New approach for treatment of radiotherapy-induced peripheral neuropathy: a pilot observational study

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ABSTRACT — OBJECTIVE: *Chronic pain represents one of the most important causes of oncological treatment discontinuation, a con-dition induced or exacerbated by the same anti-tumour therapies. Upstream to chronic pain there is the neuronal degeneration of peripheric nervous system, known as peripheric neuropathy. The aim of this study is to improve pain perception in oncological patients subjected to radiotherapy and affected by pe-ripheric neuropathy.*

MATERIALS AND METHODS: *21 oncological patients, subjected to radiation therapy for prostate, endometrial or breast cancer, reporting skeletal system pain were enrolled. All 21 patients have received a combination of L-acetylcarnitine (LAC - 500 mg), myo-inositol (MI - 500 mg) and alpha-lipoic acid (ALA - 300 mg) in sachets (Neutakis® Farmares, Rome, Italy). The treatment protocol provided for three different phases, the baseline (T0), at 30 days (T_1) and at 60 days (T_2). From T_0 to T_1, all patients have taken 2 sachets of combination, one in the morning and one in the evening, and from T_1 to T_2, the dosage was reduced to only one sachet in the morning. To evaluate treatment effects, all patients have reported their perception of stiffness, fatigue, tiredness on awakening, sleep disturbances, pain and daily activities, depression and musculoskeletal pain using Visual Analog Scale (VAS), quality of life by the Quality of Life Questionnaire SF36 and depression by Hamilton Questionnaire at the 3 timepoint.*

RESULTS: *The treatment is resulted able to improve patient perception of stiffness and fatigue sensations, facilitating their daily activities. Moreover, a greater physical functioning, social functioning, general health and vi-tality, were reported by all patients. These data were confirmed also by Hamilton Questionnaire, with the improvement of depression score in all patients.*

CONCLUSIONS: *Considering these data, we can affirm that the study supports the positive effects of these molecules help-ing physicians for chronic pain management.*

KEYWORDS
Radiotherapy, Quality of life, Myo-inositol, L-Acetylcarnitine, Alpha lipoic acid, Chronic pain.

INTRODUCTION

Chronic pain represents, without doubts, one of the most important causes of oncological treatment discontinuation[1,2]. Frequently this is a condition induced or exacerbated by the same anti-tumour therapies causing patient renunciation to medical cares or pushing the doctor to lighten therapies.

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Moreover, being diseases associated to the aging, these patients, often, are affected also by chronic pain due to skeletal pathologies, a symptom that can exacerbated by tumour or oncological treatments. Obviously, a depowered therapy represents an extreme option, often inadequate for tumour progression block or for its resolution. In this regard, the possibility to have a valid option to prevent or to limit chronic pain, counteracting the pathology impact and oncological treatment side effects, could be a fundamental. However, nowadays, to reduce the debilitant effects chronic pain induced, medications not specific as opioids, antidepressants or anticonvulsant are used, significantly complicating the clinical picture of oncological patients. To better understand how to manage this symptom is fundamental to highlight that, upstream to chronic pain there is the neuronal degeneration of peripheric nervous system, a condition known as peripheric neuropathy, easily observed in oncological patients, caused by the same anti-tumour treatments[3,4]. Peripheral nerve damage symptoms range from sensorimotor deficits as tingling sensation, burning pain in the arms, allodynia and hyperalgesia, to various functional deficits, e.g. impaired axonal transmission and reduced nutritive blood flow to nerves[5]. The impact of neuronal damage and worsen peripheric nerves functioning is also important on daily activities, as obvious considering that communication between central nervous system and internal organs, skin, muscles etc[6-8]. It is conveyed by these nerves, with consequences proportionate to the disease seriousness and to the nerve damaged[9]. This condition, therefore, represents an evident quality of life worsening for oncological patients with repercussions on social interactions and on individual activities, impairing their course of treatment[10-16]. In this regard, recently, several substances have attracted broad interest from scientific community that, even more, promotes the co-adjuvant use of molecules[17-20] such as L-acetylcarnitine (LAC)[21,22], myo-inositol (MI)[23,24] or alpha-lipoic acid (ALA)[25-27], useful to improve the neuropathic symptomatology[28]. The first one is an ester of trimethylated L-carnitine, normally synthetized in brain, liver and kidney, that plays an important metabolic role in mitochondria, participates to toxic metabolites elimination[29] and regulates acetylation of several proteins like tubulin, fundamental for neuronal protection[30]. The second one, instead, is a polyol belonging to inositols family, a fundamental element of membrane phospholipids of neurons, whose levels are reduced in neuropathic patients contribute to an altered transmission of nervous impulse, a recoverable event with MI supplementation. Finally, the last molecule, ALA, is an organic acid, characterized by an important antioxidant action[31], important for calcium homeostasis[32], for its anti-inflammatory effect[33,34], for the regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) transcription activity[35,36] and most of all essential for energetic metabolism, having regard to its involvement as initial cofactor of Krebs cycle. In light of what been said, the effect of these substances for chronic pain treatment in oncological patients subjected to radiotherapy and, therefore, potentially exposed to the risk of chronic pain onset or exacerbation of the same was studied with the aim to avoid any repercussion due to the treatment and to improve overall the patient quality of life.

