REVIEW

Chemotherapy-induced peripheral neuropathy: a literature review

Neuropatia periférica induzida por quimioterapia: uma revisão de literatura

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ABSTRACT

Peripheral neuropathy is a common side effect in patients undergoing cancer treatment with chemotherapy. This condition can affect patients in several different ways, interfering in their activities of daily living and autonomy. The present study aimed to review the literature on chemotherapy-induced peripheral neuropathy and its treatment or other possible interventions. The findings reveal that chemotherapy-induced peripheral neuropathy is a common condition that affects patients undergoing treatment with some specific drugs. Besides, several different substances have been used to treat or control this condition, although no significant evidence could be found in these studies.

Keywords: Peripheral nervous system diseases/chemically induced; Drug therapy/adverse effects

RESUMO

A neuropatia periférica é um efeito colateral comum em pacientes sob tratamento quimioterápico. Essa condição pode se manifestar de diversas maneiras, interferindo na qualidade de vida e na autonomia nas atividades de vida diária dos pacientes em questão. O presente trabalho teve como objetivo revisar a literatura referente à neuropatia periférica induzida por quimioterapia, bem como propostas de tratamento e intervenção para o efeito colateral em questão. Foi possível observar que a neuropatia periférica induzida por quimioterapia é uma condição comum a pacientes sob tratamento com alguns quimioterápicos específicos. Além disso, foi possível identificar, embora sem evidência significativa, que diversas substâncias vêm sendo utilizadas como possível tratamento ou paliativo para o efeito colateral em questão.

Descritores: Doenças do sistema nervoso periférico/induzido quimicamente; Quimioterapia/efeitos adversos

INTRODUCTION

Several studies indicate that chemotherapy is the treatment of choice for most cases of cancer[1,2]. However, despite widespread clinical use in oncology, several reports are presented in the literature of complaints associated with side effects of this treatment[3]. One of the side effects is neurotoxicity. In the literature the following drugs used in cancer chemotherapy are listed as neurotoxic: vincristine, vinblastine, vinorelbine, cisplatin, oxaliplatin, cytarabine, ifosfamide, 5-fluorouracil, methotrexate, paclitaxel, docetaxel, altretamine, procarbazine, interleukin-2, fludarabine, cladribine, and pentostatin[4].

Peripheral neuropathy is the involvement of neurons that form the peripheral nerves or nerve roots. This condition causes motor and sensory symptoms, which may include weakness, muscle atrophy and hypotonia, hyporeflexia or areflexia, hypesthesia, paresthesia, dysesthesia, sensory ataxia, leading to impaired performance of the individual in daily activities and functional independence. As to its etiology, peripheral neuropathy can be associated with general medical conditions, infectious or inflammatory processes, metabolic processes, and heredity. This study addresses the peripheral neuropathy associated with metabolic processes, due to the toxic effect of chemotherapy and its interference in the healthy metabolism of the nerve cell[5-8].

The main symptoms of chemotherapy-induced peripheral neuropathy (CIPN) may depend on the drug and dose used, but usually manifest as predominantly distal weakness, loss of sensation and reflexes. Discontinuation of the drug which induced peripheral neuropathy appears to suppress the symptoms, however, the remaining signs of toxicity should be observed, taking heed of the presence of permanent injury[7,8].

It is estimated that 30 to 40% of patients who receive chemotherapy develop peripheral neuropathy[9-11]. There are reports, however, of incidences up to 60% when the

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drugs used are cisplatin[12,13], paclitaxel[14], docetaxel[15], vincristine[16], oxaliplatin, and bortezomib[17].

This study focuses on investigating chemotherapy-induced neurotoxicity manifested as peripheral neuropathy. In the literature, there are several studies that investigate the relation among the use of chemotherapy drugs, their neurotoxicity and the presence of neurological diseases, including peripheral neuropathy[18-23].

Given the evidence shown in the literature, it is necessary to investigate the incidence, symptoms, and therapeutic procedures associated with CIPN. Thus, cancer care professionals may outline patterns in the disease development, as well as plans for early intervention and, above all, therapeutic strategies that include support and adaptation in daily activities for this population, assuring greater independence, autonomy, and quality of life.

OBJECTIVES

- To identify studies in the literature addressing CIPN.
- To identify plans in the literature for prevention and treatment of CIPN.

