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Original Article

Risk Factors for depression and efficacy of comprehensive care in advanced lung cancer patients with chemotherapy

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Abstract: Objective: To clarify the risk factors for depression in advanced lung cancer (LC) patients who undewent chemotherapy, and to explore the effectiveness of tailored comprehensive care programs in improving depression and quality of life of such patients. Methods: In Phase I of our study, from December 2014 to November 2015, 148 patients with advanced LC who underwent chemotherapy were recruited as participants. The patients completed the questionnaires with the Zung Self-Rating Depression Scale (SDS). The enrolled patients were subdivided into the case group and the control group in terms of the presence/absence of depression. A case-control analysis was conducted for investigation of the risk factors for depression in advanced lung cancer LC patients undergoing chemotherapy. In Phase II of our study, a randomized controlled trial was designed. Between December 2015 to November 2016, 140 patients with advanced LC who underwent chemotherapy admitted to our hospital were enrolled and randomly assigned to receive comprehensive care (comprehensive care group) or usual care (usual care group) according to previously identified risk factors for depression. Subsequently, the effectiveness of comprehensive care on depression and quality of life were assessed among the patients. Results: In our study, the incidence of depression was 54.7% in patients with advanced LC who underwent chemotherapy. On the univariate analysis, age, women, education and household income levels, course of disease and pain might be associated with depression in patients with advanced LC who underwent chemotherapy. Furthermore, a multivariate logistic regression analysis revealed that an age of older than 65 years, disease course of less than 6 months, the KPS score of less than 90 and pain were independent risk factors for depression in patients with advanced lung cancer who underwent chemotherapy, with adjusted OR of 1.79 (95% CI: 1.20-2.31), 1.26 (95% CI: 1.03-1.42), 1.90 (95% CI: 1.22-2.47) and 2.14 (95% CI: 1.49-3.18). Compared with the usual care group, the comprehensive care group had greater improvements in the SDS scores and the EORTCQLQ-C scores (except for the scores for several components of the quality of life, all $P<0.05$). Conclusion: Older age, shorter course of disease, a lower KPS score and pain were independent risk factors for depression in advanced LC patients undergoing chemotherapy. Compared with conventional care, comprehensive psychological care improved the depressive symptoms of the patients and enhanced their quality of life.

Keywords: Lung cancer, depression, quality of life, risk factor, psychological intervention

Introduction

In recent decades, the incidence and death from lung cancer (LC) are on the rise in China because of the prevalence of smoking, serious air pollution and aging of the population. Since the beginning of the 21st century, in particular, LC has become the leading cause of cancer-related deaths in China. In 2015, the cases of LC were 733, 300 and LC related-deaths were 610, 200 in China [1]. The prognosis of LC is poor and the 5-year survival rate of LC is only 16.1% in China [2]. This is mainly due to the fact that most of the patients are already in the advanced stage at clinical diagnosis and have missed the chance of radical surgery. Chemotherapy can inhibit proliferation, metastasis and recurrence of tumors, so it is one of recommended therapeutic methods for such patients [3]. However, the patients are susceptible to develop depression and other negative emotions because their overt symptoms, poor prog-

nosis and chemotherapy-induced damages to normal cells leading to digestive disorders, immune dysfunction and other side effects in them [4, 5]. As a result, the treatment compliance and quality of life, and survival of the patients were affected [6, 7]. Previous studies suggest that age, education level, pain, metastatic cancer, short diagnosis duration and physical conditions may increase the risk for depression in patients with LC, but the results were diverse [5, 8, 9]. Investigation of the risk factors for depression in patients with advanced lung cancer provides evidence for making appropriate care management programs to alleviate depression in such patients.

As demonstrated in numerous studies, psychological care, cognitive behavior and comprehensive care relieve negative emotions including depression and anxiety in patients with LC and improve their quality of life. Nevertheless, the results of the studies vary greatly because of different study design and outcome measures [10-13]. According to a systematic review, nursing intervention effectively improved the emotional status of the patients, but the evidence is not conclusive [14]. A meta-analysis from China indicates that psychological intervention was associated with improvements in the symptoms of anxiety and depression, as well as the quality of life of patients with LC [15]. Consequently, this study presented here was designed to investigate the risk factors for depression in advanced LC patients undergoing chemotherapy, and to evaluate the effects of comprehensive care on depression and quality of life, with an aim to identify the efficacy of the intervention and provide scientific evidence for planning effective care management programs for advanced LC patients undergoing chemotherapy.

