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Peripheral Neuropathy in Ovarian Cancer

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1. Introduction

Peripheral neuropathy is not uncommon in ovarian cancer. The incidence density of peripheral neuropathy was 21.5 per 1000 person-years in ovarian cancer, 15.3 per 1000 person-years in breast cancer and 18.3 per 1000 person-years in lung cancer for patients who received platinum-taxane combination chemotherapy (Nurgalieva et al., 2010). Carboplatin/paclitaxel is the chemotherapy of choice for advanced ovarian cancer, which has been reported to associate with chemotherapy induced neurotoxicity in as high as 54% of patients after their first-line 6 cycles of treatment and with 23% of patients with residual neuropathy after a median follow up of 18 months (Pignata et al., 2006). However, peripheral neuropathy in ovarian cancer is not always due to chemotherapeutic agents. Other etiologies of neuropathy in ovarian cancer patients are focal compression, nutritional deficiency, metabolic abnormalities, endocrine disorders, and paraneoplastic neurological syndromes.

A detailed medical history is most important for the diagnosis of neuropathy including symptoms, distribution, duration and course of the neuropathy. The past medical and social history may reveal a possible cause such as diabetes, inflammation, or a toxic or nutritional etiology. A positive family history may suggest a hereditary neuropathy. A neurologic examination is required to confirm the presence of neuropathy. Electrodiagnostic studies, including nerve conduction study and electromyography, are used to reveal the severity and its distribution pattern; underlying process demyelination or axonal loss; sensory, motor or a combination. One limitation of nerve conduction study is that it assess the function of only the large diameter nerve fibers, and not small fibers. Quantitative sensory testing, epidermal nerve fiber density, or autonomic function testing are used to evaluate small fiber neuropathy. Blood tests may reveal the etiology of nutritional, metabolic, endocrine, inflammatory, paraneoplastic, infectious, toxic, or hereditary neuropathies.

2. Chemotherapy-induced neuropathy

Seven cytotoxic chemotherapy agents have been approved by the FDA for advanced ovarian cancer since 1978. They are cisplatin, carboplatin, altretamine, paclitaxel, topotecan, liposomal doxorubicin and gemcitabine. Among them, cisplatin, caboplatin, altretamine, and paclitaxel have significant neurotoxicity. Although bone marrow suppression and neurotoxicity are the major side-effects related to chemotherapy,

neurotoxicity is often the decisive factor limiting the dose of chemotherapy agent since bone marrow suppression can be overcome with growth factors, blood transfusion, or bone marrow transplantation. Chemotherapy-induced peripheral neuropathy is clearly related to the dose per cycle, as well as the cumulative dose. However, pre-existing nerve abnormalities (debates mellitus, hereditary neuropathies, alcoholism, previous neurotoxic treatments, or malnutrition) make nerves more susceptible to chemotherapy-induced neuropathy. The incidence of chemotherapy-induced neuropathy varies in the literature due to a wide range of individual drug doses, cumulative doses, treatment schedules, and the combined use with other drugs. The other challenge is different grading systems that have been utilized, including Eastern Cooperative Oncology Group (ECOG), National Cancer Institute–Common Toxicity Criteria (NCI-CTC), and World Health Organization (WHO) toxicity criteria. The common toxicity scales are designed to allow a rapid examination of the patients with peripheral neurotoxicity by oncologists based on clinical symptoms and signs. Total Neuropathy Score (TNS) also includes neurological examination and nerve conduction study, which grade accurately and correlated well with NCI-CTC and ECOG scores (Cavaletti et al., 2006). The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire is used to evaluate symptoms and concerns associated specifically with chemotherapy-induced neuropathy, which was found to be reliable for assessing quality of life in ovarian cancer patient with neuropathy (Calhoun et al., 2003).

2.1 Platinum agents

Platinum agents cisplatin, carboplatin, and oxaliplatin have been used for the treatment of ovarian cancer. Cisplatin was approved for the treatment of ovarian cancer in 1978, and is currently administered for advanced ovarian cancer intravenously and intraperitoneally (Armstrong et al., 2006, Markman et al., 2001). Carboplatin was approved in 1989, and subsequently became a part of the first-line therapy for ovarian cancer in combination with a taxane. It was found to be less neurotoxicity than cisplatin (du Bois et al., 2003). In 2002, a third-generation platinum drug, oxaliplatin, was approved for treatment of metastatic colorectal cancer; however, 70% of the patients receiving oxaliplatin were affected by some degree of sensory neuropathy (McWhinny et al., 2009). Oxaliplatin in combination with variety of chemotherapy agents (cyclophosphamide, gemcitabine, paclitaxel and pegylated liposomal doxorubicin) has been reported in phase II clinical trials of ovarian cancer (Harnett et al., 2007, Misset et al., 2001, Nicoletto, 2006, Recchia et al., 2007, Viens et al., 2006).

