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FRAILTY AND VULNERABILITY AS PREDICTORS OF CHEMOTHERAPY TOXICITY IN OLDER ADULTS: A LONGITUDINAL STUDY IN PERU

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Abstract: *Background:* Multiple markers are used to assess frailty and vulnerability, conditions associated with the development of chemotherapy toxicity (CTT). However, there is still no consensus on which condition has stronger association with this adverse effect of chemotherapy in the elderly. *Objectives:* To evaluate the association between frailty and vulnerability with the development of CTT in oncogeriatric patients. *Design, Setting, and Participants:* Through a retrospective cohort, a secondary database of 496 male oncogeriatric military patients treated at the Geriatrics Service of the Naval Medical Centre of Peru during 2013-2015 was analyzed. *Measurements:* With prior informed consent, the presence of frailty, assessed by Fried Phenotype; and vulnerability, assessed by the Vulnerable Elders Survey-13 (VES-13) and G-8, was determined. The follow-up of patients in chemotherapy was performed every 8 weeks, to determine the development of CTT (according to the Common Terminology Criteria for Adverse Events v4.0). In addition, we included sociodemographic characteristics, medical background information and functional assessment variables. The data collected was encoded and imported into STATA v14.0 statistical package for analysis. Multivariate analysis was performed using crude and adjusted Cox regression models. The reported measure was the hazard ratio (HR) with their respective 95% confidence intervals (95%CI). *Results:* The average age was 79.2 ± 4.3 years. 129 (26.01%) developed CTT during follow-up. Similarly, 129 older adults (26.01%) were positive for frailty according to Fried phenotype; 101 (20.36%) were positive for vulnerability with VES-13, and 112 (22.58%) with G-8. In the adjusted Cox model, by type of cancer and adverse effects, a statistically significant association was found between the 3 scales evaluated and the development of CTT, with the Fried Phenotype as the scale with the strongest association (HR=2.01; 95%CI: 1.04-4.90). *Conclusions:* The frailty and vulnerability in the elderly are conditions associated with the development of CTT. The Fried phenotype was the scale with the most significant association with the outcome studied.

Key words: Drug therapy, adverse reactions, neoplasm, frailty, health vulnerability.

Introduction

Currently, more than 50% of newly treated cases of cancer correspond to people over 60 years old (1). These patients have a higher risk of developing adverse effects under treatment with antineoplastic drugs, compared to younger adults (2). Among these, chemotherapy is one of the most widely used therapeutic methods for its similar efficacy in the treatment of heterogeneous age groups. However, this benefit is accompanied by an increased risk of toxicity in geriatric patients with a certain profile of vulnerability, frailty or comorbidities, this phenomenon being known as chemotherapy toxicity (CTT) (3).

The high probability of developing CTT is due to processes involved in aging, accompanied by multimorbidity and geriatric syndromes. Among these factors, the decrease in the volume of distribution, caused by malnutrition, loss of muscle mass and adipose tissue and reduction in the percentage of total body water, besides of the poor excretion of antineoplastic agents and their active metabolites due to the decrease in the glomerular filtration rate, alter the pharmacokinetics of the antineoplastic drugs (4). However, the functional status of the elderly can be preserved through healthy activities, such as physical exercise, whose implementation could increase the patient's tolerance and suitability for oncological treatment (5, 6).

Given this situation, the International Society of Geriatric Oncology (SIOG) suggests the evaluation of the physical, cognitive, psychosocial and functional dimension of each patient, which are aspects of the comprehensive geriatric assessment (CGA), to adjust the dosage and time of medication before starting the treatment (7). However, several studies suggest as an alternative the use of risk assessment scales for the geriatric population, since their application can be faster and more effective in the external consultation, for which limited time is available (8, 9). However, laboratory tests are usually required to evaluate certain markers used on CTT predictive scales, such as the patient's hemoglobin level and creatinine clearance (10). Therefore, it is necessary to use simpler strategies, such as frailty assessment in daily clinical practice.

