Supportive Care in Cancer (2019) 27:3573–3581
https://doi.org/10.1007/s00520-019-4644-4

ORIGINAL ARTICLE

Impact of anxio-depressive symptoms and cognitive function on oral anticancer therapies adherence

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Received: 28 May 2018 / Accepted: 14 January 2019 / Published online: 28 January 2019

Abstract

Purpose Oral anticancer therapies have an important place in the therapeutic arsenal, but factors influencing adherence to oral treatment are poorly documented in oncology. The objective of this study was to assess the impact of anxio-depressive symptoms and cognitive functioning on oral medication adherence.

Methods This prospective study included cancer patients initiating a first oral therapy. Before initiation of treatment, an assessment of depression, anxiety, and cognition was performed. Using self-report questionnaires, we collected information on socio-demographic conditions and the non-adherence at 1 (M1) and 3 months (M3) after the beginning of treatment.

Results Among 129 patients enrolled, median age was 70 years and 81% of patients were treated for metastatic cancer. Before initiating treatment, 16% and 8% of patients presented respectively depression and anxiety symptoms. Global cognitive impairment was observed in 51% of patients. Ten percent of the patients were non-adherent at M1 and 13% at M3. Depression was strongly associated with non-adherence at M1 ($P = 0.046$) and M3 ($P = 0.014$), but not anxiety. Non-adherence was associated with lower working memory ($P = 0.037$) and digit memory ($P = 0.018$) at M1 and short-term memory ($P = 0.04$) at M3. Patients with more than eight co-medications were more often non-adherents ($P = 0.055$).

Conclusions Non-adherence to oral anticancer therapies was mainly associated to depression. Focusing on depressive symptoms before initiation of oral anticancer therapy could help to identify patient profiles more likely to fail self-management. Working memory, digit memory, and short-term memory also seem to play a role in non-adherence. Further studies should include a more specific population, especially according to age.

Keywords Adherence · Cancer · Depression · Anxiety · Cognitive function

Background

The incidence of cancer increased with an estimated 3.45 million new cases in Europe in 2012, partly because of the impact of screening, improvement of diagnostic and therapeutic practices, and the aging of the population [1]. Treatment options have expanded considerably with the increased use of oral anticancer therapy. Oral cytotoxic agents and more recently oral-targeted therapies are now an important part of the therapeutic arsenal in oncology [2–4]. The oral route is perceived as more convenient than the intravenous route because it improves patients' autonomy [5]. Patients with advanced stage particularly prefer this modality of treatment as long as similar efficacy can be guaranteed [6].

However, patient adherence to oral treatment can affect the effectiveness of therapies. Indeed, non-adherence can contribute to the variability observed in the treatment effect and give the impression of a lack of activity of the drug. This erroneous conclusion may lead to dosing errors, unnecessary alternative therapies, or even to suggest the end of therapeutic options [7]. There is also an impact on healthcare costs [8].

Adherence to oral treatment seems to be a complex behavior, with three main areas that may have an impact involving

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personal factors, treatment factors, and healthcare provider-related factors [7]. Moreover, there is no consensual definition of adherence even regarding the same methods [9]. In oncology, factors influencing adherence to oral treatment are poorly documented. It seems necessary to identify more precisely risk factors of non-adherence to oral treatment to judge the feasibility of initiating such therapy, especially as they are increasingly used in advanced cancers and in elderly subjects. Some studies have already highlighted the impact of depression and anxiety disorders on adherence to oral therapies [10–12]. Similarly, some studies have demonstrated that cognitive dysfunction can be induced by intravenous cancer chemotherapy [13, 14]. However, the relationship between identified cognitive disorders and oral anticancer treatment adherence remains poorly documented [10, 15]. Moreover, like the case for anxio-depressive symptoms, the few available data are mainly based on young women with adjuvant oral hormonal therapy in breast cancer.

We conducted a prospective study among a large population treated for all types of solid cancer including with new oral therapies and excluding adjuvant oral hormonal therapy in breast cancer. The aim was to evaluate the adherence to oral anticancer therapy at 1 and 3 months after treatment initiation and the link with anxio-depressive symptoms and cognitive functioning, in order to identify patient profiles more likely to be non-adherent.

