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Loss of Organic Reserve as a Detector of Frailty in Elderly Cancer Patients Treated with Chemotherapy

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Abstract

This study aims to identify the presence of frailty in elderly cancer patients by analysing their functional reserve. In order to do so, a prospective study of oncological patients over the age of 70 years, assessed on an outpatient basis at the Hospital Virgen de la Luz of Cuenca has been conducted, and data regarding functional reserve at various levels in the body have been collected: pulmonary function (peak-flow), cerebral function (cognitive assessment with the Pfeiffer Questionnaire), renal function (creatinine clearance rate test), and muscular function (grip strength, skeletal muscle mass index, and walking speed). These patients will be grouped into two blocks: patients treated with chemotherapy (Group A), and patients not receiving cytostatic drugs (Group B).

After the final cycle of chemotherapy (calculated time of 4 months), we will analyse which parameters of physiological reserve will be affected more than 30%, thereby determining which parameters are more sensitive in order to define a frail patient, prior to initiating treatment with cytostatic drugs. This could help to predict if a stressful situation for the elderly patient, such as the administration of chemotherapy for example, could precipitate or accelerate the condition of frailty.

Furthermore, we will analyse the efficiency of the VES-13 questionnaire, one of the most used questionnaires in the field of Oncogeriatrics, in the assessment of functional reserve.

Patient enrolment will take place consecutively over 36 months (December 2009-December 2012), and survival analysis will be conducted in December 2014. We are preparing the post-study analysis.

Keywords

Older, Cancer, Chemotherapy, Frailty, Toxicity, Organic reserve

Introduction

In the United States and Europe, the elderly represent between 13-15% of the total population. Life expectancy for men has risen from 48 years in 1900 to 71 years in 1980, and for women it has risen from 51 years to 77.7 years [1]. It is estimated that in industrialised countries, life expectancy for women could exceed 90 years [2].

At present, 50% of malignant tumours occur in patients over the age of 65 years; in the year 2020, if the current population growth trend is maintained, it is estimated that 60% of all cancers will affect the elderly [1]. Data regarding Survival and Epidemiology from the *SEER: Surveillance, Epidemiology and End Results* Database of the National Cancer Institute indicate that individuals of the age of 65 years or more are 11 times more at risk of developing cancer than those younger than 65 [3].

Ageing causes the multiple decline of organs and systems (cardiac, pulmonary, renal and musculoskeletal functions), leading to the deterioration of physical function and, consequently, the functional dependence of the elderly patient. There is a reduction in bone mass

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due to demineralisation of bone; women normally lose 25% and men 12%. This process is due to reduced movement, poor absorption or inadequate intake of calcium, and loss due to endocrine disorders. Over time, joint surfaces deteriorate causing pain and crepitus, and limiting movement. Similarly, there is a reduction in activity and muscle tension, and the muscular relaxation period is longer than the contraction period. With regard to the respiratory system, with aging, respiratory muscle strength decreases. In addition, rigidity and weight and volume loss cause partial filling of the lungs. The number of alveoli reduces causing dilation of the bronchioles and alveolar ducts. Alterations occur in the lung parenchyma due to a reduction in the number and the diameter of intra-alveolar capillaries; this causes reduced oxygen pressure (pO_2) and affects pulmonary ventilation and alveolar-capillary diffusion. Renal mass and kidney weight are also seen to decrease with age. Loss of kidney mass is principally cortical; the number of glomeruli reduces. Together with this, changes to the endocrine system, cardiovascular system, immune system and the organs and senses also occur, and the number of cells in the nervous system diminishes, which can vary in line with each area of the brain.

Contrary to general belief, not all elderly patients are frail [4]. Only between 3-7% of elderly patients between the ages of 65 and 75 are frail. The incidence of frailty increases with age, exceeding 32% in those over the age of 90 years [5].

The prevalence of frail elderly individuals in the Spanish population varies between 21% and 27.5% in patients over the age of 65 [6], and up to 46% in those over the age of 85 years [7]. However, these values depend greatly on the criteria employed when defining frailty, and the type of community studied.

Frailty is a biological syndrome of the elderly that is characterised by decreased reserve in multiple organs and systems. It can be triggered by a disease, lack of activity, poor nutrition, stress and/or physiological changes associated with age. Frail patients have a lower capacity to initiate the physiological responses necessary to maintain homeostasis in moments of acute stress. Once an individual becomes frail, a progressive, spiralling process is triggered that leads to the incapacity of the patient, and eventually death [8]. *Buchner* defines this as "A state of reduced physiologic reserve associated with increased susceptibility to disability" [9]. For this reason, frailty has come to be defined as "Preclinical disability" [10].

Organic systems have an "excess" capacity, with a 70% margin of loss. When normal function drops to 30% of its normal value, vulnerability is at its maximum; below said value, evidence of failure (disability) presents, and when values of 0-10% are reached, "failure to perform" or syndrome of decline ("failure to thrive") appears [11].

