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Patient-Reported Outcomes of Chemotherapy Involving Non-Small Cell Lung Cancer: Evaluation by Questionnaires of Quality of Life Regarding Anti-Aging and Anti-Cancer Drugs

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Abstract

Background: Patient-reported outcomes (PROs) of quality of life (QOL) during chemotherapy involving lung cancer are very important for the medical staffs. Patients' satisfaction and healthy changes were evaluated by the patient-self assessment. **Materials and Methods:** From July 2007 to April 2008, a total of 19 patients received chemotherapy. The QOL data were collected by using the QOL questionnaire for cancer patients treated with anticancer drugs (QOL-ACD) and the anti-aging QOL assessment (AA-QOL). The AA-QOL contained 51 items: 30 of physical and 21 of mental symptoms of the elderly and the aging population. The patients replied to the questions at two different times, *i.e.*, at pre-chemotherapy (baseline) and at post-chemotherapy (2 weeks after the chemotherapy). **Results:** Regarding the hematological toxicities, for the grade 3/4 toxicities, there were 12 neutropenia (12/19, 63.2%) and 3 thrombocytopenia (3/19, 15.8%). For the grade 3 febrile neutropenia, there were 5 cases (5/19, 26.3%). Regarding the non-hematological toxicities, there was no grade 3 and grade 4 toxicities. Based on the outcomes of the QOL-ACD, the three items ("physical condition", "social attitude", and "overall QOL") at post-chemotherapy became significantly worse compared to the baseline. Regarding the outcomes of the AA-QOL, 4 items of physical symptoms ("thirst", "anorexia", "early satiety", and "diarrhea") became significantly worse compared to the baseline. Regarding the mental symptoms, 2 items ("nothing to look forward in life" and "a sense of uselessness") became significantly worse compared to the baseline. **Conclusion:** Regarding the PROs of the QOL during the chemotherapy term, both the physical and mental symp-

toms had become worse. To clarify the changes in the QOL during chemotherapy is very important for multidisciplinary teamwork, which should play the role of providing the appropriate cares and treatment as patient-support.

Keywords

Patient-Reported Outcome, Chemotherapy, Quality of Life, Non-Small Cell Lung Cancer

1. Introduction

Lung cancer is one of the most common malignancies and remains the leading cause of cancer-related deaths in Europe and the USA [1] [2], and also in Japan [3]. The impact of chemotherapy on the survival and quality of life (QOL) on advanced non-small cell lung cancer (NSCLC) has long been the subject of debate and led to the publication of five meta-analyses of randomized trials between 1993 and 1999 testing the addition of only chemotherapy as the best supportive care [4] [5] [6] [7]. These meta-analyses concluded that chemo- therapy, mainly cisplatin-based regimens, had a modest beneficial impact on survival, with a 10% improvement in the 1-year survival and an estimated gain in the median survival of 1.5 months [6].

Although platinum-based doublets involving newer agents, such as docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan, are the standard first-line chemotherapy for most patients with advanced NSCLC [8] [9], the use of these regimens in elderly patients remains a topic of debate [10]. The main reasons given for withholding standard platinum-based doublet regimens from elderly patients are the age-related impairment of organ functions, presence of potentially complicating comorbid conditions, and a lower ability to tolerate the potential toxicity of the combination chemotherapy than younger patients.

More recent randomized trials of adjuvant cisplatin-based chemotherapy have shown only a marginally better compliance despite considerable improvements in the supportive care medications available over the past decade. North American [11], Japanese [12], and European [13] [14] [15] intergroup trials reported that only 58% - 69% of patients received all of the planned cycles of chemotherapy.

The World Health Organization defined the QOL as "individual" perceptions of their position in life in the context of their culture and value systems in which they live and in relation to their goal, expectation, standards and concerns" [16]. The impact of disease and treatment-related symptoms on the health-related quality of life (HR-QOL) was assessed using the self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) questionnaire (QLQ-C30) version 3.0 and the associated EORTC Quality of Life Lung Cancer-Specific Module (EORTC QLQ-

LC13) [17] [18]. The QOL in patients with NSCLC receiving chemotherapy was mainly studied using the EORTC QLQ questionnaire [19]-[24].