METHODS

This study was a descriptive, exploratory narrative review of the literature. Guiding questions: "How to characterize CIPN? Are there prevention and treatment for this condition?"

Selected databases during the second half of 2010: Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature on Health Sciences (LILACS), Pubmed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. Scientific studies in Portuguese, English, and Spanish published from September 2005 to September 2010 were included.

Keywords researched: "treatment" and "chemotherapy-induced peripheral neuropathy".

The cataloging of contents from the publications included in the data collection was performed according to a semi-structured routine (Chart 1).

The data were cataloged and the relevant topics addressed in the studies generated thematic categories, which were discussed in the results and discussion of this study.

RESULTS

A total of 57 studies were identified, and 26 of them met the inclusion criteria established.

From the 26 studies selected, 5 themes were identified (Figure 1). It must be highlighted that in this study only the results for the treatment of CIPN will be discussed.

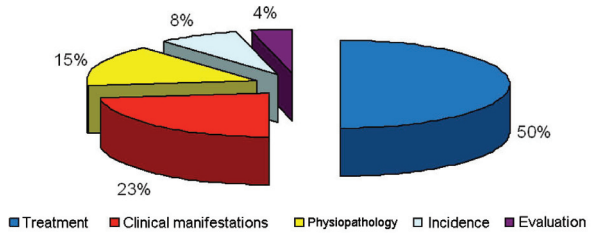

Figure 1. Main themes

DISCUSSION

In presenting the results, we found that most of the publications identified had CIPN treatment as the main theme. There was heterogeneity in the substances and techniques used in the treatment of CIPN. Thus, the following techniques and substances identified in the articles of this review are presented.

Radiofrequency ablation

An Indian study published a case study of a 63 year-old male patient diagnosed with prostate cancer with bone metastases in acetabulum, left ischium, femoral head, vertebrae, ribs, pelvis, and skull. The patient underwent surgery and subsequent radiotherapy and adjuvant chemotherapy with docetaxel and prednisone. Three months after surgery and the end of the chemotherapy cycles, the patient started to have pain and tingling in the right palm, followed by numbness in the arm, forearm, and right palm. The report indicates that the patient was refractory to CIPN treatments that included gabapentin, pregabalin, and morphine. After excluding the differential diagnosis of carpal tunnel syndrome, radiofrequency treatment was initiated. The continued radiofrequency stimulation occurred in two cycles of 90 seconds in the ulnar and median nerves. After 2 to 4 hours of stimulation, the patient reported improvement of symptoms. The next day the patient reported a 40% decrease in the pain, and 2 days later, an improvement of 90%, and the use of morphine and other pain medications was discontinued. We observed that this study addressed the technique of ablation by continued radiofrequency energy as an alternative treatment for the management of CIPN pain. However, there were no reports of decrease in sensory and motor