In all cases, frailty is a consequence of diminished reserve capacity that leads to disability, institutionalisation and death. General unanimity exists with regard to frailty not being an all-or-none process, but rather a process of continuous evolution, from being fit to becoming frail [12]. Nowadays, the term "cycle of frailty" is preferred.

The Vulnerable Elders Survey (VES-13) is a tool for identifying vulnerable elders in the community at risk of frailty. Said test, developed by *Saliba, et al.*, considers data such as age, self-rated health, limitations in physical function and functional dependency [13]. A score of ≥ 3 vs. 0-2 identifies 32% of individuals as vulnerable. This "vulnerable" group is 4 times more at risk of death or functional decline when compared to elders with lower scores [14].

This study aims to determine which parameters of functional reserve are most useful in predicting pre-chemotherapy frailty, and which are associated to the VES-13 questionnaire, which, up until now, has been the most used tool in assessing the risk of frailty in elderly oncological patients. Finally, we want to create a nomogram to calculate overall survival in elderly patients with diagnosis of cancer.

Objectives

This study was proposed with the aim of meeting a series of objectives:

The primary objectives of this project are as follows: 1) Employ parameters of functional reserve in the assessment of the state of frailty of elderly cancer patients being treated with chemotherapy. 2) Identify which of these parameters allow for the prior recognition of a frail patient (parameters which vary by ≥ 30% with the administration of chemotherapy). 3) Once said parameters have been identified, check their correlation with the VES-13 questionnaire.

The secondary objectives are as follows: 1) Determine the socio-demographic characteristics of the oncological population over the age of 70 years being treated with chemotherapy at Hospital General Virgen de la Luz of Cuenca. 2) Determine the prevalence of vulnerability in oncological elderly patients based on the administration of the VES-13 questionnaire. 3) Create a nomogram to predict overall survival in elderly oncological patients.

Material and methods

Design

Prospective, observational study in the Cancer in the Elderly Unit of the Medical Oncology Department of Hospital General Virgen de la Luz in Cuenca.

Study period

December 2009-December 2011 (SEOM [Sociedad Española de Oncología Médica (Spanish Medical Oncology Society)] Grant for Young Investigators 2009), with enrolment continuing until December 2012 (ONCOF-

RÁGIL project, implying an extension of this project) and survival analysis in December 2014.

Study subjects

All elderly patients, assessed consecutively, diagnosed with cancer who visit the Cancer in the Elderly Unit of said hospital. The inclusion criteria are as follows: Age ≥ 70 years; diagnosed with cancer of any type and stage in the period between December 2009 and December 2012; not hospitalised; not institutionalised; a speaker of Spanish or English, or accompanied by a relative that speaks either language to serve as a translator and interpreter; able to undertake all the tests we are going to apply. This implies that the patient has mobility of the upper and lower limbs (essential to measure strength of lower limbs and to use the hand dynamometer); able to give consent, in writing, to participate in this study. Patients that meet any of the following criteria cannot be included: Patients that do not meet any of the inclusion criteria; patients admitted to hospital in the two weeks prior to enrolment in the study (functional condition could be affected as a consequence of being admitted); in the case the patient is unable to read the consent, the refusal of the relatives and/or companions to collaborate with the patient to complete the questionnaire; patients with a life expectancy < 3 months.

Sample size calculation

Elderly patients over the age of 70, being treated with chemotherapy at Cancer in the Elderly Unit in the Medical Oncology Department of Hospital General Virgen de la Luz of Cuenca, have been consecutively included in this study. Taking into account that seven variables of physiological reserve have been selected, and that the results will be adjusted by age, sex and tumour stage (three additional variables), it will be necessary to enrol 110 patients. A loss of 5% is predicted; therefore a total of 115 patients treated with chemotherapy is required. At present, there is a total of approximately 400 new visits to the Medical Oncology Department per year, of which 100 correspond to the elderly, and of which 35-40 are candidates to receive chemotherapy. Taking this into account, it is expected that approximately 120-130 patients treated with chemotherapy will be included in the period of time indicated (enrolment over 3 years). This number is sufficient to be able to identify the functional reserve parameters indicative of frailty, and to create a predictive model and a nomogram.

Variables

The following variables will be included:

1) Variables regarding the study population (age; sex; cultural or educational level (illiterate; able to read and write, primary education or higher); civil status (married; widow(er); single; separated).

2) Variables related to the tumour; type of tumour (breast or gynaecological cancer; gastrointestinal cancer; lung cancer; urological or prostate cancer; others); tumour stage (stages I-III; stage IV); treatment type (cytostatic drugs as monotherapy, associated or not associated to a biological agent; polychemotherapy, associated or not associated to a biological agent).

3) Variables related to the Comprehensive Geriatric Assessment (CGA): Barthel scale; Lawton-Brody scale; Nutritive Screening Initiative (NSI) scale; Gijón's Social-Familial scale; Charlson Comorbidity Index; drug consumption.