Methods

Patients

Eligible patients were more than 18 years old, had a solid cancer, and were candidates for a first prescription of exclusive oral therapy (including new generation of hormonal agents used in prostate cancer, i.e., abiraterone acetate and enzalutamide) in Comprehensive Cancer Centre François Baclesse, Caen, France. Patients with primitive central nervous system cancer, symptomatic brain metastases, non-controlled psychiatric disorders, inability to perform cognitive tests, and documented alcohol or drug abuse were not included. Moreover, patients with hormonal therapy for breast cancer were excluded, as well as patients with adjuvant therapy. Written informed consent was obtained from all patients included. This trial was approved by a local ethics committee and French health authority (ID-RCB: 2011-A00907-34, ClinicalTrials.gov: NCT01597284) and was conducted according to the provisions of the Declaration of Helsinki.

Study design

Inclusion of patients initiating a first exclusive oral therapy in this prospective pilot study lasted from March 2012 to March 2016. At the time of the first prescription of oral therapy, information about patient characteristics (age, marital status, performance status, patients' relatives, and socio-professional level), concomitant treatments, and participation in a therapeutic education program on oral medication were collected.

Before initiation of treatment (M0), patients' anxiety, depression, and cognition were evaluated by a trained neuropsychologist with self-reported questionnaires and standardized neuropsychological tests. Neuropsychologists also have asked patient about their feeling on the clarity of the information received by the physician about the oral treatment. Non-adherence to oral therapy was assessed at 1 (M1) and 3 months (M3) after initiation (after follow-up medical visits) using two self-report questionnaires.

Measurements

Assessment of non-adherence to treatment

Non-adherence to therapy was evaluated by two self-report questionnaires. The first questionnaire indicated whether the patient had correctly observed treatment with one simple binary question: "since last month have you ever forget your treatment?", and if the answer was yes, it evaluated the number of omissions among three options (between 1 and 5 times, between 5 and 10 times, and more than 10 times). The second one, the standardized and validated French version of the Aids Clinical Trials Group (ACTG) questionnaire identified the most common causes of non-adherence in the last month with 12 items; each of them having 4-item self-report measures of adherence (never, rarely, sometimes, often) [16]. Moreover, a non-adherence sheet focusing on modalities of drug taking and on encountered difficulties was completed by the patient at M1 and M3. Any patient not taking treatment at least once during the last month was considered as non-adherent.

Assessment of depression and anxiety

The Center for Epidemiologic Studies Depression Scale (CES-D) [17] and the Spielberger State-Trait Anxiety Inventory (STAI-Trait) [18] were used to assess depression (score range 0–60) and anxiety (score range 0–80) respectively, with higher scores representing higher levels of depression or anxiety. Clinically significant symptoms of anxiety or depression were defined respectively by CES-D score ≥ 17 for men or ≥ 23 for women, and STAI score ≥ 56.

Assessment of cognition

A neuropsychologist performed a standardized test battery in a 30-min session based on a cognitive screening test and two tests corresponding to different cognitive domains (Table 1). The global cognitive status was assessed using the Montreal

Table 1 Neuropsychological tests grouped by principal cognitive domains

Cognitive domains	Test	Outcome variable	Score range
Global cognitive efficiency	MoCA	Total correct trials	0–30
Short-term memory	Delayed word recall		0–5
Visuospatial abilities and executive functions	Clock-drawing task, three-dimensional cube copy and alternation task		0–5
Naming	Three-item confrontation naming task		0–3
Language	Repetition of two complex sentences and aforementioned fluency task		0–3
Attention	Sustained attention task, serial subtraction task, and digits forward and backward		0–6
Orientation	Time and place		0–6
Abstraction	Two-item verbal abstraction task		0–2
Digit memory	WAIS-III		
Short-term memory	WAIS-III subtest: digit span forward	Total correct trials	0–16
Working memory	WAIS-III subtest: digit span backward	Total correct trials	0–14
Information processing speed	TMT A	Time to complete and number of errors	≥ 0
Executive function	TMT B	Time to complete and number of perseverative errors	≥ 0

MOCA, Montreal Cognitive Assessment; *WAIS*, Wechsler Adult Intelligence Scale; *TMT*, Trail Making Test

Cognitive assessment (MoCA) scored out of 30 points: mild cognitive impairment was defined by score < 26 [19]. This tool consists of several items to evaluate different domains: the short-term memory recall task, visuospatial abilities, executive functions, attention, concentration, language, and orientation to time and place.

