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Predictive factors of depressive symptoms of elderly patients with cancer receiving first-line chemotherapy

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Abstract

***Background*: Depression is the most common psychiatric disorder in geriatrics and oncology. For elderly cancer patients, it has a significant impact on quality of life, morbidity, and mortality. Nevertheless, depression is under-diagnosed and under-treated. Cancer management is key in improving the quality of care in this population. We aim to identify sociodemographic, clinical, and treatment-related factors of depression in elderly patients during chemotherapy, thus allowing early detection of patients in need of specific treatment. Further, we investigate whether chemotherapy efficacy and safety are associated with depression.**

***Patients and methods*: A prospective multicenter cohort composed of incident cases of cancer diagnosed in patients 70 years and older, receiving first-line chemotherapy. Depressive symptoms were measured by the Geriatric Depression Scale at baseline and after four chemotherapy cycles. Associations between depressive symptoms during chemotherapy and patients' clinical and treatment characteristics were identified by logistic regression.**

***Results*: Among 344 patients measured for depression before chemotherapy, 260 had a second assessment at the fourth treatment cycle. At baseline, 45.4% were depressed, and 44.6% were depressed after the fourth cycle. Independent factors of depression were depressive symptoms at baseline (odds ratio (OR) = 6.7, $p < 0.001$), malnutrition (OR = 5.1, $p = 0.014$), and risk of malnutrition (OR = 1.6, $p = 0.014$). After controlling for missing data, effective chemotherapy was associated with a lower risk of depression (OR = 0.4, $p = 0.018$).**

***Conclusion*: We highlight the role of depressive symptoms and nutritional status at baseline, on the occurrence of depressive symptoms during chemotherapy. These factors should be taken into account in any pre-treatment consultation and appropriate nutritional and psychiatric preventative measures established.**

Introduction

Even though depression is the most common psychiatric disorder both in the geriatric population [1,2] and in oncology [3], prevalence is difficult to estimate. Several definitions are used for depressive conditions; different diagnostic criteria exist; and population heterogeneity is common across studies. Compared with younger patients, elderly patients present specific depression features that may complicate and delay diagnosis [1]. Sadness is less expressed, and somatic symptoms including asthenia, weight loss, and sleep disturbances are frequent and can be confused with cancer symptoms or with secondary treatment effects. Factors associated with depression in the elderly include a history of previous depressive episodes, female gender, social isolation, mourning, low educational levels, dependency, cognitive disorders, or vascular risk factors [1,4,5].

Older adults with depression can have severe consequences and is associated with significant morbidity, chronicity, and an increased risk of suicide [1,4]. As well as impacting significantly on quality of life [2], it represents significant costs in health care spending [6]. Even though depression can be a predictor of mortality in cancer patients

[7], it is frequently under-diagnosed and under-treated [8]. The Geriatric Depression Scale (GDS) [9] is a specific screening scale for the elderly where somatic symptoms have been voluntarily left out. The 15-item version (GDS-15) is better known and more frequently used [10].

Our study's main objective was to identify factors associated with depressive symptoms during chemotherapy in elderly cancer patients, aged ≥70 years. Moreover, we evaluated whether the efficacy and safety of chemotherapy were associated with depressive symptoms during treatment.

Patients and methods

Patients aged ≥70 years, treated with first-line chemotherapy for various cancers (colon, pancreas, stomach, ovary, bladder, prostate, lung, non-Hodgkin's lymphoma (NHL), or cancer with unknown primary origin), were prospectively included [11]. Breast cancer patients were not eligible, because chemotherapy is rarely the first-line treatment choice. Patients with known central nervous system metastases were excluded.

Depressive symptoms were measured using the GDS-15, with a total of 0 to 15 points and a score of ≥6 indicating depression. Most data suggest that a threshold of 5 or 6 gives the best performance in terms of sensitivity and specificity, near 80% [12]. Patients who did not complete a second GDS-15 at the fourth cycle were excluded from the current analysis.

Sociodemographic and clinical characteristics were recorded at inclusion: age, sex, marital status (single, married, widower, and divorced), living alone, level of education (pre-primary, primary school certificate, and secondary studies), cancer site (colon, stomach, pancreas, NHL, prostate, ovary, bladder, lung, and unknown primary origin), and stage (advanced for solid tumors when there were metastases and for lymphomas when the International Prognosis Index was equal to 2–3). A Comprehensive Geriatric Assessment (CGA) [13] including GDS, Mini-mental State Examination (MMSE), Mini Nutritional Assessment (MNA), activities of daily living (ADL), instrumental activities of daily living, and timed get up and go (TUG) were carried out twice during chemotherapy: at baseline before treatment and before cycle 4.

