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Effects of Sertraline on Executive Function and Quality of Life in Patients with Advanced Cancer

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Background: The aim of this study was to investigate effects of the antidepressant sertraline on executive function and quality of life in patients with advanced cancer.





Material/Methods: We assigned 122 patients with stage III or IV cancer to the depressed group (DG, n=86) or the non-depressed group (NG, n=36). All subjects were given supportive treatment and patients in the DG received additional antidepressant treatment.

Results: There were significant differences in total scores of the Hamilton anxiety scale (HAMA) and the Hamilton depression scale (HAMD), performance in the Wisconsin card sorting test, and SF-36 domains. After antidepressant treatment, the level of depression and anxiety decreased significantly in the DG, but was still significantly higher than in the NG. Low executive function was enhanced in the DG, but a worsening executive function was found in total errors in the NG (-2.3 ± 3.8) ($P < 0.05$). The dimensions of SF-36 in physical functioning (PF), role limitations-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations-emotional (RE), and mental health (MH) were decreased significantly at baseline in the DG compared to the NG ($P < 0.01$). After 12-week Sertraline treatment, improvement in the DG in factors VT, SF, RE, and MH were more powerful than in the NG ($P < 0.05$). HAMA, HAMD, and VAS scores and tumor stage were significantly correlated to any one dimension of quality of life.

Conclusions: Depression is an important cause of decreased quality of life and executive function in patients with advanced cancer. The antidepressant sertraline can improve the executive function and quality of life, which may be helpful in the clinical practice of cancer treatment.

MeSH Keywords: **Depression • Executive Function • Pain Clinics • Quality of Life**

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Background

Almost all cancers are in various degrees associated with mood problems such as anxiety and depression [1,2]. Mood disorders can affect cognitive functions and severely impair cancer patient quality of life [3]. Cognitive disorders, including language abilities [4], memory [5], attention [6], speed of information processing [4], and executive function [7,8], can be seen in advanced cancer patients. The main causes of cognitive impairment in advanced cancer patients are still unclear, and may be associated with depression [9], as well as chemotherapy drugs and cancer itself [10]. Recognizing cognitive impairment and depressive symptoms and understanding their relationship with other factors is essential [11], for it determines clinical management of cancer. Sertraline hydrochloride, an antidepressant, has a clear clinical effect in improving depressive symptoms and cognitive impairment [12]. The study improved depressive symptoms of advanced cancer patients with sertraline, and re-evaluated executive function and the quality of life after depressive symptoms were improved, providing scientific evidence for comprehensive treatment of advanced cancer.

Material and Methods

Participants

From June 2010 to June 2013 122 diagnosed stage III or IV cancer patients in 3 centers (First Affiliated Hospital of Zhejiang University, Zhejiang Hospital of Oncology, and Shanxi Hospital of Oncology) were enrolled in the study. All patients were divided into 2 groups after Hospital Anxiety and Depression (HAD) scale assessment: the depressive group (HAD total score ≥ 11 , $n=86$), and the non-depressive group (HAD total score < 11 , $n=36$). The demographic and disease-related baseline characteristics are shown in Table 1. The inclusion criteria were: 1) malignant tumor diagnosis; 2) expected more than 3-month survival; 3) cooperative in cognitive evaluation and providing consent; and 4) no past history of psychiatric disorders. Exclusion criteria were: 1) dementia and cognitive disorders; 2) disorders of consciousness; 3) brain tumors and brain metastatic tumors; 4) severe organ dysfunction (brain natriuretic peptide, liver function and renal function values exceeds twice the upper limit of normal range); 5) on anti-depressants; and 6) over 80 years old. All participants and their guardians provided informed consent for the study and signed a written informed consent form.

