Patients with cancer who are cured may report fatigue even from the Earth's surface. Fatigue, fever, chills, myalgias, headaches and general malaise, but also mental fatigue and endogenous and exogenous cytokines and cause a flu-like syndrome with symptoms such as damage, or the accumulation of products derived from dead cells. From February 2016 to December 2017 we have studied 36 patients with cancer and 10% with breast cancer, 7 with lung cancer, 7 with colon cancer, 5 with renal cancer, 3 with prostate cancer, 2 with melanoma and 2 hepatocellular carcinoma). Of the 36 patients treated, 10 were during neoplastic treatment, 10 had already finished the cancer therapy and 16 were in a palliative setting. To assess the extent of fatigue in patients we used the Fatigue Severity Scale, which is used to estimate the severity of the symptom with a score from 1 to 7. Patients were treated with auto hemo transfusion (GAE) according to theSIOT (Scientific Society of Oxygen Ozone Therapy) protocols, twice a week for one month and twice a month as maintenance therapy. No side effects have been found, and 26 patients (72%) achieved a significant improvement (>50% of the symptoms).

Ozone therapy is a valid supportive therapy for fatigue in patients with cancer, both during cancer therapy and in a palliative setting without any significant side effects.

Abstract

All cancer treatments may cause fatigue and it is hypothesized that the cause is tissue damage, or the accumulation of products derived from dead cells. From February 2016 to December 2017 we have studied 36 patients with cancer and 10% with breast cancer, 7 with lung cancer, 7 with colon cancer, 5 with renal cancer, 3 with prostate cancer, 2 with melanoma and 2 hepatocellular carcinoma). Of the 36 patients treated, 10 were during neoplastic treatment, 10 had already finished the cancer therapy and 16 were in a palliative setting. To assess the extent of fatigue in patients we used the Fatigue Severity Scale, which is used to estimate the severity of the symptom with a score from 1 to 7. Patients were treated with auto hemo transfusion (GAE) according to theSIOT (Scientific Society of Oxygen Ozone Therapy) protocols, twice a week for one month and twice a month as maintenance therapy. No side effects have been found, and 26 patients (72%) achieved a significant improvement (>50% of the symptoms).

Ozone therapy is a valid supportive therapy for fatigue in patients with cancer, both during cancer therapy and in a palliative setting without any significant side effects.

Introduction

Ozone, a gas discovered in the mid-nineteenth century, is a molecule consisting of three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states. The gas is colorless, acidic in odor and explosive in liquid or solid form. It has a half-life of 40 min at 20°C and about 140 min at 0°C. Its basic function is to protect humans from harmful effects of UV radiation. Ozone occurs at less than 20μg/m³ from the Earth’s surface at concentrations that are perfectly compatible with life. Although ozone has dangerous effects, yet researchers believe it has many therapeutic effects [1–3]. The beginning of precise medical ozone generators has only recently allowed the mechanisms, action and possible toxicity of ozone to be evaluated by clinical trials [2]. Ozone has a capacity to oxidize organic compounds, [4] and has well-known toxic effects on the respiratory tract when present in smog [5–6]. In medical use the gas produced from medical grade oxygen is administered in precise therapeutic doses, and never via inhalation, and advocates that it has excellent health benefits in dental caries, decrease blood cholesterol and stimulation of antioxidative responses, modifies oxygenation in resting muscle and is used in complementary treatment of hypoxic and ischemic syndromes [7–10].

The National Comprehensive Cancer Network describes fatigue as a universal symptom present at different levels in all subjects with cancer undergoing chemotherapy, radiotherapy, bone marrow transplantation. Among the subjects with metastases, the prevalence reaches the 78%. Patients with cancer who are cured may report fatigue even after the end of the therapy and according to some studies it can persist up to 5 years after healing [11–15].

Except for situations in which fatigue is caused by chemotherapy induced anemia, in other cases the underlying pathophysiological mechanism is unknown. It seems that its origin is multi-factorial: on one hand the tumor and the therapy and on the other the biological and genetic characteristics of each person. These are risk factors: sleeping disorders, insufficient physical activity, chronic pain and emotional stress [16].

All cancer treatments may cause fatigue, it is hypothesized that the cause is tissue damage, or the accumulation of products derived from dead cells. Cancer treatments also cause pro-inflammatory cytokines formation, high in patients who accuse fatigue after the treatment. Fatigue increases during radiotherapy and reaches its peak at about half cycle, generally improving after two months from the end. Biotherapies expose patients to endogenous and exogenous cytokines and cause a flu-like syndrome with symptoms such as fatigue, fever, chills, myalgias, headaches and general malaise, but also mental fatigue and cognitive deficits. Chemotherapy is associated with fatigue, which worsens if pain, anxiety and depression are also present. The characteristics of patients associated with worsening

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or remission of fatigue are not known. Overall, fatigue and pain are often associated with cancer therapies [17-19].