MATERIALS AND METHODS

Patients involvement

For this pilot study, 21 oncological patients, men and women, with age between 50-80 years (62.74 ± 7.01), subjected to radiation therapy for prostate, endometrial or breast cancer at Radiotherapy Oncology Center, Azienda Ospedaliera of Cosenza and reporting a skeletal system pain of 7 on 10 at a semiquantitative scale (Visual Analog Scale - VAS)[37], were enrolled from January 2019 to June 2019. Included patients have Tumor, Node, Metastasis (TNM) classification between T1-2, with the lymph nodes involvement only for breast cancer cases, following the Associazione Italiana di Oncologia Medica (AIOM) guidelines for the management of prostate, endometrial or breast cancers, to evaluate treatment efficacy in patients with tumours at initial stage[38-40]. Any chemotherapy treatment, concomitant pain management with opioids, presence of metastases or no compliance to the treatment were considered exclusion criteria. All subjects involved provided written Informed Consent Form before participation, according to the Declaration of Helsinki. More patients' details are available in Table 1.

TNM classification and radiation treatment

According to the TNM classification, all prostate cancer (PC) patients (6 patients) staging between T1b (Tumor incidental histologic finding in more than 5% of tissue resected) and T2 (Tumor confined within prostate)[41] without involvement of lymph nodes or presence of metastases. Relatively all endometrial cancer (EC) patients, following the International Federation of Gynecology and Obstetrics, these staging between T1B (Invasion to less than half of the myometrium) and T2 (Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus) without involvement of lymph nodes or presence of metastases[42]. Finally, all breast cancer (BC) patients staging between T1 (≤2 cm across) and T2 (between 2 cm and <5 cm across) with also the involvement of lymph nodes between N1 (cancer

Table II. Baseline patient characteristics.