However, regarding the HR-QOL in the chemotherapy of lung cancer, it is important to assess the clinical outcome based on the patient's aspect. There are very few studies about the QOL, especially about patient-reported outcomes (PROs). It is also difficult for doctors and nurses to evaluate the patients' QOL as comprehensive and objective indicators. PROs include areas of the HR-QOL, but also broader concepts such as patient satisfaction with care and treatment.

We previously reported the PRO of the surgery of lung cancer by an evaluation based on the questionnaires of the anti-aging quality of life (AA-QOL) and EORTC-C30 QLQ [25]. In case of the surgical modality, the healthy changes represented that the physical symptoms became worse compared to the mental symptoms. The PRO for surgery is very important for multidisciplinary teamwork, which should play a role in providing the appropriate care and treatments and useful information for a preoperative patient's decision making of receiving surgical treatment.

The aim of the present study is to clarify the patient's satisfaction and healthy changes of the patients receiving chemotherapy for lung cancer, which is an evaluation to be performed by the patient's self-assessment. We did not use the famous and the most world-widely-used EORTC QLQ questionnaire survey in this study. However, we used two patient-reported questionnaire surveys of the QOL; one is the QOL questionnaire for cancer patients treated with anticancer drugs (QOL-ACD), which consists of four domains (functional, physical, mental, and psychosocial), and a global face scale developed as a generic questionnaire for Japanese cancer patients undergoing chemotherapy [26]. The other is the anti-aging QOL assessment (AA-QOL), which is specific for 30 physical and 21 mental symptoms for the Japanese elderly population [27].

2. Materials and Methods

2.1. Patients

This study was approved by the University of Miyazaki Hospital Clinical Research Ethics Board. The procedures used in this study were in accordance with the Helsinki Declaration. From July 2007 to April 2008, a total of 19 patients, who received neoadjuvant therapy, adjuvant therapy, and intensive chemotherapy for recurring cases of the CBDCA-GEM or CBDCA-PTX or CDDP + DOC doublet combinations and DOC monotherapy. The characteristics of the 19 patients entered in this study are summarized in **Table 1**. The TNM classification is based on the Union for International Cancer Control (UICC) [28]. The histological analysis of the tumor was based on the World Health Organization classification for cell types [29]. Patients with histologically documented NSCLC and pathologically staged were eligible to receive induction chemotherapy, adjuvant chemotherapy after complete resection of the primary tumor and mediastinal lymph nodes in our department. The patient selection was at the discretion of the attending physicians. All patients provided informed consent before the

treatment.

2.2. Each Patient Had to Meet the Following Eligibility Criteria

Pathological stage diagnosed with IB to IV, Eastern Cooperative Oncology Group Performance Status of 0, 1 or 2, adequate bone marrow function (total leukocyte count ≥4.0 × 10^9/ L, hemoglobin concentration ≥10.0 g/dl, platelet count ≥100 × 10^9/L), adequate liver and renal function (serum transaminase ≤2 times normal value; serum creatinine ≤1.5 times normal value), partial pressure of arterial oxygen (paO_2) ≥60 torr, past history of severe allergic reaction to drugs, interstitial pneumonia identified by computed-tomography of chest, cirrhosis, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, and uncontrolled massive pleural effusion or ascites, no postoperative complications, able to undergo first course treatment in an inpatient setting within 4 to 8 weeks after surgery, and written informed consent.

Table 1. Patient characteristics (n = 19).

Gender	Male/Female	13/6
Age (year)	Mean ± SD	66.2 ± 10.1
	Range	44 - 86
ECOG-PS	0/1	19/0
Surgery	Lobectomy	19
Histology	Adenocarcinoma	17
	Squamous cell carcinoma	2
Pathological stage	IIA	2
	IIIA	9
	IIIB	3
	IV	5
Chemotherapy	Neoadjuvant therapy	3
	Adjuvant therapy	11
	Intensive chemotherapy for recurrence	5
Regimen	GEM + CBDCA	13
	PTX + CBDCA	3
	DOC + CDDP	2
	DOC	1
Planned cycles	2/3/4 cycles	8/3/8
Received cycles	2/3/4 cycles	8/3/8
Compliance	Dose reduction	5/19 (26.3%)
	Delayed	1/19 (5.3%)
Response evaluation	Partial response	3 (37.5%, 3/8)
	Stable disease	5 (62.5%, 5/8)
Toxicities	≥Grade 3/4	14/19 (73.7%)

ECOG-PS: Eastern Cooperative Oncology Group Performance Status, GEM: Gemcitabine, CBDCA: Carboplatin, PTX: Paclitaxel, CDDP: Cisplatin, DOC: Docetaxel.

