

Title: The assessment of fatigue and quality of life in patients with bone tumor, undergoing chemotherapy treatment and possible predictive factors.

Code: Fatigue-ONCO

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Acronyms used in the text

BFI: Brief Fatigue Inventory

EORTC QLQ C-30

TESS: Toronto Extremity Salvage Score

BMI: Body mass index

NRS: Numering Rate Scale

CRF: Case Report Form

Introduction

Fatigue syndrome is defined as an altered physical, emotional and / or cognitive feeling of tiredness that is not proportional to the activities performed by the subject and interferes with the activity of daily life (NCCN, 2018, Bower, 2014). It is a clinical condition, linked to the oncological pathology, extremely widespread and in patients undergoing chemotherapy and / or radiotherapy it is common in 80% of patients (NCCN, 2018; Bower, 2014; Arajuo, 2017).

At the same time this symptomatology is identified as under-estimated and under-treated. Hubbard et al (2014), in accordance with the guidelines, suggest the need to introduce assessment of fatigue as a screening element for normal clinical practice. Interventions aimed at increasing physical activity, psychosocial and pharmacological support can benefit patients even if a standard treatment model has not been described to date (Bower, 2014). One of the difficulties highlighted in the literature is the correct identification of this syndrome. Scott et al (2011) stress the need for systematic studies in cancer populations with different types of cancer and at different stages of the disease using patient-oriented fatigue assessment tools. The Brief Fatigue Inventory (BFI) is one of the scales used precisely in the evaluation of this syndrome and has proved to be a reliable and easy to use tool, also validated in Italian (Mendoza et al 1999, Catania et al. 2013). Several authors have also shown that reduced physical activity and a worse quality of life are associated with fatigue (Witt et al 2002; Stark et al 2012, Warner et al 2008), particularly in young patients (Poort et al 2017) .

In the area of bone tumors, the available data on fatigue syndrome are extremely poor and only two studies have emerged from the literature search. The study by Granada-Cameron et al (2011) describes the experience of 11 new sarcoma patients undergoing chemotherapy treatment. Fatigue had been described as the prevalent symptom and was related to a worse quality of life.

Serveas et al (2003) observing patients two years after the conclusion of treatment for bone cancer found that in 28% of cases fatigue is a severe problem for patients.

Objective

The aim of the present study is to evaluate and describe the evolution over time of the fatigue and the quality of life of patients with bone tumor during the chemotherapy treatment and in the first phase of follow-up and to identify possible prognostic factors. Such knowledge is a necessary precondition for identifying patients and the periods most at risk due to the onset of fatigue, so as to be able to hypothesize adequate containment strategies.

Setting: Rizzoli Orthopedic Institute. Department of Chemotherapy

Methods

Design: observational study

Population: all patients belonging to the Chemotherapy ward will be recruited consecutively for a new antineoplastic treatment protocol. The process of informing and collecting the participants' consent will take place during the first admission in which intravenous administration of the chemotherapy will be started. Potential participants will be identified / selected for recruitment through inclusion and exclusion criteria described below. Enrolled patients who will not continue the chemotherapy protocol within our Institute but at another facility will exit the study.

Inclusion criteria:

all patients diagnosed with bone tumors who start a new chemotherapy treatment protocol, both on admission and on an outpatient basis at the Chemotherapy ward for its antineoplastic treatment over 12 years of age. The NCCN Guidelines Cancer-Related Fatigue identifies appropriate screening with rating scales with scores from 0 to 10 precisely for patients older than 12 years.

Exclusion criteria:

patients with little knowledge of the Italian language due to the impossibility of completing the assessment scales.

Primary outcome:

the patient's Fatigue will be measured during the treatment period with antineoplastic drugs and part of the followup period. To this end the BFI scale validated in Italian will be used (Mendoza et al 1999; Catania et al, 2013) which includes 9 items with a score for each of 0 to 10 and a consequent total score from 0 to 90. The measurement will take place in 4 times: the day of enrollment, 6 months, 12 months and 24 months after enrollment.

Secondary outcome:

the quality of life of patients measured by the EORTC QLQ C-30 scale (Aaronson et al, 1993) and the level of autonomy measured by the TESS scale (Davis et al, 1996) in 4 steps: the enrollment day , at 6 months, at 12 months and at 24 months from enrollment.

Variables taken into consideration: through the literature search and the comparison between professionals of different disciplines (nurses, physiotherapists, oncologists) involved, a panel of variables was established to collect:

- Age
- sex
- BMI
- Smoking
- diabetes

- cardiopathies (hypertension, previous heart attack, ...)
- Comorbidity (pulmonary, renal, anemia, arthritis, neuromuscular complications, sleep disorders, pain, emotional distress)
- Diagnosis,
- presence of metastases at the entrance
- type of chemotherapeutic protocol / drug that will be administered from the time of enrollment (Methotrexate, Cisplatin, Adriamycin, Ifosfamide, Elastomer Ifosfamide, Gemcitabine, Taxotere, Vincristine-Adriamycin-ifosfamide, Vincristine - phosphamide-Dactomycin, Ifosfamide-etoposide, Temiri, Topotecan, Cyclophosphamide, Eribulin)
- previous chemotherapy treatments: chemotherapy protocol / drugs already performed (Methotrexate, Cisplatin, Adriamycin, Ifosfamide, Elastomer Ifosfamide, Gemcitabine, Taxotere, Vincristine-Adriamycin-ifosfamide, Vincristine - phosphamide-Dactomycin, Ifosfamide-etoposide, Temiri, Topotecan, Cyclophosphamide , Eribulina) and number of cycles already carried out.
- number of therapy cycles carried out from the moment of enrollment (to be collected at the 24th month)
- tumor location
- surgery (date and type)
- Perceived pain measured with the NRS scale in the 4 expected data collection times