Materials and methods

Patients

This study got approval from the ethics committee of the Second Hospital of Dalian Medical University. From December 2014 to November 2016, a total of 288 patients with advanced LC admitted to our department and treated with chemotherapy were enrolled in this study. Patients were eligible for enrollment if they had confirmed LC on pathological and/or cytological examination, Stage III or IV of LC, chemotherapy, an age of more than 18 years, no mental disorders or disturbance of consciousness, and provided written informed consent. Patients were ineligible for enrollment if they had other severe disease, cognitive or mental dysfunction; unstable or rapidly exacerbating symptoms of LC.

Study design

This study consist of two phases, with phase I investigating the risk factors for depression in advanced LC patients with chemotherapy and phase II exploring the effectiveness of comprehensive care on depression and quality of life of the patients.

Phase I: From December 2014 to November 2015, 148 patients with advanced LC admitted to our hospital were recruited as participants, and demographic and clinical data were pooled from the patients. The Karnofsky Performance Scale (KPS) was used to evaluate whether the patients were resistant to chemotherapy according to their abilities to carry out normal activity, severity of the disease and self-care. On a scale of 0-100 points, 10 points was rated as a grade, and higher scores indicates better physical performance status, with 60 indicating the patients were able to care for most of their own personal needs but require occasional assistance, and 100 indicating good physical performance status [16]. The enrolled patients were assigned to the case group or the control group in terms of whether depression was present during the study period. The risk factors for depression in patients with advanced LC were explored in this case-control analysis.

Phase II: Between December 2015 and November 2016, 140 advanced LC patients with chemotherapy were randomly subdivided into two groups, with 70 patients in each group. One group of patients (usual care group) were instructed to complete usual cancer care programs, including management of artificial airway and chemotherapy-related adverse events, and other symptomatic management; the other group of patients (comprehensive care group) received comprehensive care in addition to usual care, including health education and psychological intervention. As far as health education was concerned, physicians and nurses made regular lectures on health care education related to LC for once or twice a week; the lec-

Table 1. Univariate analysis of depression of patients in the control group and the case groups

Characteristic	Control group (n=67)	Case group (n=81)	x^2	P
Age			7.159	0.007
<65	37 (55.2)	27 (33.3)		
≥65	30 (44.8)	54 (66.7)		
Gender			4.494	0.034
Male	55 (82.1)	54 (66.7)		
Female	12 (17.9)	27 (33.3)		
Smoking			3.457	0.063
No	27 (40.3)	21 (25.9)		
Yes	40 (59.7)	60 (74.1)		
Education			4.122	0.042
HSOB	26 (38.8)	45 (55.6)		
COA	41 (61.2)	36 (44.4)		
MHI			4.479	0.034
<4,000	28 (41.8)	48 (59.3)		
≥4,000	39 (58.2)	33 (40.7)		
CS			0.951	0.329
III	36 (53.7)	37 (45.7)		
IV	31 (46.3)	44 (54.3)		
DC			3.990	0.046
<6 mon	27 (40.3)	46 (56.8)		
≥6 mon	40 (59.7)	35 (43.2)		
PT			2.950	0.086
NSCLC	58 (86.6)	61(75.3)		
SCLC	9 (13.4)	20 (24.7)		
KPS score			6.900	0.009
70-80	26 (38.8)	49 (60.5)		
90-100	41 (61.2)	32 (39.5)		
PS			7.049	0.008
N/M	36 (53.7)	26 (32.1)		
M/S	31 (46.3)	55 (67.9)		

Note: HSOB denotes high school or below, COA college or above, MHI monthly household income, CS clinical stage, DC disease course, PT pathologic type, NSCLC non-small cell lung cancer, SCLC small cell lung cancer, PS pain severity, N/M none/mild, and M/S moderate/severity.