Short-term memory and working memory performances were evaluated by the digit span of the Wechsler Adult Intelligence Scale (WAIS) III [20]. Digit memory, evaluated with the WAIS-III-combined digit span backward and forward. Executive functioning was measured with the part B of Trail Making Test (TMT), and processing speed with the part A of this tool [21].

Assessment of autonomy

For patients ≥ 65 years old, the Instrumental Activities of Daily Living (IADL) focusing on the ability to perform eight household tasks was used [22]. The global score, computed by adding the scores on the eight tasks, ranged from 0 to 8 in order to assess the functional abilities of older adults. Lower scores indicate greater autonomy.

Statistical analysis

The study was designed to control the α error risk of 0.05 with a power of 80%. Required sample size was estimated as 115 patients based on the following assumptions: 30% of patients without cognitive deficits representing two thirds of the study population, in order to highlight a 30% difference between the proportion of non-adherent patients according to the presence or not of cognitive disorders. Published normative data were used to convert patients' raw neuropsychological test scores into standardized scores (z scores; mean, 0; standard deviation (SD), 1). For patients who could not perform the test because of its difficulty, they were considered as having pathological scores. Descriptive statistics (relative frequency, mean value, and SD) were generated for the socio-demographic and clinical variables from the total population included in the trial. Comparison of means for sub-groups of patients was realized by Student's or Wilcoxon's tests as appropriate. Comparisons of the proportions of non-adherent patients according to their cognitive status or other baseline characteristics were performed using chi square or exact Fisher's test. Predictive relationships between patient characteristics, domains of cognitive function (MOCA score and its sub items of executive functions, attention, and short-term memory, WAIS III, TMT A and B), depression, anxiety, and autonomy at baseline and non-adherence data were estimated with univariate logistic regression models with results presented by odds ratio (OR) and their 95% confidence intervals (CI). All analyses were conducted using SAS (version 9.3).

Results

Patients' characteristics

A total of 129 patients were enrolled. Baseline demographic and clinical characteristics of all patients are presented in

Table 2 Baseline characteristics ($N = 129$ patients)

Baseline patients' characteristics	*N*	%
Median age, years (range)	70 (41–96)	
Male sex	78	60
Marital status		
Married/in couple	89	69
Widowed	19	15
Divorced	11	8
Single	10	8
Patient's living situation		
Not alone	87	69
Lives alone	39	31
Performance status		
ECOG 0–1	99	77
ECOG 2	22	17
ECOG 3	8	6
Education level		
Primary school	34	27
Middle school	43	33
High school	23	18
University	28	22
Medication		
Median co-medications number (range)	6.5 (0–15)	
Analgesic class II	20	16
Analgesic class III	13	10
Cancer disease		
Cancer type		
Renal cell	29	22.2
Lung	29	22.5
Prostate	24	19
Colorectal	17	13
Breast	16	12
Other	14	11
Presence of metastases	105	81
Prior anticancer therapies		
Surgery	51	40
Chemotherapy	48	37
Hormonal therapy	42	33
Radiotherapy	49	38
Actual therapy		
Study drug		
Targeted therapy	71	55
Chemotherapy alone	18	14
Chemoradiotherapy	16	12
New generation hormonal therapy	24	19
Information received about treatment		
Very clear	70	54
Clear	52	41
Moderately clear	4	3
Not clear at all	0	0
Missing data	3	2
Therapeutic education program on oral medication	34	26

ECOG, Eastern Cooperative Oncology Group

Table 2. Among the 129 participants, median age was 70 years, with 66% patients aged 65 years or older. Furthermore, 60% were male and 69% were married or living in couple. Only 6% of patients had performance status evaluated greater than 2 according to Eastern Cooperative Oncology Group (ECOG) and 40% were high school graduate or more. The number of concomitant medications ranged from 0 to 15 (median = 6.5) and 83% of the patients had more than three concomitant treatments while 37% had more than eight treatments. Classes II/III analgesics were used in 26% of patients. A large proportion of patients (81%) were treated for a metastatic disease. The most common cancer type included urological tumors (41.5%). Targeted therapies (55%) represented the majority of oral treatments. Almost all patients (95%) declared receiving clear information by the physician concerning oral treatment. One quarter of patients benefited from therapeutic education consultations.