Platinum-induced peripheral neuropathy has elements common to all three agents with some distinctive patterns. The severity of neurotoxicity in platinum agents from greatest to least is cisplatin, oxaliplatin, and carboplatin (McWhinny et al., 2009). Cisplatin produces a predominantly sensory neuropathy characterized by painful paresthesia, numbness, and diminished vibratory sense. Symptoms often begin in the feet, and typically occur during the first few cycles of treatment. When severe, gait ataxia may appear. Lhermitte sign may occur. Large fiber function is more affected than small fiber function. Autonomic neuropathy in general is not prominent. Weakness and motor neuropathy are less common. Sensory disturbance is typical in a symmetrical stocking and glove distribution, with decreasing proprioception and vibratory sensation. Deep tendon reflexes are reduced or absent. Peripheral neuropathy is often not completely

reversible. Symptoms may be worse transiently after therapy is discontinued (coasting effect). Neurotoxicity has been reported in 47% of the patients treated with cisplatin compared with 25% of those treated with the non-cisplatin regimen in 387 patients with ovarian cancer. The severity was much higher at cumulative doses of cisplatin between 500 and 600 mg/m² (Van Der Hoop et al., 1990). Carboplatin induced neuropathy has similar symptoms to those of cisplatin, but absent Lhermitte sign. The neurotoxicity of carboplatin is generally considered to be less frequent, and less severe than cisplatin. Grade 3/4 sensory neuropathy was 13.5% in the cisplatin regimen versus 7.2% in the carboplatin regimen (du Bois et al., 2003). In addition to chronic sensory neuropathy similar to cisplatin, oxaliplatin also causes acute cold-aggravated transient painful paresthesia, which occurs within hours of each infusion, and typically resolves within hours to days. These symptoms can be accompanied by jaw and eye pain, possibly due to muscle cramps.

Cisplatin and oxaliplatin undergo hydrolysis to a greater extent than carboplatin, and may associate with more severe patterns of neurotoxicity (McWhinny et al., 2009). In addition, cisplatin produces about three times more platinum-DNA adducts in the dorsal root ganglion than does oxaliplatin and with greater neurotoxicity (Ta et al., 2006). The neurotoxicity is the result of platinum compounds accumulating in the dorsal root ganglia, leading to shrinking or loss of dorsal root ganglia neurons and a resultant sensory neuronopathy (Krarup-Hansen et al., 1999), which is likely why the motor fibers are primarily spared. Platinum-DNA-protein cross-links have been proposed as a mechanism for the platinum antitumor activities (Chválová et al., 2007). Platinum compounds interfere with DNA replication and metabolic function of the dorsal root ganglia. The "coasting" phenomenon may result from platinum accumulation in the dorsal root ganglia over a long period time. Cisplatin also induces apoptosis in dorsal root ganglion by binding to nuclear DNA and mitochondrial DNA (Podratz et al., 2011). There is also the secondary degeneration of the posterior columns, which likely accounts for the Lhermitte sign. Oxaliplatin affects nerve excitability through voltage-dependent mechanisms, with specific effects mediated through axonal Na+ channel inactivation. It may be the cause of the acute neurotoxicity of oxaliplatin (Park et al., 2011a).

2.2 Taxanes (paclilaxel / Docetaxel)

Paclitaxel and docetaxel are frequently used taxanes in ovarian cancer. Paclitaxel combined with carboplatin is now considered as a standard first-line therapy for advanced ovarian cancer, but neurological toxicity is a clinically significant adverse effect (Mayerhofer et al., 2000). Docetaxel combined with carboplatin has been suggested to be a promising alternative, particularly in terms of minimizing the incidence and severity of peripheral neuropathy (Pfisterer et al., 2004 and Vasey et al., 2004). Nab-paclitaxel is an albumin-bound paclitaxel that has lesser hypersensitivity reactions, but seems to be similar to paclitaxel for inducing neuropathy.

Paclitaxel induces a progressive, predominantly sensory neuropathy. Symptoms can occur after the first dose, and include painful paresthesia as well as numbness of the hands and feet. Transient myalgia is common after each dose, which usually resolves within days. Sensory loss presents in a stocking-glove distribution. Ankle jerks and other reflexes may be diminished or absent, which progresses with cumulative doses. Both small and large fiber sensory functions are affected. Muscle strength is frequently

preserved or only minimally affected. Docetaxel presents similar clinical manifestations as paclitaxel, but with different toxicity profiles. Docetaxel/carboplatin was associated with 11% grade 2 or higher sensory neuropathy compared with 30% in paclitaxel/carboplatin. Motor neuropathy grade 2 or higher was 3% in Docetaxel/carboplatin versus 7% in paclitaxel/carboplatin. However, docetaxel/carboplatin was associated with significantly more grade 3-4 neutropenia as 94% versus 84% (Vasey et al., 2004). Docetaxel was tolerated better by patients because of less neuropathic pain and myalgia (Pan & Kao 2007). Overall, either single or cumulative dose is the most important factor to consider in taxanes-induced neuropathy. Most symptoms usually improve or resolve after discontinuation of treatment, however, severe symptoms may persist for a long period of time (Argyriou et al., 2008).