Design and processing

This was an open perspective study with 2 follow-ups, which happened at baseline and endpoint, and the total follow-up period was 12 weeks. At baseline, patient screening, confirming diagnosis, physical examination, electric cardiograph, cranial computed

tomography or magnetic resonance imaging, and other associated laboratory tests (routine blood test, biochemical blood test, BNP, thyroid function, and tumor markers) were done. The 122 patients who met the criteria underwent HAD assessment and were divided into 2 groups (the dividing line was a total score of 14, with a higher score indicating a more severe state of depression). During the follow-up period, the depression group was given sertraline hydrochloride (brand name Zoloft, provided by Pfizer Pharmaceuticals Limited), a selective serotonin reuptake receptor inhibitor, at a dose of 25–75 mg/d, which was increased to an effective therapeutic level at 2 weeks after the beginning of the treatment. The 2 groups of patients underwent mainly supportive care under the same circumstances. During the treatment, medications that have a potential effect in cognitive functions were not allowed to be used for more than 3 days. At endpoint, 3 trained clinical staff evaluated anxiety, depression, executive function, and quality of life. Before formal evaluation began, staff were trained, performance was standardized, and internal consistency testing was done, with a κ value of 0.81.

Evaluation scale

Anxiety and depression was evaluated with the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAM-D) 17-item version. Executive function was evaluated with the Wisconsin Card Sorting Test (WCST). Quality of life was evaluated with the Short Form 36 (SF-36) Chinese version. Pain was measured with a 0–10 visual analogue scale.

WCST is a classical test in executive function testing, and showed remarkable validity and reliability in various studies [13,14]. The evaluation markers include: 1) Total Errors (TE); 2) Perseverative Errors (PE); 3) Non-perseverative Errors (NPE), 4) Categories Achieved (CA), and 5) Failure to Maintain Set (FMS), $FMS = \text{number of withdrawn participants} / \text{total participants} \times 100$. The evaluation of analysis of WCST was conducted by computer software.

SF-36 has good validity and reliability [15], and a Chinese norm has been established [16,17]. It has been widely used in studying the quality of life in cancer patients [18–20]. The SF-36 includes a total of 8 dimensions: Physical Functioning (PF), Role limitations-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role limitations-Emotional (RE), and Mental Health (MH). The original score was transformed into a standard score using the formula: $(\text{original score} - \text{the lowest possible score}) / \text{the possible score range} \times 100$. The standard score of each dimension ranges from 0 to 100, with a higher score indicating a better state of health.

Statistical analysis

All data were input into the computer and processed with SPSS 15.0 for Windows. Means were compared using t-test, rates

Table 1. Demographic and disease-related baseline characteristics.

	Depression group (n=86)	Non-depressive group (n=36)		P	
Gender (male: female)	45: 41	20: 16	$\chi^2=0.11$	0.75	
Age (years)	59.6±12.2	61.7±13.5	t=0.84	0.40	
Years of education (years)	10.8±4.5	12.4±5.1	t=1.72	0.09	
BMI (Kg/m ²)	18.6±3.2	20.4±3.5	t=2.76	<0.01	
Smoking (%)	43 (50.0)	17 (47.2)	$\chi^2=0.08$	0.78	
Drinking (%)	57 (66.3)	21 (61.1)	$\chi^2=0.70$	0.41	
Coffee consumption (%)	32 (37.2)	14 (38.9)	$\chi^2=0.03$	0.86	
Tumor duration (years)	2.5±1.4	2.7±1.5	t=0.70	0.48	
Tumor stage (III: IV)	35: 51	16: 20	t=0.94	0.35	
Surgical operation (%)	32 (37.2)	11 (30.6)	$\chi^2=1.83$	0.07	
Radio- and chemo-therapy (%)	75 (87.2)	30 (83.3)	$\chi^2=0.12$	0.73	
Tumor location	Gastrointestinal system (%)	38 (44.2)	17 (47.2)	$\chi^2=0.86$	0.84
	Respiratory system (%)	22 (25.6)	9 (25.0)		
	Hemopoietic system (%)	14 (16.3)	7 (19.4)		
	Others (%)	12 (14.0)	3 (8.3)		
HAD total score	24.2±5.6	10.5±3.2	t=17.04	<0.01	
Pain score	7.4±2.5	6.8±2.3	t=1.24	0.22	

or proportions were compared using chi-square test or Fisher exact test, and the correlations between quality of life and other variables were analyzed using multiple regression analysis. P<0.05 means the difference has statistical significance.

