. Nurs Res 2007; 56: 323-331 [PMID: 17846553 DOI: 10.1097/01.NNR.0000289503.22414.79]
12. Tofthagen C. Surviving chemotherapy for colon cancer and living with the consequences. J Palliat Med 2010; 13: 1389-1391 [PMID: 21091028 DOI: 10.1089/jpm.2010.0124]
13. Mols F, Beijers J, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. Support Care Cancer 2014; 22: 2261-2269 [PMID: 24789421 DOI: 10.1007/s00520-014-2255-7]
14. Zis P, Varrassi G, Vadalouka A, Paladini A. Psychological Aspects and Quality of Life in Chronic Pain. Pain Res Manag 2019; 2019: 8346161 [PMID: 31281559 DOI: 10.1155/2019/8346161]
15. Zis P, Daskalaki A, Bountouni I, Sykioti P, Varrassi G, Paladini A. Depression and chronic pain in the elderly: links and management challenges. Clin Interv Aging 2017; 12: 709-720 [PMID: 28461745 DOI: 10.2147/CIA.S113576]
16. Herschman DL, Lacchetti C, Loprinzi CL. Prevention and Management of Chemotherapy-Induced
Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline Summary. *J Oncol Pract* 2014; 10: e421-e424 [PMID: 24924607 DOI: 10.1200/JOP.2014.001776]

Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL.; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013; 309: 1359-1367 [PMID: 23549581 DOI: 10.1001/jama.2013.28213]

Magnowska M, Iżycka N, Kapolka-Czyż J, Romala A, Lorek J, Spaczyński M, Nowak-Markwiez E. Effectiveness of gabapentin pharmacotherapy in chemotherapy-induced peripheral neuropathy. *Ginekol Pol* 2018; 89: 200-204 [PMID: 29781075 DOI: 10.5603/GP.a2018.0034]

Kim BS, Jin JY, Kwon JH, Woo IS, Ko YH, Park SY, Park HJ, Kang JH. Efficacy and safety of oxycodone/naloxone as add-on therapy to gabapentin or pregabalin for the management of chemotherapy-induced peripheral neuropathy in Korea. *Asia Pac J Clin Oncol* 2018; 14: e448-e454 [PMID: 29280313 DOI: 10.1111/ajco.12822]

van den Heuvel SAS, van der Wal SEI, Smedes LA, Radema SA, van Alfen N, Vissers KCP, Steegers MAH. Intravenous Lidocaine: Old-School Drug, New Purpose-Reduction of Intractable Pain in Patients with Chemotherapy Induced Peripheral Neuropathy. *Pain Res Manag* 2017: 8053474 [PMID: 28485893 DOI: 10.1155/2017/8053474]

Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD 3rd, Kugler JW, Hoff KL, Reddy PS, Rowland KM Jr, Riepl M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCTCG trial N06CA. *Support Care Cancer* 2011; 19: 833-841 [PMID: 21946177 DOI: 10.1007/s00520-010-0911-0]

Radkin M, Batashi R, Elmaleh S, Debi R, Schaffer P, Schaffer M, Asna N. Management of Peripheral Neuropathy Induced by Chemotherapy. *Curr Med Chem* 2019; 26: 4698-4708 [PMID: 30621555 DOI: 10.2174/0929867326666190107163756]

Ibrahim EY, Ehrlich BE. Prevention of chemotherapy-induced peripheral neuropathy—a review of recent findings. *Crit Rev Oncol Hematol* 2020; 145: 102831 [PMID: 31783290 DOI: 10.1016/j.critrevonc.2019.102831]

Mo M, Erdelyi I, Szigiét-Buck K, Benbow JH, Ehrlich BE. Prevention of paclitaxel-induced peripheral neuropathy by lithium pretreatment. *FASEB J* 2012; 26: 4696-4709 [PMID: 22889322 DOI: 10.1096/fj.12-214647]

Wadia RJ, Stolar M, Greens C, Ehrlich BE, Chao HH. The prevention of chemotherapy induced peripheral neuropathy by concurrent treatment with drugs used for bipolar disease: a retrospective chart analysis in human cancer patients. *Oncotarget* 2018; 9: 7322-7331 [PMID: 29484113 DOI: 10.18632/oncotarget.23467]

Pignata S, Scambia G, Ferrandina G, Savarese A, Sorio R, Breda E, Gobbia V, Musso P, Frigerio L, Del Medico P, Lombardi AV, Febraro A, Scollo P, Ferro A, Tamberi S, Brandes A, Ravaoli A, Valerio MR, Aiini E, Natale D, Sciallriti L, Greggi S, Pisanos C, Lorusso D, Salutari V, Legge F, Di Maio M, Morabito A, Gallo C, Perrone F. Carboplatin plus paclitaxel plus paclitaxel vs carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. *J Clin Oncol* 2011; 29: 3628-3635 [PMID: 21844495 DOI: 10.1200/JCO.2010.33.8566]

