


Effect of Wellness Education on Quality of Life of Patients With Non–Small Cell Lung Cancer Treated With First-Line Icotinib and on Their Family Caregivers

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Abstract

Objective: To examine the effects of a wellness-education intervention on quality of life (QOL) of patients with NSCLC treated with icotinib and on their caregivers. **Methods:** This feasibility study was a prospective pilot randomized controlled trial to evaluate a wellness-education intervention in NSCLC patients and caregivers undergoing icotinib treatment. The participants in the wellness-education group were provided with well-being information over 8 weeks. The Family Environment Scale (FES), Functional Assessment of Cancer Therapy–Lung (FACT-L), Caregiver QOL Index–Cancer Scale (CQOLC), and Hospital Anxiety and Depression Scale (HADS) were measured at baseline prior to randomization and after 8 weeks. Patients completed the FACT-L and HADS, caregivers completed the CQOLC and FES. **Results:** 67 patients/caregivers in the wellness-education group and 71 in the control group could be analyzed. Feasibility targets were the following: (1) >70% study enrollment of eligible patients; (2) >90% of participants completing this study; (3) <10% missing data. Wellness-education group had better change scores at 8 weeks for the emotional well-being subscale of FACT-L (12.8 vs 15.6, $P = .014$), anxiety subscale of HADS (6.1 vs 6.7, $P = .030$), adaptation (66.0 vs 54.7, $P = .037$) and financial subscales of CQOLC (70.8 vs 69.8, $P = .044$), and the cohesion (7.3 ± 1.8 vs 5.7 ± 1.7 , $P = .021$) and conflict (3.4 ± 1.9 vs 4.5 ± 1.7 , $P = .031$) subscales of the FES. **Conclusion:** Wellness-education in patients/caregivers with NSCLC treated with icotinib are feasible and could improve patients' QOL and their relationship with caregivers.

Keywords

non–small cell lung cancer, icotinib, quality of life, wellness education, caregiver

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Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide. Non–small cell lung cancer (NSCLC) represents approximately 84% of lung cancer cases with more than half in advanced stages at presentation.^{1,2} NSCLC patients have high rates of psychological symptoms, and many of their family caregivers experience significant distress.^{3–5}

Epidermal growth factor receptor (EGFR) mutations facilitated drugs such as erlotinib, icotinib, and afatinib, which have been approved as first-line treatments for NSCLC with EGFR mutations.^{6,7} The EGFR mutation rate in East-Asian populations is relatively high.^{7,8} Several studies confirmed that EGFR-tyrosine kinase inhibitors (TKIs) could improve the quality of life (QOL) of patients.^{6,8–10}

Nevertheless, despite improvements in cancer-related QOL, current treatments are associated with toxicities and proper management is necessary to further improve the QOL.^{11,12}

Previous studies showed that patients with NSCLC and their caregivers are highly vulnerable to psychosocial morbidity and high levels of distress including depression, anxiety, and reduced QOL.^{3,13,14} Distress is a frequently reported

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adverse event, and early recognition and effective management of psychosocial morbidity can improve the QOL of patients and their caregivers,^{3,4,15-18} while preventing unnecessary disruption of cancer care. It has been shown that caregivers should be involved in the management of patients with advanced NSCLC.^{3-5,19} Some nonpharmacologic interventions were tried and showed promising results, such as biofeedback-assisted stress management,²⁰ psycho-oncologic interventions,²¹ early palliative care,²² and couple-based yoga,²³ among others. Nevertheless, the conclusions often suffer from low-quality trials,²¹ and well-designed randomized controlled trials (RCTs) are necessary.

Despite the probable benefits of physical activity in cancer patients,²⁴⁻²⁶ a recent preliminary clinical investigation performed by our group in our patient population showed that <2% of 410 patients with incurable lung cancer and 8% of their caregivers engage in regular physical activity. Considering disability, social behavior, and economic costs associated with lung cancer, we advocate paying close attention to the development of nonpharmacological approaches that include education and mindfulness.

