Medicine®

OPEN

Clinical observation on the benefits of antidepressant intervention in advanced cancer patients

Bing Pu, MDa iD, Ning Wang, MDa, Chuansheng Wang, MDb, Bo Sun, MDb,* iD

Abstract

To observe the interventional effect of antidepressants on advanced cancer patients from the perspective of patient benefit and analyze patient characteristics to explore reasonable drug use.

Pharmaceutical care was administered to patients with advanced cancer. From June 2018 to June 2020, 152 advanced cancer patients underwent sertraline intervention. The Hospital Anxiety/Depression Scale (HADS) was used to screen for the risk of anxiety and depression, and patients were divided into 4 groups: high, medium, low, and no risk. Concomitant clinical symptoms and antidepressant intervention results were recorded. HADS score change and symptom improvement were used to evaluate the antidepressant intervention effect, and effective intervention time for both indicators was recorded. The guidelines for antidepressant medication for these patients were analyzed, and depression/anxiety assessments and treatment models in this population were discussed.

We observed that concomitant refractory clinical symptoms were the main target for the antidepressant intervention. Of those considered high risk on the basis of the HADS score (i.e., ≥15 points), 41.5% had depression, 26.3% had anxiety, and 20.4% had comorbid anxiety and depression. For the 142 patients who completed the study, the improvement rate of mood-related symptoms based on the efficacy index was 78.2%, with a median of 7 days until improvement was observed. The improvement rate based on the HADS score was 57.0%, with a median of 19 days for improvement. Improvement rate and median days until improvement under both indices were statistically significant. Comparisons by risk group showed that improvement in clinical symptoms was significantly greater in the high- and medium-risk groups than in the low-risk group, and HADS score improvement was significantly greater in the high-risk group than in the other 2 groups. Moreover, sertraline improved chemotherapy tolerance, unhealthy emotions, and clinical symptoms such as fear, dyspnea, agrypnia, fatigue, and intractable pain.

We observed a positive effect of antidepressant drug intervention on refractory clinical symptoms in patients with advanced cancer that was particularly pronounced in those with a high-to-medium risk of depression and anxiety. However, the effect was not correlated with improved HADS score. Antidepression treatment improves concomitant clinical symptoms and benefits patients.

Abbreviations: CGI = clinical global impression, EI = efficacy index, HADS = Hospital Anxiety/Depression Scale.

Keywords: advanced cancer patients, clinical observation, diazepam, HADS screening, rational drug use, sertraline

1. Introduction

Patients with malignant tumors often experience varied depression and anxiety symptoms, which are referred to as cancer-related depression. These affect quality of life and treatment effects.[1,2] Long-term survivors of advanced cancer and those with potential for disease progression have a higher incidence of depression and often require drug intervention.[3,4] In patients with tumors accompanied by refractory clinical symptoms, antidepressant treatment is common; however, although some effects have been observed,

the intervention goals were not clear, and the medication effects were inconsistent. At present, there is an urgent need for accurate screening and assessments and active treatment of depression to improve the quality of life of cancer patients.[5] Clinical pharmacists are part of the clinical treatment team that monitors and evaluates drug treatments for tumor patients. We used the Hospital Anxiety/Depression Scale (HADS) to screen and evaluate the risk of depression and anxiety in cancer patients, as recommended by previous literature.[6,7] The purpose of this observational study was to observe the intervention effect of antidepressants in advanced

cancer patients with clinical symptoms, to provide a reference for improving the recognition and treatment rates of anxiety and depression symptoms, and to promote the rational use of antidepressants in patients with advanced cancer.

2. Methods

2.1. Patients

We recruited 152 inpatients with advanced cancer who received sertraline antidepressant intervention, comprising 54 men and 98 women, aged 59.5 ± 5.2 years. We included patients with advanced tumors who had been diagnosed with a malignant tumor >1 year previously, who were in the advanced or recurrent metastatic stages, had experienced at least 2 courses of combined chemotherapy, radiotherapy, or targeted therapeutics, had refractory clinical symptoms, did not respond to routine symptomatic (according to the Chinese Society of Clinical Oncology guidelines) treatment, and had undergone sertraline intervention. Exclusion criteria were history of mental illness and age under 18 years. This study was approved by the Ethics Committee of The First Hospital of Zibo. The ethics committee waived the need for patient consent due to the observational nature of this study.