tures were focused on the issues related to LC and chemotherapy, including the necessity of chemotherapy, adverse events and skills of psychological adjustment. For psychological intervention, efforts were made to know the psychological pressure of patients through communicating with them and their families; the risks for depression in the patients were determined based on the risk factors reported in the literature and previous studies; programs of behavioral, cognitive, and psychological care were individually tailored to each patient's needs and personal priorities [17]. Since the second week, the care providers instructed the patients according to their distinctive psychological features to learn to reasonably cope with the situations, correct their self-concepts, arouse their initiatives, correct their mistakes with rational cognition, and reconstruct cognitive structure. The patients also received progressive relaxation trainings. Placed in a supine position and under the voice guidance, the patients closed the eyes and relaxed the muscles gradually from the head to the feet; then they made active self-relaxation to enhance their emotional stability. Specialized tailored psychological counseling was implemented to the individuals with negative emotions and at high risks in accordance with their personal traits. In our current study, the personnel providing psychological intervention had received relevant trainings on psychological intervention.

Outcome measures

Depression: The Zung Self-Rating Depression Scale (SDS) was employed at admission and at the end of this chemotherapy cycle for evaluation of the depression symptoms of the patients [18]. The SDS score <50 indicates no depression, 50-69 mild depression, 60-69 moderate depression, and 70 or more severe depression.

Quality of life: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, Chinese version) at admission and at the end of this chemotherapy cycle was used for assessment of the quality of life of patients. The QLQ-C30 incorporates five functional subscales (physical, role, emotional, cognitive, and social); three symptom subscales (fatigue, pain, and nausea and vomiting); a global health subscale and 6

Table 2. Multivariate logistic regression analysis of the risk factors for depression among the advanced LC patients with chemotherapy

Characteristic	Adjusted OR*	95% CI	P
Age		1.20-2.31	0.035
<65	Reference		
≥65	1.79		
DC		1.03-1.42	0.042
<6 mon	Reference		
≥6 mon	1.26		
KPS score		1.22-2.47	0.033
90-100	Reference		
70-80	1.90		
PS		1.49-3.18	0.018
N/M	Reference		
M/S	2.14		

Note: *Adjusted gender, education and monthly income levels. DC denotes disease course, PS pain severity, N/M none/mild, and M/S moderate/severity.

items for specificity reflecting symptoms and economic status. The global health subscale consists of 7 grades, with scores ranging from 1 to 7; other items are rated into 4 grades, with scores varying from 1 to 4. The initial sore of each entry is derived from the sum of the scores for all the items included divided by the total number of items. The initial sores are conversed into the standard score of 0-100 through linear transformation. The EORTCQLQ-C30 scale was recommended to be used for assessment of the quality of life of the patients with LC due to its favorable reliability, validity and responsiveness [3].

Statistical analysis

Measurement data were presented as mean ± standard deviation, and the two-sample independent t-test was utilized for comparisons of the mean values of measurement data between the groups. Categorical variables were described as constituent ratio, and the differences between the categorical variables were compared by the two-sided chi-square test. Multivariate logistic regression analysis was made for investigating the risk factors of depression in patients with advanced LC who underwent chemotherapy. On the multivariate analysis, the likelihood ratio test was performed on the base of the maximum local likelihood for stepwise selection of independent variables. In evaluation of the interventions for depression and quality of life, the paired t-test was utilized to compare the changes in depression and quality of life before and after intervention between the two groups. The differences in the scores of depression and quality of life between the two groups were compared with the application of the two sample independent t test. The level for significance was set as two-tailed α of 0.05. Statistical analyses of the data were performed using the SPSS software, version 20.0.

Results

Baseline characteristics of patients

Among the 148 advanced LC patients with chemotherapy admitted to our hospital from December 2014 to November 2015, 81 showed depression on the SDS score, with a depression rate of 54.7%, including 34.5% (51) of mild depression and 20.2% (30) of depression.