2.3. Treatment Schedule

All patients received one protocol from the prepared four treatment regimens by the attending doctors' direction and/or patients' favorable selection depending on the regimen's toxicities. The body surface area was calculated using the Du-Bois equation. The carboplatin dosage calculation was based on the glome- rular filtration rate according to the Calvert formula [30], and evaluated by the Cock-croft-Gault equation [31]. The administration of the carboplatin dosage was adjusted prior to each cycle through redetermination of the glomerular filtration rate.

2.3.1. Gemcitabine plus Carboplatin Regimen

Gemcitabine (Gemzar®, Eli Lilly Japan K.K., Kobe, Japan) was administered at a dose of 1000 mg/m^2 on days 1 and 8, and carboplatin (Paraplatin®, Bristol-Myers K.K., Tokyo, Japan) with the target dose of area under the curve (AUC) of 4 on day 8 every 28 days. Premedication was intravenously performed by drip infusion of 100 ml of isotonic sodium chloride solution containing 8 mg of dexamethasone sodium phosphate and 3 mg of granisetron hydrochloride. On days 1 and 8, the intravenous (i.v.) administration of 1000 mg/m^2 gemcitabine mixed in 100 ml of isotonic sodium chloride solution was performed by drip infusion for 30 minutes. On day 8, carboplatin with the calculated dose of the AUC mixed in 250 ml of a 5% glucose solution was administered for 1 hour, following the drip infusion of gemcitabine.

2.3.2. Paclitaxel plus Carboplatin Regimen

Paclitaxel (Paclitaxel®, Bristol-Myers K.K., Tokyo, Japan) was administered at a dose of 70 mg/m^2 on days 1, 8 and 15, and carboplatin (Paraplatin®, Bristol-Myers K.K., Tokyo, Japan) with the target dose of AUC of 5 on day 1 every 28 days. As a premedication, 50 mg of diphenhydramine hydrochloride was intravenously infused. The drip infusion of 50 ml of an isotonic sodium chloride solution containing 8 mg of dexamethasone sodium phosphate, 50 mg of ranitidine hydrochloride and 10 mg of azasetron hydrochloride was performed. After the administration of seventy mg/m^2 of paclitaxel in 250 ml of a 5% glucose solution for over 1 hour, carboplatin with the calculated dose of the AUC mixed in 250 ml of a 5% glucose solution was intravenously infused for 1 hour.

2.3.3. Docetaxel plus Cisplatin Regimen

Docetaxel (Taxotere®, Sanofi K.K., Tokyo, Japan) was administered at a dose of 60 mg/m^2 on day 1, and cisplatin (Platosin®, Phizer Japan, Inc., Tokyo, Japan) on day 1 every 28 days. The drip infusion of 100 ml of an isotonic sodium chloride solution containing 8 mg of dexamethasone sodium phosphate and 3 mg of granisetron hydrochloride was performed. After the administration of 60 mg/m^2 of docetaxel in 250 ml of a 5% glucose solution for over 1 hour, 80 mg/m^2 of cisplatin in 500 ml of an isotonic sodium chloride solution was intravenously infused for 2 hours. As hydration, drip infusions of 500 ml of an isotonic sodium chloride solution for over 2 hours, 500 ml of a 5% glucose solution for over 2 hours,

and 500 ml of a maintenance solution with electrolyte for over 2 hours were performed. The drip infusion of 300 ml of a 20% of D-mannitol for over 1 hour was performed. A 20 mg amount of furosemide was intravenously injected.

2.3.4. Docetaxel Regimen

Docetaxel (Taxotere®, Sanofi K.K., Tokyo, Japan) was administered at a dose of 60 mg/m^2 on day 1 every 21 days. The drip infusion of 100 ml of an isotonic sodium chloride solution containing 8 mg of dexamethasone sodium phosphate and 3 mg of granisetron hydrochloride was performed. The drip infusion of 250 ml of an isotonic sodium chloride solution containing 60 mg/m^2 of docetaxel (Taxotere®, Sanofi K.K., Tokyo, Japan) for over 1 hour was performed.