Therefore, we hypothesized that a psycho-oncologic wellness education (WE) could improve the QOL of patients and their caregivers. We designed a feasibility prospective pilot RCT study that encourages patients with NSCLC and their caregivers to join a WE group during icotinib treatment. This intervention, received on a voluntary basis, involves instruction on exercise, balanced diet and nutrition, pharmacological management, legal issues relevant to health, and mental health issues. In addition, particular attention is given to the individual's treatment experiences, including thoughts, feelings, and physical sensations. The present study aimed to evaluate the participant recruitment, intervention provision, data collection, and the efficacy of the WE intervention on patients with advanced NSCLC treated with icotinib as first-line treatment and on their caregivers. The primary outcome was QOL after 8 weeks.

Methods

Study Design and Participants

This study was a prospective randomized 8-week WE intervention feasibility study of patients undergoing icotinib treatment, carried on from December 2016 to December 2017 at the Department of Medical Oncology of the Tianjin Cancer Hospital. The eligibility criteria were the following: (1) outpatients initiated icotinib hydrochloride as first-line treatment (125 mg tid [3 times a day]; Zhejiang Beta Pharma, Zhejiang, China); (2) Eastern Cooperative Oncology Group performance status 0 to 2; (3) >18 years of age; (4) histologically confirmed stage III-IV NSCLC (*UICC/AJCC Staging Manual*, 6th edition²⁷); and (5) confirmed activating mutation in EGFR, that is, exon 19

deletion or exon 21 L858R point mutation.²⁸ The exclusion criteria were the following: (1) poor therapeutic compliance during the initial observation period judged by the patient or the caretaker or (2) the patient/caretaker did not come to the hospital as scheduled to take obtain the drugs.

Ethical approval was obtained from the Research Ethics Committee of Tianjin Cancer Hospital. All participants and their families, who were interested in participating, signed a "permission to contact" form and were subsequently contacted by the research team to assess eligibility and obtain consent.

The patients were enrolled within 2 weeks after beginning TKI treatment if good compliance was observed. The authors were responsible for drug distribution and patient education at the hospital. The patients were approached for participation when they came to obtain the drugs.

The eligibility criteria of the main caregiver were the following: (1) at least 18 years of age; (2) spouse or adult child of the patient; (3) living with the patient; and (4) no apparent cognitive impairment.

All patients and their family caregivers were from the Tianjin Cancer Hospital. All participants signed an informed consent.

Randomization

The participants were randomized after the baseline evaluation. The participants were randomized and assigned 1:1 to the WE and control groups using sequential sealed envelopes prepared by an independent statistician using a computer-generated random number table.

Blinding

Due to the nature of the intervention, the participants could not be blinded. On the other hand, all assessors responsible to fill out the questionnaires with the participants were blinded to the grouping.

Data Collection

Sociodemographic data (eg, educational status and smoking history) were collected at baseline by questionnaire. Smoking was defined as smoking, irrespective of the amount of tobacco and frequency. Assessment of the QOL, psychological distress, and family relationships was performed at baseline (T0, week 0) and at the end of study (T1, week 8).

Outcomes

The primary outcomes were feasibility of participant recruitment, intervention provision, and data collection; and sample size needed to detect differences in the rates of

unnecessary referral. Additional secondary outcomes included patient QOL and changes in the way of life and family relationships, anxiety, and depression.

Intervention

The intervention was composed of six 45-minute sessions of multidisciplinary components over 8 weeks. The intervention team was composed of 1 chief director physician, 1 deputy director physician, 2 graduate physicians, and 3 nurses. The sessions were offered on 3 different days each week, and the patients attended the session of their choice. The sessions included physical therapy, coping and communication strategies, mental health education, spirituality, social needs, knowledge about lung cancer, TKI treatment, nutrition, physical activity, symptoms, and pain management.