Chart 1. Characterization of selected studies

N	Database	Title	Authors	Year	Origin	Type of study	Main themes
1	PUBMED	Persistent mobility disability after neurotoxic chemotherapy	Hile ES, Fitzgerald GK, Studenski SA	2010	United States	Case Study	Clinical manifestations
2	PUBMED	BNP7787-mediated modulation of paclitaxel- and cisplatin-induced aberrant microtubule protein polymerization in vitro	Parker AR, Petluru PN, Wu M, Zhao M, Kochat H, Hausheer FH	2010	United States	Review	Pathophysiology
3	PUBMED	Glutamate carboxypeptidase inhibition reduces the severity of chemotherapy-induced peripheral neurotoxicity in rat	Carozzi VA, Chiorazzi A, Canta A, Lapidus RG, Slusher BS, Wozniak KM, Cavaletti G	2010	Italy	Experimental	Treatment
4	CINAHL	Radio frequency ablation in drug resistant chemotherapy-induced peripheral neuropathy: a case report and review of literature	Yadav N, Philip FA, Gogia V, Choudhary P, Rana SPS, Mishra S, Bhatnagar B	2010	India	Review	Treatment
5	PUBMED	Patient perceptions associated with chemotherapy-induced peripheral neuropathy	Tofthagen C	2010	United States	Clinical trial	Clinical manifestations
6	WEB OF SCIENCE	Neurophysiological, histological and immunohistochemical characterization of bortezomib-induced neuropathy in mice	Bruna J, Udina E, Alé A, Vilches JJ, Vynckier A, Monbaliu J, Silverman L, Navarro X	2010	Spain	Experimental	Physiopathology
7	PUBMED	A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA	Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD, Kugler JW, Hoff KL, Reddy PS, Rowland KM, Riepl M, Christensen B, Loprinzi CL	2010	United States	Clinical trial	Treatment
8	PUBMED	Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies	Gutiérreza GG, Serenoa M, Miralles A, Casado-Sáenz E, Gutiérrez-Rivas E	2010	Spain	Review	Clinical manifestations
9	PUBMED	Animal models of chemotherapy-evoked painful peripheral neuropathies	Authier N, Balayssac D, Marchand F, Ling B, Zangarelli A, Descoeur J, Coudore F, Bourinet E, Eschalier A	2009	France	Review	Treatment
10	PUBMED	Neuropatia inducida por quimioterapia: um problema no resuelto	Velasco R, Bruna J	2009	Spain	Review	Clinical manifestations
11	PUBMED	Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated With Paclitaxel	Reyes-Gibby CC, Morrow PK, Buzdar A, Shete S	2009	United States	Clinical trial	Incidence
12	WEB OF SCIENCE	Therapy of chemotherapy-induced peripheral neuropathy	Kaley TJ, DeAngelis LM	2009	United States	Review	Treatment
13	PUBMED	Compartmentalized microfluidic culture platform to study mechanism of paclitaxel-induced axonal degeneration	Yang IH, Siddique R, Hosmane S, Thakor N, Höke A	2009	United States	Experimental	Pathophysiology
14	PUBMED	Feasibility and validity of the Patient Neurotoxicity Questionnaire during taxane chemotherapy in a phase III randomized trial in patients with breast cancer: N-SAS BC 02	Shimozuma K, Ohashi Y, Takeuchi A, Aranishi T, Morita S, Kuroi K, Ohsumi S, Makino H, Mukai H, Katsumata N, Sunada Y, Watanabe T, Hausheer FH	2009	Japan	Clinical trial	Evaluation
15	PUBMED	Prospective assessment of chemotherapy induced peripheral neuropathy due to weekly paclitaxel in patients with advanced or metastatic breast cancer (CSP-HOR 02 study)	Kuroi K, Shimozuma K, Ohashi Y, Hisamatsu K, Masuda N, Takeuchi A, Aranishi T, Morita S, Ohsumi S, Hausheer FH	2009	Japan	Clinical trial	Incidence
16	WEB OF SCIENCE	The use of cannabinoids (CBs) for the treatment of chemotherapy-induced peripheral neuropathy (CIPN): A retrospective review	Gingerich J, Wadhwa D, Lemanski L, Krahn M, Daeninck PJ	2009	Canada	Review	Treatment

continue...

Chart 1. Continuation

N	Database	Title	Authors	Year	Origin	Type of study	Main themes
17	WEB OF SCIENCE	Peripheral neuropathy in survivors of childhood acute lymphoblastic leukemia	Ramchandren S, Leonard M, Mody RJ, Donohue JE, Moyer J, Hutchinson R, Gurney JG	2009	United States	Clinical trial	Clinical manifestations
18	PUBMED	Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy	Amara S	2008	United States	Review	Treatment
19	CINAHL	Chemotherapy-induced peripheral neuropathy was described as background noise affecting daily life	Alford M	2008	United States	Clinical trial	Clinical manifestations
20	CINAHL	Chemotherapy-induced peripheral neuropathy: Prevention and treatment strategies	Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C	2008	United States	Review	Treatment
21	PUBMED	Acetyl-L-carnitine for the treatment of chemotherapy-induced peripheral neuropathy: a short review	De Grandis D	2007	Italy	Review	Treatment
22	PUBMED	Vitamin E for the prevention of CIPN: rationale for an ongoing clinical trial	Kottschade L, Loprinzi C, Rao R	2007	United States	Clinical trial	Treatment
23	PUBMED	Putting evidence into practice®: evidence-based interventions for chemotherapy-induced peripheral neuropathy	Visovsky C, Collins M, Abbott L, Aschenbrenner J, Hart C	2007	United States	Review	Treatment
24	PUBMED	Therapeutic angiogenesis inhibits or rescues chemotherapy-induced peripheral neuropathy: taxol- and thalidomide-induced injury of vasa nervorum is ameliorated by VEGF	Kirchmair R, Tietz AB, Panagiotou E, Walter DH, Silver M, Young-Sup, Yoon Y, Schratzberger P, Weber A, Kusano K, Weinberg DH, Ropper AH, Isner JF, Losordo DW	2007	United States	Clinical trial	Treatment
25	PUBMED	Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy	Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F	2006	United States	Review	Pathophysiology
26	PUBMED	Acupuncture treatment of CIPN – a case series	Wong R, Sagar S	2006	Canada	Case study	Treatment

deficits that could interfere in improving quality of life related to greater independence in daily activities[24].