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Frailty, a syndrome prevalent in the elderly, expresses the risk of developing functional dependence or death from the exposure to a stressor (11). This is highly accentuated by the comorbidities of cancer, such as anemia (12). On the other hand, vulnerability, specifically oncological, would be linked to the possible benefit of performing the CGA before starting antineoplastic treatment (13). Both conditions are part of the cumulative functional impairment evaluation in the geriatric patient, being among the shortest and simplest instruments included in the Fried Phenotype, for frailty; and the Vulnerable Elders Survey-13 (VES-13) with the G-8, for vulnerability (13–15).

Although the scales presented can be used as predictors of CTT, we have not found previous research where they have compared both scales for this purpose. For this reason, the present study had the aim to evaluate the association between frailty and vulnerability, with the development of CTT in oncogeriatric patients.

Material and methods

Design and population

Retrospective cohort study, with a secondary analysis of a study, carried out during 2013-2015 in oncogeriatric patients of the Geriatrics Service of the Naval Medical Centre of Peru (Centro Médico Naval, CEMENA for its initials in Spanish) (16, 17).

We included patients older or equal to 60 years with a pathological diagnosis of cancer, made at CEMENA, between September 2012 and February 2013. We excluded those participants who obtained a score less than or equal to 23 points in the Mini-Mental State Examination (MMSE), who have not wanted to enter the study, who have not given their informed consent or who have not provided all the relevant information in their data collection sheets (16, 17).

Procedure

The patients were invited to participate in the study when the oncological diagnosis was confirmed, previous voluntary authorization of informed consent. After that, the measurements of all the variables evaluated in the first consultation were made. This included the application of the 3 scales in the study (Fried Frailty Phenotype, VES-13, and G-8) to determine the frailty and vulnerability of the population, in addition to the evaluation of their sociodemographic characteristics, medical background information and functional assessment variables.

Chemotherapy sessions were conducted in the medical oncology service. The participants were followed up every 8 weeks in the CEMENA Geriatrics Service, to determine CTT. For this procedure, we used the Common Terminology Criteria for Adverse Events v4.0.

Exposure: Frailty and vulnerability

Frailty: Fried Phenotype

The instrument used to assess frailty was the Fried Phenotype, while vulnerability was determined by VES-13 with G-8. Fried Frailty Phenotype considers the following 5 criteria: grip strength, gait speed, physical exhaustion, weight loss, and physical activity. These were individually evaluated in each patient, and were classified as non-frail if they presented 1 or 2 positive values; and frail, with 3 or more positive values (15), considering positive values as follow: 1) Inability to perform the grip strength test with a hand dynamometer or if they obtained a maximum grip strength value of 30 kg or less for men and 20 kg or less for women in two trials (18); 2) Inability to perform the timed walk test of 4 meters at the speed «as fast as you felt safe" or slow gait considered as <0.8 m/s; 3) If they answered «No» to the question Do you feel full of energy? 4) If they answered «Yes» to the question, have you lost weight recently so that your clothes have loosened? and 5) If they obtained a score lower than 64 for men and 52 for women on the Physical Activity Scale for the Elderly (PASE), respectively (18–22).

Vulnerability: VES-13 and G-8

The VES-13 includes 13 items distributed in 4 criteria: age, self-perceived health, functional and physical evaluation. Through its application, it is possible to obtain a value from 0 to 10, being considered as positive for vulnerability if the participant achieve a score ≥3 (23).

The G-8 evaluates the criteria of age, mobility, food intake, body mass index, weight loss, polypharmacy, neuropsychiatric impairment, and self-perceived health. This score varies between 0 to 17, and it is considered positive for vulnerability when a score ≤14 is obtained (24).