2.2. Assessments

The HADS score was used to screen and evaluate the degree of anxiety and depression for inpatients before and after sertraline intervention. In accordance with the commonly used HADS scoring standard, patients were categorized into 4 risk groups: high (HADS score, ≥15), medium (10–14 points), low (8–10 points), and no (≤7 points) risk. The improvement in clinical symptoms, changes in HADS score, effective intervention time, drug reactions, and drug interactions following sertraline and diazepam intervention were analyzed for each group. We paid specific attention to the impact of a high risk of anxiety on the effect of sertraline intervention. Diazepam (10 mg) was added for patients with a high risk of anxiety or when sertraline did not provide an adequate response in 1 week, and sertraline was stopped for 4 weeks. Improvement in clinical symptoms was assessed in accordance with the efficacy index (EI) standard of the World Health Organization clinical global impression (CGI) evaluation as effective or markedly effective; that is, treatment in those with some improvement in symptoms or disappearance of some symptoms was evaluated as effective and was judged as effective in those with a reduction in risk grade or HADS risk score of ≥3 points. We recorded the changes in the above 2 indicators and the sertraline intervention period and performed group statistics on patients on the basis of whether patients took chemotherapy drugs. The refractory clinical symptom items (poor efficacy of conventional symptomatic treatment) were added to the HADS evaluation table, and the intervention effect was evaluated in accordance with the 4 criteria of the CGI EI series: significant effect, effective, slight effect, and ineffective. The effective and significant effects were considered effective and were thus included in the statistical analyses.

2.3. Statistical tests

SPSS, version 19.0 (IBM, NY), was used for data inspection and processing. The Wilcoxon rank–sum test was used for the comparison of measurement data, and the χ^2 test was used to compare count data. $P < .05$ was considered statistically significant.

3. Results

From July 2018 to June 2020, a total of 152 patients with an advanced tumor who had clinical symptoms that affected their quality of life were included in the study. The top 6 primary tumor diseases were 32 cases of non–small cell lung cancer, 29 cases of colorectal cancer, 21 cases of esophageal cancer, 18 cases of gastric cancer, 17 cases of breast cancer, and 10 cases of head and neck cancer. Concurrent treatment measures included second-line or above combined chemotherapy or single-drug chemotherapy, targeted therapies, such as gefitinib-bevacizumab and apatinib, and symptomatic supportive therapies, such as analgesia and antiemesis nutrition. A total of 142 patients who had completed sertraline intervention for ≥1 week were included in the data analysis, and 10 patients were excluded because of sertraline toxicity or loss to follow-up after discharge. Diazepam was added for 45 patients. We found that patients with advanced tumors were accompanied by refractory clinical symptoms, and poor response to symptomatic treatment was the primary reason for requiring the addition of antidepressants.

3.1. HADS screening risk and sertraline intervention period in patients with advanced tumors

The average duration of sertraline intervention in the 152 patients was 16.5 ± 6.6 days. Among the patients screened as high risk by the HADS score, 63 had depression (41.5%), 40 had anxiety (26.3%), and 31 had a high risk of comorbid depression and anxiety (20.4%). The HADS scores of other patients who received sertraline intervention indicated medium or low risk in 75 patients and no risk in 2 cases.

3.2. Comparison of the intervention effect of sertraline between different indicators of efficiency and effective intervention time

The refractory clinical symptoms evaluated using the EI criteria showed that the effective improvement rate of antidepressant intervention was 78.2% and that the effective improvement rate based on the HADS score was 57.0%. The sertraline intervention course and the effective intervention time of the 2 observation indices were recorded in days. Drug tolerance was evaluated by observing the duration of time for which patients took the antidepressant intervention. The effective intervention time and efficiency of the different indices were observed to evaluate the relationship between the applicability of antidepressant observation indicators and clinical benefit. As shown in Table 1, the effective rate of the clinical symptom intervention was 78.2%, and the median effective intervention time was 7 days. The effective improvement rate based on the HADS score was 57.0%, and the median effective intervention time was 19 days. These were significantly different between the 2 indices (Table 1).

Table 1

Data of the sertraline intervention course and the onset times of observation indices in 142 patients.