The taxanes block tubulin depolymerisation, leading to the inhibition of microtubule dynamics and cell cycle arrest. Paclitaxel and docetaxel accumulate microtubules in axon, dorsal root ganglia, and Schwann cells. These defective microtubules inhibit axonal transport, axonal sprouting, or nerve regeneration (Manfredi & Horwitz 1984, Rowinsky and Donehower 1995). In rat model, both paclitaxel and docetaxel equally induced severe and dose-dependent neuropathy measured with neurophysiological methods, however, the morphometric examination demonstrated more detrimental effect of paclitaxel on nerve fibers (Persohn et al., 2005). In patients, paclitaxel produced early sensory dysfunction in 4 weeks as increasing in stimulus threshold and reduction in sensory amplitudes on neurophysiological and nerve excitability studies; 71% of patients developed symptoms by 6 weeks after administration of about 500 mg/m^2 (Park et al., 2011b). Reduced sensory amplitudes or abolishment of sensory responses on neurophysiology studies were also found in patients treated with docetaxel (New et al., 1996, Pan & Kao 2007). Taxanes-induced peripheral neuropathy is a predominant axonal sensory neuropathy.

2.3 Altretamine

Altretamine was approved by the FDA to treat refractory ovarian cancer in 1990. It is an alkylating agent, binding to and cross-linking of nucleic acid chains. Altretamine induces a mild sensorimotor axonal polyneuropathy that is reversible on cessation of the drug. The neuropathy consists of paresthesia, decreased position and vibrating sense, hyporeftexia, and motor weakness. The incidence of neuropathy (primarily sensory) was between 5-10%(Manetta et al., 1990, Olver et al., 2001, Vergote et al., 1992**).** Prognosis is usually good with the reversal of the neuropathy upon discontinuation of treatment.

2.4 Neuroprotection

There is currently no standard treatment for the prevention of chemotherapy induced neuropathy. However, neuroprotection studies revealed some potential agents although none of them are commonly employed at present. The ideal candidate for neuroprotection should be safe, well-tolerated, and effective. Most importantly it should not interfere with the cytotoxic activity of chemotherapy.

2.4.1 Acetyl-L-carnitine

Acetyl-L-carnitine, the acetyl ester of L-carnitine, naturally occurs in plants and animals. Acetyl-L-carnitine plays an essential role in metabolism to facilitation of fatty acid

utilization. Acetyl-L-carnitine has demonstrated neuroprotective and neurotrophic actions in other neuropathies. In a multicenter, randomized, double-blind, placebo-controlled, diabetic neuropathy study with 333 patients, acetyl-L-carnitine or placebo was administered intramuscularly at a dosage of 1000 mg/day for 10 days and continued orally at a dosage of 2000 mg/day for 355 days (De Grandis & Minardi 2002). Acetyl-L-carnitine showed a statistically significant improvement in mean nerve conduction velocity and amplitude compared with placebo. The greatest changes were observed in sural and ulnar sensory nerves, and the peroneal motor nerve. After 12 months of treatment, pain was reduced 39% from baseline in the acetyl-L-carnitine group, but only 8% in the placebo group (De Grandis & Minardi 2002). Acetyl-L-carnitine also showed significant improvements in sural nerve fiber numbers and regenerating nerve fiber clusters in two 52-week randomized placebo-controlled clinical diabetic neuropathy trials (Sima et al., 2005). Low levels of serum acetyl-L-carnitine were found in patients with antiretroviral toxic neuropathy (James 1997). After 6 months of acetyl-L-carnitine (1500 mg twice daily, oral), small sensory fibers increased from skin biopsy in HIV-positive patients with antiretroviral toxic neuropathy. Improvement of innervation continued in the epidermis and dermis after 24 months of treatment (Hart et al., 2004). In a randomized study, acetyl-L-carnitine treatment produced a significantly greater reduction in pain compared with placebo (P=0.022) when administered 500 mg intramuscularly twice daily for 14 days, followed by orally 1000 mg twice daily for 42 days in patients with antiretroviral toxic neuropathy (Youle et al., 2007).

Acetyl-L-carnitine was found to be able to reduce the neurotoxicity of cisplatin and paclitaxel without interfering with antineoplastic effects of either medication (Pisano et al., 2003) as well as the neurotoxicity of oxaliplatin in rat models (Ghirardi et al., 2005). It was also confirmed that acetyl-L-carnitine does not affect the cytotoxicity of paclitaxel or carboplatin on ovarian cancer cells (Engle et al., 2009). In rats, acetyl-L-carnitine prevented paclitaxel-induced neuropathic pain, the swollen and vacuolated mitochondria caused by paclitaxel in C-fibers, but not in A-fibers (Jin et al., 2008). In addition, acetyl-L-carnitine decreased the spontaneous discharge of A-fibers and C-fibers, and blocked the development of the paclitaxel-evoked pain in the sural nerve of rats (Xiao and Bennett 2008). Acetyl-L-carnitine has been investigated in 2 open label clinical trials in chemotherapy-induced neuropathy. Acetyl-L-carnitine was administrated orally 1g 3 times a day for 8 weeks in 25 patients with neuropathy during paclitaxel or cisplatin therapy (Bianchi et al. 2005). All patients except one reported symptomatic relief, and only two reported nausea. Sensory neuropathy improved in 15 of 25 patients, and motor neuropathy improved in 11 of 14 patients. Total neuropathy score that included neurophysiological studies improved in 23 (92%) patients. Symptomatic improvement persisted in 12 of 13 evaluable patients at median 13 months. Acetyl-L-carnitine (1 g intravenous infusion over 1-2 hours) was also investigated in 26 patients with paclitaxel and/or cisplatin-induced neuropathy (Maestri et al. 2005). At least one WHO grade improvement in the peripheral neuropathy severity was shown in 73% of the patients. Insomnia related to acetyl-L-carnitine was reported in one patient. At present, there is no double-blind, placebo controlled studies to confirm the effect of acetyl-L-carnitine in chemotherapy-induced neuropathy.