Non-adherence outcomes

Flow chart of adherence assessments is presented in Fig. 1

At M1, assessment of non-adherence was available for 114 (88%) patients. Based on self-report questionnaires, 11 (10%) of them were non-adherent to their oral anticancer therapy. They reported between one and five treatment omissions during the previous month. The most common reasons given for missing doses of their anticancer medications, according to the ACTG questionnaire, were having simply forgotten or being sick. None of them related their omission to the excessive number of pills or any difficulties to take them, and only one of them wanted to avoid side effects.

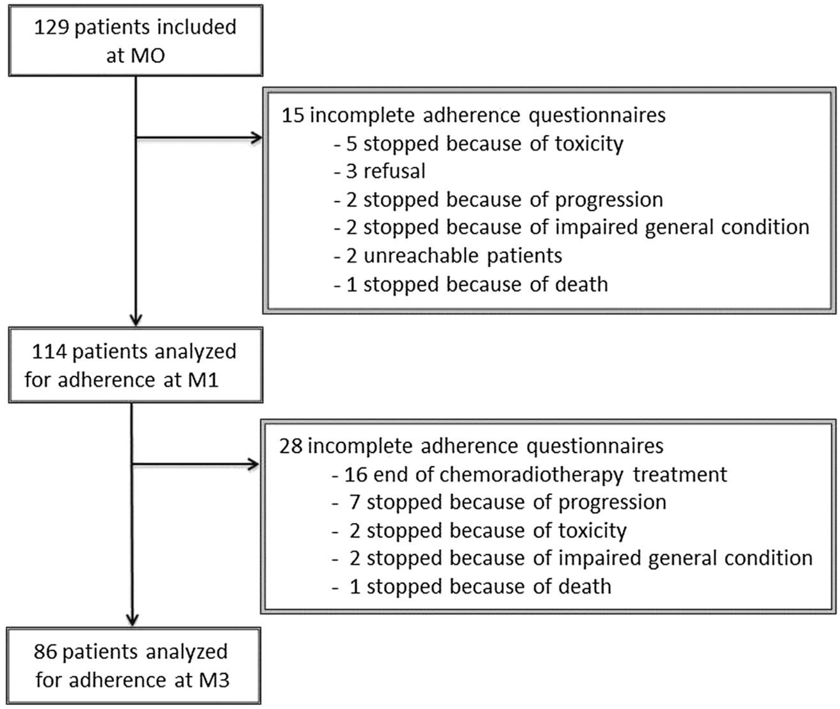
Adherence assessed at M3 was available for 86 (67%) patients, and 11 (13%) considered were non-adherent. Among the non-adherent, 4 were already non-adherent at M1. Moreover, when patients who performed both M1 and M3 assessments were combined, 84 patients were evaluable with 15 patients (18%) who were non-adherent.

Regarding these non-observant patients, the median age was 71 years with about 80% of patients with a status performance ≤ 1 and 27% living alone at the two-point assessment. Sex ratio, level of education, and participation to the therapeutic education program were similar to those of the all study population, exepted for the median number of concommitant medications which was higher (8 at M1 and 9 at M3). At M1, non-observant patients were mostly treated for kidney and colon cancers with 72% of metastatic disease versus mostly lung cancers at M3 and metastatic disease for all patients. Information received by the physician about the treatment was considered clear in more than 85% of cases.

Anxio-depressive outcomes

Details of the results of analyzable patients for adherence ($N = 114$) are provided in Table 3. Among these patients, 16% and 8% of them presented respectively depressive or anxiety symptoms, knowing that only 10% had reported a history of anxiodepressive disorder. No association was found between anxio-depressive symptoms and age.