Data collection: the data will be collected at the Chemotherapy ward at the time of admission of the patient in the ward or of his access to the outpatient service. Nurses and the research physiotherapist will be responsible for collecting data by administering the assessment scales and consulting the patient's clinical documentation. Data collection times and specific collection methods are shown in the following tables:

1° day			
DIAGNOSIS/new protocol			
Consent/CRF	6 months		
BFI	BFI	12 months	
QLQ	QLQ	BFI	24 months
TESS	TESS	QLQ	BFI
		TESS	QLQ
			TESS

Variables	Collection methods	Responsible for the collection
Age	Health documentation - to be included in the enrollment form, then a calculation sheet	Nurse
Sex	Health documentation - to be included in the enrollment form, then a calculation sheet	Nurse
BMI	To be calculated: report the patient's weight and height at the entrance	Nurse
Smoking	OBSERVATION sheet (CRF): report in a calculation sheet	Nurse
diabetes	OBSERVATION sheet (CRF): report in a calculation sheet	Nurse
cardiopathies	OBSERVATION sheet (CRF): report in a calculation sheet	Nurse
Diagnosis	Enrollment form: to be reported in the calculation sheet	Nurse
presence of	Sanitary documentation: to be included in the	Nurse

metastases at the entrance	OBSERVATION (CRF) form, then calculation sheet	
type of chemotherapeutic protocol	Enrollment form: to be reported in the calculation sheet	Nurse
previous chemotherapy treatments	Health documentation - to be included in the enrollment form, then a calculation sheet	Nurse
number of therapy cycles	OBSERVATION sheet (CRF): to be found in health documentation and then in the calculation sheet)	Nurse
tumor location	Enrollment form: to be reported in the calculation sheet	Nurse
surgery (date and type)	OBSERVATION sheet (CRF): report in a calculation sheet	Nurse
Pain	Measured with NRS scale. Data present in the BFI Sheet: to be reported in the calculation sheet	Nurse
Autonomy level	TESS scale: self-filled by the patient (6-12-24 months from enrollment)	Physiotherapist

Statistical analysis: The characteristics of the sample will be described using the mean and standard or median deviation and interquartile range for quantitative variables and absolute and percentage frequencies for qualitative variables. Simple and multiple linear regression analyzes will be performed and to identify predictors of primary and secondary outcome.

Sample size: In a pilot study of 19 patients at the Chemotherapy SSD the average BFI score was 31.6 with DS 19.1 at a mean follow-up of 5.2 months and DS 3.7. On the basis of this data, the number of variables taken into consideration equal to 15 in a multiple linear regression, an effect size of 0.1, an alpha value of 0.05 and a power of 80% the

number of patients to be enrolled is equal to 183. The sample size was calculated with Stata 15.0.

Duration of the study: The project lasted 5 years as follows:

Month 1-3 Meeting and training of the team involved in the study

Months 3–36 Patient enrollment and data collection.

Months 36-48 Construction of the database and preliminary analysis

Months 48-60 Follow-up and Statistical analysis of data

The approval date of the Ethics Committee will be considered as the starting date of the trial.

Safety assessment: as this is an observational study, patients will be treated in accordance with the rules of good clinical practice and in accordance with the protocols regularly used in the operating unit involved.

Data management and informed consent: the personnel designated by the Investigator must report the information required by the protocol in the CRF form and subsequently in the prepared database. Each potential participant will be fully explained the progress of the study and will be given the opportunity to ask questions and receive answers to all his doubts. The informed consent form must be signed by the participant or a legally authorized representative prior to his participation. Patient documentation must be able to demonstrate that consent was given prior to participation in the study. A copy of the informed consent form must be left to the patient. The consent form, signed by the patient, must be kept at the site.

Approval by the Ethics Committee: This protocol, the informed consent form and all the necessary relevant information related to the study must be submitted to the Ethics Committee for evaluation and must be approved before the start of the study. The study will be conducted in accordance with international standards ISO 14: 155, with the Good Clinical Practice and with the national laws in force.

Confidentiality of data and ownership of results: Adequate documentation will be maintained for everything concerning the patient's clinical data, work sheets, nursing notes; the database will be available in a protected environment and access allowed only with Password. The confidentiality of the patient's sensitive data is guaranteed by the Investigator.

Publication of Results: The main investigator undertakes to produce the final report, publish all the data collected as described in the protocol and ensure that the data is reported responsibly and consistently. In particular, the publication of the data deriving from this study will take place regardless of the results obtained. The transmission or diffusion of the data, through scientific publications and / or presentation at congresses, conferences and seminars, will take place exclusively following the merely statistical elaboration of the same, or in any case in an absolutely anonymous form.

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