Pignata S, De Placido S, Bianmonte R, Scambia G, Di Vagno G, Colucci G, Febraro A, Marinaccio M, Lombardi AV, Manzione L, Carteni G, Nardi M, Danese S, Valerio MR, de Matteis A, Massidda B, Gasparini G, Di Maio M, Pisanos C, Perrone F. Residual neurotoxicity in ovarian cancer patients in clinical remission after first-line chemotherapy with carboplatin and paclitaxel: the Multicenter Italian Trial in Ovarian cancer (MITO-4) retrospective study. *BMC Cancer* 2006; 6: 5 [PMID: 16398939 DOI: 10.1186/1471-2407-6-5]

Pignata S, Scambia G, Katsaros D, Gallo C, Pujade-Lauraine E, Reddy PS, Rowland KM Jr, Riepl M, Pisanos C, Greggi S, Lauria R, Lorusso D, Marchetti C, Ricci C, Salutari V, Ricci C, Lauria R, Lorusso D, Marchetti C, Pignata S, Scambia G, Katsaros D, Gallo C, Pujade-Lauraine E, De Placido S, Ferrandina G, Savarese A, Sorio R, Breda E, Gobbia V, Musso P, Frigerio L, Del Medico P, Lombardi AV, Febraro A, Scollo P, Ferro A, Tamberi S, Brandes A, Ravaoli A, Valerio MR, Aiini E, Natale D, Sciallriti L, Greggi S, Pisanos C, Lorusso D, Salutari V, Legge F, Di Maio M, Morabito A, Gallo C, Perrone F. Carboplatin plus paclitaxel vs carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. *J Clin Oncol* 2011; 29: 3628-3635 [PMID: 21844495 DOI: 10.1200/JCO.2010.33.8566]

Katsurata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, Tsuda H, Sugiyama T, Kodama S, Kimura E, Ochiai K, Noda K; Japanese Gynecologic Oncology Group. Dose-dense paclitaxel once a week in combination with carboplatin every 3 wk for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009; 374: 1331-1338 [PMID: 19767092 DOI: 10.1016/S0140-6736(09)61157-0]

Harano K, Terauchi F, Katsurata N, Takahashi F, Yasuda M, Takakura S, Takano M, Yamamoto Y, Sugiyama T. Quality-of-life outcomes from a randomized phase III trial of dose-dense weekly paclitaxel and carboplatin compared with conventional paclitaxel and carboplatin as a first-line treatment for stage II-IV ovarian cancer: Japanese Gynecologic Oncology Group Trial (JGOG3016). *Ann Oncol* 2014; 25: 251-257 [PMID: 24356636 DOI: 10.1093/annonc/mdt527]
Oneda E et al. CIPN prevention in gynecological cancer

31 Chan JK, Brady MF, Penso RT, Huang H, Birrer MJ, Walker JL, DiSilvestro PA, Rubin SC, Martin LP, Davidson SA, Huh WK, O’Malley DM, Boente MP, Michael H, Monk BJ. Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer. *N Engl J Med* 2016; 374: 738-748 [PMID: 26933849 DOI: 10.1056/NEJMoa1505067]

32 Clamp AR, James EC, McNeish IA, Dean A, Kim JW, O’Donnell DM, Hook J, Coyle C, Blagden S, Brenton JD, Naik R, Perren T, Sundar S, Cook AD, Gopalakrishnan GS, Gabra H, Lord R, Dark G, Earl HM, Hall M, Banejee S, Glasspool RM, Jones R, Williams S, Swart AM, Stening S, Parmar M, Kaplan R, Ledermann JA. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *Lancet* 2019; 394: 2084-2095 [PMID: 31791688 DOI: 10.1016/S1474-4422(19)32259-7]

33 Vasey PA, Jayson GC, Gordon A, Gabra H, Coleman R, Atkinson R, Parkin D, Paul J, Hay A, Kaye SB; Scottish Gynaecological Cancer Trials Group. Phase III randomized trial of docetaxel-cobalatin vs paclitaxel-cobalatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004; 96: 1682-1691 [PMID: 15547181 DOI: 10.1093/jnci/djh323]

