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ORIGINAL PAPER

Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera®) for chemotherapy-induced peripheral neuropathy management, a prospective study

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Abstract Chemotherapy-induced peripheral neuropathy (CIPN) is a major clinical problem associated with a number of cytotoxic agents. OPERA® (GAMFARMA srl, Milan, Italy) is a new dietary supplement where α-lipoic acid, Boswellia Serrata, methylsulfonylmethane and bromelain are combined in a single capsule. The aim of this prospective study was to determine the efficacy and safety of OPERA® supplementation in a series of patients affected by CIPN. We selected 25 subjects with CIPN evolving during or after chemotherapy with potentially neurotoxic agents. Patients were enrolled at the first clinical manifestation of neuropathy. CIPN was assessed at the enrollment visit and subsequently repeated every 3 weeks until 12 weeks. Primary endpoint was the evaluation of changes of measured scores after 12 weeks of therapy compared to baseline evaluation. Secondary endpoints were the evaluation of neuropathy reduction at 12 weeks after beginning of therapy with OPERA®. Analysis of VAS data showed reduction in pain perceived by patients. According to NCI-CTC sensor and motor score, mISS scale and TNSc scale, both pain and both sensor and motor neuropathic impairment decreased after 12 weeks of treatments. Treatment with OPERA supplement was well tolerated; no increase in the toxicity profile of any of the therapeutic regimen that the patients were undergoing was reported. OPERA® was able to improve CIPN symptoms in a prospective series of patients treated with neurotoxic chemotherapy, with no significant toxicity or interaction. Prospective RCT in a selected patients' population is warranted to confirm its promising activity.

Keywords Neuropathy · Management · Dietary supplement · Neurotoxic chemotherapy

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a major clinical problem associated with a number of cytotoxic agents, sometimes requiring treatment modification or even withdrawal [1–3], resulting in reduced chemotherapeutic benefit for patients. Currently, evidence of drugs efficacy to prevent these side effects is sparse [4, 5]. The effectiveness of drugs used to treat other types of neuropathy may not be translated to CIPN, as in the case of the tricyclic antidepressant amitriptyline, gabapentin, opioids or other interventions such as calcium and magnesium infusion [6]. α-Lipoic acid (ALA) is a potent lipophilic antioxidant that has been shown to be effective in the treatment of diabetic neuropathy with few side effects [7]. Boswellia Serrata (BS) resins contain several different boswellic acids such as acetyl-keto-beta-boswellic acid (AKBA), an inhibitor of the lipoxygenase pathway, which are suggested to have anti-inflammatory properties [8]. Methylsulfonylmethane (MSM) is an organosulfur molecule that can be synthesized commercially from dimethylsulfoxide (DMSO). Many properties have been attributed to MSM, some of which include chemopreventive properties, anti-inflammatory activities, anti-atherosclerotic action, prostacyclin (PGI2) synthesis inhibition and free radical scavenging activity [9, 10].

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Bromelain is the crude extract of the pineapple stems. It has fibrinolytic, antithrombotic and anti-inflammatory properties; these effects have been well documented in animal and human studies [11]. OPERA® (GAMFARMA srl, Milan, Italy) is a new dietary supplement where α-lipoic acid (240 mg), BS (40 mg), MSM (200 mg) and Bromelain (20 mg) are combined together in a single hard gelatin capsule. Those capsules are equipped with ACTIBOX® system, a programmable carrier technology capable to deliver biologically active substances selectively at pH value around 7.01, typically detected in the early stages of inflammation of various tissues, such as myelin sheaths of the nerves. The aim of our prospective study was to determine the efficacy and safety of OPERA® supplementation in a series of patients affected by CIPN.

Materials and methods

Our clinical study consisted of a convenience sample of 25 adult Caucasian subjects treated at the Radiation Oncology Unit of the Careggi University Hospital, Florence (Italy). Study design and study procedures were reviewed and approved by institutional ethics committee ("Comitato Etico Area Vasta Centro").

Informed consent was obtained from all individual participants included in the study. The inclusion criteria were as follows: 18 years or older; Karnofsky performance score (KPS) $\geq$70; treatment with one of the following agents: paclitaxel, docetaxel, nab-paclitaxel, oxaliplatin, cisplatin, carboplatin, vinorelbine, vincristine, etoposide, eribulin mesylate; the presence of CIPN that evolved after or during standard chemotherapy. The exclusion criteria were as follows: concomitant diseases or neurologic conditions that would complicate interpretation (e.g. diabetes, renal insufficiency, alcohol abuse >5 IU/day); treatment with antiepileptic drugs, antidepressants and major analgesics, unless stable dosing and conditions have been reached; the presence of peripheral nerve damage due to another illness or medication; concurrent potentially neurotoxic medication.