Specific treatments for depression were not proposed by the clinician. The treatment (standard, standard reduced (defined in study protocol), or adapted (i.e., adapted chemotherapy or best supportive care)) was determined by a clinician blinded to the CGA results. Chemotherapy protocols were chosen according to standard guidelines at the time of trial registration, as described previously [11,14]. Efficacy was defined by RECIST and CHESON criteria and coded dichotomously: progression versus partial or complete response. Severe toxicities requiring dose decreases or interruption were coded with two variables: hospitalizations for toxicity and grades 3–4 toxicities according to the World Health Organization definition. Patients provided written informed consent. The protocol was approved by institutional review boards and ethics committees and was conducted in accordance with the Declaration of Helsinki Good Clinical Practices and local ethical and legal requirements (clinical trials: NCT00210249).

Statistical analysis

The relationships between clinical and demographic factors and presence of depressive symptoms at baseline were tested using chi-square and *t*-tests. Missing data were specified if necessary. The significance level was 0.05. Odds ratio (OR) and 95% confidence intervals were obtained using logistic regression models. Univariate models were fitted for all clinical and demographic variables: age (70–75, 75–80, 80–85, or >85 years), sex (male/female), living alone (yes/no), marital status (married/not married), education level (pre-primary, primary school certificate, and secondary studies), response to chemotherapy (progression or stabilization/partial or complete response), toxicity grade 3 or 4 (yes/no), hospitalization for toxicity (yes/no), advanced stage (yes/no), MMSE (abnormal if <24), MNA (17–23.5: malnutrition risk, <17: malnutrition), TUG test (abnormal if <20 s), ADL (no dependencies / >1), and GDS at baseline (abnormal if >5). Variables significant at the 0.15 level in univariate analysis were selected for a multivariate logistic model to predict depressive symptoms at the fourth treatment cycle. No interaction terms were identified. A backward stepwise manual method was used for the reduced final multivariate model adjusted for age and sex. We checked model fit with the Hosmer and Lemeshow test [15]. Because of the high number of missing data in geriatric assessment and clinical data (only 195 patients had complete data at four cycles), the complete case analysis was compared with an analysis after multiple imputations. This method [16] consisted in imputing several values for each missing data point across all patients with GDS-15 at baseline, creating several completed data sets that were analyzed separately and then combined to have an overall score. Estimated parameters after imputation can be compared with those in complete case analysis. All analyses were performed in SAS, 9.3.

Results

Between September 2002 and September 2005, 364 patients were included from 12 centers in south-western France: two cancer referral centers and ten community hospitals. Of the 344 patients that completed the GDS-15 before starting chemotherapy, 260 also completed the

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GDS-15 before the fourth cycle, constituting the study population.

The reason for absent GDS at the fourth cycle was known for 66 of 84 patients (Figure 1). Data were missing because of organizational problems for 33% of patients, because of the difficulty of carrying out chemotherapy and geriatric assessment on the same day. Forty percent of patients were dead. Baseline characteristics of the 84 patients with missing GDS-15 at the fourth cycle were compared in an exploratory analysis with those of patients with at least two GDS-15 measures. The 84 non-respondents were mostly men, with advanced disease and cancers with worst prognosis (data not shown). They had more cognitive impairment and poor performance status, which may explain missing data (data not shown).

In the study population, mean age was 77.6 years. Most patients were male (55.4%) and married (63.9%) (Table 1). Tumor sites included 44% digestive, 34% NHL, and 22% other types (bladder, ovary, and prostate). Sixty percent of patients had advanced cancer. Baseline CGA highlighted the following points (Table 2): Patients were mostly independent for ADL (83.1%) and without cognitive and mobility impairment. Only 37% had a good nutritional status (MNA > 23.5), and 27% had preserved instrumental activities of daily living. According to GDS-15 results at baseline, 120 (46.2%) patients had depressive symptoms before beginning chemotherapy. After four cycles, 116 (44.6%) had depressive symptoms, of whom 25% were not depressed at baseline. One hundred and eleven patients (42.7%) did not have depressive symptoms both before and during chemotherapy. Thirty-three patients (23.0%) had depressive symptoms at baseline and were no longer depressed during chemotherapy.