BASELINE PATIENT DATA	
Age (Years)	62.74 ± 7.01
Weight (kg)	70.16 ± 8.52
Height (cm)	166.95 ± 8.62
BMI (kg/m^2)	24.91 ± 1.58
Hamilton Score (HDRS)	18.37 ± 1.32
GENDER	
Male	6 (30 %)
Female	14 (70 %)
CANCER TYPES AND TNM CLASSIFICATION	
Prostate cancer	7 (30 %): T1b-2;N0;M0
Uterine cancer	8 (40 %): T1b (G1-G2) - T2 (G1-G2)
Breast cancer	6 (30 %): T1-2;N1-3;M0
RADIATION THERAPY	
Prostate cancer	76 Gy / 38 fr
Endometrial cancer (Brachytherapy)	50 Gy / 25 fr + Boost 18 Gy / 3 fr
Breast cancer	50 Gy / 25 fr + Boost 10 Gy / 4 fr
SF-36 QUALITY OF LIFE (QOL) SCORING SYSTEM	
Physical Functioning	48.05 ± 3.33
Role-Physical	44.26 ± 2.46
Bodily Pain	37.26 ± 2.06
General Health	32.37 ± 2.31
Vitality	37.74 ± 2.11
Social Functioning	50.79 ± 1.89
Role-Emotional	58.00 ± 1.70
Mental Health	50.37 ± 2.56
VISUAL ANALOG SCALE	
Stiffness	6.63 ± 0.49
Fatigue	7.32 ± 0.46
Tiredness on awakening	7.37 ± 0.74
Sleep disturbances	6.63 ± 0.74
Pain and daily activities	7.37 ± 0.49
Depression	6.84 ± 0.66
Musculoskeletal pain	6.89 ± 0.47

cells are in the lymph nodes in the armpit but the nodes are not stuck to surrounding tissues) and N3 (cancer cells are in lymph nodes below the collarbone (N3a) or in the armpit and behind the breastbone (N3b) or in lymph nodes above the collarbone (N3c)) and without metastases. Relatively to PC patients, these were subjected to external beam radiotherapy with a total dosage of 76 Gy fractioned in 38 sessions (divided in 7.5 weeks). Instead, with regards of all EC patients, these where previously subjected to hysteron-annessiectomy and subsequently were subjected to radiation therapy by brachytherapy for a total dosage of 50 Gy fractioned in 25 sessions (divided in 5 weeks) with the addition of 18 Gy divided in 3 fractions as boost. Finally, all BC patients were subjected previously to breast conserving surgery and subsequently to radiation therapy on lymph nodes for a total of 50 Gy divided in 25 fractions (divided in 5 weeks) with the addition of a boost of 10 Gy divided in 4 fractions.

Treatments and patient evaluation

In this observational study, at baseline, all 21 patients have received a combination of LAC (500 mg), MI (500 mg) and ALA (300 mg) in sachets (Neutakis® Farmares, Rome, Italy). The treatment protocol provided for three different phases, the baseline (T_0), from baseline to the 30th day after radiation therapy initiation (T_1) and from 30th day to 60th day, corresponding with the end of radiation therapy (T_2). From T_0 to T_1, all patients have taken 2 sachets of combination, one in the morning and one in the evening, and from T_1 to T_2, the dosage was reduced to only one sachet in the morning. To evaluate the treatment effect on skeletal chronic pain, all patients have reported their perception of stiffness, fatigue, tiredness on awakening, sleep disturbances, pain and daily activities, depression and musculoskeletal pain using VAS at T_0, T_1 and T_2. Finally, to complete the evaluation of treatment impact, also quality of life and depression of all patients were analyzed by the SF36 Quality of Life Questionnaire and the Hamilton Questionnaire at baseline, T_1 and T_2.

Statistical Analysis

Data belonging to all the patients that followed the protocol were included in the statistical analysis. Results are expressed as means ± SD. For all outcomes, primary differences were compared using the two-tailed Student's *t* test for independent data. A *p*-value <0.05 was considered statistically significant.

RESULTS

In this pilot observational study, 20 oncological patients of 21 involved, have completed the protocol treatment. Only 1 patient was dropped out from the study after the beginning of pain therapy with opioids between T_0 and T_1. Interestingly, all patients have reported clearly a subjective improvement of perceived pain as showed in Figure 1. In particular, all patients have reported a reduction of stiffness and fatigue sensations. The treatment is resulted useful to improve their mood, facilitating their daily activities. Relatively to their quality of life, as reported in Figure 2, all patients have shown a better physical functioning, an improved general health, a greater vitality and social functioning, with an overall improvement of mental health. These data were con-