2.4.2 Amifostine

Amifostine is approved as a cytoprotective adjuvant for use in cancer chemotherapy and radiotherapy involving DNA-binding chemotherapeutic agents including platinum and

alkylating agents. The cytoprotective activity of amifostine is proposed to decrease DNA interstrand crosslinks of platinum and alkylating agents, and to scavenge free radicals. Common side effects are hypotension, nausea and vomiting.

Amifostine cytoprotection was investigated in a multicenter randomized controlled trial in 242 advanced ovarian carcinoma patients with the first-line treatment of cisplatin and cyclophosphamide. The study demonstrated a significant reduction in hematologic, renal, and neurologic toxicities with equivalent therapeutic response and survival (Rose 1996). Later, a phase II study was conducted by the Gynecologic Oncology Group. Twenty-seven patients received intravenous paclitaxel (175 mg/m^2) followed by amifostine (740 mg/m^2) and cisplatin (75 mg/m^2). Four of 27 patients developed grade 2 to 4 neurotoxicity based on clinical assessments, Cancer Institute–Common Toxicity Criteria and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity. The neuropathic events exceeded the predetermined threshold level, and the study was closed (Moore et al., 2003). In a double-blind randomized placebo-controlled amifostine study of 72 patients in first-line treatment of advanced ovarian cancer with carboplatin/paclitaxel with or without epirubicin, amifostine improved sensory neuropathy according to Cancer Institute–Common Toxicity Criteria with objective neurological assessment. The improvement included two-point discrimination, vibration perception and tendon reflex, but there were almost no differences in self-estimated specific sensory or motor symptoms comparing with placebo. In addition, amifostine failed to improve the global health status quality of life score, and worsened nausea and vomiting (Hilpert et al., 2005). The other randomized study in 90 ovarian cancer patients treated with standard carboplatin/paclitaxel with or without amifostine reported no symptoms of neurotoxicity in 40% of the carboplatin/paclitaxel group versus 49% of the carboplatin/paclitaxel/ amifostine group. Grad II sensory neuropathy was in 12% of the carboplatin/paclitaxel group versus 2% of the carboplatin/paclitaxel/amifostine group. Amifostine was temporarily interrupted in five patients due to hypotension. Quality of life questionnaires showed no difference in neurotoxicity scores between both study arms (De Vos et al., 2005).

American Society of Clinical Oncology published 2008 clinical practice guideline. Amifostine may be considered for prevention of cisplatin-associated nephrotoxicity, reduction of grade 3 to 4 neutropenia. It is not recommended for protection against platinum or paclitaxel associated neuropathy (Hensley et al., 2009).

2.4.3 Glutamate

The amino acid glutamate is naturally in many foods. Glutamate is the most abundant excitatory neurotransmitter in the vertebrate nervous system. Like the closely related amino acid glutamine, glutamate was investigated in a randomized, placebo-controlled, double-blinded clinical and electrodiagnostic study. Forty-three ovarian cancer patients were available for analysis following six cycles of paclitaxel treatment. Twenty-three patients were supplemented by glutamate at a daily dose of 500 mg three times, while 20 patients received a placebo. The only statistical difference was found in lower pain scores in the glutamate group. There was no significant difference in neurological examinations, questionnaires and sensory-motor nerve conduction studies between the two groups (Loven et al., 2009). Therefore, based on limited study, glutamate has not demonstrated neuroprotective properties against peripheral neurotoxicity.

