Patients with gastrointestinal cancer are more susceptible to unintentional weight loss after chemotherapy treatment

Pacientes com câncer gastrointestinal apresentam maior susceptibilidade para a perda involuntaria de peso após tratamento quimioterápico

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ABSTRACT
There is growing evidence showing that some chemotherapeutic agents employed for oncology treatments contribute to the induction of anorexia, leading to weight loss and the reduction of muscle mass due to the effects of treatment and the tumor, which may trigger the cachexia syndrome. Owing to the complexity of the diagnosis and body evaluation in these patients, the objective of this study was to evaluate the nutritional status of oncology patients submitted to chemotherapy treatment showing a weight loss greater than 5%. We screened 220 oncology patients and shortlisted 10 patients diagnosed with different types of tumors assisted by the Instituto Ribeirão Pretano de Combate ao Câncer under chemotherapy treatment and who presented weight loss greater than 5%. Anthropometric data such as weight, height and arm circumference (AC) was used for the calculation of Body Mass Index (BMI). We also used the Arm Muscle Circumference (AMC) and Arm Muscle Area (AMB) and the application of the Oncology Patient Global Nutrition Questionnaire. The results point out that cancer patients presented different anthropometric classification pre-diagnosis and after the beginning of anticancer treatment resulting from the side effects of chemotherapeutic agents and the reduction in the volume of food ingested. Gastrointestinal tract cancer patients presented greater short-term weight loss when compared to other types of tumors. We suggest that the observed weight loss may be related to the MFLOX and FOLFOX treatment protocols, in addition to the reduction in food intake (while maintaining good nutritional quality). These factors together may lead to the reduction of life quality and life expectancy and worsened patients’ prognosis.

Keywords: cachexia, cancer, chemotherapy.

RESUMO
Caquexia associada ao câncer é definida como uma síndrome multifatorial onde ocorre perda contínua de massa muscular, tendo ou não perda de massa gorda. As suas manifestações clínicas e os agentes quimioterápicos contribuem para o desenvolvimento e progressão, tornando seu diagnóstico ainda mais complexo. Devido a complexidade de diagnóstico e de avaliação corporal nesses pacientes, o objetivo deste trabalho foi avaliar o estado nutricional de pacientes oncológicos com perda de peso ponderal maior que 5%, submetidos a tratamento quimioterápico. Foram triados 220 pacientes oncológicos e selecionados 10 pacientes com diagnóstico de diferentes tipos de tumores atendidos pelo Instituto Ribeirão Pretano de Combate ao Câncer em tratamento quimioterápico e que apresentaram perda de peso maior que 5%. Realizamos o levantamento dos dados antropométricos como peso, estatura e circunferência do braço (CB) para o cálculo do
Índice de Massa Corporal (IMC), Circunferência Muscular do Braço (CMB) e a Área Muscular do Braço (AMB) e aplicação do Questionário Global Alimentar Do Paciente Oncológico. Os resultados demonstram que os pacientes oncológicos apresentaram diferentes classificações antropométricas pré-diagnóstico e após o início do tratamento anticâncer decorrentes dos efeitos colaterais dos agentes quimioterápicos e da redução do volume de alimentos ingeridos. Os pacientes com câncer do trato gastrointestinal apresentaram maior perda de peso em curto prazo quando comparados aos demais tipo de tumores. Sugerimos que a perda de peso observada pode estar relacionada com o protocolo de tratamento MFLOX e FOLFOX, além da redução do volume de alimentos consumidos (mesmo mantendo uma boa qualidade nutricional). Esses fatores em conjunto podem ter como consequência a redução da qualidade e expectativa de vida e piora no prognóstico do paciente.

**Palavras-chave:** caquexia, câncer e quimioterapia.

**1 INTRODUCTION**

The Pan American Health Organization [1] defines cancer as a generic term for a large group of diseases that can affect any part of the body. The estimated number of new cancer cases worldwide between 2020 to 2040 is 30 million, with skin cancer being the most incident (177 thousand), followed by breast and prostate cancer (66 thousand each), colon and rectum (41 thousand), lung (30 thousand), and stomach (21 thousand) [2,3].