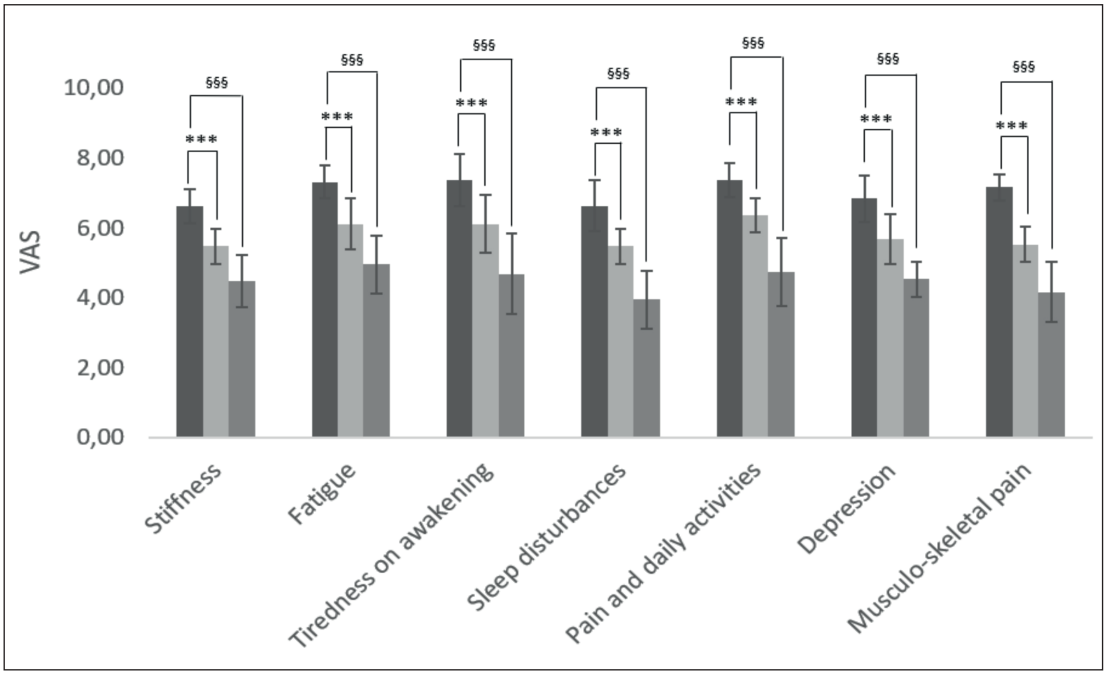

Figure 1. Evolution of stiffness, fatigue, tiredness on awakening, sleep disturbances, pain impact on daily activities, depression and musculoskeletal pain at T0, T1 and T2 using VAS scale 0-10. Error bars are ± SD. Significance: ***$p \leq 0.001$ T1 *vs.* Baseline, §§§$p \leq 0.001$ T2 *vs.* T1.

firmed also by the Hamilton Questionnaire, as shown in Figure 3. All patients have reported an improvement of their depression score between the T_0 and T_2.

DISCUSSION

One of the main obstacles for patient compliance subjected to radiation therapy is chronic pain onset. The impact of this side effect is evident in their quality of life, impairing daily activities, physical and mental health, social interactions and the oncological therapies. Frequently, because of this condition, patients feel tired and demotivated to continue the treatments which are often responsible of this state. Indeed, chronic pain is a typical side effect of these therapies, induced or exacerbated when already present, especially in aged persons. To avoid this condition, preserving, for the most possible, patient compliance, often, medical doctors prefer to reduce treatment intensity, improving patient quality of life but conditioning treatment efficacy. For this reason, a therapeutic support for these patients would be important, useful to counteract chronic pain onset, improving their compliance to the treatments. In this regard, the effect of a combination with LAC, MI and ALA, in oncological patients, subjected to radiation treatments was evaluated, considering what is reported in scientific literature.