Outcome: Chemotherapy toxicity

Our outcome variable was CTT, expressed as positive if after the application of chemotherapy there was evidence of clinical or laboratory adverse effects of grade III, IV or V. This calculation was performed using the Common Terminology Criteria for Adverse Events v4.0 (National Cancer Institute), a tool developed based on international consensus to assess this adverse effect (25).

Other variables

Sociodemographic characteristics

The sociodemographic characteristics were included and evaluated by self-report: age (in years) and marital status (single, married/living together, divorced, widower).

Medical background

We included the following variables by self-report: smoking history (yes or no), falls in the last year (yes or no). In addition, we obtained from the geriatric medical history the

Table 1
Characteristics of the study sample and bivariate analysis (N=496)

Variables	n	%	Mean ± SD	Chemotherapy toxicity		p value
				Yes	No	
				n=129 (26.01%)	n=367 (73.99%)	
Age (in years)			79.2 ± 4.3	86.7 ± 4.3	77.6 ± 3.8	0.01
Marital status						0.4
Single	44	8.87		12 (27.27)	32 (72.73)	
Married/living together	287	57.86		88 (30.66)	199 (69.34)	
Divorced	66	13.31		15 (22.73)	51 (77.27)	
Widower	99	19.96		14 (14.14)	85 (85.86)	
Family history of cancer	39	7.86		13 (33.33)	26 (66.68)	0.1
Comorbidities						0.001
0	76	15.32		10 (13.16)	66 (86.84)	
1	198	39.92		19 (9.60)	179 (90.40)	
2	123	24.80		29 (23.58)	94 (76.42)	
3 or more	99	19.96		71 (71.72)	28 (28.28)	
Smoking history	104	20.97		65 (62.50)	39 (37.50)	0.01
No	392	79.03		64 (16.33)	328 (83.67)	
Calf circumference ≤31cm	99	19.96		77 (77.78)	22 (22.22)	0.01
No	397	80.04		52 (13.10)	345 (86.90)	
Poor physical activity	250	50.40		79 (31.60)	171 (68.40)	0.004
No	246	49.60		50 (20.33)	196 (79.67)	
Dependency in ADL	102	20.56		80 (78.43)	22 (21.57)	0.001
No	394	79.44		49 (12.44)	345 (87.56)	
Falls during the year	111	22.38		69 (62.16)	42 (37.84)	0.0001
No	385	77.62		60 (15.58)	325 (84.42)	
Polypharmacy	261	52.62		77 (29.50)	184 (70.50)	0.06
No	235	47.38		52 (22.13)	183 (77.87)	
Fried phenothype						0.0001
Frail (3-5)	129	26.01		81 (62.79)	48 (37.21)	
Non-frail (1-2)	367	73.99		48 (13.08)	319 (86.92)	
VES-13						0.0001
Vulnerable (3 - 10)	101	20.36		71 (70.30)	30.00 (29.70)	
Normal (0 - 2)	395	79.64		58 (14.68)	337.00 (85.32)	
G-8						0.0001
Vulnerable (0 - 14)	112	22.58		68 (60.71)	44.00 (39.29)	
Normal (15 - 17)	384	77.42		61 (15.89)	323.00 (84.11)	

SD: standard deviation; ADL: activities of daily living; VES-13: Vulnerable Elders Survey-13.

following: family history of cancer (yes or no), comorbidities (high blood pressure, type 2 Diabetes Mellitus, chronic kidney disease, chronic obstructive pulmonary disease, osteoarthritis, overweight/obesity according to body mass index, osteoporosis, and dyslipidemia) and polypharmacy (≥5 drugs consumed under medical prescription) (26). We constructed a variable including the comorbidities from the older adult medical history (0, 1, 2, 3 or more) (27).

The body mass index (BMI) was determined by the formula: weight (kg)/[height (m2)]. Both measures were assessed without shoes or belt with a calibrated scale and height gauge, respectively (VEGA brand, PT-CLX model, 2085 series).