Results

Demographic and disease-related characteristics

As shown in Table 1, two groups of patients showed no significant differences in gender, age, years of education, tobacco use, alcohol and coffee consumption, tumor location and stage, proportion of surgical operation, and proportion and duration of chemo- and radio-therapy. However, the body mass index (BMI) difference between the 2 groups reached statistical significance (t=2.76, p<0.01) and the HAD score difference between the 2 groups also had a statistical significance (t=17.04, p<0.01).

Comparison of anxiety and depression scores

At baseline, the HAMA and HAMD scores of the depression group were 25.6±6.5, 27.4±5.4, respectively; the HAMA and HAMD scores of the non-depressive group were 10.6±4.2, 9.7±2.1, respectively. At endpoint, HAMA and HAMD score of

the depression group were 12.5±4.0, 14.6±5.3; and HAMA and HAMD score of non-depressive group were 10.4±4.5, 10.3±3.5, respectively. At baseline, the anxiety and depression scores were statistically different between the 2 groups (t=12.76 and t=19.05, respectively, both p<0.01). At endpoint, the anxiety and depression scores were still significantly different (t=2.37 and t=4.15, respectively, both p<0.05).

WCST result comparison

Table 2 shows that at baseline there was no statistically significant difference in FMS (p>0.05), but there were statistically significant differences in all other markers, including TE, PE, NPE, and CA (p<0.01). After 12 weeks of anti-depression treatment, the depression symptoms in the depression group improved; therefore, WCST performance also improved. At endpoint, the WCST performance in the 2 groups had no significant difference. Comparing TE in the depression group before and after the treatment, it improved (12.1±4.5) points, but in the non-depressive group it declined (-2.3±3.8) points. Compared to the non-depressive group, the improvement of performance in depression group most benefitted from the improvement in PE (10.8±3.7 vs. -2.4±3.5), whereas the most important reason for the decline in the non-depressive group was probably the significant increase in NPE (-8.1±4.7 vs. 1.7±4.2), and both differences reached statistical significance (p<0.05).

Table 2. Comparison of the WCST.

	TE	PE	NPE	CA	FMS
Baseline					
Depression group	54.8±24.3	31.6±12.3	22.0±10.2	4.2±1.1	1.1±1.2
Non-depressive group	38.6±17.8	15.2±9.5	13.4±11.7	3.5±1.3	0.8±1.1
<i>t</i>	3.61	7.15	4.06	3.04	1.29
<i>P</i>	<0.01	<0.01	<0.01	<0.01	0.20
Endpoint					
Depression group	41.2±20.1	21.5±11.7	20.1±10.6	3.6±1.2	0.9±1.0
Non-depressive group	40.5±22.4	17.6±10.2	22.7±15.4	3.4±1.1	0.8±1.0
<i>t</i>	0.16	1.62	1.00	0.80	0.47
<i>P</i>	0.87	0.11	0.32	0.43	0.64

Table 3. Comparison of the SF-36 scale scores.

	Depression group		Non-depressive group	
	Baseline (n=86)	Endpoint (n=75)	Baseline (n=36)	Endpoint (n=31)
PF	60.7±17.8	68.5±19.1 ^{##}	70.3±18.4 ^{**}	72.2±20.6
RP	61.5±26.3	64.3±30.6 ^{##}	61.9±30.3 ^{**}	60.5±33.5
BP	50.7±17.3	65.2±19.8 ^{##}	63.2±17.2 ^{**}	66.9±20.2
GH	31.4±13.6	36.6±19.2 [#]	52.0±19.0 ^{**}	50.1±21.3 ^{**}
VT	21.7±10.2	42.1±20.1 ^{##}	55.1±19.2 ^{**}	47.3±17.8
SF	33.7±10.0	62.3±17.4 ^{##}	69.5±17.4 ^{**}	58.2±19.6
RE	30.2±22.3	56.5±28.2 ^{##}	62.9±34.3 ^{**}	54.1±30.1
MH	25.3±10.2	50.7±20.8 ^{##}	58.6±16.6 ^{**}	53.8±19.8

t-test, # *P*<0.05; ## *P*<0.01, comparison within the same group before and after the treatment; ** *P*<0.01, comparison across the groups at the same time point.