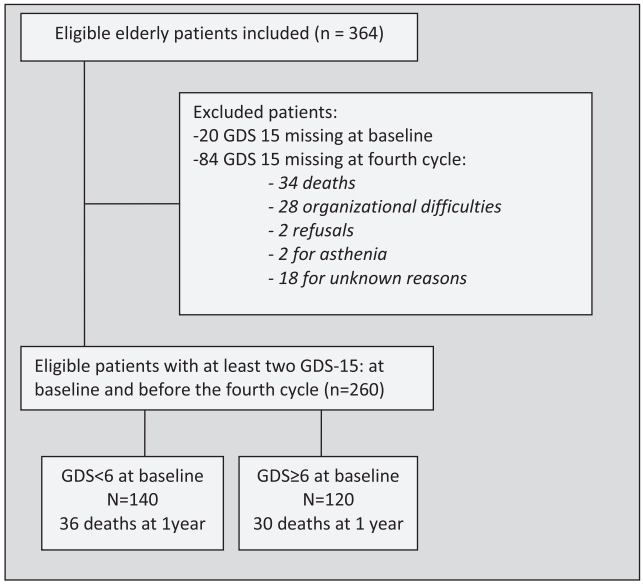

Figure 1. Patient inclusions in study investigating depressive symptoms in elderly during first-line chemotherapy

Patients with depressive symptoms at baseline were significantly older than those without ($p = 0.004$). They were most often women ($p < 0.001$), living alone ($p = 0.009$), single, widowed, or divorced ($p = 0.005$), and with lymphomas, cancers of the colon or pancreas ($p = 0.007$) (Table 1). Malnourished patients, dependent or with impaired mobility, were statistically ($p \leq 0.001$) more likely to be depressed at baseline (Table 2). Level of education, stage of cancer at diagnosis, type of treatment, and cognitive status did not have a significant effect on depression at baseline.

Older age, living alone, unmarried, women, ineffective chemotherapy, high GDS-15 at baseline, low MNA, low ADL, low MMSE, and slow TUG were significantly associated with a higher risk of depressive symptoms in univariate analysis and were selected for a multivariate logistic model. We found no associations between depressive symptoms during chemotherapy and education level, stage of disease at diagnosis, or toxicity of chemotherapy. In the final multiple model (Table 3) adjusted for age and sex, independent associated factors were as follows: GDS at baseline, MNA, living alone, and the effects of chemotherapy. In complete case analysis (195 patients), the presence of depressive symptoms at baseline (OR = 6.4, $p < 0.001$), poor nutritional status at baseline (OR = 6.2, $p = 0.03$), and living alone (OR = 2.31, $p = 0.03$) increased the risk of possible depressive symptomatology during chemotherapy. In contrast, an effective chemotherapy (i.e., partial or complete response) seemed to lower the risk (OR = 0.48, $p = 0.054$), but the result was of borderline statistical significance.

After multiple imputation, estimated parameters were similar for GDS-15 (OR = 6.93, $p < 0.001$) and MNA at baseline (OR = 5.54, $p = 0.02$). Living alone was no longer significantly associated with a higher risk for depressive symptomatology during treatment (OR = 1.44, $p = 0.262$), and effective chemotherapy became significantly associated with a lower risk (OR = 0.42, $p = 0.018$).

Discussion

The prospective multicenter cohort included patients aged ≥70 years, monitored during first-line chemotherapy, aiming to identify factors associated with depression during early chemotherapy. To our knowledge, no previous study on depression has covered this specific population group. The average age was high, almost 78 years, enabling an extrapolation of results to elderly cancer patients, for which there are limited published data.

Our population had various types of cancer, principally lymphomas and digestive tumors, and mostly presenting at an advanced stage at diagnosis. At baseline, most patients were malnourished or at risk of malnutrition, but independent for ADL and without cognitive or mobility impairment. We found that depressive symptoms were

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Table 1. Sociodemographic and clinical characteristics among 260 patients at baseline