34 Dizon DS, Hensley ML, Poynor EA, Sabbatini P, Aghajanian C, Hummer A, Venkatraman E, Spriggs DR. Retrospective analysis of carboplatin and paclitaxel as initial second-line therapy for recurrent epithelial ovarian carcinoma: application toward a dynamic disease state model of ovarian cancer. *J Clin Oncol* 2002; 20: 1238-1247 [PMID: 11870166 DOI: 10.1200/jco.2002.20.5.1238]

35 Mao T, Seidman AD, Piulson L, Vertosick E, Chen X, Vickers AJ, Blinder VS, Zhi W, Li Q, Vahdat LT, Dickler MN, Robson ME, Mao J. A phase IIa trial of acupuncture to reduce chemotherapy-induced peripheral neuropathy severity during neoadjuvant or adjuvant weekly paclitaxel chemotherapy in breast cancer patients. *Eur J Cancer* 2018; 101: 12-19 [PMID: 30007894 DOI: 10.1016/j.ejca.2018.06.008]

36 Smith TJ, Coyne PJ, Parker GL, Dodson P, Ramakrishnan V. Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare®) for chemotherapy-induced peripheral neuropathy. *J Pain Symptom Manage* 2010; 40: 883-891 [PMID: 20813492 DOI: 10.1016/j.jpainsymman.2010.03.022]

37 Pachman DR, Weisbrod BL, Seisler DK, Barton DL, Fee-Schroeder KC, Smith TJ, Lachance DH, Liu H, Shehurud RA, Cheville AL, Loprinzi CL. Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. *Support Care Cancer* 2015; 23: 943-951 [PMID: 25245776 DOI: 10.1007/s00520-014-2424-8]

38 Majithia N, Smith TJ, Coyne PJ, Abdi S, Pachman DR, Lachance D, Shehurud R, Cheville A, Basford JR, Farley D, O’Neill C, Ruddy KJ, Sparadero F, Beutler A, Loprinzi CL. Scrambler Therapy for the management of chronic pain. *Support Care Cancer* 2016; 24: 2807-2814 [PMID: 27041741 DOI: 10.1007/s00520-016-3177-3]

39 Coyne PJ, Wan W, Dodson P, Swainey C, Smith TJ. A trial of Scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *Support Care Cancer Pharmacother* 2013; 27: 359-364 [PMID: 24143893 DOI: 10.1007/s00520-013-2475-8]

40 Park HS, Sin WK, Kim HY, Moon JY, Park SY, Kim YC, Lee SC. Scrambler therapy for patients with cancer pain - case series -. *Korean J Pain* 2013; 26: 65-71 [PMID: 23342211 DOI: 10.3344/kjp.2013.26.1.65]

41 Loprinzi C, Le-Rademacher JG, Majithia N, McMurray RP, O’Neill CR, Bendel MA, Beutler A, Lachance DH, Cheville A, Strick DM, Black DF, Tilburt JC, Smith TJ. Scrambler therapy for chemotherapy neuropathy: a randomized phase II pilot trial. *Support Care Cancer* 2020; 28: 1183-1197 [PMID: 31209630 DOI: 10.1007/s00520-019-04881-3]

42 Tsuyuki S, Yamagami K, Yoshiyabasho H, Sugie T, Mizuno Y, Tanaka S, Kato H, Okuno T, Ogura N, Yamashiro H, Takawa H, Kikawa Y, Hashimoto T, Kato T, Takahara S, Katayama T, Yamachia A, Inamoto T. Effectiveness and safety of surgical glove compression therapy as a prophylactic method against nanoparticle albumin-bound-paclitaxel-induced peripheral neuropathy. *Breast* 2019; 47: 22-27 [PMID: 3102389 DOI: 10.1016/j.breast.2019.06.008]

43 Hochberg J. A randomized prospective study to assess the efficacy of two cold therapy treatments following carpal tunnel release. *J Hand Ther* 2001; 14: 208-215 [PMID: 11511016 DOI: 10.1197/j.jht001.1103(01).80055-7]

44 McGuire DA, Hendricks SD. Incidences of frostbite in arthroscopic knee surgery postoperative cryotherapy rehabilitation. *Arthroscopy* 2006; 22: 1141.e1-1141.e6 [PMID: 17024220 DOI: 10.1016/j.arthro.2005.06.027]

45 Rosenback F, Holm HS, Hjelmberg JVB, Ewertz M, Jensen JD. Effect of cryotherapy on dose of adjuvant paclitaxel in early-stage breast cancer. *Support Care Cancer* 2020; 28: 3763-3769 [PMID: 31828491 DOI: 10.1007/s00520-019-05196-z]