Patients were considered to have dropped out if they had low attendance rate (not due to a physical or health problem), or became physically unfit and unable to continue or finish final evaluation, withdrew consent, or died.

Participants Report Measures

The questionnaires used to assess patient QOL were the Functional Assessment of Cancer Therapy–Lung (FACT-L²⁹; validated Chinese version³⁰) and the Caregiver QOL Index–Cancer Scale (CQOLC³¹; validated Chinese version³²). The FACT-L consists of 36 items grouped into 5 different categories: physical, social, emotional, and functional well-being, as well as the Lung Cancer Subscale²⁹ assessing the symptoms typical for lung cancer (validated in Chinese³³) and the Trial Outcome Index³⁴ (validated in Chinese³⁵). The CQOLC consists of 35 items on 5-point Likert-type scales to assess various domains of caregiver QOL and burden. A total score is obtained, as well as scores for subscales of burden, disruptiveness, adaptation, and financial concerns.

Psychological distress was measured using the Hospital Anxiety and Depression Scale (HADS)³⁶ that measures generalized anxiety and depression experienced during the past week with 2 subscales. A cutoff value of ≥ 8 was used to indicate at least mild distress on each subscale. In addition, a total HADS score (HADS-T) of ≥ 15 was used to indicate clinically significant distress.

Family relationships were evaluated using the relationship dimensions subscale of the Family Environment Scale (FES),³⁷ which is composed of 27 items (3 subscales) that measure cohesion, expressiveness, and conflict. High scores reflect better family relationships. Patients completed the FACT-L and HADS, and caregivers completed the CQOLC and FES–Chinese Version.

Statistical Analysis

The distribution of the continuous data was tested using the Kolmogorov-Smirnov test. Normally distributed continuous

data were presented as mean \pm standard deviation and analyzed using the Student's *t* test. Nonnormally distributed data were presented as median (range) and analyzed using the Kruskal-Wallis test. Categorical data were presented as frequencies and analyzed using the χ^2 test or the Fisher's exact test, as appropriate. SAS 9.1 (SAS Institute, Cary, NY) was used for analysis. Two-sided *P* values $< .05$ were considered as statistically significant. As this was a feasibility study, statistical analyses were exploratory in nature. Thus, although hypothesis tests were performed, statistical significance was understood to be interpretable as a signal rather than a formal probability. Accordingly, no adjustment for multiple testing was performed. QOL, family relationships, anxiety, and depression were analyzed using the per-protocol set.

Results

Enrollment

Figure 1 presents the patient flowchart. Between December 2016 and December 2017, 220 patients/caregivers were assessed for eligibility and 159 met the eligibility criteria and were randomized to the WE group ($n = 80$) and the control group ($n = 79$). At the end of the study period, 67 patients in the WE group and 71 in the control group could be analyzed and included in the per-protocol set.

Characteristics of the Patients

The baseline characteristics of the patients are shown in Table 1. There were no differences between the 2 groups for age, gender, marital status, Eastern Cooperative Oncology Group, brain metastases, initial cancer therapy, and smoking status (all $P > .05$).

Characteristics of the Caregivers

The baseline characteristics of the caregivers are shown in Table 2. There were no differences between the 2 groups for age, gender, relationship to the patient, education, income, employment status, duration of caregiving, and private insurance (all $P > .05$).

Outcomes

The main feasibility outcomes were recruitment and questionnaire completion rates. Feasibility targets were the following: (1) $>70\%$ study enrollment of eligible patients; (2) $>90\%$ of participants completing this study; and (3) $<10\%$ missing data. Preliminary effectiveness outcomes were assessed to inform a future larger scale RCT.