4) Frailty variables related to the body's reserve: muscular reserve, measured using skeletal muscle mass index; functional reserve, in upper limbs, measured using cylindrical grasp or handgrip, and in lower limbs, measured using walking speed at a comfortable pace for 5 metres; cognitive reserve, analysed using Pfeiffer's Short Portable Mental Status Questionnaire; respiratory reserve, measured using peak-flow or peak expiratory flow (PEF); and kidney reserve, determined using creatinine clearance calculated in accordance with the Cockcroft-Gault equation.

5) Frailty variables based on questionnaires: VES-13 Questionnaire. Other questionnaires/criteria that will also be recorded are: the Barber Questionnaire and phenotype of frailty defined by Linda Fried.

Methodology

Data collection will be carried out by the principal investigator in the patient's first visit, after the patient has been informed and has given his/her consent to participate.

In order to determine the skeletal muscular mass index, a body composition analyser (Tanita 300 model) will be used. Using this, values for skeletal muscle mass and impedance will be obtained; said values can then be used to calculate the skeletal muscle mass index using the height of the patient and applying the *Janssen* formula [15].

In order to determine hand grip strength, the JAMAR adjustable hand dynamometer with a step scale of 0.5 kg will be used. To use the dynamometer, the subject must be in a standing position. The required hand must be in line with the forearm, the elbow must be extended and the arm positioned alongside the body, yet not touching it, with the palm of the hand facing the thigh. The subject will squeeze using his/her fingers with the maximum strength possible, maintaining the starting position. Two readings with the dominant hand will be recorded and it will be selected the higher value.

In order to determine walking speed at a quick or comfortable pace, the patient will walk 5 metres. A 0.1 m/s decrease in walking speed in one year increases the risk of mortality within 5 years [16].

The Pfeiffer Questionnaire consists of 10 items. The cut-off point is at 3 or more errors, in the case of individuals that can read and write, and at 4 or more for those who cannot. Cognitive deterioration is suspected for anything above this score [17].

Peak Expiratory Flow (PEF) or Peak-Flow is expressed in litres/minute. Peak-flow is measured in a standing position. The marker must be placed at zero. The meter must be held horizontally so as not to interfere with the movement of the marker. The patient must breathe in and place their lips around the mouthpiece, making sure they do not place their tongue in the hole; they must blow out, in one single blow, as hard and as fast as they can. The process must be repeated two more times and will be recordedthe highest value. Recent studies indicate that pulmonary function is an independent predictor of mortality in the elderly [18].

Creatinine clearance will be calculated using the Cockcroft-Gault equation [19].

Frailty will be determined using the VES-13 questionnaire (score of ≥ 3). They will also be used the Barber questionnaire (score of ≥ 1), and the phenotype defined by Linda Fried (score ≥ 3) [20]. According to this phenotype, elderly patients that meet ≥ 3 of the following criteria will be considered frail: a) unintentional weight loss of 5% or more in the last year; b) muscle weakness; c) self-reported exhaustion or tiredness; d) slow walking speed; e) low daily physical activity.

In both groups, both the group treated with chemotherapy (Group A) and the group not receiving chemotherapy (Group B), these physiological reserve variables will be determined on the same day of inclusion in the study (baseline), and 4 months after starting the study (post-baseline).

Ethical Aspects

The investigation complies with Helsinki regulations [21]. The study was submitted to the Clinical Research Committee of Hospital General Virgen de la Luz of Cuenca for the approval thereof, and authorisation was obtained. All participants have signed a specific informed consent prior to inclusion in this project.

Statistical analysis

The statistical analysis corresponding to this type of study will be performed using the SPSS statistical analysis software package for Windows version 19.0. Said analysis will include a series of steps: 1) Descriptive data analysis, using mean, median, standard deviation and range for the quantitative variables, and percentages for the qualitative variables. 2) Analysis of differences between both groups, the group treated with chemotherapy (Group A) and the group not receiving chemotherapy (Group B), by means of mean difference analysis for the quantitative variables, and the chi-square test for the qualitative variables. 3) In order to determine if there are significant differences between each of the study variables (pre- and post-chemotherapy), the Student-Fisher t-test will be used for independent groups, following a pre- and post-test design, including a control group of oncological patients not receiving treatment with chemotherapy. The variables in which the difference is ≥ 30% will be the predictor variables of frailty, and they will be used for the following analysis. 4) Logistic regression analysis, in order to determine which of the parameters, in which a ≥ 30% loss was produced, received a score of ≥ 3 in the VES-13 questionnaire administered before chemotherapy. 5) Cox regression, in order to identify which parameters of the elderly patient's organic reserve can be associated to their survival, adjusted by age, sex and tumour stage. The latter analysis will be performed using the total number of patients included in the study (Group A and Group B). It will be elaborated a nomogram to predict overall survival in an elderly patient with diagnosis of cancer, by using the integrated statistics package Stata.

Study Limitations

A priori, the main limitation that may compromise the fulfilment of the proposed objectives is the excessive workload experienced by outpatient clinics within the Medical Oncology Department. Another limitation to take into account is the level of participation of the patients seen.

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Author Contributions

MJMG wrote the manuscript. CGP, MJMG and AM reviewed the manuscript. AM made the statistical analysis. All of them approved the final version of the article.

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