There is growing evidence that some chemotherapeutic agents employed for oncology treatment contribute to the induction of anorexia generating weight loss, and the reduction of muscle mass arising from the effects of the treatment and the tumor, and may trigger the cachexia syndrome [4]. The weight loss and muscle mass resulting from the effects of chemotherapy are similar to those of cachexia, making its diagnosis even more complex [5].

Cancer-associated cachexia is considered common in patients who have advanced disease, affecting up to 80% of these patients and representing the cause of 20% of all cancer deaths [6]. It is defined as a multifactorial syndrome where there is a continuous loss of muscle mass, with or without loss of fat mass [7]. The main associated clinical manifestations include lack of appetite, change in taste, exacerbated weight loss, anemia, nausea, asthenia, loss of motor and physical abilities, and fatigue.

This is related to the hypermetabolism of carbohydrates, proteins and lipids. It is worsened due to the pre-existing loss of muscle mass and it is exacerbated by the cancer therapy due to several factors that increase the catabolic response, leading to the
mobilization of muscle mass and high levels of muscle depletion, causing significant morbidity and mortality in the patient [5].

Stronger emetic and anorexic effects were observed after the administration of cisplatin, dacarbazine, cyclophosphamide, carboplatin, and streptozotocin, and minimal after administration of 5-fluorouracil, vincristine, etoposide, and mitomycin. This occurred because these agents inhibit the growth of tumors and normal tissues, such as the gastrointestinal mucosa, causing malabsorption or altered bowel movements, sending signals of emesis to the central nervous system [8].

The drugs - cisplatin, irinotecan hydrochloride, doxorubicin and etoposide cause muscle loss by means of the direct activation of the transcription factor NF-kB, increased proteolysis, mitochondrial damage, oxidative stress and inflammatory cytokines (IL-1, IL-6 and TNF-alpha). Moreover, muscle atrophy by chemotherapy is associated with positive regulation of the ERK1/2 and p39 MAPS pathways that impair the protein synthesis pathway by inhibiting the AKT/mTOR pathway [9].

The evaluation of the body composition in patients with cachexia is difficult to interpret due to physiological changes, fluid retention, increased tumor mass, hormonal changes due to treatment or paraneoplastic syndromes, effects of antineoplastic treatment and syndrome on metabolism and body composition [10]. Thus, the present study aimed to evaluate the nutritional status of cancer patients with weight loss greater than 5%, undergoing chemotherapy treatment assisted by the Unified Health System (SUS) at the Instituto Ribeirãopretano de Combate ao Câncer.

2 MATERIALS AND METHODS

2.1 SAMPLE STUDY VENUE AND CHARACTERIZATION OF THE SAMPLE OF THE ONCOLOGY PATIENTS

The project was approved by the Research Ethics Committee CEP-CONEP - Plataforma-Brasil (authorization number 4.192.874). The work was developed at the Instituto Ribeirãopretano de Combate ao Câncer, located at the Hospital Beneficiencia Portuguesa in Ribeirão Preto/SP. We screened 220 patients and shortlisted 10 patients diagnosed with cancer between February and April 2021, who were seen by the Unified Health System (SUS). The inclusion criteria were adult patients (over 18 years) and elderly (up to 80 years), of both genders, with or without metabolic changes (such as cholesterol, hypertension, Diabetes Mellitus type 1 or 2, triglycerides, among other pathologies), diagnosed with different types of tumors, who have already started
chemotherapy treatment, and who presented weight loss greater than 5% on average during 3 months. The patients included in the sample signed the Informed Consent Form. Patients were excluded from the sample if they were under 18 years of age, over 80 years of age, and who had no medical records.

2.2 QUESTIONNAIRE ON THE NUTRITIONAL QUALITY OF CANCER PATIENTS

The Questionnaire for Global Assessment and Feeding in the Oncology Patient was applied based on a compilation of questions taken from the questionnaires: Brazilian Consensus of Cachexia/Anorexia in Palliative Care [11], Subjective Global Assessment Produced by the Patient (ASG-PPP) [12], Food Frequency Questionnaire (QFA [13], QLQ-C30 instrument (Quality of Life Questionnaire) [14].

2.3 ANTHROPOMETRIC EVALUATION

The patients’ medical records containing data regarding height and body weight before and after chemotherapy were collected. This data was used to calculate the Body Mass Index.

The arm circumference was performed and evaluated according to WHO recommendations (2000) [15] and muscle composition was obtained through the equations that quantify the arm muscle circumference (AMC) and arm muscle area (AMB), classifying them according to Blackburn and Thornton (1979) [16].

