Abstract. – OBJECTIVE: Fatigue may be cause by all cancer treatments, maybe because the tissue damage or the build-up of dead cells derived products.

PATIENTS AND METHODS: At the Mede Clinic in Sacile, Pordenone, Italy, from February 2016 to May 2018 we studied 50 patients with cancer and fatigue (15 with breast cancer, 12 with lung cancer, 11 with colon cancer, 5 with renal cancer, 3 with prostate cancer, 2 with melanoma and 2 hepatocellular carcinoma). Patients were treated with Auto Hemotransfusion (GAE) according to the SIOOT (Scientific Society of Oxygen Ozone Therapy) protocols, two times a week for one month and then twice monthly as maintenance therapy.

RESULTS: Nineteen of them were undergoing neoplastic treatment, 10 had already ended the cancer therapy and 21 were in a palliative setting. The Fatigue Severity Scale was used to assess the extent of fatigue in patients, in order to estimate the severity of the symptom with a score from 1 to 7. No side effects were found, and 35 patients (70%) achieved a significant improvement (> 50%) of the symptoms.

CONCLUSIONS: Our preliminary data demonstrate that ozone therapy is a valid supportive therapy for fatigue in cancer patients, both during cancer therapy and in a palliative setting with no significant side effects.

Key Words
Cancer, Fatigue, Ozono therapy.

Introduction

Ozone is a gas discovered in the mid-1800; its molecule consists in three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states. Ozone is colorless, has an acrid smell and is explosive in its liquid or solid forms. Its half-life is 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 20 μg/m³ from the Earth’s surface, at concentrations that are perfectly compatible with life. Despite ozone has hazardous effects, researchers believe it has many therapeutic effects. The development of accurate medical ozone generators has recently allowed the evaluation of mechanisms, action and possible toxicity of ozone in clinical trials. Ozone is capable to oxidize organic compounds, and has well-known poisonous effects on the respiratory tract when present in smog. In medical use ozone derived from medical grade oxygen is administered in precise therapeutic doses, but never through inhalation, and advocates that it has exceptional 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. The National Comprehensive Cancer Network has described fatigue as a general sign present at different levels in all cancer patients undergoing chemotherapy (AC), radiotherapy, or bone marrow transplantation. Among the subjects with metastases, the prevalence can be up to 78%. Patients with cancer who are healed, may report fatigue even after the end of treatments and according to some studies, it can persist up to 5 years after they have been cured. Apart from fatigue caused by chemotherapy-induced anemia, in other cases the underlying pathophysiological mechanism is unknown. It seems that fatigue origin is multi-factorial: the tumor and the therapy on one hand and the biological and genetic characteristics of each person on the other. Sleeping disorders, insufficient physical activity, chronic pain and emotional stress are risk factors. All cancer treatments may cause fatigue, it is hypothesized that the reason is tissue damage, or the accumulation of products derived from dead...
cells. Cancer treatments also produce the pro-inflammatory cytokines formation that is high in patients complaining for fatigue after the therapy. During radiotherapy fatigue increases, reaching its peak at about half cycle, but generally improving after two months from the conclusion of treatments. Patients undergoing biotherapies are expose to endogenous and exogenous cytokines causing a flu-like syndrome with symptoms such as fatigue, fever, chills, myalgia, headaches and general malaise, but also mental fatigue and cognitive deficits. Antiblastic chemotherapy is associated with fatigue, worsening when pain, anxiety or depression are concomitant. Still unknown are the characteristics of patients associated with worsening or remission of fatigue. Overall, fatigue and pain are often associated with cancer therapies.

### Patients and Methods

In order to evaluate the efficacy of oxygen-ozone therapy on cancer patients with fatigue, either during or after cancer therapy or in a palliative setting, we decided to undertake a study collecting the samples at the Tumor Center, CFS, Fibromyalgia and Oxygen Ozone Therapy Unit, Mede Clinic, Sacile (Pordenone, Italy). This work has been performed in compliance with the ethical values laid down by the Declaration of Helsinki, and informed consent documentation have been reviewed and agreed by the independent Ethics Committee at the Mede Clinic.

### Statistical Analysis

The $\chi^2$ test has been used to calculate the differences according to age, gender, and adverse events. 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 gender and age have been used to calculate adjusted odds ratios and 95% confident ratios; $p<0.05$ has been considered statistically significant.

### Results

Between February 2016 to May 2018 we have enrolled in the study 50 consecutive patients with cancer and fatigue, 15 with breast cancer (9 during cancer therapy, 6 after having finished cancer therapy, all females, aged 38 to 72 years), 12 with lung cancer (all in a palliative setting, i.e. after AC and/or radiotherapy have been used and patients were in progression without any potential further effective therapy available, 10 males and 2 female, aged 50 to 78 years), 11 with colon cancer (5 during AC, 3 after therapy was finished and 3 in a palliative setting, 7 males and 4 females, aged 48 to 78 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 50 patients treated, 19 were during AC, 10 had already finished the cancer therapy and 21 were in a palliative setting (Table 1). To assess the extent of fatigue in patients with cancer we have used the Fatigue Severity Scale, in order to estimate the severity of the symptom with a score from 1 to 7. Patients have been treated

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>N. of patients</th>
<th>During therapy</th>
<th>After therapy was finished</th>
<th>Palliative setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brest</td>
<td>11</td>
<td>5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Colon</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Prostate</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>35 (70%)</td>
<td>12</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>
with auto hemotransfusion (GAE) according to the Scientific Society of Oxygen Ozone Therapy (SIOOT) protocols, twice a week for one month and then twice a month as maintenance therapy. No significant side effects have been found, while 35 patients (70%) achieved a significant improvement (>50% of the symptoms) of fatigue during therapy, after therapy was terminated, 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. Because the short period of follow up, we have 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 a proper management. Fatigue can be treated with pharmacological and non-pharmacological interventions. It is generally recommended to use both. Pharmacological therapies differ depending on the cause of fatigue (erythropoietin for anemia, sleep inducers for insomnia, antidepressants for depression). Among the non-pharmacological interventions, physical exercise seems to be the most effective. The scientific community considers ozone therapy among the integrative but not substitutive for treatments. Ozone therapy may be used as adjuvant for palliative care in tumors. 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 it may be considered a therapy improves oxygenation in most tumor tissues with hypoxia and it may be considered a therapy for fatigue in cancer patients, both during cancer therapy and in a palliative setting, without any significant side effects. In the next future we hope to increase the number of patients to some more different kinds of cancer either in therapy of in a palliative setting and in a vision of complementary and integrative medicine. Considering the small number of patients treated and evaluated we firmly believe that others confirmatory randomized trial are needed to improve the amount of data and quality of scientific results.

Conclusions

At our knowledge, this is among the largest studies reported in the literature of cancer patients treated with oxygen-ozone therapy. Oxygen-ozone therapy seems to be a valid supportive therapy for fatigue in cancer patients, both during cancer therapy and in a palliative setting, without any significant side effects. In the next future we hope to increase the number of patients to some more different kinds of cancer either in therapy of in a palliative setting and in a vision of complementary and integrative medicine. Considering the small number of patients treated and evaluated we firmly believe that others confirmatory randomized trial are needed to improve the amount of data and quality of scientific results.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

Oxygen-ozone therapy as support and palliative therapy in 50 cancer patients with fatigue


19) National Cancer Institute, Fatigue (PDQ), National Cancer Institute 2014.