Univariate logistic regression analysis

Table 1 shows the individual and clinical characteristics of 81 patients with depression (case group) and 67 patients without depression (control group). In the case group of patients, 66.7% were 65 years or older, and 33.3% were female, significantly higher than 44.8% (P=0.007) and 17.9% (P=0.034) of the control group; 44.4% received education of college or above, which was considerably lower than that of the control group (P=0.042). In addition, the case group, as compared with the control group, demonstrated lower income, shorter course of disease, but a larger proportion of patients with pain (all P<0.05).

Multivariate logistic regression analysis

Table 1 also shows that age, women, education and household income levels, course of disease, and pain were associated with depression in advanced LC patients undergoing chemotherapy. On multivariate logistic regression analysis including the above-mentioned factors, older age, shorter course of disease, lower KPS score and pain were independent risk factors for presence of depression in patients with advanced LC patients undergoing chemotherapy, with adjusted OR of 1.79 (95% CI: 1.20-2.31), 1.26 (95% CI: 1.03-1.42), 1.90 (95% CI:

Table 3. Characteristics of patients with comprehensive or usual care

Characteristic	CC (n=70)	UC (n=70)	x^2	P
Age			1.830	0.176
<65	38 (55.3)	30 (42.9)		
≥65	32 (45.7)	40 (57.1)		
Gender			0.331	0.565
Male	53 (75.7)	50 (71.4)		
Female	17 (24.3)	20 (28.6)		
Smoking			1.467	0.226
No	24 (34.3)	31 (44.3)		
Yes	46 (65.7)	39 (55.1)		
Education			2.326	0.127
HSOB	28 (40.0)	37 (52.9)		
COA	42 (60.0)	33 (47.1)		
MHI			1.101	0.294
<4,000	47 (67.1)	41 (58.6)		
≥4,000	23 (32.9)	29 (41.4)		
CS			1.036	0.309
III	29 (41.4)	35 (50.0)		
IV	41 (58.6)	35 (50.0)		
DC			1.841	0.175
<6 mon	36 (51.4)	28 (40.0)		
≥6 mon	34 (48.6)	42 (60.0)		
PT			0.714	0.396
NSCLC	54 (77.1)	58 (82.7)		
SCLC	16 (22.9)	12 (17.1)		
KPS score			2.319	0.128
70-80	41 (58.6)	32 (45.7)		
90-100	29 (41.4)	38 (54.3)		
PS			2.338	0.126
N/M	36 (51.4)	27 (38.6)		
M/S	34 (48.6)	43 (61.4)		

Note: HSOB denotes high school or below, COA college or above, MHI monthly household income, CS clinical stage, DC disease course, PT pathologic type, NSCLC non-small cell lung cancer, SCLC small cell lung cancer, PS pain severity, N/M none/mild, M/S moderate/severity, CC comprehensive care, and UC usual care.

Table 4. Improvements of depression in patients with comprehensive or usual care

Item	Intervention	CC (n=70)	UC (n=70)	t	P
SDS	Pro-intervention	57.6±9.9	58.9±11.2	0.728	0.234
	Post-intervention	55.8±8.7	58.3±19.7		
	Difference	1.8±4.2	0.6±2.7	2.011	0.047
	t	8.167	1.859		
	P	0.001	0.067		

Note: CC denotes comprehensive care, and UC usual care.

1.22-2.47), and 2.14 (95% CI:1.49-3.18), respectively (**Table 2**).

Depression and quality of life in patients with usual or comprehensive care

Between December 2015 and November 2016, 140 advanced LC patients undergoing chemotherapy admitted to our hospital were enrolled in this phase II study, and randomly assigned to the usual care group or the comprehensive care group according to their respective care interventions received. No significant differences in the individual and clinical characteristics were noted between the two groups (all P>0.05, **Table 3**).

The depression scores were largely similar among the patients in the two groups before intervention, but decreased substantially in the patients with comprehensive care at the end of the intervention (P=0.01). The depression scores of the patients with usual care alone also decreased, though insignificantly. A greater improvement in depression was observed with comprehensive care than with usual care alone (P=0.047; **Table 4**).