Comparison of the quality of life

It can be seen from Table 3 that at baseline, compared to non-depressive group, the depression group's quality of life in all dimensions, including PF, RP, BP, GH, VT, SF, RE, and MH, were significantly lower (*p*<0.01). After 12 weeks of anti-depression and supportive treatment, 8 dimensions of quality of life in the depression group significantly increased (*p*<0.05). Except for GH, the other 7 markers reached the non-depressive group's level. In the non-depressive group, there was no significant change before or after the treatment.

Multiple regression analysis

To analyze the correlation between various factors and the quality of life, we merged all the data together, and made the 8 dimensions of quality of life dependant variables; general

information, anxiety and depression scores, and tumor stage were made independent variables; and then we performed a multiple regression analysis. Table 4 shows that the change in quality of life in advanced cancer patients has little relationship with age, gender, years of education, BMI, smoking, drinking, coffee consumption, or the type of cancer, but was associated with anxiety and depression score, pain degree, and tumor stage.

Discussion

As the Chinese population ages, cancer has become one of the biggest killers of middle-aged and elderly people. Depressive symptoms in cancer patients are common, and Massie et al. showed that 38% of hospitalized cancer patients reached the diagnostic criteria, and 58% of the patients had depressive

Table 4. The relationship between quality of life and various in the study population (beta values).

	PF	RP	BP	GH	VT	SF	RE	MH
Age	0.08	0.09	0.03	0.13	0.08	0.05	0.07	0.12
Gender	0.03	0.07	0.06	0.10	0.13	0.05	0.04	0.06
Years of education	0.14	0.07	0.11	0.09	0.05	0.08	0.13	0.05
BMI	-0.13	-0.14	-0.05	-0.17	-0.16	-0.08	-0.12	-0.07
Smoking	-0.03	-0.06	-0.11	-0.13	-0.14	-0.06	-0.12	-0.10
Drinking	-0.11	-0.04	-0.12	-0.13	-0.09	-0.07	-0.05	-0.12
Coffee consumption	0.10	0.13	0.09	0.07	0.12	0.04	0.05	0.11
HAMA score change	0.59*	0.71*	0.82**	0.93**	0.48*	0.74*	0.59*	0.49*
HAMD score change	0.57*	0.11	0.55*	0.30	0.67*	0.26	0.56*	0.47*
Pain degree change	0.68*	0.83**	0.90**	0.76*	0.54*	0.66*	0.71*	0.67*
Tumor stage	0.60*	0.76**	0.45*	0.91**	0.65*	0.70*	0.52*	0.41
Tumor type	0.16	0.03	0.17	0.15	0.08	0.24	0.07	0.13
R ²	0.79	0.92	0.71	0.62	0.85	0.66	0.87	0.83
F	101.33	140.35	106.40	90.21	124.50	94.37	132.51	115.26
P	0.62	0.00	0.00	0.00	0.00	0.00	0.00	0.00

t-test, * P<0.05; ** P<0.01.

symptoms [21]. The existence of depressive symptoms exacerbates patient cognitive impairment and quality of life. This study aimed to explore the impact of anxiety and depression on executive function and quality of life in cancer patients, and to analyze the main factors influencing quality of life, thus contributing to better treatment of advanced cancer. In this study, a total of 122 cancer patients were enrolled, and the 2 groups of patients showed no significant difference in gender, age, years of education, tobacco use, drinking alcohol, coffee consumption, and tumor location, stage, and time since diagnosis at baseline ($p>0.05$), thus making 2 groups equivalent. We found that the comorbidity rate of advanced cancer and major depressive disorder can be as high as 70.5% (slightly higher than in Massie's report), which may be because the participants we enrolled were all stage III or IV advanced cancer patients, or due to differences in evaluation tools. At baseline, the BMI of the depression group is significantly lower than in the non-depressive group, which may suggest that depression worsens physical function [22], or depression itself results in weight loss [23,24]. Depression also may indirectly promote cancer progression and cause weight loss [25].