Observational index	Effectively improve	No improvement	Rate (%)	Median improvement time (d)
Symptoms improve	111	31	78.20	7
HADS effective improvement	81	61	57.00	19
P			<.05	<.01

Improvement times of the 2 observation indicators were tested using the Wilcoxon rank–sum test.
Improvement rates of observation indices were tested using the χ^2 test with $P < .05$.
HADS = Hospital Anxiety/Depression Scale.

3.3. Comparison of the intervention effect of sertraline and diazepam among HADS screening risk groups

Results of the drug intervention for the 4 HADS risk groups are summarized in Table 2. The improvement rate of clinical symptoms and the effective improvement rate of the HADS score were higher in the high-risk group than those of other risk groups, and there was no significant difference in the 2 indicators between the groups. However, the medium-risk group had a higher rate of effectiveness for clinical symptoms and a lower HADS improvement rate, but improvement for both criteria was significant. Only a few patients in the low-risk group showed an improvement in clinical symptoms. There was no significant difference in the improvement of clinical symptoms between the high- and medium-risk groups; however, that in the low-risk group was significantly lower than that in the high- and medium-risk groups. The decrease in HADS score was significant in the high-risk group and was significantly different from that in the medium- and low-risk groups. Furthermore, significant differences were found in the 2 observation indicators between the medium- and low-risk groups. This suggested that there was a low correlation between the clinical symptom improvement rate and the risk improvement rate based on the HADS score following sertraline intervention, and their improvement patterns were inconsistent. This reflected the characteristics of drug use in this population, as shown in Table 2. Because there were only a few cases in the risk-free group, these patients were not included in the comparison.

3.4. Relationship between clinical symptoms and the benefits of sertraline and diazepam intervention statistics of the effectiveness of the sertraline intervention for clinical symptoms in this study provide a reference for peers

The patients were divided into 2 groups according to whether they received chemotherapy drugs, and refractory clinical symptoms (1–2 types) were defined by patients' chief complaints before sertraline intervention was started. We tried to combine symptoms causally to avoid duplication, and we observed the intervention effect after the sertraline regimen was added. In this study, refractory clinical symptoms with an intervention effectiveness rate of ≥70% for clinical symptoms included refractory nausea and vomiting, adverse emotions such as anxiety and irritability, dyspnea, insomnia, fatigue, fear, and stubborn cancer pain (Table 3). A positive intervention effect was observed for patients with poor symptomatic treatment who were at high and medium risk based on the HADS screening score. Sertraline was found to be safe and effective at an initial dose of 50 mg. A total of 45 patients received diazepam as a supplement, which was shown to be synergistic with sertraline. The main sertraline-associated adverse events were nausea, vomiting, dizziness, and drowsiness, all of which had an acceptably low incidence. Serious interactions with commonly used antitumor therapies were not observed. Sertraline had a comprehensive intervention effect on the symptomatic treatment of end-stage (survival <3 months) cancer patients, especially in patients who were at high and medium risk based on HADS screening.

4. Discussion

The incidence of tumor-related depression in patients with a malignant tumor is high at both the initial diagnosis and advanced diagnosis stages.[4] With developments in cancer treatments, advanced cancer patients achieve long-term survival; therefore, it is particularly important to establish effective depression screening and treatments for patients with advanced cancer. The incidence of depressive symptoms in tumor patients is higher than that in the general population; yet, the rate of recognition and treatment is lower. For example, a survey[8] conducted by an affiliated hospital of the Peking University in China found that the prevalence rates of depressive disorder and severe depressive disorder in 460 cancer patients were 25.9% and 12.6%, respectively, of which only 6.9% were identified by doctors. There is a gap in the utilization rate of antidepressants between China and other developed countries; according to a survey of 87 medical institutions in China, antidepressant spending and prescription rates in cancer patients were ≤3.29%.[9] The average rate of antidepressant use in cancer

---

Table 2

The intervention effect of sertraline and diazepam on the Hospital Anxiety and Depression Scale score and clinical symptoms in different HADS risk groups.

HAD grouping before intervention	Cases	Proportion (%)	HADS valid/invalid*	Symptoms valid/invalid†	P value
High (A/D ≥ 15)	65	45.8	55/10	56/9Δ	>.05
Medium (11–14 points)	55	39.7	28/27	47/8Δ	<.01
Low (8–10 points)	20	14.1	1/19	9/11	<.01
None (≤7 points)	2	1.4	0/2	0/2	–
Total	142	100	84/58	112/30	<.01

Comparisons between any other pair of groups were tested using χ^2, $P < .01$.
HAD = hospital anxiety and depression, HADS = Hospital Anxiety/Depression Scale.
* Column pairwise comparisons were tested using χ^2 or continuity corrected by χ^2, $P < .01$.
† Column comparison between Δgroups was tested using χ^2, $P > .05$.