2.4 PATIENTS’ CLINICAL DATA

Patients’ data such as age, ethnicity, and time of diagnosis, tumor type, and type of chemotherapy treatment used were collected. This data was compared to the anthropometric data obtained and nutritional quality questionnaire to evaluate correlations between weight loss after diagnosis, tumor type and type of chemotherapy treatment.

3 RESULTS

3.1 SAMPLE CLINICAL DATA CHARACTERIZATION

Among the 220 cancer patients screened through the medical record along 3 months, we spotted 10 patients who presented weight loss greater than 5%, where 60%
(n=6) were male and 40% (n=4) were female, with ages ranging from 30 to 72 years. Regarding ethnicity, 60% (n=6) were white and 40% (n=4) were of mixed ethnicity.

Regarding the type of cancer, 30% (n=3) were diagnosed with Colon Adenocarcinoma, 30% (n=3) Esophageal Squamous Cell Carcinoma, 10% (n=1) Rectal Adenocarcinoma, 10% (n=1) Embryonal Carcinoma, 10% (n=1) Oral Squamous Cell Carcinoma, and 10% (n=1) Gastric Bell Ring Cell Adenocarcinoma. Remarkably, 80% of the patients who were included in the study had GIT cancer.

All patients were undergoing chemotherapy, 30% (n=3) and using MFLOX protocol (Oxaliplatin 85mg², 5-Fluorouracil 500mg/m, Leucovorin 35mg/m²), 30% (n=3) Carbo AUV2 (Carbo 25mg², Toxol 50mg²), 20% (n=2) FOLFOX (Oxaliplatin 85mg/m, 5-Fluorouracil 400mg/m, 5-Fluorouracil 2400mg/m, Leucovorin 400mg/m²), 10% (n=1) Cisplatin (40mgm²) and 10% (n=1) the CHOPP (Etoposide + Cisplatin) therapy.

3.2 USUAL WEIGHT AND POST-DIAGNOSIS WEIGHT EVALUATION

The usual weight reported by the patients ranged from 58 to 100 kg before the diagnosis and through the BMI calculation, it was found that about 60% (n=6) were obese or overweight, and 40% (n=4) were eutrophic. As for post-treatment weight, there was a variation of 37 to 78.8 kg, with 40% (n=4) classified as lean or malnourished, 30% (n=3) overweight, and 30% (n=3) eutrophic.

The time frame for the diagnosis of cancer ranged from 2 to 10 months, and among the shortlisted cancer patients, those with GIT cancer stood out for presenting great weight loss in the short-term when compared to other types of tumors (Table 1). It was also observed that the oncology patients through the BMI calculation presented a pre-diagnostic weight that classified them as: eutrophic, overweight, and obese. However, after the cancer diagnosis and treatment, they were classified as eutrophic, overweight, and lean. In addition, the anthropometric evaluations through CMB and AMB of the post-treatment patients place them into cases of severe, mild or moderate malnutrition.