Sertraline is a first-line SSRI anti-depressant with definite therapeutic effect and improves cognitive function [26] and pain [27]. The mechanism is to inhibit the reuptake of serotonin on the presynaptic membrane to increase the function

of monoamine neurotransmitters. In this study, we gave patients the dose of 25–75 mg/d. Advanced cancer patients are generally weak and on multiple medications, but this dose range is enough to have therapeutic effects, and at the same time does not increase the risk of adverse events. In this study, after 12 weeks of sertraline treatment, HAMA and HAMD scores in the depression group greatly decreased, further proving its therapeutic effects. From the results, after 12-week anti-depressive and supportive treatment, although anxiety and depression scores greatly declined, they were still higher than in the non-depressive group at endpoint, and the difference was statistically significant ($p<0.01$). This shows that depression in comorbidity with cancer needs long-term medical treatment, but also shows that the mechanism of depression in cancer patients is complicated and cannot be attributed solely to reduction of monoamine neurotransmitters. In addition, the effect of sertraline in improving depression is somewhat limited, with an effective rate of approximately 60–80% [28]. The anxiety and depression scores in the depressive group was still higher than in the non-depressive group after the treatment due to 2 reasons: 1) the treatment regimen for depressive disorders is relatively long, usually 1–3 years, but in this study the regimen was only 12 weeks; and 2) depression in comorbidity with cancer may have a different etiology from that of common depression [29] and needs further study.

Executive function is an important higher-level cognitive function, which is a cognitive psychological process that integrates and coordinates different cognitive processes for a special purpose. The significant impact cognitive dysfunction has on cancer patients' work, study, and social activities has drawn great attention. WCST is widely used in cognitive evaluation in depressive state, not only because it reveals the executive function of frontal lobe, but also because it helps predict the severity [30], recurrence, and symptoms of depressive state [31]. This study used WCST to test abstract thinking ability such as categorization and ranking. The results showed that at baseline the 2 groups had significant difference in TE, PE, NPE, and CA ($p < 0.01$) and no difference in FMS ($p > 0.05$). After 12 weeks of anti-depressant treatment, the depression group improved in depressive symptoms and WCST performance, among which TE improved (12.1 ± 4.5) points, but in the non-depressive group it declined (2.3 ± 3.8) points. This shows that in advanced cancer patients executive function worsens, especially in those with depressive symptoms. The tumor itself can cause a decline in executive functions, but the depressive state is the main reason. There has been a long debate about whether cognitive dysfunction in cancer patients is a trait or a state. In this study, the depression group had improved symptoms, executive functions, and quality of life, suggesting the characteristics of a state. At endpoint, the executive function had not recovered to the non-depressive group's level, but it should not be concluded that it is a trait, because depressive symptoms were not totally relieved. Thus, this study tends to support the conclusion that cancer patient cognitive impairment is caused more by the accompanying depression. Clinical practitioners should pay more

attention to evaluation of patient mood. Early evaluation improves patient quality of life, as well as cognitive functions.

This study shows that the main factors affecting advanced cancer patients' quality of life are severity of tumor, pain, and anxiety and depressive mood. The stage of cancer is irreversible, but the accompanying pain and mood problems can be well controlled in clinical practice. Thus, to improve quality of life, a thorough evaluation of mood and pain symptoms is suggested, and a wise use of anti-depressants can be a good choice, for this study further confirms anti-depressants not only improves depressive symptoms, but also improves cognitive dysfunction and quality of life.

As shown above, cancer patients are not only impaired physically, but also psychologically. Early discovery and treatment of cancer patients' depressive symptoms and pain symptoms not only improves patient mood, but also executive functions and quality of life.

Conclusions

Depression is an important factor leading to the decline of quality of life and executive function in patients with advanced cancer. The antidepressant sertraline can improve executive function and quality of life, which may be helpful for the clinical practice of cancer treatment. However, this study was based on a small sample size, so there is still need for further investigations.

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