Functional assessment

We used the Barthel Index, an instrument that evaluates the execution of 10 Activities of Daily Living (ADL), with a score between 0 to 100. Participants are considered as dependent with a score <100 (28). Finally, the calf circumference (cm) was evaluated, establishing as cut-off point ≤31 cm.

Statistical analysis

We used the statistical package STATA v14.0 for our analysis. For the descriptive analysis, we used measures of central tendency, dispersion measures, absolute and relative frequencies. The bivariate analysis comparing the results of patients with and without CTT was performed using the Chi-square test, Fisher exact test, and the Student t-test, as appropriate.

Multivariate analysis to assess the association between exposure variables and the development of CTT was performed using crude and adjusted Cox regression models. Five models (1 crude and 4 adjusted models) were constructed to evaluate the association between exposure variables (frailty and vulnerability scales) and the development of CTT. The models were adjusted for type of cancer and adverse effects. The reported measure was the hazard ratio (HR) with their respective 95% confidence intervals (95%CI). Finally, the Kaplan-Meier estimator was used to graph the survival analysis.

Ethical aspects

The study was conducted according to the ethical principles for human research, presented in the Declaration of Helsinki. Therefore, the physical, psychological and social integrity of the participants was preserved at each stage of the study. We obtained the informed consent from participants previous data collection. Additionally, the research project was approved by CEMENA's Ethics Institutional Review Board.

Results

General characteristics of the study sample

A total of 496 older adults were analyzed. The average age was 79.2 ± 4.3 years and all participants were men. 129 (26.01%) developed CTT during follow-up. Similarly, 129 (26.01%) older adults were positive for frailty based on Fried phenotype, 101 (20.36%) were positive for vulnerability according to VES-13, and 112 (22.58%) using G-8 (Table 1).

The 129 patients who developed CTT had a total of 199 CTT events, and the more frequent were the following: 65 (32.66%) presented gastrointestinal CTT; 29 (14.57%) developed lymphatic/hematologic CTT; 24 (12.06%) expressed dermal CTT, and 19 (9.55%) developed respiratory CTT (Table 2). On the other hand, the groups with lymphomas/leukemia (9.48%) and multiple myeloma (11.09%) had the highest proportion of participants affected with this outcome, being 82.98% and 81.82%, respectively (Table 3).

Table 2
Classification of chemotherapy toxicity effects

Chemotherapy adverse effects (Common Terminology Criteria for Adverse Events v4.0 - National Cancer Institute)	n (%)
Gastrointestinal	65 (32.66)
Lymphatic/hematological	29 (14.57)
Dermal	24 (12.06)
Respiratory	19 (9.55)
Related to the route of administration	14 (7.04)
Cardiac	10 (5.03)
Endocrine	9 (4.52)
Musculoskeletal	8 (4.02)
Neurological	7 (3.52)
Infectious	5 (2.51)
Immunological	4 (2.01)
Vascular	3 (1.51)

Table 3
Frequency of chemotherapy toxicity according to cancer location

Cancer Location	n	%	Chemotherapy toxicity	No Chemotherapy toxicity
			n (%)	n (%)
Prostate	161	32.46	65 (40.37)	96 (59.63)
Stomach	101	20.36	59 (58.42)	42 (41.58)
Colon/rectum	66	13.31	35 (53.03)	31 (46.97)
Lung	66	13.31	40 (60.61)	26 (39.39)
Multiple myeloma	55	11.09	45 (81.82)	10 (18.18)
Lymphomas/Leukemia	47	9.48	39 (82.98)	8 (17.02)

Frailty and vulnerability as predictors of chemotherapy toxicity

The development of CTT was more frequent in patients with frailty and vulnerability compared to those without these conditions, according to the usual cut-off points of the Fried

Table 4
Cox regression models to evaluate the development of chemotherapy toxicity according to frailty and vulnerability scales