Fig. 1. Flow chart of adherence assessment



Cognition outcomes

Table 3 shows patient performances on each of the neuropsychological tests. Before starting the oral therapy, global cognitive impairment, assessed with the MoCA, was observed in 51% patients. Digit memory disorders were identified in 11% of patients. Eight participants were not able to realize the TMT B (executive function). Pathological scores were noted for 19% and 25% patients for the time and perseverative errors scores, respectively. As for information processing speed, TMT A scores were respectively altered in 5% and 19% of patients concerning the time and errors.

We found a positive association between working memory and MoCA score ($P < 0.0001$). Similarly, we found a positive association between age (continuous) and an impaired MoCA score ($P = 0.0493$). As compared to younger patients, more than 70-year-old patients had an almost threefold increased odds of impaired MoCA score [OR (95% CI) 2.95 (1.40–6.31); $P = 0.0048$]. A positive association was found between age (continuous) and working memory score ($P = 0.0029$). When comparing patients less than 70 years old to older ones, working memory impairment appeared more pronounced for elderly ($P = 0.0014$).

Autonomy outcomes

Autonomy was assessed for 62% patients over 65 years: mean score was 4.12 (SD = 4.03).

Factors associated with non-adherence (Table 4)

Depression was strongly associated with non-adherence at M1 [OR (95% CI), 4.13 (1.02–16.69); $P = 0.046$] and at M3 [OR (95% CI), 5.58 (1.41–22.03); $P = 0.014$] respectively. Anxiety did not emerge as a risk factor at M1 or M3.

Concerning cognitive disorders, even if the overall MOCA score was not associated with non-adherence, we observed a link between the short-term memory sub-test and non-adherence at M3 [OR (95% CI), 1.51 (1.01–2.26); $P = 0.04$]. We also found a relation between non-adherence and declined score of digit memory [OR (95% CI), 2.13 (1.14–3.97); $P = 0.018$] and working memory [OR (95% CI), 1.37 (1.02–1.83); $P = 0.037$], both at M1.

A number of concomitant medications greater than eight appeared to have an impact on adherence, at M1 and M3 ($P = 0.055$). Age, sex, education level, marital status, living situation, and performance status as well as the types of cancer or the therapy received were not significantly associated with medication adherence.

Conclusions

This prospective study investigated the relationship between anxio-depressive symptoms and cognitive functioning and non-adherence of patients treated with a first oral anticancer therapy including chemotherapy, targeted therapies, and prostate new generation hormonal therapy. More than half of the patients were over 70 years. Only 10% of patients were non-

Table 3 Anxio-depressive, neuropsychological, and autonomy baseline outcomes ($N = 114$ patients)

Cognitive domain and test	*N*	Score Mean (SD)	Z scores Mean (SD)	Pathological score *N* (%)
depression				
CES-D (/60)	114	13.11 (8.08)		18 (16)
Anxiety				
STAI-Trait (/80)	114	36.35 (12.24)		9 (8)
Mild cognitive dysfunction				
MoCA	114	24.98 (3.65)		58 (51)
Digit memory				
WAIS-III	114		− 0.36 (1.07)	13 (11)
Short term memory				
WAIS-III subtest: digit span forward	114	8.30 (2.064)		
Working memory				
WAIS-III subtest: digit span backward	114	4.81 (1.92)		
Information processing speed				
TMT A time	114	47.24 (19.92)	− 0.14 (0.81)	5 (5)
TMT A errors	114	0.29 (0.64)	0.76 (2.37)	21 (19)
Executive function				
TMT B time	106*	138.27 (72.59)	0.30 (1.23)	22/114 (19)
TMT B perseverative errors	106*	0.57 (1.01)	0.66 (1.82)	28/114 (25)
Autonomy				
IADL (/8)	71**	4.12 (4.03)		

CES-D, Center for Epidemiologic Studies Depression Scale; *STAI-Trait*, Spielberger State-Trait Anxiety Inventory; *MoCA*, Montreal Cognitive Assessment; *WAIS*, Wechsler Adult Intelligence Scale; *TMT*, Trail Making Test; IADL, Instrumental Activities of Daily Living; *SD*, standard deviation. *8 patients did not perform the test because of its difficulty. These patients had been classified with a pathological score**43 patients/114 under 65 years, with no assessment of autonomy by IADL

adherent after 1 month of treatment and 13% after 3 months. There was a significant negative association between depression and non-adherence. Furthermore, a positive association between cognitive function (working memory, digit memory, and short-term memory) and adherence was observed. The number of concomitant medications was also closely related to non-adherence.