The changes in quality of life of the two groups before and after intervention are shown in **Table 5**. The scores of all the items before intervention were balanced between the two groups (all P>0.05). Due to the impact of chemotherapy, the scores for the components of quality of life (with the exception of the specificity components of cognitive function, dyspnea and diarrhea) of the two groups were lowered considerably during the study; however, the comprehensive care group, as compared with the usual care group, had remarkably higher scores for other functions except cognitive function and dyspnea and diarrhea, but con-

Table 5. Improvements in quality of life in patients with usual or comprehensive care

QoL	CC (n=70)					UC (n=70)					COD	
	Pre-I	Post-I	Difference	t	P	Pre-I	Post-I	Difference	t	P	t	p
GH	65.9±11.2	58.2±10.8	7.7±8.5	7.579	<0.001	66.3±12.9	54.1±10.2	12.1±9.3	10.886	<0.001	2.922	0.004
Function												
Physical	67.8±12.7	56.9±11.3	9.9±9.6	8.628	<0.001	69.5±13.8	55.9±10.4	13.6±11.2	10.159	<0.001	2.099	0.038
Role	64.2±13.1	57.7±10.4	6.5±6.9	7.882	<0.001	63.7±12.3	53.5±11.2	10.2±9.8	8.708	<0.001	2.583	0.011
Emotional	61.4±10.5	52.7±9.6	8.7±10.1	7.207	<0.001	64.2±11.6	51.8±10.7	12.4±11.7	8.867	<0.001	2.104	0.037
Cognitive	66.7±11.9	66.3±12.9	0.4±2.1	1.594	0.058	64.3±10.4	63.2±11.3	0.7±3.2	1.830	0.072	0.656	0.513
Social	70.1±14.2	61.9±11.7	8.2±10.7	6.411	<0.001	72.8±15.4	59.9±13.1	12.9±16.4	6.581	<0.001	2.008	0.047
Symptom												
Fatigue	44.6±8.6	52.4±10.8	7.8±9.4	6.942	<0.001	46.1±9.7	58.6±15.5	12.5±14.7	7.114	<0.001	2.254	0.026
Pain	32.9±7.1	38.2±8.2	5.3±10.4	4.263	<0.001	34.6±9.2	44.2±14.9	9.6±14.1	5.696	<0.001	2.053	0.042
NV	23.6±5.7	32.0±7.5	8.4±12.9	5.448	<0.001	25.1±6.8	38.6±9.2	13.5±15.7	7.194	<0.001	2.100	0.038
Specificity												
Dyspnea	48.9±8.4	47.6±9.1	1.3±5.9	1.843	0.070	50.7±10.3	49.1±9.8	1.6±7.8	1.716	0.091	0.257	0.798
Insomnia	35.7±7.9	43.2±9.6	7.5±12.7	4.941	<0.001	37.7±8.6	50.3±10.2	12.6±16.9	6.238	<0.001	2.018	0.045
Appetite	32.3±8.1	39.6±10.1	7.3±13.9	4.394	<0.001	34.8±9.7	47.3±12.5	12.5±16.1	6.496	<0.001	2.045	0.043
Constipation	29.5±7.7	35.8±9.8	6.3±11.5	4.583	<0.001	31.7±10.4	42.1±11.9	10.4±16.3	5.338	<0.001	1.720	0.088
Diarrhea	34.2±8.5	35.3±11.8	1.1±4.9	1.878	0.065	37.1±11.9	38.7±13.4	1.6±6.9	1.940	0.056	0.494	0.622
ES	41.8±10.7	48.3±14.3	6.5±10.9	4.989	<0.001	43.9±13.5	52.3±15.8	8.4±15.7	4.476	<0.001	0.832	0.407

Note: CC denotes comprehensive care, UC usual care, COD comparison of differences, Pre-I pre-intervention, Post-I post-intervention, QoL quality of life, GH global health, NV nausea and vomiting, and ES economic status.

siderable reductions in the scores for insomnia and appetite at the end of the intervention (P= 0.045, and 0.043, respectively).