Table 3

The intervention effect of sertraline and diazepam on clinical symptoms in advanced tumor inpatients (concurrent symptoms, effective ratio ≥ 70%).

Chemo group	Valid/total	Effective ratio (%)	Non-chemo group	Valid/total	Effective ratio (%)
Nausea/vomiting	15/20	75.0	Dyspnea, chest distress	12/16	80.0
Fatigue, numbness	20/25	80.0	Fidgety, irritability	28/30	93.3
Insomnia	36/40	90.0	Intractable cancer pain	40/44	91.0
Fear, worry	20/25	80.0	Fear, worry	36/38	94.7
Fidgety, irritability	30/36	83.3	Fatigue, numbness	36/42	85.7
Depression, apathy	25/35	71.4	Insomnia	52/57	91.2

patients in the United States from 1999 to 2012 was 18.3% and has shown an increasing trend over the past decade.[10] The rates of diagnosis and treatment of cancer-associated depression are lower in China than in other countries. Therefore, establishing a model for depression screening and evaluation for patients with advanced cancer is crucial.

The traditional intervention for tumor-related depression is psychological counseling to improve mood states. For example, mindfulness counseling, family interventions, traditional Chinese medicine treatments, and acupuncture treatment have demonstrated some positive effects.[11–13] However, the treatment period is relatively long; for instance, the effect of group psychotherapy is evaluated after >4 weeks of treatment. In recent years, there have been numerous reports on the benefits of antidepressants in cancer patients.[14–17] The use of antidepressants in inpatients with stubborn clinical symptoms is common, and the evaluation of the rational use of drugs has become a novel issue for clinical pharmacists. The observational data of our study highlighted the high comorbidity of depression and anxiety in patients with advanced cancer, and sertraline combined with diazepam provided relief for both conditions and had good clinical tolerance. The improvement rate of clinical symptoms following sertraline treatment was higher than that of the HADS score. The intervention effect of sertraline in advanced cancer patients differed among those with different HADS screening risk levels. The clinical symptoms of patients in the high- and medium-risk groups improved significantly. There was no difference in the clinical symptom improvement rate between the high- and medium-risk groups; however, there was a significant decrease in the low-risk group. There was a correlation between the improvement rate of clinical symptoms and risk group based on the HADS assessment but not between the improvement rate of clinical symptoms and the improvement in HADS score. The difference between the 2 indicators reflects the characteristics of patients with advanced tumors; namely, that drug treatment characteristics differed between those with depression and anxiety. Our findings suggested that the evaluation and treatment of anxiety and depression in patients with advanced cancer should be implemented differently than in patients without cancer, and further targeted studies are needed.

The HADS score has been recommended worldwide for screening cancer patients for depression risk.[6,7] The evaluation items are relatively simple, easy to implement in the clinic, and allow simultaneous anxiety screening, which enables the identification of the combined factors of anxiety and depression in patients with advanced cancer. The success rate of interventions may be improved by combining drugs. However, the HADS score does not replace diagnosis of depression and anxiety, which requires confirmation by assessments such as the Hamilton Anxiety Scale/Hamilton Depression Scale. Sertraline is a new serotonin reuptake inhibitor antidepressant that improves executive functions and quality of life of advanced cancer patients.[17] It is effective for treating anxiety and depression and is as safe and well tolerated as other similar drugs. A 50-mg dose of sertraline as an initial dose was safe and effective, and only 2 patients required a dose increase to 100 mg to observe an intervention effect. In addition, sertraline has the potential to induce antitumor cell proliferation activity and is considered the first choice for antianxiety and depression therapy in tumor patients.[18] The main side effects associated with sertraline were nausea and vomiting, dizziness, and drowsiness. Moreover, there was no interaction between sertraline and common antitumor therapies. Thus, our findings suggest that mood improvement therapy for tumor patients should be initiated with a low dose and those with hyposmolarity or electrolyte disturbances should use sertraline with caution.