Patients were enrolled at the first clinical manifestation of neuropathy. The diagnosis of CIPN was based on the National Cancer Institute–Common Toxicity Criteria for Adverse Event (NCI-CTCAE) v4.0 grade of $\geq$1 for sensory neuropathy, with at least a report of paresthesia of fingers or toes (grade 1). All patients were required to take an OPERA® capsule once daily, without regard to administration of food.

CIPN was assessed using the following items: the National Cancer Institute–Common Toxicity Criteria (NCI-CTC) v3, sensory and motor neuropathy score [12]; the clinical version of the Total Neuropathy Score clinical version (TNSc) [13]; the modified Inflammatory Neuropathy Cause and Treatment (INCAT) group sensory sum score (mISS) [14]; the Visual Analog pain Scale (VAS) assessed to determine the amount of pain perceived by the patients, who were explicitly asked to score the pain considered to be CIPN related [15].

All the evaluation tools were utilized during the first assessment at the enrollment visit, and subsequently repeated every 3 weeks until 12 weeks. All the evaluations were carried out by the Chemotherapy Day Unit medical staff (doctors, nurses), after an adequate training has been performed in the previous weeks.

Primary endpoint was the evaluation of changes of measured scores after 12 weeks of therapy compared to baseline evaluation (done at the beginning of neuropathy). Secondary endpoints were the evaluation of neuropathy reduction at 12 weeks after beginning of therapy with OPERA®.

Results

Population characteristics

Twenty-five patients met study eligibility criteria and were enrolled between January 1, 2016, and April 1, 2016. Twenty-three patients (92%) received chemotherapy with neurotoxic agent at enrollment, while 2 patients (8%) had completed chemotherapy with neurotoxic drug (docetaxel and paclitaxel, respectively) one month prior enrollment and presented signs and symptoms of neuropathy. Ten patients received a combined chemotherapy with 2 drugs, not necessarily both classified as neurotoxic; only 2 patients (8%) received a combination of 2 neurotoxic drugs (paclitaxel and carboplatin). Of the 25 patients enrolled, 7 patients (28%) had undergone previous neurotoxic therapies. Table 1 summarizes patients' and treatments characteristics. All enrolled patients started therapy with OPERA® at enrollment and completed consumption of OPERA® at twelfth week. All enrolled patients have taken regularly one capsule, once a day.

Pain assessment

Analysis of VAS data showed a progressive reduction in pain perceived by enrolled patients during study period. At enrollment (T0), 12% of patients signaled pain G0, 40% pain G1, 44% pain G2 and 4% pain G3, while at the last assessment (T4) the percentage of pain G0 increased to 32% and G1 and G2 pain percentage decreased, respectively, to 36 and 32% (Fig. 1). No G3 pain toxicity was found at last evaluation: The only patients that showed pain G3 at first assessment reported a reduction in pain relief to grade G2 after 6 weeks from first assumption of OPERA®.

Table 1 Patients and treatments characteristics

Variable	
Sex	
Male	6 (24%)
Female	19 (76%)
Age (mean-range)	64 (40–76)
Tumor type	
CNS cancer	1 (4%)
Breast cancer	17 (68%)
Head and neck cancer	1 (4%)
Lung cancer (NSCLC)	2 (8%)
Endometrial cancer	2 (8%)
Prostate cancer	1 (4%)
Genitourinary cancer	1 (4%)
Current chemotherapy with neurotoxic agent	23 (92%)
Mono-chemotherapy	13 (52%)
Multiple agents	10 (40%)
Current neurotoxic agent type	
Platins (cisplatin, carboplatin)	4 (16%)
Vinca alkaloid	2 (8%)
Taxanes	17 (68%)
Eribuline	2 (8%)
Current use of opioids or other pain medications	2 (8%)
Previous exposure to neurotoxic agent	9 (36%)
Platins (cisplatin, carboplatin)	3 (12%)
Vinca alkaloid	2 (8%)
Taxanes	7 (28%)
Total	25 (100%)