Table 3 shows the trial outcomes. Within the control group, the anxiety (from 10.4 to 7.6, $P = .041$) and depression (from 10.5 to 6.8, $P = .034$) subscales of the HADS

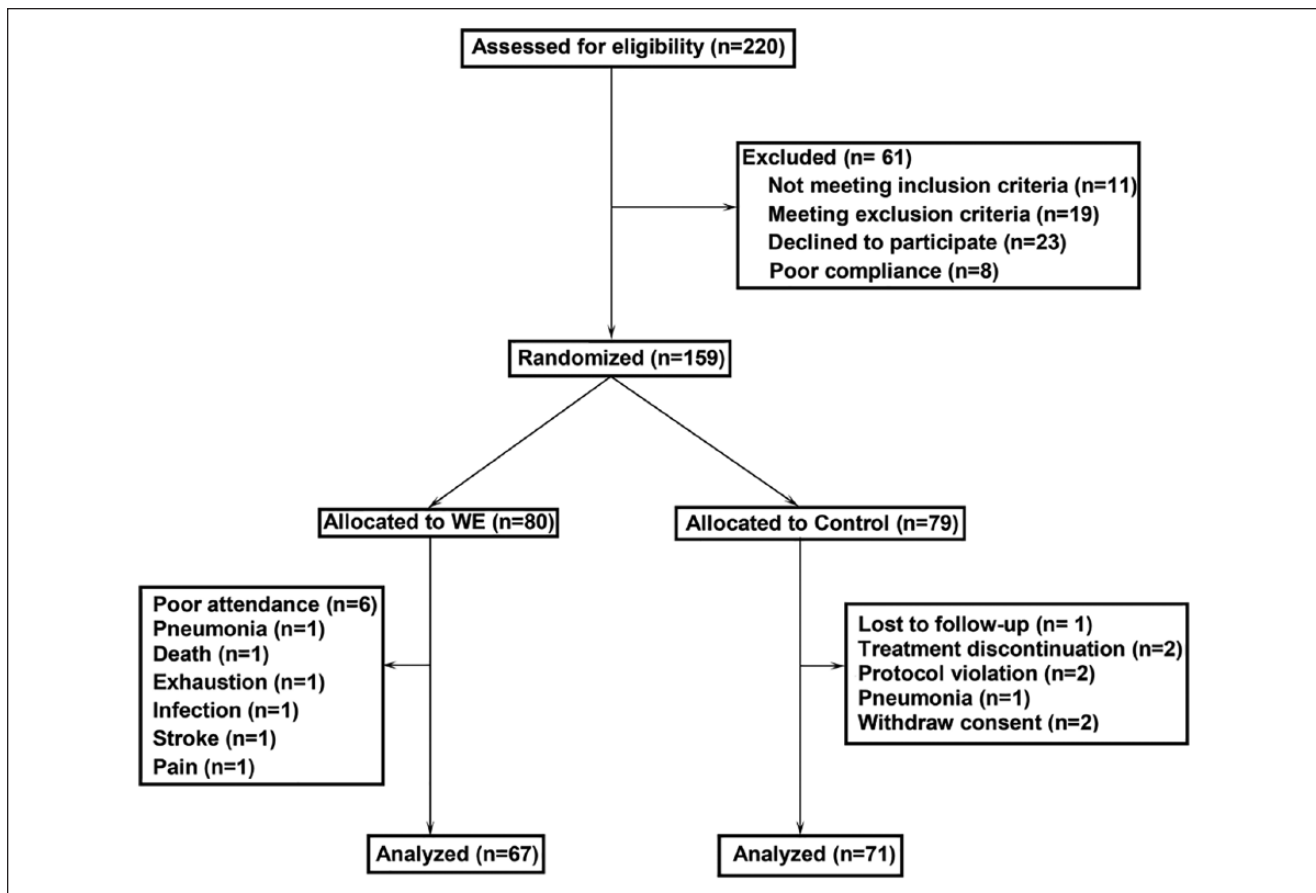


Figure 1. Flow chart of the study.