In this regard, several studies have reported the capability of LAC to improve pain perception, as reported by Rossini et al. on patients affected by fibromyalgia[43], or by Bianchi et al[44] that have shown the beneficial effect of a continuative administration of this molecule, for 8 weeks, in patients with sensorial and motor neuropathies due to chemotherapy (Paclitaxel, Cisplatin, etc.). Moreover, these studies have confirmed clearly the good LAC tolerability, also for extended treatment periods. For this reason, administration of LAC is strongly recommendable to prevent and to treat neuropathic symptoms due to oncological treatments. Relatively to MI, as previously referred, several studies have reported reduced levels of this molecule, fundamental for neurons, in neuropathic patients with important repercussions on nervous impulse transmission, a recoverable event with MI supplementation. Indeed, some studies have shown that, in neuropathic subjects, MI levels are lower than normal, a reduction coherent with a reduced activity of Na^+/K^+ ATPase, responsible of a slowed nerve transmission about of 25-30% and of an increased axonal atrophy and demyelination. Moreover, clinical studies have reported the ability of MI administration to prevent signs of nerve degeneration[45], to counteract the arise of typical neuropathy symptoms[46] and to amplify, in patients with diabetic neuropathy, the action potential, increasing conduction velocity, at medial level of leg (76%), at level of sural triceps (160%) and at popliteal level (40%)[47]. As clearly reported in literature, therefore, MI administration, in patients with peripheric neuropathy seems to be useful to improve the overall symptomatology, optimising neuronal flow.

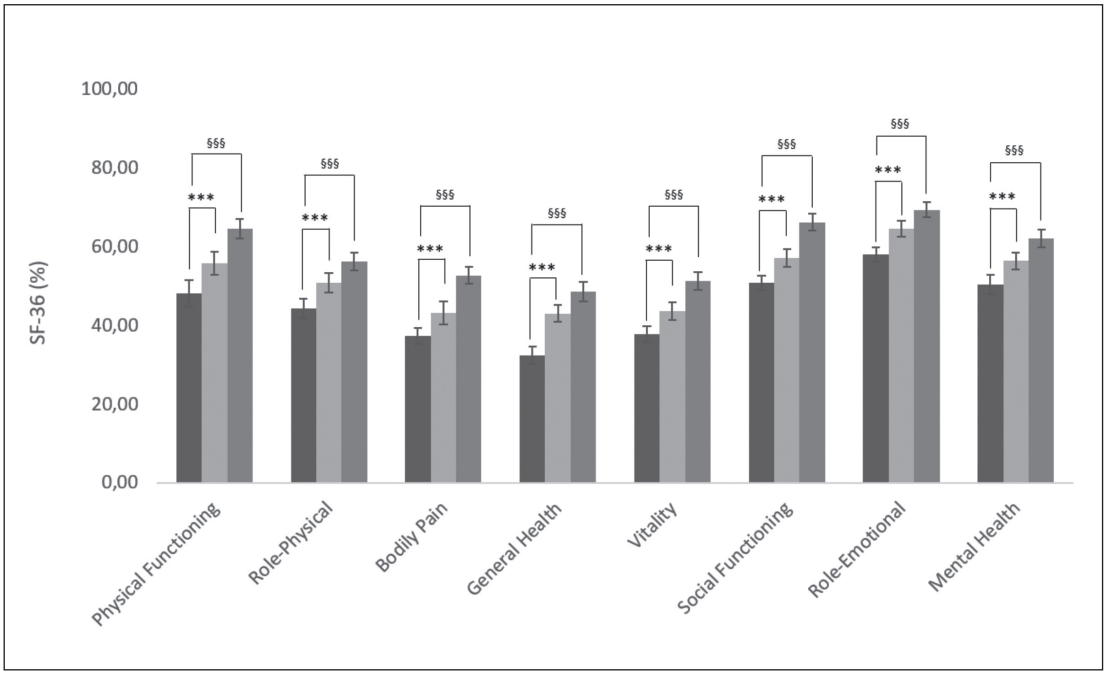

Figure 2. Evolution of Quality of Life (QoL) at T0, T1 and T2 using SF36 Quality of Life Questionnaire. Error bars are ± SD. Significance: *** $p \leq 0.001$ T1 *vs.* Baseline, §§§ $p \leq 0.001$ T2 *vs.* T1. PF: Physical Function-ing; RP: Role-Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role-Emotional; MH: Mental Health.