Baclofen, amitriptyline HCL, and ketamine

In a randomized, placebo-controlled study, American researchers investigated the efficacy of a topic lecithin organogel composed of baclofen 10 mg, amitriptyline HCL 40 mg, and ketamine 20 mg, in 203 CIPN patients under treatment with various chemotherapeutic agents (vinca alkaloids, oxaliplatin, cisplatin , taxanes, thalidomide, and others). The selection of the organogel compounds was based on the mechanism of action of the drugs: baclofen is a GABA receptor agonist, amitriptyline HCL affects adenosine A receptors and sodium channels, and ketamine inhibits glutaminergic NMDA receptors. The patients in the study were instructed to apply a tablespoon of the gel in the body region affected by pain, loss of sensation and/or tingling, twice a day – upon rising and at bedtime – for 4 weeks. CIPN was assessed using a 20-item questionnaire entitled European Organization for Research and Treatment of Cancer – Chemotherapy Induced Peripheral Neuropathy (EORTC – CIPN20), containing questions that evaluates sensory, motor, autonomic and functional symptoms. After statistical analysis of recorded data, researchers found that patients who applied the topical gel, compared to placebo-control group, showed improvement trends in sensory components ($p = 0.053$), and statistically significant improvement ($p = 0.021$) in motor components[25].

Vitamin E

Some researchers suggest that CIPN symptoms – such as loss of reflexes and glove-and-stocking paresthesia – are similar to those presented by patients with

peripheral neuropathy caused by vitamin E deficiency syndromes, such as lipid malabsorption and cystic fibrosis. Furthermore, it is noted that cisplatin treatment significantly reduces vitamin E levels, and as a result patients may experience CIPN[26,27].

Based on these assumptions, a clinical study was conducted to evaluate the neuroprotective effects of vitamin E, in 47 patients receiving cisplatin (median cumulative dose of 420 mg/m^2). Patients were randomly divided into two groups: one group received only cisplatin, and the other group received cisplatin and vitamin E (300 mg/day). A significant decrease in the incidence of CIPN was observed in the group receiving vitamin E with chemotherapy (31 *versus* 86%)[27].

A second randomized study evaluated 40 patients undergoing chemotherapy with cisplatin and paclitaxel, using the same methodology described in the study above, except for a difference in dose: some patients received 300 mg of vitamin E twice a day, in addition to chemotherapy. The results from the comparison between the two groups are similar to the findings of the previous study. There was a 25% incidence of CIPN in the group treated with vitamin E, and 73% incidence of CIPN in the control group[28].

Both studies showed a protective effect of vitamin E on the incidence of CIPN. However, these studies did not have quantitatively representative samples to confirm that this substance actually has similar effects on other samples of patients undergoing chemotherapy. However, we found a phase III, double-blind, randomized, placebo-controlled study in progress in the North Central Cancer Treatment Group, in the United States. This research will include the analysis of the neuroprotective effects of vitamin E in 200 patients undergoing chemotherapy. It is hoped that the results of the study may elucidate the effects of vitamin E on CIPN, and provide data about the efficacy of the substance in the treatment of CIPN[29].

Glutamine

Several studies suggest that glutamine may affect several side effects experienced by patients undergoing chemotherapy, including: mucositis, myalgia, arthralgia, diarrhea, cardiotoxicity, and cachexia. In addition, due to the regulatory function of the neuronal growth factor, it is believed that glutamine may have a potentially neuroprotective effects, thereby reducing CIPN[30-32].

Some researchers evaluated the neuroprotective effects of glutamine in 45 patients with stage 4 breast cancer receiving treatment with high doses of paclitaxel. The first cohort (n = 33) received no glutamine, whereas the second (n = 12) received 10 g of glutamine orally, 3 times a day, for 4 days, starting 24 hours after the administration of paclitaxel. The results of the study showed that patients receiving glutamine had significantly fewer paresthesia symptoms and moderate to severe reduction in proprioception in the fingers and toes. Also, patients treated with glutamine had less loss of reflexes and less impairment in daily activities. It is noteworthy that all symptoms of toxicity proved to be reversible over time[33].