Two patients with greater weight loss stood out, one diagnosed with Colon Adenocarcinoma with a loss of 10.1kg/month and a percentage of 25.25% in two months. The other had a diagnosis of gastric Adenocarcinoma of signet ring cells with a loss of 6kg/month and a percentage of 44.77% in five months.
Table 1 – The relationship between the time of diagnosis, weight loss (PP), habitual and current BMI with tumor type and chemotherapy of patients (n=10) who are under treatment at the Instituto Ribeirão Preto de Combate ao Câncer, Ribeirão Preto, 2021.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time of diagnosis (months)</th>
<th>Usual Weight (Kg)</th>
<th>Usual MCI (Kg/m²)</th>
<th>WHO Classification (2000)</th>
<th>Curren t Weight (Kg)</th>
<th>Curren t MCI (Kg/m²)</th>
<th>WHO Classification (2000)</th>
<th>PP (KG)</th>
<th>(%) PP</th>
<th>PP Average (Kg/month)</th>
<th>Tumor Location</th>
<th>Metastasis</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>90</td>
<td>30.42</td>
<td>Obesity GI</td>
<td>77</td>
<td>26.02</td>
<td>Overweight</td>
<td>13</td>
<td>14.4</td>
<td>3.25</td>
<td>Colon</td>
<td>Lymphnodes</td>
<td>Mflox</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>100</td>
<td>35.43</td>
<td>Obesity GII</td>
<td>78.8</td>
<td>27.91</td>
<td>Overweight</td>
<td>21.2</td>
<td>21.2</td>
<td>5.3</td>
<td>Recto</td>
<td>No</td>
<td>Mflox</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>96</td>
<td>32.07</td>
<td>Obesity GI</td>
<td>75.5</td>
<td>25.22</td>
<td>Overweight</td>
<td>20.5</td>
<td>21.3</td>
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<td>Embryo</td>
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<tr>
<td>4</td>
<td>10</td>
<td>87</td>
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<td>Eutrophic</td>
<td>73.05</td>
<td>21.34</td>
<td>Thinness</td>
<td>13.9</td>
<td>15.9</td>
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<tr>
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<td>76</td>
<td>26.92</td>
<td>Eutrophic</td>
<td>68</td>
<td>24.09</td>
<td>Eutrophic</td>
<td>8</td>
<td>10.5</td>
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<td>Cisplatin</td>
</tr>
<tr>
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<td>5</td>
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<td>31</td>
<td>Obesity GI</td>
<td>37</td>
<td>17.12</td>
<td>Malnutrition GI</td>
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<td>44.7</td>
<td>6</td>
<td>Gastric</td>
<td>Ovaries</td>
<td>Folfox</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>73</td>
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<td>Overweight</td>
<td>67</td>
<td>24.9</td>
<td>Eutrophic</td>
<td>6</td>
<td>8.2</td>
<td>1</td>
<td>Colon</td>
<td>No</td>
<td>Folfox</td>
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<td>8</td>
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<td>76</td>
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<td>Eutrophic</td>
<td>60</td>
<td>18.3</td>
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<td>21.0</td>
<td>2.28</td>
<td>Esophagus</td>
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<td>Carbo AUC2</td>
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<td>59.8</td>
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<td>20.2</td>
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<td>Lung and Liver</td>
<td>Mflox</td>
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<td>Eutrophic</td>
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<td>22.47</td>
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<td>4</td>
<td>6.89</td>
<td>3.44</td>
<td>Esophagus</td>
<td>No</td>
<td>Carbo AUC2</td>
</tr>
</tbody>
</table>

Source: Author
3.3 PATIENTS’ MUSCLE MASS ANALYSIS THROUGH THE ANTHROPOMETRIC DATA

Regarding the classification of the BC, 50% (n=5) had been classified with moderate malnutrition, 40% (n=4) eutrophic and 10% (n=1) overweight. As for the WCD classification, 10% (n=1) presented severe malnutrition, 40% (n=4) moderate malnutrition and 50% (n=5) eutrophic.

As for the AMB, 20% (n=2) were severely malnourished, 30% (n=3) mild/moderate malnourished and 50% (n=5) eutrophic. These three analyzed groups showed that 50% (n=5) of the patients were eutrophic, i.e., with an adequate amount of muscle tissue for their age, and 50% (n=5) showed some degree of malnutrition, i.e., with an amount of muscle tissue below for their age.

3.4 THE RELATIONSHIP BETWEEN THE CHANGES IN THE CURRENT DIETARY INTAKE OF PATIENTS WITH GASTROINTESTINAL SYMPTOMS RELATED TO CHEMOTHERAPY

Among the 10 patients analyzed 20% (n=2) reported that the diet presented the usual consistency and volume, 30% (n=3) normal diet, but in small quantity, 20% (n=2) complete liquid diet, 20% (n=2) liquid diet plus enteral diet and 10% (n=1) with enteral diet.

Some gastrointestinal symptoms are common among patients on chemotherapy treatment, and the most cited in the present study were: 90% pain, 80% nausea, 80% vomiting, 70% dysphagia, 70% nauseating smells, 50% diarrhea, 50% xerostomia, 40% taste alteration, 20% constipation, 10% low salivation and 10% mastitis.

4 DISCUSSION

Among the 220 cancer patients screened along the 3-month period, we found 10 patients who presented a weight loss greater than 5% after the diagnosis and the beginning of the chemotherapy treatment. According to Fearon et al [17] this is one of the classification criteria for cachexia.