Discussion

The diagnosis and subsequent treatment of cancer tend to cause anxiety and depression in patients. According to a study conducted in China, depression is considerably more prevalent in cancer patients, patients with LC in particular, than in the general population [4]. The LC patients with depression account for 2.5% to 77% of all the LC patients in previous studies; the differences are not only associated with the outcome measures and the source of patients, but also the clinical staging and the treatment they have received [4, 20, 21]. Some researchers also imply that chemotherapy enhances the risk for depression in cancer patients [22, 23]. In our current study, the rate of depression in patients with advanced LC and chemotherapy was 54.7%, which was similar to those of some studies, but lower or higher than those of other studies, [4, 5, 23-26].

In our study, we found that older age, shorter course of disease, lower KPS score and pain were independent risk factors for depression in patients with advanced LC and chemotherapy, which were consistent with the findings of other studies [4, 5, 27]. However, the findings of different studies vary greatly. For example, some studies reveal that younger age correlates with depression instead [28, 29]. A study from China indicated that low education level significantly enhanced the risk of depression in patients with LC, but this result was merely derived from a univariate analysis as the author did not conduct a multivariate analysis [4]. In our study, the significance of education level was also reflected in the univariate analysis. Likewise, the association of gender with depression in LC patients was also observed merely in the univariate analysis. Conversely, another study revealed that women were an independent risk factor for depression in patients with LC [21]. The reports that shorter course of disease, poor performance status and pain were independent risk factor for depression in patients with LC were more consistent among the studies. Additionally, clinical staging, solitude, drinking and other factors have been reported to be associated with depression in patients with LC, though the results are not consistent [8, 30]. Therefore, additional studies are required for exploring the association between the abovementioned factors and depression in patients with advanced LC.

Depression has an adverse effect on the quality of life of LC patients, and it is associated with

a substantial reduction of quality of life of the patients with advanced LC and chemotherapy [23]. As demonstrated in our study, the quality of life of all the patients with comprehensive care or care was decreased considerably during chemotherapy.

Therefore, care intervention in the course of chemotherapy is of great significance to improve the patients' emotion, quality of life and survival. Currently, multiple psychological interventions including behavioral cognition therapy, health education, and physical-mental treatment, have been evaluated in exploring depression control of LC patients [31]. A meta-analysis from China reviewing eight clinical studies indicates that psychological intervention improves the quality of life of LC patients; however, the number of the studies included was inadequate [15]. Different results were derived from a systematic review in which two different indexes were used in evaluating quality of life of patients [32]. In our study, we found that the quality of life of the two groups of patients declined remarkably due to the impact of chemotherapy, with a more significant reduction in the patients with comprehensive care than those with usual care, which corresponded to the results of other studies [11]. In another study, the quality of life of the patients in both study groups after two cycles of chemotherapy was higher than that before chemotherapy, with a greater improvement in the intervention group versus the control group [33]. This might be explained by the fact that our study was only involved in one chemotherapy cycle with a shorter duration of observation. Moreover, some studies show that comprehensive care significantly improves the quality of life of patients, while others have not brought about such significant results [17, 34]. In general, with the differences in intervention methods, personal characteristics of patients, outcome measures, randomization and analysis methods, the efficacy of comprehensive care on the quality of life of LC patients undergoing chemotherapy is required for further evaluation.

The advantages of our study lies in that we investigated the risk factors for depression in patients with advanced LC in a case-control analysis before comprehensive care was conducted, and also performed specific tailored care programs based on the previous literature and the patients' conditions. However, there are still several limitations in this study. For example, it is difficult to fully eliminate the impacts of bias due to the retrospective nature of the case-control analysis. What's more, no blinding in intervention evaluation and the short study duration added difficulties to observe the long-term effects of comprehensive care management on quality of life of patients.

In conclusion, this study was firstly to explore the risk factors for depression in advanced LC patients undergoing chemotherapy, and then tailored comprehensive care programs were carried out in these patients. The results demonstrated that compared with usual care, comprehensive care improved depression and quality of life of patients more effectively. Additional randomized controlled studies with larger sample size should be made in the future. Moreover, unified methods of assessment and treatment are required to assess the effectiveness of comprehensive care on negative emotions and quality of life of advanced LC patients undergoing chemotherapy through long-term intervention and follow-up.

Disclosure of conflict of interest

None.

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