Another group of researchers evaluated the role of oral glutamine in 86 patients with metastatic colorectal cancer treated with oxaliplatin (85 mg/m^2 on days 1 and 15 of each 28-day cycle). Patients were randomized to receive glutamine (n = 42) or not (n = 44). The group that received glutamine at a dose of 15 g, twice a day, for 7 days, every 2 weeks, was compared to the group that received glutamine according to the CIPN symptoms evaluated after 2, 4, and 6 cycles of treatment, using the NCI-CTC scale. The study also evaluated nerve conduction, response to chemotherapy, and impaired daily activities. The results showed that patients receiving glutamine had fewer CIPN symptoms and less interference in daily activities when compared to controls. The researchers noted that there were no differences in nerve conduction, response to chemotherapy, or median survival for these patients. This study therefore suggests that glutamine may reduce the occurrence of CIPN, avoiding both the efficacy of oxaliplatin and the need for lowering the dose of the drug[34].

Therefore, although the studies showed favorable results with the use of oral glutamine in patients undergoing chemotherapy, they fail to evaluate the neuroprotective effects of the substance in quantitatively adequate samples that can provide statistically significant data to prove the efficacy of glutamine in reducing the incidence of CIPN[35].

Cannabinoids

Canadian researchers investigated the impact of cannabinoids in reducing CIPN symptoms in eight patients, of whom six received treatment with platinum derivatives. After the administration of cannabinoids to these patients, an improvement was noted in seven of eight patients, by comparing the scores of the NCI-CTC scale before and after treatment. As this was a study with a very small sample, the authors pointed out limitations of the study concerning its replication in quantitatively

more significant samples. They also identified the need for more extensive investigations on the therapeutic effects of cannabinoids in patients with CIPN[36].

FINAL COMMENTS

This review achieved its objectives, since it identified studies that explored CIPN, and its several interrelated aspects, particularly some interventions proposed to minimize the damage caused by involvement of peripheral nerve fibers.

CONCLUSIONS

The field for study, research, and intervention in the area is large and needs further investigation. It was noted that several studies have been conducted recently to evaluate the response of drugs and procedures that hypothetically minimize CIPN symptoms and bouts. However, the studies have limitations that converge on the need for methodological adjustments, such as selection of quantitatively representative samples and research designs that may yield more reliable data, which can be generalized to other samples of patients with similar pathological conditions.