5. Conclusion

In the distinct group of patients with advanced cancer, psychological intervention is one element of best supportive therapy (i.e., BestSupportCare).[19] Although there are numerous influencing factors, such as tumor type, family environment, educational background, and economic conditions, in patients with advanced cancer, we showed that patients with advanced cancer can benefit from antidepressant intervention, and this was correlated with a high-to-medium risk of depression and anxiety but not with improvement in the HADS score. Sertraline and diazepam benefit patients by improving concomitant clinical symptoms. However, the sample size of this study was limited, and more high-level studies are needed in this patient group.

References

[1] Lv SJ, Zhang YJ, Wang PP. Research progess on cancer-related depression [J]. Chinese J Gerontol. 2018;38:4326–30.

[2] Svetlákova L, Slama O, Svetlak M, et al. Prevalence of anxiety and depression and their impact on the quality of life of cancer patients treated with palliative antineoplasic therapy – results of the PALINT trial. Klin Onkol. 2019;32:201–7.

[3] Huang WK, Juang YY, Chung CC, et al. Timing and risk of mood disorders requiring psychotropics in long-term survivors of adult cancers: a nationwide cohort study. J C Disord. 2018;236:80–7.

[4] Valderrama Rios MC, Sánchez Pedraza R. Anxiety and depression disorders in relation to the quality of life of breast cancer patients with locally advanced or disseminated stage. Rev Colomb Psiquiatr. 2018;47:211–20.

[5] Lin BJ, Zhang HZ. Research progress of mood disorders in patients with malignant tumor [J]. Chinese J Cancer Prev Treat. 2020;27:2006–12.

[6] Villoria E, Lara L. Assessment of the Hospital Anxiety and Depression Scale for cancer patients. Rev Med Chil. 2018;146:300–7.

[7] Miljanovic M, Sindik J, Milunović V, et al. Factor structure and cut-off scores of the Hospital Anxiety and Depression Scale (HADS) in a Croatian sample of adult patients suffering from advanced cancer. Psychiatr Danub. 2017;29:451–8.

[8] Zhao L, Li X, Zhang Z, et al. Prevalence, correlates and recognition of depression in Chinese inpatients with cancer [J]. Gen Hosp Psychiatry. 2014;36:477–82.

[9] Lin P, Zhen JC, Chen N, et al. Utilization analysis of antidepressants in cancer patients from 87 hospitals in China[J]. Chinese J Drug Appl Monit. 2017;14:48–51.

[10] Xiang X, An R, Ghlert S. Trends in antidepressant use among U.S. cancer survivors,1999-2012 [J]. Psychiatr Serv. 2015;66:564.

[11] Li P, Cao WB, Chen XG, et al. Analysis on the incidence group psychotherapy improves the emotional state of tumor patients[J]. China J Health Psychol. 2017;25:387–90.

[12] Wang XY. Progressive muscle relaxation training combined with traditional Chinese medicine music intervention to improve anxiety, depression and quality of life in cancer patients[J]. J Mod Oncol. 2017;25:3509–12.

[13] Lu WJ, Duan LH, Zhou YQ, et al. The primary clinical study of mental depression in 45 patients with malignant tumor was conducted with traditional Chinese medicine and psychological intervention[J]. Chinese Archives Tradit Chin Med. 2011;29:2346–8.

[14] Zhang LJ, Ding ZS. Research progress of drugs for the treatment of tumor-related depression [J]. China Pharmacy. 2013;24:2859–62.

[15] Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat. 2005;89:243–9.

[16] Liu JL, Qiu H, Liu DB, et al. Analysis on the incidence of anxiety and depression in cancer patients and its influencing factors[J]. Drug Eval. 2012;3:24–8.

[17] Li XJ, Dai ZY, Zhu BY, et al. Effects of sertraline on executive function and quality of life in patients with advanced cancer. Med Sci Monit. 2014;20:1267–73.

[18] Sullivan DR, Mongoue-Tchokote S, Mori M, et al. Randomized, double-blind, placebo-controlled study of methylphenidate for the treatment of depression in SSRI-treated cancer patients receiving palliative care.[J]. Psychooncology. 2017;26:1763–9.

[19] Li XN. Application of active psychological intervention in hospice care for patients with advanced tumor[J]. Chinese J Cancer Prev Treat. 2018;25:273–5.