	Total population		GDS < 6 at baseline		GDS ≥ 6 at baseline		
	n = 260 (%)		*n* = 140 (%)		*n* = 120 (%)		*p* value
Age, mean (SD)	77.6	(4.8)	76.9	(4.6)	78.5	(4.7)	0.004
Women (%)	116	(44.6)	49	(35.0)	67	(55.8)	<0.001
Living alone	77	(29.6)	32	(22.9)	45	(37.5)	0.009
Education level							0.314
Pre-primary	47	(18.1)	23	(16.4)	24	(20.0)	
Primary school certificate	130	(50.0)	69	(49.3)	61	(50.8)	
Secondary studies	56	(21.5)	29	(20.7)	27	(22.5)	
Higher studies	27	(10.4)	19	(13.6)	8	(6.7)	
Marital status							0.005
Single	10	(3.8)	3	(2.1)	7	(5.8)	
Married	166	(63.9)	103	(73.6)	63	(52.5)	
Widower	69	(26.5)	28	(20.0)	41	(34.2)	
Divorced	15	(5.8)	6	(4.3)	9	(7.5)	
Cancer site							0.007
Colon	69	(26.5)	33	(23.6)	36	(30.0)	
Stomach	34	(13.1)	23	(16.4)	11	(9.2)	
Pancreas	12	(4.6)	2	(1.4)	10	(8.3)	
NHL*	88	(33.9)	43	(30.7)	45	(37.5)	
Prostate	13	(5.0)	10	(7.1)	3	(2.5)	
Ovary	12	(4.6)	7	(5.0)	(5.0)	(4.2)	
Bladder	11	(4.2)	9	(6.4)	2	(1.6)	
Lung	17	(6.5)	12	(8.6)	5	(4.2)	
Unknown primary origin	4	(1.4)	1	(0.7)	3	(2.5)	
Performance index (WHO)							0.031
0–2	243	(93.5)	134	(95.7)	109	(90.8)	
3–4	14	(5.4)	3	(2.1)	11	(9.2)	
Missing data	3	(1.1)	3	(2.1)	0	(0.00)	
Advanced disease *n* = 256	156	(61.0)	80	(51.3)	76	(48.7)	0.065
Treatment							0.216
Standard	117	(45.0)	70	(50.0)	47	(39.2)	
Standard reduced	43	(16.5)	21	(15.0)	22	(18.3)	
Adapted	100	(38.5)	49	(35.0)	51	(42.5)	

GDS, Geriatric Depression Scale; NHL, non-Hodgkin's lymphoma; SD, standard deviation; WHO, World Health Organization.

common and persistent during chemotherapy: 45% of patients presented depressive symptoms, both at the beginning and at the fourth chemotherapy cycle. During chemotherapy, the depressive symptoms have disappeared in 23% of patient and appeared in 25%. Because we had no information on the previous history of depression of patients, we could not draw any conclusion regarding the nature (reactional, constitutional, or persistent depression) from these observations. In addition, no specific therapeutic option was proposed as part of the protocol, and the treatment for depression was left to the oncologist's or general practitioner's discretion.

Prevalence estimated in the literature is heterogeneous, and comparisons between studies are difficult. Several studies in prostate cancer using the 'Hospital Anxiety and Depression Scale' have reported prevalence rates ranging from 5% to 38% [17–19]. In ovarian tumors, the prevalence of depressive symptoms measured with the scale 'Center for Epidemiologic Studies Depression' (CES-D) was estimated at 21% [20], or 38% in the year following diagnosis, and 67.5% at 12 months in elderly cancer patients, or myocardial infarction, heart failure, and falls with injuries [21]. Kurtz *et al.* [22] studied depressive symptoms with the CES-D, in elderly patients with colorectal cancer, and estimated prevalence around 18%. We found a prevalence rate before treatment of 45% that remained high after four cycles of chemotherapy. Several reasons including the lack of diagnostic confirmation, the chosen GDS-15 threshold [23], the high rate of advanced cancers in our population, the recent diagnosis of cancer, or the concomitant chemotherapy could explain the higher prevalence of depression in our study. Advanced stage and early evaluation of depression after cancer diagnosis have been reported to be associated with higher prevalence of depression [24]. Several studies have shown that depressive symptoms tend to be higher at diagnosis or during treatment [25].

Depressive symptoms at baseline manifested more often in women, living alone, unmarried, dependent, and malnourished. In accordance with the literature, female gender [22], advanced cancer [26,27], unmarried status [28], and dependence on ADL [22] were significantly

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Table 2. Comprehensive Geriatric Assessment among 260 patients at baseline and depending on screening for depression by the GDS-15 (before chemotherapy)

Geriatric assessment	Total population		GDS < 6 at baseline		GDS ≥ 6 at baseline		*p* value
	n	(%)	*n* = 140	(%)	*n* = 120	(%)	
ADL	216	(83.1)	129	(92.1)	87	(72.5)	<0.001
Normal	44	(16.9)	11	(7.9)	33	(27.5)	
Abnormal							
IADL	70	(26.9)	51	(36.4)	19	(15.8)	<0.001
Normal	190	(73.1)	89	(63.6)	101	(84.2)	
Abnormal							
MMSE	218	(83.9)	122	(87.1)	96	(80.0)	0.146
Normal	42	(16.1)	18	(12.9)	24	(20.0)	
Abnormal							
MNA	97	(37.3)	74	(52.9)	23	(19.2)	<0.001
Normal	163	(62.7)	66	(47.1)	97	(80.8)	
Abnormal							
TUG	197	(75.8)	118	(84.3)	79	(65.8)	0.001
Normal	63	(24.2)	22	(15.7)	41	(34.2)	
Abnormal							