were decreased. The adaptation score of the CQOLC was decreased (from 65.7 to 54.7, $P = .018$). Within the WE group, the WE intervention improved the emotional well-being (from 18.9 to 12.8, $P = .037$) and Trial Outcome Index (from 56.2 to 44.6, $P = .021$) scores of FACT-L, improved anxiety (from 10.4 to 6.1, $P = .022$) and depression (from 10.5 to 5.8, $P = .039$) subscales of HADS, lowered the burden (from 54.6 to 44.6, $P = .039$) and disruptiveness (from 79.7 to 57.0, $P = .027$) and adaptation score (from 63.6 to 46.4, $P = .011$) subscales of CQOLC, and improved the cohesion (from 5.6 ± 2.7 to 7.3 ± 1.8 , $P = .027$) and conflict (from 4.5 ± 2.8 to 3.4 ± 1.9 , $P = .041$) subscales of FES.

When comparing the 2 groups, the analyses showed that compared with the control group, the WE group had better scores at 8 weeks for the emotional well-being subscale of FACT-L (12.8 vs 15.6, $P = .014$), anxiety subscale of HADS (6.1 vs 6.7, $P = .030$), adaptation (66.0 vs 54.7, $P = .037$) and financial subscales of CQOLC (70.8 vs 69.8, $P = .044$), and the cohesion (7.3 ± 1.8 vs 5.7 ± 1.7 , $P = .021$) and conflict (3.4 ± 1.9 vs 4.5 ± 1.7 , $P = .031$) subscales of the FES.

Discussion

Patients with advanced NSCLC suffer from distress. Approaches have been tried to manage distress,²⁰⁻²³ but there is a lack of well-designed trials.²¹ Therefore, this study aimed to examine the effects of a WE intervention on QOL of patients with stages IIIB-IV NSCLC treated with icotinib and on their caregivers. The results showed that WE interventions in patients and caregivers with stages IIIB-IV NSCLC treated with icotinib are feasible and could improve the QOL of the patients and their relationship with their caregiver.

NSCLC is a difficult experience for a patient and for his or her family. Facing the threat of death and dealing with treatments can strain the family's coping abilities, placing the members into considerable burden, even despair. Psychological stress cannot only be considered a psychological impairment, but also a threat to the whole family relationship. Previous findings indicated that depression might be fostered by age and the level of education; older and less educated people are prone to a higher risk of depression.³⁸

Table 1. Characteristics of the Patients.

	TKI (n = 71), n (%)	TKI + WE (n = 67), n (%)	P
Age	54	57	>.05
Gender			>.05
Male	20 (28.2%)	21 (31.3%)	
Female	51 (71.8%)	46 (68.7%)	
Marital status			>.05
Married	63 (88.7%)	62 (92.5%)	
Single	1 (1.4%)	0	
Divorced	4 (5.6%)	3 (4.5%)	
Widowed	3 (4.2%)	2 (3.0%)	
ECOG performance			>.05
0	2 (2.8%)	3 (4.5%)	
1	4 (5.6%)	6 (9.0%)	
2	65 (91.6%)	58 (86.5%)	
Brain metastases	8 (11.3%)	11 (16.4%)	>.05
Initial anticancer therapy			>.05
Oral EGFR-TKI	71	67	
Radiotherapy (brain)	3 (4.2%)	6 (9.0%)	
Smoking status			>.05
Never smoked	51 (71.8%)	49 (73.1%)	
Smoking	20 (28.2%)	18 (26.9%)	
HADS	19.3	18.9	>.05
Stage of disease			>.05
III	22 (31.0%)	15 (22.4%)	
IV	49 (69.0%)	52 (77.6%)	
Time since diagnosis			
Within 1 month	71	67	

Abbreviations: TKI, tyrosine kinase inhibitor; WE, wellness education; ECOG, Eastern Cooperative Oncology Group functional status; EGFR, epidermal growth factor receptor; HADS, Hospital Anxiety and Depression Scale cutoff scores (0-7 = normal, 8-10 = borderline abnormal [borderline case]; 11-21 = abnormal).