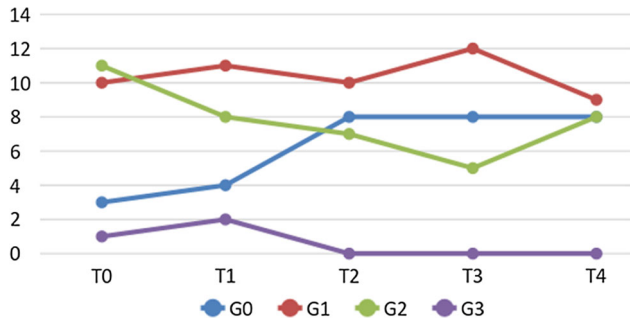

Fig. 1 Pain assessment with VAS over 12 weeks

CIPN assessment

NCI-CTC

According to NCI-CTC sensory and motor neuropathy score, at enrollment the major grade of neurological impairment registered was G3, and no G4 or G5 neurological toxicity was reported. Sensory rather than motor component was more likely to be impaired, considering rate of G3 toxicity (20% G3 vs 4% G3, respectively). After 12 weeks of therapy with Opera, a progressive modification of toxicities' incidences among this cohort was registered: The percentage of G0 sensory and motor neuropathy increased from 0 to 4% and 16%, respectively, as the percentage of G1 toxicity (from 28 and 56% to 61 and 72%, respectively), while there was a decrease in G2 (from 52 and 40%, respectively, to 20 and 8%) and G3 (from 20 and 4% to 8 and 0%, respectively) as shown in Fig. 2.

mISS

According to mISS scale, the median value of sensorial impairment at first assessment was 11.5 (range 1–17) that reduced to a median value of 7.5 (range 1–15) at second assessment (after 4 weeks) and further diminished to a median value of 4.5 (range 0–9) at the last evaluation (12th week) (Fig. 3).

TNSc

The median value of TNSc scale (range 0–28) was 8.5 (range 2–12) at enrollment; after 4 weeks of treatment with OPERA the median value decreases to 6 (range 1–11) and it stabilized to 4.5 (range 0–9) from the third assessment to the 12th week (Fig. 4). The evaluation of individual items showed a greater impairment of sensory component of

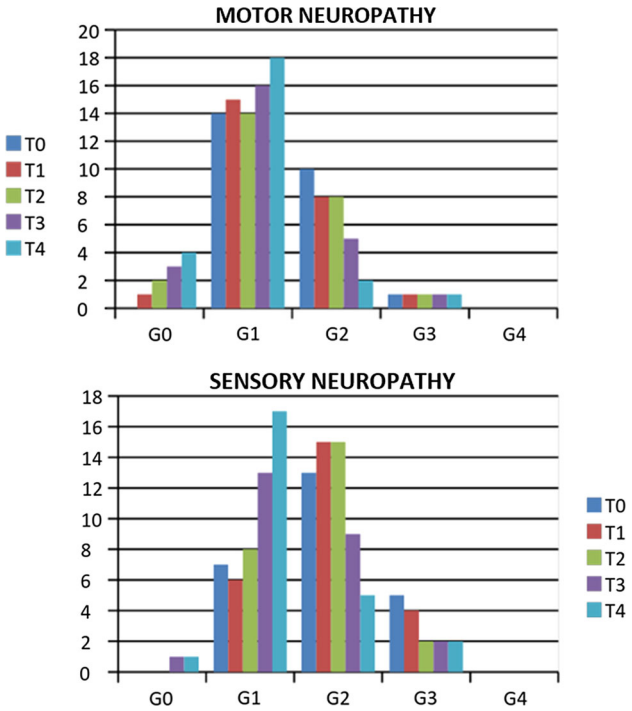

Fig. 2 NCI-CTC sensory and motor neuropathy score assessment over 12 weeks

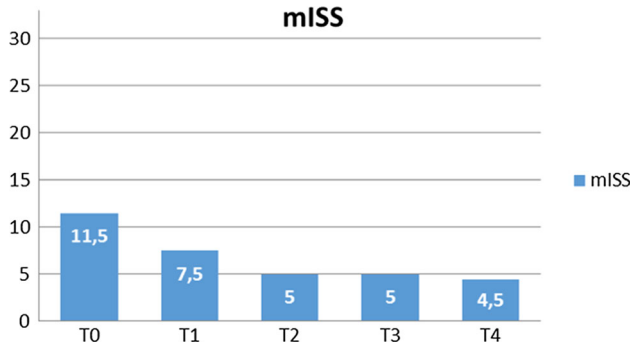

Fig. 3 Trend over time in mISS medians (considering 0.33 scale)

CIPN compared to motor component; the most affected sensitive item was vibration, with a median value of 1.5 at first assessment.