Very few data are available in oncology about the risk factors of non-adherence, especially for targeted therapies and new generation of hormonal therapy.

Our study suggests a strong relationship between depressive symptoms and non-adherence. The results of some other studies are also in favor of a significant relationship between depression and adherence. However, these studies focused on adjuvant hormone therapy for breast cancer among young women, with a mean age was around 55 years [10–12]. Our study is therefore the first one to prospectively focus on the impact of depression on adherence in an older population treated for cancers of all types at fairly advanced stages. This psychological factor can be managed and controlled, making it a very interesting target to improve adherence to oral therapies. Indeed, effective management of depressive symptoms before starting oral anticancer therapies may help in treatment adherence. Depression is prevalent and often underestimated in older age. The prevalence of depression in older age ranges from 10 to 20% [23] and can promote accelerated cognitive impairment and disability in this population [24]. A comprehensive geriatric oncology consultation is commonly proposed when decision on oral cancer treatment for elderly patients seems difficult, with a significant impact on decision [25, 26]. Depression should be systematically evaluated during these consultations, and more generally before starting oral therapy whatever the age, to detect disorders that could impact on oral treatment adherence.

Cognitive dysfunction has already been reported to be an important risk factor of non-adherence in other non-cancer areas. Indeed, deficits in working memory, but also in attention flexibility, have been recognized as mainly implicated in non-adherence among patients receiving oral treatment for diabetes, dyslipidemia, or menopause [27].

We found 51% of the patients with mild global cognitive impairment detected by the MoCA. One of the cognitive domains significantly impacting adherence was working memory. It refers to systems that are assumed to be necessary in order to keep things in mind while performing complex tasks such as reasoning, comprehension, and learning [28].

Table 4 Univariate odds ratio of non-adherence

	M1 evaluation (N = 114) OR (95% CI)	Evaluation at M3 (N = 86) OR (95% CI)
Depression		
CES-D < 17 (men) or 26 (women)	1.0	1.0
CES-D ≥ 17 (men) or 23 (women)	**4.13 (1.02–16.69)***	**5.58 (1.41–22.03)***
Anxiety		
STAI-Trait < 56	1.0	1.0
STAI-Trait ≥ 56	1.19 (0.13–10.49)	1.15 (0.13–10.57)
Mild cognitive impairment		
MoCA ≥ 26	1.0	1.0
MoCA < 26	0.52 (0.14–1.88)	0.94 (0.26–3.36)
Short-term memory sub-test (MoCA)	0.99 (0.68–1.44)	**1.51 (1.01–2.26)***
Attention sub-test (MoCA)	0.94 (0.56–1.58)	1.12 (0.71–1.76)
Executive function sub-test (MoCA)	0.75 (0.40–1.42)	0.70 (0.37–1.33)
Digit memory	**2.13 (1.14–3.97)***	1.21 (0.66–2.22)
Short term memory	1.20 (0.89–1.64)	0.89 (0.64–1.23)
Working memory	**1.37 (1.02–1.83)***	1.03 (0.72–1.46)
Information processing speed		
TMT A time (*Z*-score)	1.04 (0.48–2.22)	1.41 (0.60–3.31)
TMT A errors (*Z*-score)	NE	0.79 (0.46–1.35)
Executive function		
TMT B time (*Z*-score)	1.03 (0.63–1.7)	1.58 (0.95–2.64)
TMT B errors (*Z*-score)	1.02 (0.73–1.42)	1.05 (0.67–1.63)
IADL	1.08 (0.67–1.74)	1.19 (0.77–1.82)
Number of co-medication	1.04 (0.88–1.23)	1.13 (0.95–1.35)
Co-medication ≤ 8	1.0	1.0
Co-medication > 8	3.37 (0.92–12.34)	3.98 (0.97–16.28)
Grade II/III analgesics		
No	1.0	1.0
Yes	1.44 (0.29–7.12)	1.03 (0.25–4.28)

OR, odds ratio; *CI*, confidence interval; *CES-D*, Center for Epidemiologic Studies Depression Scale; *STAI-Trait*, Spielberger State-Trait Anxiety Inventory; *MoCA*, Montreal Cognitive Assessment; *TMT*, Trail Making Test; *IADL*, Instrumental Activities of Daily Living; *NE*, not estimable

*$P < 0.05$

Alteration of working memory induces daily difficulties in the temporary maintenance of memory and manipulation of information during short periods and when carrying out activity. In comparison with the working memory test, the MoCA is a screening tool and remains maybe too general. However, we observed that the short-term memory assessed by the delayed word recall of the MOCA test was related to non-adherence. Moreover, there is also a link between digit memory of the WAIS-III and non-adherence.