Few reports have examined how the experience of cancer diagnosis and treatment affects family caregivers in patients with NSCLC in China. The present study suggests benefits of a WE intervention in patients and their caregivers, including improvements in QOL and psychological well-being. Caregivers face experiences that are different from those faced by patients, and thus different strategies could be beneficial. Indeed, through qualitative analyses of the participants' verbatim, the WE intervention was well received by the patients and caregivers, and showed positive effects on family relationships, even though not all scores were strong enough for statistical significance. Second, the intervention had positive effects on some parameters of QOL, suggesting that it could be used in combination with other means to improve the overall QOL of the patients. Nevertheless, QOL scores were improved, but lung symptom scores were not, indicating that this approach could be complementary to medical interventions improving QOL.

The WE approach used here is a kind of psycho-oncologic intervention that is based on the voluntary participation of the patients and their caregivers. For the purpose of

the study, the participants were required to attend 6 sessions over 8 weeks, but the participants had the choice to attend the session that fitted with their schedule. Such flexibility could increase the adherence of the participants to the intervention. Indeed, 84% of the patients/caregivers completed the entire study as per protocol. Compared with the control group, the WE group had better scores at 8 weeks for the emotional well-being subscale of FACT-L, anxiety subscale of HADS, adaptation and financial subscales of CQOLC, and the cohesion and conflict subscales of the FES. Although preliminary, the results were consistent with the general effect of psycho-oncologic interventions on the QOL of cancer patients and their caregivers. Indeed, as reviewed by Faller et al²¹ and by Northouse et al,³⁹ the general trend of psycho-oncologic interventions is to improve the QOL of the patients and their caregivers, but the previous studies have to be taken with caution considering the wide variability in quality. In this article, a RCT was designed. Unfortunately, blinding was not possible for the participants, and some bias could be responsible for the observed differences.

Table 2. Characteristics of the Caregivers.

	TKI (n = 71), n (%)	TKI + WE (n = 67), n (%)	P
Age	47	54	>.05
Gender			>.05
Male	11 (15.5%)	8 (11.9%)	
Female	60 (84.5%)	59 (88.1%)	
Relationship to patient			>.05
Spouse	45 (63.4%)	46 (68.7%)	
Daughter/son	23 (32.4%)	21 (31.3%)	
Other	3 (4.2%)	0	
Education			>.05
Primary school	21 (29.6%)	26 (38.8%)	
Middle school	23 (32.4%)	18 (26.9%)	
High school and above	27 (38.0%)	23 (34.3%)	
Annual household income (RMB)			>.05
<60 000	0	0	
61 000-111 999	20 (28.2%)	13 (19.4%)	
>120 000	51 (71.8%)	54 (80.6%)	
Employment status			>.05
Employed	26 (36.6%)	30 (44.8%)	
Unemployed	5 (7.0%)	4 (6.0%)	
Retired	40 (56.3%)	43 (64.2%)	
Duration of caregiving (months)	2	2	
Private insurance			>.05
Yes	6 (8.5%)	4 (6.0%)	
No	65 (91.5%)	63 (94.0%)	

Abbreviations: TKI, tyrosine kinase inhibitor; WE, wellness education; RMB, renminbi.

Table 3. Study Endpoints.