2.4.4 Glutamine

Glutamine is a neutral amino acid that plays a critical role in protein synthesis, as a source of cellular energy, and nitrogen donation. The neuroprotective role in chemotherapy induced neuropathy has not been reported in ovarian cancer. Two non-randomized, controlled studies investigated the effect of glutamine (10 g orally three times a day) in single high-dose paclitaxel (825 mg/m^2) induced peripheral neuropathy in breast cancer with a total of 91 patients (Stubblefield et al., 2005, Vahdat et al., 2001). Both paired pre- and post-paclitaxel evaluations shown that the glutamine group had a statistically significant reduction in the incidence and severity of peripheral neuropathy, reduced symptoms and sign in dysesthesias, numbness, weakness and abnormal vibration sense. There were significant reductions in the amplitude and conduction velocity of the motor and sensory nerves from the baseline in both groups, and glutamine did not appear to exert a protective effect (Stubblefield et al., 2005, Vahdat et al., 2001). The role of oral glutamine in preventing oxaliplatin-induced neuropathy was evaluated in 86 patients with colorectal cancer (wang et al., 2007). Patients were randomized to receive or not receive glutamine (15 g twice a day). Glutamine had significantly lower incidence of grade 1-2 peripheral neuropathy, reduced interference with activities of daily living, and did not result in a need for oxaliplatin dose reduction. There were no significant differences between groups in electrophysiological abnormalities, or survival (wang et al., 2007). All 3 clinical trials found that oral glutamine reduces the symptoms of chemotherapy-induced neuropathy, but it does not prevent declining nerve function as measured by nerve conduction study. In addition, none of these studies was randomized, or placebo-controlled. There is a lack of sufficient evidence to recommend oral glutamine for the prevention of chemotherapy induced neuropathy.

2.4.5 Glutathione

Glutathione is a tripeptide. It is an antioxidant to prevent cellular damage by reactive oxygen species such as free radicals. Glutathione was postulated to reduced the toxicity of cisplatin, and a multi-center, double-blind, randomized, placebo controlled phase III trial was conducted in 151 ovarian cancer patients with 74 patients in cisplatin/glutathione group, and 77 patients in cisplatin/placebo group (Smyth et al.,1997). The objective was to determine whether glutathione would enhance the feasibility of giving six cycles of cisplatin at 100 mg/m^2. Glutathione (3 g/m^2) or placebo was given with cisplatin every 3 weeks. Fifty-eight percent of patients completed 6 cycles of treatment in the glutathione group versus 39% of patients in the control group (P = 0.04). The glutathione group also showed significantly less nephrotoxicity, and better quality of life scores. Glutathione only suggested a trend towards less neurotoxicity. Sensory neuropathy was 39% in the glutathione group versus 49% in the control group. Motor neuropathy was 9% in the glutathione group versus 12% in the control group measured with common toxicity criteria.

Shortly before the clinical trial for ovarian cancer, glutathione showed efficacy in the prevention of cisplatin induced neurotoxicity, and did not reduce the clinical activity of cisplatin in a randomized double-blind placebo-controlled trial with 50 gastric cancer patients (Cascinu et al., 1995). Glutathione was given intravenously at a dose of 1.5 g/m^2 immediately before cisplatin administration, and at a dose of 600 mg by intramuscular injection on days 2 to 5. Normal saline was administered to patients in the placebo group. Clinical neurologic evaluation and electrophysiologic investigations were performed at

baseline, after 9 (cisplatin cumulative dose, 360 mg/m2) and 15 (cisplatin cumulative dose, 600 mg/m2) weeks of treatment. At the 9th week, no patients showed clinically evident neuropathy in the glutathione group, compared to 16 patients in the placebo group. After the 15th week, 4 of 24 patients in the glutathione group suffered from neurotoxicity versus 16 of 18 in the placebo group (P = .0001). Neurophisiologic studies showed a significant reduction of sensory nerve amplitude in the placebo group but not in the glutathione group (Cascinu et al., 1995). Later, glutathione in oxaliplatin-induced neurotoxicity was also demonstrated in a randomized, double-blind, placebo-controlled trial by the same authors with a similar study design (Cascinu et al., 2002). After 12 cycles (oxaliplatin cumulative dose 1,200 mg/m^2), grade 2 to 4 neurotoxicity was observed in 3 of 21 patients in the glutathione group, and in 8 of 19 patients in the placebo group (P=.004). Sural sensory nerve conduction study showed a statistically significant reduction in the placebo group but not in the glutathione group. This study provides evidence that glutathione is a promising drug for the prevention of oxaliplatin induced neuropathy without a reduction of the clinical activity of oxaliplatin. The results from above clinical trials on the efficacy of glutathione are encouraging, but it should be further confirmed in large scale randomized, double-blind, placebo-controlled trials.

2.4.6 Vitamin E

Vitamin E is a fat soluble vitamin with antioxidant property. Low plasmatic levels of vitamin E had been found in patients with severe cisplatin induced neurotoxicity (Bove et al., 2001). Supplementation of vitamin E has shown neuroprotection in patients receiving cisplatin, paclitaxel, or their combination.