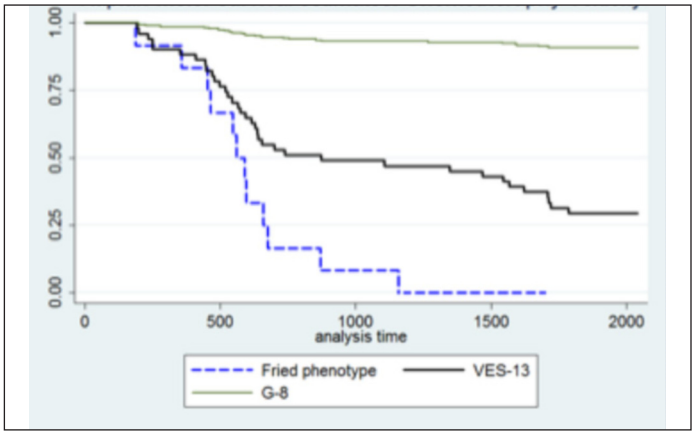
	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)	Model 5 HR (95%CI)
Fried Phenotype					
Non-frail (1-2)	Reference	Reference	-	-	Reference
Frail (3-5)	10.20 (7.01-16.91)	4.21 (4.03-7.80)	-	-	2.01 (1.04-4.90)
VES-13					
Normal (0 - 2)	Reference	-	Reference	-	Reference
Vulnerable (3 - 10)	7.75 (6.26-12.89)	-	2.75 (1.23-3.44)	-	1.05 (1.02-1.09)
G-8					
Normal (15 - 17)	Reference	-	-	Reference	Reference
Vulnerable (0 - 14)	8.18 (5.13-13.06)	-	-	1.08 (1.03-1.26)	1.05 (1.03-1.10)

Model 1: crude; Models 2, 3, 4 y 5: adjusted for type of cancer and adverse effects; CI: confidence interval; HR: hazard ratio; VES-13: Vulnerable Elders Survey-13.

phenotype (62.79% vs. 13.08%), VES-13 (70.30% vs. 14.68%) and G-8 (60.71% vs. 15.89%) (p <0.001) (Table 1).

In the Cox regression model, adjusted for type of cancer and adverse effects, a statistically significant association was found between Fried phenotype (HR=2.01; 95%CI: 1.04-4.90), VES-13 (HR=1.05; 95%CI: 1.02-1.09), and G-8 (HR=1.05; 95%CI: 1.03-1.10), and the development of CTT (Table 4).

Figure 1
Kaplan-Meier estimator for frailty and vulnerability scales as mortality predictors in patients who developed chemotherapy toxicity



Other factors associated with chemotherapy toxicity

Other factors associated with CTT were: the presence of 3 or more comorbidities (p<0.001), smoking history (p<0.01), calf circumference ≤31 cm (p<0.01), dependency in ADL (p<0.001), poor physical activity (p <0.004) and have suffered falls during the year (p<0.001) (Table 1).

Survival estimated by Kaplan-Meier for chemotherapy toxicity

Fried phenotype was the scale that predicted the highest risk of mortality in patients evaluated who suffered from CTT, followed by VES-13 and G-8, respectively (Figure 1).

Discussion

Main results

496 older adults submitted to chemotherapy for some type of cancer were evaluated, of which 26% developed CTT. An increased risk of CTT was found in those patients diagnosed with frailty according to the Fried phenotype, as well as in those who presented vulnerability assessed by the VES-13 and G-8 scales; being frailty screened with Fried phenotype the marker associated with the highest risk. This outcome was more frequent in geriatric patients who had lymphomas or leukemia and lower in those affected with prostate cancer, being these data usually not reported in previous studies (9, 13, 24). On the other hand, the most common adverse effects of CTT were gastrointestinal, lymphatic/hematologic and dermal.