Finally, about ALA, several studies have shown that this molecule can prevent nerve degeneration[48], as the study of Melli et al[49] where is demonstrated, in vitro, the harmfulness of chemotherapy for neurons and the ability of this molecule to prevent nervous degeneration, suggesting a beneficial role for this substance in patients subjected to anti-neoplastic treatments[50]. To confirm the beneficial effect of ALA for the treatment of peripheric neuropathies, a meta-analysis study on 1.258 patients was performed. All patients have received 600 mg/die of ALA for three months[51] reporting an overall improvement of energetic metabolism with also an increased neuronal flow[52]. In light of what been said, the effect of these substances for chronic pain treatment in oncological patients subjected to radiotherapy and, therefore, potentially exposed to the risk of chronic pain onset or exacerbation of the same was studied with the aim to avoid any repercussion due to the treatment and to improve overall the patient quality of life. The results obtained have widely confirmed the ability of these molecules to favour a better manage-

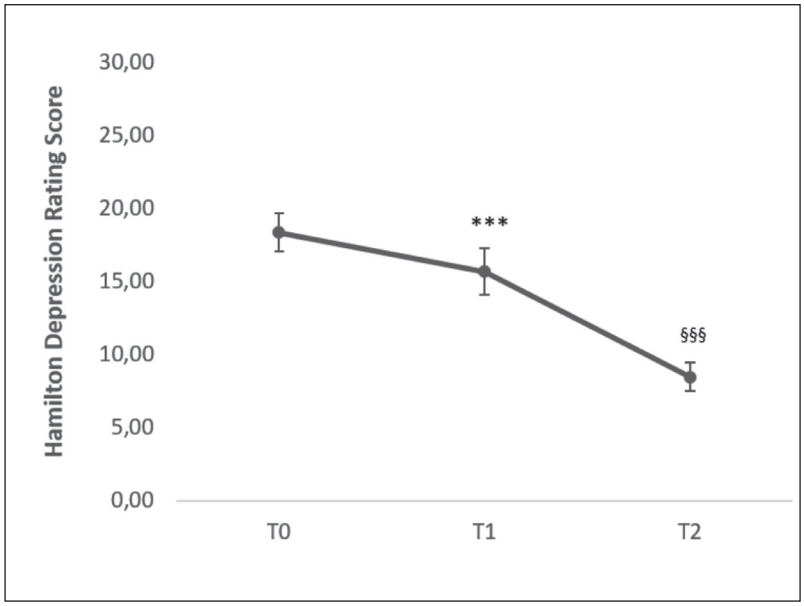

Figure 3. Graphical representation of Hamilton score trend. Error bars are ± SD. Significance: ***$p \leq 0.001$ T1 *vs.* Baseline, §§§$p \leq 0.001$ T2 vs. T1.

ment of pain as reported by the patients involved in this study. The widespread perception, though subjective, allow to affirm that the treatment improves chronic pain, fatigue, mood and patient sociality, inducing, consequently, a depression improvement, a fundamental effect to guarantee a greater patients compliance to the oncological scheduled treatments.

CONCLUSIONS

Considering these data, we can affirm that the study supports, as known in literature, the positive effects of these molecules. Indeed, this combination is resulted useful to physicians for chronic pain management avoiding a cancer treatment impairment. However, despite the encouraging results, this study should be considered as a preliminary step and, for this reason, new and broader studies will have to be performed to confirm data obtained in this work.

Conflicts of interest:
The authors declare that they have no conflict of interest.

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