Pace and colleagues performed both preclinical study and a pilot clinical trial to evaluate the neuroprotective effect of vitamin E in cisplatin induced neuropathy (Pace et al., 2003). In preclinical studies, nude mice carrying the human melanoma tumor were treated with cisplatin alone or in combination with vitamin E. Cisplatin combined with vitamin E showed no differences in tumor growth, tumor weight, or life span of nude mice as compared to treatment with cisplatin alone. Forty-seven patients were randomly assigned to the vitamin E group during cisplatin chemotherapy, or the control group with cisplatin chemotherapy alone. Vitamin E 300 mg daily was administered orally before cisplatin chemotherapy and continued for 3 months after the suspension of treatment in the vitamin E group. Twenty-seven patients completed six cycles of cisplatin chemotherapy: 13 patients in the vitamin E group and 14 patients in the control group. The incidence of neurotoxicity was significantly lower in the vitamin E group (30.7%) than it was in the control group (85.7%). The severity of neurotoxicity, measured with a comprehensive neurotoxicity score based on clinical and neurophysiological parameters, was significantly lower in patients of the vitamin E group than in patients in the control group (2 versus 4.7) (Pace et al., 2003). Later, Pace and colleagues performed a 2 center, double-blind, randomized, placebo controlled study of cisplatin induced neuropathy in solid tumor patients (Pace et al., 2010). A total of 108 patients treated with cisplatin chemotherapy were randomly assigned to receive vitamin E (400 mg/day) or placebo orally. Only 41 patients who received a cumulative dose of cisplatin higher than 300 mg/m^2 were eligible for statistical analysis with 17 in the vitamin E group and 24 in the placebo group. The incidence of neurotoxicity was significantly lower in the vitamin E group (5.9%) than in the placebo group (41.7%) ($p< 0.01$). Neurotoxicity was measured with Total Neuropathy Score, and revealed a mean score

of 1.4 in the vitamin E group versus 4.1 in the placebo group ($p < 0.01$). On sensory nerve conduction study, mean sural and median sensory amplitudes were both significantly reduced in the control group, while only mildly reduced in the sural nerve and unchanged in the median nerve in the vitamin E group (Pace et al., 2010).

Argyriou and colleagues conducted 3 randomized, open label with blind assessment, controlled trials to determine whether vitamin E has a neuroprotective effect in chemotherapy-induced peripheral nerve damage. In 3 trials, a total 93 patients treated with six cycles of cisplatin, paclitaxel, or their combination were randomly assigned to a vitamin E group or a control group. Patients were followed by neurologic examination and electrophysiologic study. Patients assigned to the vitamin E group received oral vitamin E at a daily dose of 600 mg/day during chemotherapy and 3 months after its cessation were compared to patients of the control group. The incidence of neurotoxicity differed significantly between the two groups. The percentage of patients with neurotoxicity was 18.7-25% in the vitamin E group and in 62.5-73.3% in the control group. Mean peripheral neuropathy scores were 2.25-4.99 for patients of the vitamin E group and 10.62-11.5 for patients of the control group (Argyriou et al., 2005, 2006a, 2006b). Their studies showed that vitamin E effectively protects patients with cisplatin/paclitaxel induced peripheral neuropathy. Interestingly, vitamin E supplement at dose from 300 mg to 600 mg daily in all above clinical trials seems to have a similar range of reduction of the incidence of peripheral neurotoxicity. The promising results warrant additional double-blind, randomized, placebo controlled trials in ovarian cancer with carboplatin/paclitaxel treatment for the safety, and efficacy.

Acetyl-L-carnitine, amifostine, glutamate, glutamine, glutathione and vitamin E, reviewed here, are only some of the possible neuroprotective agents investigated for chemotherapy induced neuropathy. Other agents, such as acetylcysteine, calcium and magnesium, diethyldithiocarbamate, and Org 2766 have been investigated , but only limited data is available. At present, the neuroprotection data is insufficient to conclude that any of these agents prevent or limit the neurotoxicity in chemotherapy-induced neuropathy (Albers et al., 2011).

Future research for neuroprotective agents needs well designed clinical trials in chemotherapy-induced neuropathy with a validated grading system, quality of life measurement and evidence of improvement in nerve structure or function, such as epidermal nerve fiber density or electrophysiology study. Otherwise, clinical measurement alone may be symptomatic treatment instead of neuroprotection.

2.4.7 Symptomatic treatment of neuropathic pain

Chemotherapy induced sensory neuropathy may cause neuropathic pain reported as burning, tingling, pins and needles sensation, shooting, cramping, and deep aching. Neuropathic pain is frequently treated with antidepressants, anticonvulsants, topical agents, and analgesics. This treatment must be individualized. Combinations of different agents should be considered in some patients. Slow dose escalation may improve drug tolerability (Pan and Thomas 2001). A new evidence-based guideline for treating painful diabetic neuropathy was issued by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation based on a systematic review of literature from 1960 to 2008 (Bril et al., 2011). This guideline recommends using pregabalin for painful diabetic neuropathy if clinically appropriate; venlafaxine, duloxetine, amitriptyline, gabapentin,

valproate, opioids, capsaicine and percutaneous electrical nerve stimulation are probably effective and should be considered. This guideline can be used for the treatment of chemotherapy induced neuropathic pain.

Pregabalin is an anticonvulsant, which does not bind to plasma proteins or interact with other drugs. It has demonstrated efficacy in 4 randomized, double-blind, multicenter studies of painful diabetic neuropathy (Frampton & Scott 2004, Satoh et al., 2011). Pregabalin is given 2 to 3 times daily. From an initial dose of 50 or 75 mg/day, may be increased to 300 mg/day gradually, and later, to 600 mg/day as needed. Adverse effects of pregabalin include dizziness, somnolence, peripheral edema, headache, blurred vision, and constipation.