46 Kanbayashi Y, Sakaguchi K, Ishikawa T, Ouchi Y, Nakatsukasa K, Tabuchi Y, Kaneshi F, Hiramatsu M, Takagi R, Yokota I, Kato H, Taguchi T. Comparison of the efficacy of cryotherapy and compression therapy for preventing nanoparticle albumin-bound-paclitaxel-induced peripheral neuropathy: A prospective self-controlled trial. *Breast* 2020; 49: 219-224 [PMID: 31901783 DOI: 10.1016/j.breast.2019.12.011]

47 Ng DQ, Tan CJ, Soh BC, Tan MML, Loh SY, Tan YE, Ong HH, Teng PPC, Chan JJ, Chay WY, Lee J, Lai G, Beh SY, Tan TJJ, Yap YS, Lee GE, Wong M, Dent R, Lo YL, Chan A, Loh KW. Impact of Cryotherapy on Sensory, Motor, and Autonomic Neuropathy in Breast Cancer Patients Receiving Paclitaxel: A Randomized, Controlled Trial. *Front Neurol* 2020; 11: 604688 [PMID: 33424755 DOI: 10.3389/fneur.2020.00688]
48 Schaper T. Hilotherapy for the Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy. [cited 29 April 2020]. In: Hilotherm [Internet]. Available from: https://www.hilotherm.co.uk/cipn-hand-foot-syndrome

49 Oneda E, Meriggi F, Zanotti L, Zaina E, Bighè S, Andreis F, Rueda S, Zaniboni A. Innovative Approach for the Prevention of Chemotherapy-Induced Peripheral Neuropathy in Cancer Patients: A Pilot Study With the Hilotherm Device, the Poliambulanza Hospital Experience. *Integr Cancer Ther* 2020; 19: 1534735420943287 [PMID: 32856475 DOI: 10.1177/1534735420943287]

50 Su Y, Huang J, Wang S, Unger JM, Arias-Fuenzalida J, Shi Y, Li J, Gao Y, Shi W, Wang X, Peng R, Xu F, An X, Xue C, Xia W, Hong R, Zhong Y, Lin Y, Huang H, Zhang A, Zhang L, Cai L, Zhang J, Yuan Z. The Effects of Ganglioside-Monosialic Acid in Taxane-Induced Peripheral Neuropathy in Patients with Breast Cancer: A Randomized Trial. *J Natl Cancer Inst* 2020; 112: 55-62 [PMID: 31093677 DOI: 10.1093/jnci/djz086]

51 Greenlee H, Hershman DL, Shi Z, Kwan ML, Ergas JJ, Roh JM, Kushi LH. BMI, Lifestyle Factors and Taxane-Induced Neuropathy in Breast Cancer Patients: The Pathways Study. *J Natl Cancer Inst* 2017; 109 [PMID: 27794123 DOI: 10.1093/jnci/djw206]

52 Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, Zucker DS, Matthews CE, Ligibel JA, Gerber LH, Morris GS, Patel AV, Hue TF, Perna FM, Schmitz KH. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019; 51: 2375-2390 [PMID: 31626055 DOI: 10.1249/MSS.0000000000002116]

53 Andersen Hammond E, Fritz M, Shay B. Neuropathic Pain in Taxane-Induced Peripheral Neuropathy: Evidence for Exercise in Treatment. *Neurorehabil Neural Repair* 2019; 33: 792-799 [PMID: 31342880 DOI: 10.1177/1545968319860486]

54 Jiménez-López J, Bravo-Caparrós I, Cabeza L, Nieto FR, Ortiz R, Perazzoli G, Fernández-Segura E, Cañizares FJ, Baeyens JM, Melguizo C, Prados J. Paclitaxel antitumor effect improvement in lung cancer and prevention of the painful neuropathy using large pegylated cationic liposomes. *Biomed Pharmacother* 2021; 133: 111059 [PMID: 33378963 DOI: 10.1016/j.biopha.2020.111059]

55 Scotté F, Banu E, Medioni J, Levy E, Ebenezer C, Marsan S, Banu A, Tourani JM, Andrieu JM, Oudard S. Matched case-control phase 2 study to evaluate the use of a frozen sock to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot. *Cancer* 2008; 112: 1625-1631 [PMID: 18286527 DOI: 10.1002/cncr.23333]

56 Miskowski C, Mastick J, Paul SM, Abrams G, Cheung S, Sabes JH, Kober KM, Schumacher M, Conley YP, Topp K, Smoot B, Mausisa G, Mazor M, Wallhagen M, Levine JD. Impact of chemotherapy-induced neurotoxicities on adult cancer survivors' symptom burden and quality of life. *J Cancer Surviv* 2018; 12: 234-245 [PMID: 29159795 DOI: 10.1007/s11764-017-0662-8]