**Materials, Methods and Results**

Within the Tumor Center, CFS, Fibromyalgia and Oxygen Ozone Therapy Unit, MEDE Clinic, Sarajevo, Pordenone (Italy), we decided to undertake a study with the aim to evaluate the efficacy of oxygen-ozone therapy on cancer patients with fatigue, either during cancer therapy or after cancer therapy or in a palliative setting. The samples were collected to the MEDE Clinic, Sarajevo (Pordenone), Italy. This retrospective work was performed in compliance with the ethical values laid down by the Declaration of Helsinki, and informed consent documentation was reviewed and agreed by the independent ethics committee at the MEDE Clinic. Differences according to age, gender, and adverse events have been calculated using the Chi-square test. Univariate analyses have been performed to match the study arms and the unadjusted logic regression method has been used to assess crude odds ratios and 95% confident intervals. Logistic progression models adjusted for major confounders like age and gender have been used to calculate adjusted odds ratios and 95% confident ratios. P<0.05 has been considered statistically significant. From February 2013 to December 2017 we have included in the study 36 patients with cancer and fatigue, 10 with breast cancer (during cancer therapy, 6 after having finished cancer therapy, all females, aged 41 to 72 years), 7 with lung cancer (all in a palliative setting, i.e. after chemotherapy and/or radiotherapy have been used and patients were in progression without any potential further effective therapy available, 6 males and 1 female, aged 51 to 78 years), 7 with colon cancer (1 during chemotherapy, 3 after therapy was finished and 3 in a palliative setting, 5 males and 2 females, aged 48 to 75 years), 5 with renal cancer (2 during cancer therapy, 1 after finishing cancer therapy and 2 in a palliative setting, 3 males and 2 females, aged 41 to 68 years), 3 with prostate cancer (all during cancer therapy, aged 60 to 81 years), 2 with melanoma (all in a palliative setting, both females and aged 39 to 52 years) and 2 hepatocellular carcinoma (both in a palliative setting, both males, aged 61 to 71 years); therefore, of the 36 patients treated, 10 were during neoplastic therapy, 10 had already finished the cancer therapy and 16 were in a palliative setting. To assess the extent of fatigue in patients with cancer we used the Fatigue Severity Scale, which is used to estimate the severity of the symptom with a score from 1 to 7 [20].

Patients were treated with auto hemo transfusion (GAE) according to the SIOOT (Scientific Society of Oxygen Ozone Therapy) protocols, twice a week for one month and twice a month as maintenance therapy. No side effects have been found, while 26 patients (72%) achieved a significant improvement (>50% of the symptoms) of fatigue during therapy, or after therapy was finished, or in a palliative setting, without any significant difference among the three groups of patients, also due to the small numbers of patients in each group. Due to the short period of follow up, we did not yet evaluate the duration of response obtained.

**Discussion**

When a patient begins an anticancer treatment, it is very important to explain that fatigue may occur. Informing the patient is the first step towards proper management. Fatigue can be treated with pharmacological and non-pharmacological interventions. It is generally recommended to use both. Pharmacological therapies vary depending on the cause of fatigue (erythropoetin for anemia, sleep inducers for insomnia, antidepressants for depression). Among the non-pharmacological interventions, physical exercise seems to be the most effective [21-28].

Ozone therapy is one of the therapies that the scientific community considers as integrative but not substitutive for treatments. Regarding tumors, ozone therapy may be used as adjuvant for palliative care. The procedure aims to increase oxygenation and cell metabolism and improve the quality of life. Ozone therapy improves oxygenation in most tumor tissues with hypoxia and can be considered a potential adjuvant to chemotherapy and radiotherapy [11-20]. At our knowledge, there are few reports published in literature regarding ozone therapy in cancer patients [29-31].

In our experience, ozone therapy seems to be effective either in patients with fatigue related to antineoplastic therapy, after therapy has been finished and also in palliative setting. Due to the overall small number of patients in each group, it has not yet been evaluated in detail the outcome in each group of patients.

In conclusion, at our knowledge, this is the largest study of patients with cancer treated with ozone therapy reported in the literature. Oxygen-ozone therapy seems a valid supportive therapy for fatigue in patients with cancer, both during cancer therapy and in a palliative setting, without any significant side effects. We hope to increase the number of patients to some more different kinds of cancer either in therapy of in a palliative setting.

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