Venlafaxine is an antidepressant. It is a serotonin, norepinephrine, and dopamine reuptake inhibitor. A moderate effect of pain relief was found compared with placebo (Rowbotham et al., 2004). Venlafaxine XR 75 mg daily may be increased to 150 mg daily. Venlafaxine is well tolerated; the adverse events are nausea, headache, somnolence, dry mouth, and dizziness.

Duloxetine is an antidepressant, a reuptake inhibitor of serotonin and norepinephrine. Duloxetine at doses of 60 and 120 mg a day improved neuropathic pain in several randomized, double-blind studies of diabetic neuropathy and was rather well tolerated (Goldstein et al., 2005). A more common initial side effect, nausea, can be curtailed if the drug is started at a low dose of 20 or 30 mg during the first week.

Amitriptyline has been investigated in several double-blind, randomized trials. Amitriptyline, desipramine, and fluoxetine were compared at a mean daily dose of 105, 111, and 40 mg respectively in 2 randomized, double-blind, crossover studies of painful diabetic neuropathy. Amitriptyline and desipramine relieved pain in 74% and 61% of 38 patients respectively, whereas fluoxetine showed no difference compared with placebo in 46 patients (Max et al., 1992). Amitriptyline should be started at a dosage of 10 to 25 mg/day and increased by 10 to 25 mg/week to the maximum effect or tolerated dosage. Bedtime administration may help to reduce day time sedation. The adverse events most commonly reported are dry mouth, sedation, constipation, nausea, and urinary retention as well as orthostatic hypotension and tachycardia in elderly patients. Amitriptyline should be administrated with caution in patients with urinary retention, glaucoma, constipation, impaired liver function, or cardiovascular disease.

Gabapentin is currently the most frequently used anticonvulsant for painful neuropathy, and also does not bind to plasma proteins or interact with other drugs. A double-blind, placebo-controlled trial demonstrated pain reduction with gabapentin at 900 to 3600 mg/day in 165 patients with diabetic neuropathy (Backonja et al., 1998). Gabapentin can reduce chemotherapy-induced neuropathic pain at a low dose of 800 mg/day (Tsavaris et al., 2008). Adverse events may include fatigue, dizziness, somnolence, and weight gain. Gabapentin should be started at a dose of 100 to 300 mg/day and slowly increased to the maximum effect or tolerated dosage. Occasionally, a previously effective dose needs to be increased to maintain pain control in the absence of objective evidence of disease progression, possibly due to habituation.

3. Entrapment neuropathy

Entrapment neuropathy is caused by focal compression, restriction, or mechanical distortion of a nerve in a fibrous or fibro-osseous tunnel. Chemotherapy-induced peripheral neuropathy can make nerves more vulnerable to compression or to stretching

nerve injury. Minor compression may lead to focal demyelination or axonal injury. Entrapment neuropathy should be suspected if symptoms are focal or unilateral instead of symmetrical, length dependent or generalized. Positive Tinel's sing may be found at the entrapment site. Nerve conduction study and electromyography can localize the abnormality and reveal the severity. Several common entrapment neuropathies should be recognized as below.

Median nerve entrapment at the wrist is the most common entrapment neuropathy as median nerve passes the carpal tunnel. Symptoms involve the thumb, index and middle fingers with numbness, tingling and burning, but referred pain can radiate to forearm or arm. Symptoms may be worse at night, or after using of the hand. Examination may reveal sensory deficit for light touch in the median nerve distribution distal to carpal tunnel. Thenar weakness and atrophy are seen in the severe entrapment cases. Nerve conduction study frequently demonstrates prolonged sensory nerve latency, reduced amplitude, and prolonged distal motor latency. The initial treatment is wrist splint in neutral position. Severe entrapment needs surgical carpal tunnel release.

Ulnar nerve entrapment at the elbow is the second most common entrapment neuropathy. The ulnar nerve may be directly compressed in the retrocondylar grove or entrapped through cubital tunnel. Symptoms present as tingling or numbness in the fifth and part of the fourth fingers, hypothenar eminence and the dorsum of the hand. Weakness or atrophy of the interossei muscles causes clawing of the fourth and fifth fingers in severe entrapment. Nerve conduction study reveals slow conduction velocity across the elbow segment. Electromyography may reveal acute and chronic denervation in ulnar nerve innervated muscles. Elbow protector, avoidance of repetitive elbow flexion and extension, and direct pressure from excessive elbow leaning may resolve the symptoms. Surgical release of compression or anterior translocation may be considered if symptoms persist after conservative treatment.

Common peroneal nerve entrapment at the fibular head is the most common entrapment neuropathy in the leg. Direct pressure to the fibular head, or habitual leg crossing can result foot drop, inversion, and sensory deficits at the lateral lower leg. Nerve conduction study may reveal slow motor conduction velocity across the fibular head. Electromyography may reveal acute and chronic denervation in common peroneal or deep nerve innervated muscles. Ankle-foot orthosis can improve the gait when foot drop is present.