In our investigation, age was significantly correlated with global cognitive and working memory impairment and more especially for patients of 70 years or more but age was not associated to treatment adherence. Nevertheless, several studies among adults with human immunodeficiency virus have shown that older participants who were cognitively impaired had disproportionate difficulty in adequately adhering to their medication regimen [29, 30]. Indeed, our findings suggest that age strongly impacts on cognitive function. Appropriate tests in the elderly population are needed to identify patient profiles who are more likely to fail self-management of oral anticancer therapy.

We also found a relationship between number of concomitant medications age-adjusted higher than eight and non-adherence. This result is consistent with previous studies in digestive oncology and hematology which found a negative impact of the number of co-medication on non-adherence [31, 32].

The percentage of non-adherent patients in our study may be underestimated because of the declarative and therefore subjective nature of this information collected by self-report questionnaires. Although various methods for measuring adherence are available, there is no gold standard, and self-reporting is the most widely used, notably in routine clinical practice because of its low cost, simplicity, and real-time feedback [8, 9, 33]. Moreover, half of the patients had mild cognitive impairment, which may induce a lack of insight to acknowledge to remember medication omission.

In our study, adherence assessment was made at 1 and 3 months. This early assessment may overestimate the proportion of adherent patients. It would be interesting to compare these results with longer-term assessment of adherence. Nevertheless, another study assessing adjuvant oral hormonotherapy adherence in breast cancer patients found similar non-adherence rate (14%) [15]. In the latest study, the adherence was assessed every 6 months, and patients were considered as adherent if they followed the treatment at least 4 years (≥ 80% of their expected time on therapy), which is a long period of follow-up. Our adherence rate at 1 and 3 months are therefore not so low in comparison with these long-term data and would certainly be higher on a new evaluation few months later. Nevertheless, our population had advanced cancer and several subsequent lines of treatment, for which oral therapy is often discontinued after a few months for progression or deterioration of the general condition. Finally, one quarter of patients were involved in the therapeutic education program that could increase the number of adherent patients. Indeed, in the Comprehensive Cancer Centre where the study was conducted, in addition to the explanations given by the doctor, a therapeutic education session is proposed before the implementation of an oral treatment.

Our study may have insufficient statistical power to show a robust association between domains of cognition and non-adherence. It would be interesting to conduct a similar study with a patient sample most important, especially regarding to age, such as a study specifically in elderly patients. Furthermore, accordingly, our study was monocentric, conducting a multicenter and prospective study with a large population would support our results. These results could have important clinical implications, especially with the assessment of depression in clinical practice before the initiation of oral treatment, for example, from a short self-report questionnaire such as the Hospital Anxiety and Depression Scale (HADS) or CES-D, not only in elderly patients during the comprehensive geriatric assessment. In the presence of depressive symptoms, the pre-therapy management might allow adequate adherence to oral treatments. Besides, we have only assess cognition before oral treatment initiation. The evolution of cognitive disorders could be interesting to assess and more specifically according to the fact that some cancer treatment could induced cognitive decline, especially in older patients [34]. The evolution of co-medication would also have been interesting and could be included in future studies.

Depression seems to play an important role on adherence. The impact of psychological factors must not be neglected. Indeed, special attention including a systematic short screening for depression before the initiation of oral therapy should be considered whatever the age of the patient to detect risk of non-adherence and therefore to implement an additional support and help decision-making. Impaired cognitive functions and especially working memory, digit memory, and short-term memory also appear to be risk factors for non-adherence and may be important to detect before starting oral therapy, especially among elderly population.

Acknowledgments The authors would like to thank all patients who generously participated in this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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