	TKI		P Within Group	TKI + WE		P Within Group	Change Score, Between Group	
	Baseline	Endpoint		Baseline	Endpoint		(95% CI)	P
<i>Patient</i>								
FACT-L scale								
PWB	21.8 ± 5.3	16.9 ± 7.1	.052	21.4 ± 5.3	17.4 ± 5.7	.089	0.08 (-0.02 to 0.22)	.103
SWB	19.7 ± 5.0	18.9 ± 6.2	.065	19.3 ± 3.8	17.1 ± 5.5	.078	0.11 (-0.08 to 0.16)	.122
EWB	16.1 ± 5.1	15.6 ± 5.9	.050	18.9 ± 6.0	12.8 ± 5.7	.037	1.44 (0.75 to 2.13)	.014
FWB	17.5 ± 6.7	14.9 ± 6.3	.077	14.1 ± 5.8	13.1 ± 5.4	.07	0.52 (-0.41 to 1.46)	.098
LCS	19.3 ± 3.8	19.4 ± 5.7	.151	20.4 ± 5.1	17.4 ± 5.7	.09	1.60 (-1.34 to 1.62)	.159
TOI	57.6 ± 12.5	58.4 ± 12.6	.105	56.2 ± 10.8	44.6 ± 10.6	.021	1.38 (-0.96 to 3.72)	.123
HADS								
Anxiety subscale	10.4 ± 3.1	7.6 ± (3.0)	.041	10.4 ± 3.1	6.1 ± (2.2)	.022	1.9 (0.6 to 3.3)	.030
Depression subscale	10.5 ± 3.6	6.8 ± (5.8)	.034	10.5 ± 3.6	5.8 ± (3.5)	.039	0.50 (-0.46 to 1.46)	.221
<i>Caregiver</i>								
CQOLC								
Burden	55.9 ± 17.3	50.9 ± 7.3	≥.05	54.6 ± 12.1	44.6 ± 10.7	.039	1.5 (0.6 to 3.3)	.077
Disruptiveness	76.5 ± 20.7	71.5 ± 22.7	≥.05	79.7 ± 22.4	57.7 ± 20.9	.027	3.4 (2.5 to 4.3)	.057
Adaptation	65.7 ± 13.7	54.7 ± 11.7	.028	63.6 ± 19.7	46.4 ± 18.7	.011	6.7 (5.3 to 8.2)	.037
Financial	67.8 ± 21.9	69.8 ± 11.9	≥.05	76.8 ± 14.5	70.8 ± 19.3	.141	5.9 (4.4 to 7.3)	.044
FES-CV								
Cohesion	5.1 ± 1.6	5.7 ± 1.7	≥.05	5.6 ± 2.7	7.3 ± 1.8	.027	0.07 (0.04 to 0.12)	.021
Conflict	4.9 ± 1.9	4.5 ± 1.7	≥.05	4.5 ± 2.8	3.4 ± 1.9	.041	1.08 (0.14 to 0.77)	.031
Expressiveness	4.1 ± 1.8	4.7 ± 2.2	≥.05	4.2 ± 1.9	4.1 ± 1.8	.056	0.03 (0.21 to 0.91)	.056

Abbreviations: TKI, tyrosine kinase inhibitor; WE, wellness education; CI, confidence interval; FACT-L, Functional Assessment of Cancer Therapy–Lung; PWB, physical well-being; SWB, social well-being; EWB, emotional well-being; FWB, functional well-being; LCS, lung cancer subscale; TOI, Trial Outcome Index; HADS, Hospital Anxiety and Depression Scale; CQOLC, Caregiver QOL Index–Cancer Scale; FES-CV, Family relationship Chinese version of the Family Environment Scale.

Note: The significance of values in bold in table 3 are all $P < .05$.

Study Limitations

The study has some limitations. First, because the participants volunteered, the sample may have been subjected to some selection bias in that these patients may have been more motivated to participate in research activities than other persons. Therefore, the entire target population may have been misrepresented. Second, the follow-up was short, as the authors were only responsible for drug distribution for the first few months (patients could later receive free medication from charity if the drug was effective, and they no longer went to the hospital). Another study limitation is that only an immediate follow-up time point was used. Third, the participants might be physically healthier and therefore more willing to participate in the present study. Fourth, though the participants were randomized, blinding was impossible. Finally, participants in the control group formally requesting psycho-oncologic consultation or detected to be with clinically significant distress could not be denied any intervention. Additional multicenter study is necessary to determine the real effectiveness of the WE approach.

Conclusion

In conclusion, WE interventions in patients and caregivers with stages IIIB-IV NSCLC treated with icotinib are feasible and could improve the QOL of the patients and their relationship with their caregiver.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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