Safety

Treatment with OPERA supplement was well tolerated by patients, and no acute toxicity directly related to the intake of OPERA was reported during the study period. No increase in the toxicity profile of any of the therapeutic regimen that the patients were undergoing was reported.

Discussion

Despite intensive efforts in recent years, CIPN still represents an unmet clinical need in the management of chemotherapy side effects. The morbidity associated with CIPN can lead to pronounced alterations in quality of life, thus impairing independent performance of activities of daily living [16]. Current CIPN guidelines moderately recommend duloxetine as the only effective treatment for painful CIPN [17]. Nevertheless, duloxetine obtained only modest results with considerable associated side effects and a high dropout rate [4]. New safe and effective treatments are clearly warranted. A rising interest has developed in recent years for the use of natural products or complementary medicine; published experience showed encouraging results with vitamin E in preventing CIPN [18]. L-Glutamine, goshajinkigan and omega-3 are also promising [18]. On the other hand, acetyl-l-carnitine may worsen CIPN and alpha lipoic acid activity is unknown [18]. Alpha lipoic acid has strong antioxidant and chelating activity, neurotrophic and neuroprotective properties; therefore, it can eliminate the free radicals produced by platinum-based chemotherapy, reactivate the normal axonal flow and reduce the effects of neuropathic anticancer therapies [19]. An in vitro study showed effectiveness of alpha lipoic acid in preventing neurotoxicity induced by taxanes, through a mitochondrial action [20]. A study of patients with advanced gastric cancer demonstrated effectiveness of alpha lipoic acid in reducing peripheral neuropathy induced by docetaxel/cisplatin [21]. To date only one RCT evaluated whether alpha lipoic acid could prevent neuropathy from platinum-based chemotherapy. Guo et al. [22] randomized 243 patients to oral alpha lipoic acid 1800 mg daily or placebo for 24 weeks; treatment was stopped between 2 days before and 4 days after each dose of platinum to avoid interactions, potentially compromising chemotherapy efficacy. CIPN was measured by the 11-item Gynecologic Oncologic Group-Neurotoxicity component of FACT at week 24. Only 70 patients (29%) completed the study due to change of regimens, non-compliance, missing data or unknown reasons. No statistical differences were found between the two groups. Interestingly, the dose of ALA used in Author's experience was considerably larger than what was adopted in the current study. The ACTIBOX programmable carrier technology in fact does not require such large dose to obtain a sufficient concentration in the blood. Our study conducted in a miscellaneous series of 25 patients affected by CIPN showed that after 12 weeks of treatment with OPERA® both pain and CIPN symptoms assessed with internationally validated tools [23] showed an improvement. No worsening of pain or CIPN symptoms was recorded in the study population during the study period. Nine patients (36%) have already been treated with neurotoxic agents such as platinum salts and taxanes. A clear limitation of this study is represented by the limited sample size and the non-homogenous patients population affected by CIPN. Of note, detection and assessment of CIPN were always made with validated tools [24], and all the involved healthcare providers in this study were specifically trained in using the tools before the beginning of the study.

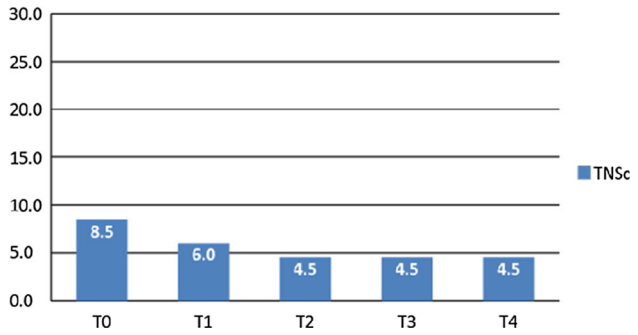

Fig. 4 Median value of TNSc scale over 12 weeks

Conclusion

OPERA® dietary supplement was able to improve CIPN symptoms in a prospective series of patients treated with neurotoxic chemotherapy, with no significant toxicity or

interaction. Prospective RCT in a selected population is warranted to confirm its promising activity.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee ("Comitato Etico Area Vasta Centro") and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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