GDS, Geriatric Depression Scale; ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini-mental State Examination; MNA, Mini Nutritional Assessment; TUG, timed up and go test. [Normal scores: ADL = 6/6; IADL = 8/8; TUG <20 s; MMSE ≥24/30; GDS <6/15; MNA ≥24/30]

Table 3. Multivariate logistic regression – complete case analysis (*n* = 195) and analysis after multiple imputation (*n* = 344). Study of the association between patient and clinical characteristics and the risk of depression after the fourth cycle of chemotherapy

	Complete case analysis (*n* = 195)			Multiple imputation (*n* = 344)		
	OR	95%CI	*p*	OR	95%CI	*p*
Age (years)	1.03	0.95–1.11	0.440	1.04	0.97–1.12	0.165
Female	1.47	0.72–3.02	0.286	1.58	0.88–2.82	0.122
MNA>24: well nourished	1	—	0.027	1	—	
17 to 23.5: at risk of malnutrition	1.43	0.66–3.09		1.46	0.75–2.83	0.260
<17: malnourished	6.20	1.63–23.60		5.54	1.36–22.55	0.019
GDS at baseline	6.42	3.09–13.32	<0.001	6.93	2.74–17.50	<0.001
<6						
≥6/15						
Living alone	2.31	1.06–5.02	0.034	1.44	0.75–2.77	0.262
Ineffective chemotherapy	2.08	0.99–3.12	0.054	2.38	1.17–5.00	0.018

OR, odds ratio; CI, confidence interval; MNA, Mini Nutritional Assessment; GDS, Geriatric Depression Scale.

associated with depression during chemotherapy in univariate analysis. These results were not confirmed in the multivariate analysis, which identified the following independent factors, both in complete case analysis and after multiple imputation: depressive symptoms at baseline and poor nutritional status. Living alone was identified only in the full case analysis. Disease progression during chemotherapy was significantly associated with a higher risk of depression after multiple imputation. A causal relationship between chemotherapy and depressive symptoms could not be identified. A partial or complete response after chemotherapy was significantly associated with a lower risk of depression only after multiple imputation. The other demographical and clinical characteristics, such as advanced disease, ADL, TUG, MMSE, and chemotherapy toxicity showed no association with depression.

Malnutrition at baseline was identified as a risk factor for depressive symptoms during treatment. The role of nutritional status on depressive symptoms, and vice versa, is well described in the literature [29–31]. Our results highlight this link but fail to identify a causal relationship.

The screening of depression using the GDS-15 has been well validated in older patients [10,32,33] and in cancer patients receiving palliative care [34]. The lack of diagnostic confirmation and the low correlation between screening tests and psychiatric diagnosis are an important limitation [35]; nevertheless, the study of depression was not an objective of the pilot study. In addition, even though the GDS score may vary over time, we did not use regression to the mean, because of the dichotomous nature of this screening tool and the availability of only two measures. Missing data, especially for the GDS-15 at the fourth cycle, resulted in a reduced population in the final multivariate analysis. Of the initial 364 patients, the final complete case analysis model included 195

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patients. The reason for absent GDS was known for 66 of 84 patients, with early death (40%) and organizational problems (33%) as the main reasons. However, despite these missing data, the multiple imputation method is a real strength of this article, demonstrating the reliability of our results.

In conclusion, this work highlights the frequency of depressive symptoms during chemotherapy and the need to evaluate specific psychiatric intervention. These findings indicate that depressive symptoms and malnutrition at baseline are independent factors associated with depression during chemotherapy. These assessment scales (GDS-15 and MNA) are easy to complete and allow early detection of patients requiring nutritional management, psychiatric diagnosis, and specific treatment. Depressive symptoms at baseline should not be overlooked and considered only as an expected reaction to a cancer diagnosis. Furthermore, depressive symptoms can appear during chemotherapy and should be cautiously followed during treatment. The role of chemotherapy and treatment failure or success on depressive symptoms requires additional focused studies. For example, the next step could be to have a diagnostic confirmation by a psychiatrist and evaluate the effectiveness of specific interventions in this vulnerable and ever-growing population.

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Conflict of interest

The authors have declared no conflicts of interest.

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