REFERENCES

1. Butters DJ, Ghersi D, Wilcken N, Kirk SJ, Mallon PT. Addition of drug/s to a chemotherapy regimen for metastatic breast cancer. Cochrane Database Syst Rev. 2010;(11):CD003368.
2. Mauri D, Polyzos NP, Salanti G, Pavlidis N, Ioannidis JP. Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. J Natl Cancer Inst. 2008;100(24):1780-91.
3. National Cancer Institute. What you need to know about cancer [Internet]. Bethesda: National Institutes of Health; 2006 [cited 2011 Nov 24]. p. 66. Available from: http://www.cancer.gov/cancertopics/covers-wyntk-cancer.pdf.
4. DeVita VT Jr, Hellman S, Rosenberg SA. Cancer: principles and practice of oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins. 2001. Section 8, Miscellaneous toxicities; p.2964-76.
5. Misra UK, Kalita J. Toxic neuropathies. Neurol India. 2009;57(6):697-705.
6. Acebal RM, Muñoz MC. Polineuropatías. In: Gutiérrez-Rivas E, Hernandés MD, Pardo J, Acebal RM. Manual del IX Curso de electromiografia básica para neurólogos. Barcelona: Novartis; 2006. p. 107-12.
7. Schestatsky P, Zanonato A, Lladó-Carbó A. Polineuropatias. In: Chavez ML, Finkelsztejn A, Stefani MA. Rotinas em neurologia e neurocirurgia. Porto Alegre: Artmed; 2009. p. 223-34.
8. Kimura J. Electrodiagnosis in diseases of nerve and muscle: principles and practice. 2nd ed. Philadelphia: FA Davis; 1989. Chapter 25, Polyneuropathies; p. 462-81.
9. Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. Eur J Cancer. 2008;44(11):1507-15.
10. Bhagra A, Rao RD. Chemotherapy-induced neuropathy. Curr Oncol Rep. 2007;9(4):290-9.
11. Cavaletti G, Marmiroli P. The role of growth factors in the prevention and treatment of chemotherapy-induced peripheral neurotoxicity. Curr Drug Saf. 2006;1(1):35-42.
12. Chaudhry V, Rowinsky EK, Sartorius SE, Donehower RC, Cornblath DR. Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies. Ann Neurol. 1994;35(3):304-11.
13. von Schlippe M, Fowler CJ, Harland SJ. Cisplatin neurotoxicity in the treatment of metastatic germ cell tumour: time course and prognosis. Br J Cancer. 2001;85(6):823-6.
14. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008;358(16):1663-71.
15. Pronk LC, Hilkens PH, van den Bent MJ, van Putten WL, Stoter G, Verweij J. Corticosteroid co-medication does not reduce the incidence and severity of neurotoxicity induced by docetaxel. Anticancer Drugs. 1998;9(9):759-64.
16. Sarris AH, Hagemeister F, Romaguera J, Rodriguez MA, McLaughlin P, Tsimberidou AM, et al. Liposomal vincristine in relapsed non-Hodgkin's lymphomas: early results of na ongoing phase II trial. Ann Oncol. 2000;11(1):69-72.
17. Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. J Clin Oncol. 2005;23(20):4553-60.
18. Grothey A. Clinical management of oxaliplatin-associated neurotoxicity. Clin Colorectal Cancer. 2005;5 Suppl 1:S38-46.
19. De Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18(16):2938-47.
20. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-17.
21. Hile ES, Fitzgerald GK, Studenski SA. Persistent mobility disability after neurotoxic chemotherapy. Phys Ther. 2010;90(11):1649-57.
22. Authier N, Balayssac D, Marchand F, Ling B, Zangarelli A, Descoeur J, et al. Animal models of chemotherapy-evoked painful peripheral neuropathies. Neurotherapeutics. 2009;6(4):620-9.
23. Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. Semin Oncol. 2006;33(1):15-49.
24. Yadav N, Philip FA, Gogia V, Choudhary P, Rana SP, Mishra S, et al. Radio Frequency Ablation in Drug Resistant Chemotherapy-induced Peripheral Neuropathy: A Case Report and Review of Literature. Indian J Palliat Care. 2010;16(1):48-51.
25. Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer. 2011;19(6):833-41.
26. Bove L, Picardo M, Maresca V, Jandolo B, Pace A. A pilot study on the relation between cisplatin neuropathy and vitamin E. J Exp Clin Cancer Res. 2001;20(2):277-80.
27. Pace A, Savarese A, Picardo M, Maresca V, Pacetti U, Del Monte G, et al. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. J Clin Oncol. 2003;21(5):927-31.
28. Argyriou AA, Chroni E, Koutras A, Ellul J, Papapetropoulos S, Katsoulas G, et al. Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. Neurology. 2005;64(1):26-31.
29. Kottschade L, Loprinzi C, Rao R. Vitamin e for the prevention of chemotherapy-induced peripheral neuropathy: rationale for an ongoing clinical trial. Support Cancer Ther. 2007;4(4):251-3.
30. Visovsky C, Collins M, Abbott L, Aschenbrenner J, Hart C. Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. Clin J Oncol Nurs. 2007;11(6):901-13.

31. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev. 2003;29(6):501-13.

32. Decker GM. Glutamine: indicated in cancer care? Clin J Oncol Nurs. 2002;6(2):112-5.

33. Vahdat L, Papadopoulos K, Lange D, Leuin S, Kaufman E, Donovan D, et al. Reduction of paclitaxel-induced peripheral neuropathy with glutamine. Clin Cancer Res. 2001;7(5):1192-7.

34. Wang WS, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, et al. Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. Oncologist. 2007;12(3):312-9.

35. Amara S. Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2008;42(10):1481-5.

36. Gingerich J, Wadhwa D, Lemanski L, Krahn M, Daeninck PJ. The use of cannabinoids (CBs) for the treatment of chemotherapy-induced peripheral neuropathy (CIPN): a retrospective review [abstract]. J Clin Oncol. 2009;27(15):e20743.