Comparison with other studies

The main finding of our study was that suffering from frailty evaluated by the Fried phenotype, or vulnerability according to VES-13 and G-8, was associated with an increased risk of developing chemotoxicity. This outcome is supported by studies that have evaluated the association between the alteration in the scores of the G-8 and VES-13 scales with the development of the adverse effect studied (29, 30). However, a systematic review recommended continuing with the application of the comprehensive geriatric assessment (CGA), because the G-8 and VES-13 have low specificity and negative predictive value (31). Despite this, due to the short time required for their employment, they are still used as

practical scales to assess the risk of chemotoxicity (32).

Currently, frailty scales, such as the Cancer-specific Geriatric Assessment (GA) and the Functional Autonomy Measuring System (SMAF), support the association between frailty and CTT (33, 34). However, in a cohort that compared the utility of three geriatric assessment tools for usual outcomes of cancer, such as functional loss and death, VES-13 scale demonstrated a greater predictive value than Fried Phenotype (11). In addition, among the criteria evaluated by this frailty scale, only the decrease in the grip strength has previously shown an independent predictive value for CTT or mortality (25).

Factors associated with chemotoxicity

Among the factors evaluated, multimorbidity (three or more comorbidities), smoking history, calf circumference equal or less than 31 cm, dependency in ADL, poor physical activity and have suffered falls during the year were associated with the development of CTT in oncogeriatric patients. Regarding these points, the presence of comorbidities has been associated with a higher risk of suffering from grade III/IV non-hematologic toxicity due to chemotherapy in males, being reported as a more effective predictor of early cessation of treatment than the decrease of functional state (35). On the other hand, a calf with reduced circumference is an anthropometric indicator of the detriment of muscle mass and nutrition of the patient, which predisposes to early cessation of chemotherapeutic treatment due to the risk of cachexia (36). Also, the consumption of tobacco, which is a systemic risk factor, worsens the functional capacity in the patient, which would predispose to the alteration in the pharmacokinetics of antineoplastic drugs and a worse prognosis (4). In addition, dependency in ADL has been previously associated with development of adverse effects in geriatric patients with cancer undergoing surgeries and systemic treatments (37). Similarly, physical activity has been shown to have a positive effect on muscle strength, mood and immunity, which possibly induces an increase in the rate of successful completion of chemotherapy treatment (38). Finally, the increase in the number of falls is one of the most common manifestations of peripheral neurotoxicity induced by chemotherapy, and this is one of the main reasons for the dose reduction and early cessation of treatment (39).

The relevance of the findings

This is one of the first studies to compare the efficiency of various vulnerability and frailty scales, specifically VES-13, G-8, and Fried Phenotype, as predictors of the development of CTT in oncogeriatric patients. Therefore, through these findings, the use of faster methods than CGA to verify the benefit of chemotherapy can be endorsed. In addition, because the study was carried out in a poorly studied sample such as retired military sailors, whose risk factors and health deficiencies differ from those of the general population (40), the results obtained have important relevance for them.

Limitations

This study has certain limitations: 1) Due the follow-up of patients was only for 2 years, exists the probability that later CTT events have not been recorded; 2) Different types of cancer were evaluated, so determining whether the predictive value of the tests used differs according to cancer nature was not possible; 3) The dose of chemotherapy applied was not recorded, making it a potential unmeasured confounder, as it could lead to underestimating or overestimating the association between frailty or vulnerability with CTT; 4) Due to studying a population formed solely by ex-military men, who have been exposed to risk or protector factors for the development of different cancer and CTT, and have access to a health system different from the general population, these results could not be extrapolated to other oncogeriatric patients. However, it is plausible to emphasize in the importance of these novel results since few studies evaluate this kind of population; 5) We did not measure the creatinine clearance in our study; however, we included the presence of chronic kidney disease within the comorbidities evaluated.

Conclusions

In conclusion, frailty and vulnerability in older adults are conditions associated with the development of CTT, finding additionally that Fried Phenotype, a scale to evaluate frailty, had the most valuable association with CTT. We suggest to develop further studies to clarify the chemotherapy dose of choice for oncogeriatric patients, using the scales studied.

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