Our results show that 50% (n=5) of patients with greater weight loss were undergoing the MFLOX and FOLFOX chemotherapy treatment protocols. The other 50% (n=5) were on the CHOPP, Carbo AUC2 and Cisplatin chemotherapy protocols.

A greater reserve of adipose tissue in obese and/or overweight cancer patients may be a detrimental factor in the early diagnosis of cancer-related cachexia, since the
degradation of muscle tissue may be occurring and it may not be evident due to its high adipose reserve, a fact called "hidden cachexia" and/or "sarcopenic obesity" [18], as observed in the patients of this study, who despite being overweight after starting chemotherapy, had a weight loss above 5%, indicating one of the criteria for the diagnosis of cachexia.

Thus, malnutrition associated with cancer can occur due to metabolic and endocrine changes resulting from systemic inflammation due to the tumor, anabolic deficiency, proteolysis, lipolysis, insulin resistance, mechanical and physiological changes of the gastrointestinal system and the effects caused by oncology treatment [19]. This malnutrition can generate a low tolerance to treatment, resulting in delayed cycles and decreased doses of chemotherapeutic drugs, leading to a worse prognosis, poor quality of life and survival.

It was found that 80% (n=8) of patients who showed greater weight loss had a tumor in the gastrointestinal tract, this was a factor responsible for patients’ weight loss, as well as the location of the tumor, as seen in this study, patients with cancer of the gastrointestinal tract, head and neck, liver and lung present a high risk of malnutrition [20]. Shaw [21] described that cancers of the upper gastrointestinal tract posed a higher risk for developing malnutrition; 22% may be severely malnourished and 63% moderately malnourished or at risk of malnutrition. Lower gastrointestinal tract cancers, on the other hand, present a lower risk of malnutrition, 10 to 17% being severely malnourished and 25 to 60% being moderately malnourished or at risk of malnutrition. This malnutrition in gastrointestinal tract cancer occurs due to the difficulty in feeding, digesting, absorbing nutrients and the side effects of treatment [22].

The physical state of the patient may reflect on food intake, as patients undergoing chemotherapy often reduce the volume of their consumption, a fact also observed in this study. Thus, the quantities and distribution are inadequate for nutrition in this phase, hyper catabolism caused by cachexia associated with tumor factors that alter the metabolism of carbohydrates, proteins and fats and the side effects of cancer treatment contribute to the worsening of the patient's nutritional status [22].

The main side effects caused by chemotherapeutic agents include: nausea, xerostomia, dysphagia, abdominal pain, vomiting, fatigue, taste abnormality, stomatitis, mucositis, diarrhea, constipation, changes in food preferences, and anorexia, contributing to weight and muscle mass loss [5,23].
The etiology related to the nutritional deterioration in cancer patients is complex and can occur at any stage of the disease, treatment modality and tumor type, influencing the degradation of nutritional status [19].

The patients’ quality of life is jeopardized by malnutrition, causing fatigue, reduced functional capacity, emotional distress, and decreased life expectancy [24]. Weight loss with depletion of muscle mass and adipose tissue stores, characterized by sarcopenia and/or cachexia is installed, lowering patients’ quality of life and posing a higher risk of toxicity related to anticancer treatment, resulting in the decrease of the dose intensity, in lower response rates to treatment, increased surgical complications, and higher mortality [25,26].

Cachexia remains as a neglected medical condition indeed. Considering that cachexia is a multifactorial syndrome, a multidisciplinary therapeutic approach targeting the various pathophysiological pathways that has shown to be more efficient. Nutritional therapy, physical training and pharmacological interventions can effectively contribute to minimize the impact of cachexia on weight loss, muscle mass and the risk of drugs causing toxicity in patients [27].

5 CONCLUSION

When comparing the patients admitted to the study and the results found, we can state that it is necessary to perform evaluations beyond weight, to observe the behavior and food intake of patients undergoing oncology treatment, and offer attention and prevention to patients with GIT cancer because they are the most affected regarding weight loss, the framework of time to lose weight, and side effects due to drugs.

We suggest that the weight loss observed in the oncology patients in the present study may be related to the MFLOX and FOLFOX treatment protocol in individuals with gastrointestinal tumors, in addition to the reduction in the volume of food intake (even while maintaining good nutritional quality). Together, these factors may lead to consequences such as patients’ quality and life expectancy being reduced, poor compliance to treatment, and worse prognosis.

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