Posterior tibial nerve is more frequently entraped distally at the tarsal tunnel instead of the proximal segment. The most common pathology relates to external compression from shoes that are too tight or to plaster casts. Others include posttraumatic fibrosis, tendon sheath cysts, and rheumatoid arthritis. The plantar nerves may be damaged within the tarsal tunnel or more distally as they course through the arch and sole of the foot. The medial plantar nerve is injured more commonly than the lateral, and may cause burning pain in the toes and the sole of the foot, which is difficult to deferential from chemotherapy-induced neuropathy if it involves both feet. Nerve conduction study may confirm entrapment at the tarsal tunnel, however, planter nerve sensory response is not easy to elicit, may be absent even without tarsal tunnel syndrome. If the sural sensory study is abnormal, absent planter nerve sensory response may be due to generalized peripheral neuropathy. Tarsal tunnel syndrome treatment, at least initially, should be conservative to remove possible outside compression, such as shoes. When conservative measures fail, surgical release may be considered.

Lateral femoral cutaneous nerve entrapment is usually entrapped at the inguinal ligament with obesity, direct compression by a belt, but rarely in the proximal segment of femoral nerve by retroperitoneal tumor, hematoma, ascites or other conditions with increased intra-abdominal pressure. This nerve is a pure sensory nerve and entrapment causes numbness, burning, and/or pain on the anteriorlateral thigh. Most patients with lateral femoral cutaneous nerve neuropathy, except for those with iliacus or retroperitoneal hematoma that might require surgical intervention, are treated conservatively, while waiting for spontaneous remyelination or reinnervation.

Dellon and colleagues reported clinical success of surgical decompression in 80 percent of their patients, including chemotherapy-induced neuropathy if patients had positive Tinel's sign on the known anatomic compression sites. Five of 9 in the report were ovarian cancer patients treated with cisplatin or paclitaxel or both. Three patients had complaints of pain localized in a single extremity with single nerve compression. Single nerve decompression was successful for those patients. The other 2 ovarian cancer patients had multiple decompression in lower extremities. Surgical decompression has resulted in restoration of sensation and relief of pain. (Dellon et al., 2004).

4. Neurologic paraneoplastic syndromes

Paraneoplastic syndromes are rare, and occur as a remote effect of tumor, not by mass lesions, metastases, or anti-tumor treatment. The prevalence of paraneoplastic syndromes is very low, as only one patient was found with neurological paraneoplastic syndrome as cerebellar degeneration in 908 patients with primary ovarian malignancy (Hudson et al., 1993). Neurologic paraneoplastic disorders are autoimmune diseases, and can affect any part of the central (cerebellar degeneration, limbic encephalitis, opsoclonus-myoclonus, and brainstem encephalitis), or peripheral nervous system (subacute sensory neuronopathy, and autonomic insufficiency). Unlike chemotherapy-induced neuropathy, subacute sensory neuronopathy can begin in arm, legs, or face, and spread proximally to trunk, with progressively loss all sensations. Neurological paraneoplastic syndromes are caused by an autoimmune response to proteins (onconeural antigents) that are shared by the cancer and the peripheral or central nerve systems. They are Hu, Yo, Ri, CV2, amphiphysin, Ma, Ta, Tr, NMDA. Ovarian cancer patients may express proteins Hu, Yo, Ri and anti-amphiphysin (Titulaer et al., 2011). Therefore, test antibodies for Hu, Yo, Ri and anti-amphiphysin can help to diagnose neurological paraneoplastic syndrome in ovarian cancer. In a retrospective study of 73 Hu-antibody positive patients, neurological paraneoplastic syndromes are 55% sensory neuropathy, 22% cerebellar degeneration, 15% limbic encephalitis, and 16% brainstem encephalitis (Sillevis Smitt et al., 2002).

Treatment of paraneoplastic syndromes in ovarian cancer should primarily treat the malignancy. Corticosteroids, cyclophosphamide and other immunosuppressant may be used. Intravenous immune globulin **or** plasma exchange can be tried. However, all treatment may not be beneficial to subacute sensory neuronopathy.

5. Conclusion

Peripheral neuropathy in ovarian cancer is complex. When patients develop neuropathy symptoms in ovarian cancer, we cannot simply conclude that it is chemotherapy-induce neuropathy. It is a challenge to treat this condition. Diagnosis of the etiology of the neuropathy, treating the underlying disease, correction of metabolic, nutritional, and

endocrine abnormalities, and decompression of the nerve entrapment will preserve nerve function. The goals of treatment are reduction of symptoms, improvement of function and patient's quality of life.

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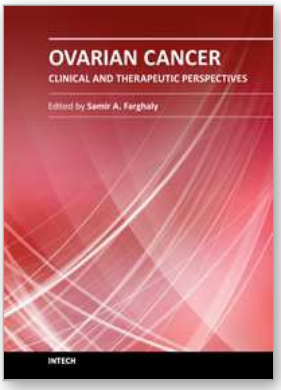

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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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