2.3.5. The Exclusion Criteria

The exclusion criteria included serious infection, fever (≥38˚C), impairments of an organ function (bone marrow, central nervous and cardiovascular system, liver, kidneys, interstitial pneumonia, and disseminated intravascular coagulation), patient's refusal and attending doctor's decision.

2.4. Toxicity

Prior to receiving the chemotherapy, all patients provided a complete medical history and underwent a physical examination. Patients were monitored weekly throughout the treatment by physical examination, recording of toxic effects, complete blood cell counts, and blood chemistry. These patients were examined for their background characteristics, adverse events, treatment compliance and relapse-free survival. Adverse events (AE) were evaluated for 4 weeks after the completion of the chemotherapy according to the Common Terminology Criteria for Adverse Events Version. 3.0 (CTCAE v3.0). The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on this general guideline: Grade 1, mild AE; Grade 2, moderate AE; Grade 3, severe AE; Grade 4, life-threatening or disabling AE; grade 5, Death related to AE. Grade 3/4 thrombocytopenia (grade 3, <50.0 – 25.0 × 10^9/l; grade 4, <25.0 × 10^9/l) and grade 1/2 alopecia (grade 1, thinning or patchy; grade 2, complete) were defined.

2.5. The Patient-Centered Outcomes of Quality of Life

The QOL data were collected using questionnaires from the QOL questionnaire for cancer patients treated with anticancer drugs (QOL-ACD) and the Anti-aging Quality-of-Life Assessment (AA-QOL). The questionnaires of the QOL-ACD and the AA-QOL were used to obtain the patient-centered QOL during the chemotherapy treatment period. The patients replied to the questionnaires at different times. *i.e.*, before and after chemotherapy, which was at the pre-chemotherapy (baseline) and at the post-chemotherapy (2 weeks after the chemotherapy). The obtained data of these scores at the pre-chemotherapy and the post-chemotherapy times were averaged and compared between the two groups, of which the changes were represented as the second evaluation of the QOL.

2.5.1. The Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD)

The QOL questionnaire for cancer patients treated with anticancer drugs (QOL-ACD), which consists of four domains (functional, physical, mental, and psychosocial) and a global face scale, was developed as a generic questionnaire for Japanese cancer patients undergoing chemotherapy [26]. Matsumoto T. *et al*. [32] examined the validity and reliability of this questionnaire of Japanese patients with advanced NSCLC who participated in two randomized phase III trials. The results confirmed the high reliability of the questionnaire. The results of a factor analysis provided strong support for the domain structure used in the questionnaire. Each of the four domains had a moderate to strong association with important clinical variables, such as performance status or weight loss, and a correlation analysis showed that the face scale provided an appropriate measure of the global QOL. The QOL-ACD is potentially useful for clinical research regarding Japanese patients with advanced NSCLC.

2.5.2. Anti-Aging Quality of Life Assessment (AA-QOL)

Observation of improvement in the QOL was used by a common interview sheet. At the baseline and after surgery, any improvement in the QOL, *i.e*., "physical symptoms" and "mental symptoms" as subjective symptoms, were evaluated using a five-point scale (1-point: absolutely none; 2-point: almost not; 3-point: mild, 4-point: moderate; 5-point:severe) using the Anti-aging QOL Common Questionnaire (AA-QOL) [27].

The symptomatic evaluated items are 30 physical symptoms and 21 mental ones. The physical symptoms are listed as "tired eyes", "blurry eyes", "eye pain", "stiff shoulders", "muscular pain/stiffness", "palpitations", "dyspnea", "tendency to gain weight", "weight loss; thin", "lethargy", "no feeling of good health", "thirst", "skin problems", "anorexia", "early satiety", "epigastralgia", "liable to catch colds", "coughing and sputum", "diarrhea', "constipation", "headaches", "dizziness", "tinnitus", "lumbago", "arthralgia", "edematous", "easily breaking into a sweat", "frequent urination", "hot flash", and "cold skin". Mental symptoms are listed as "irritability", "easily angered", "loss of motivation", "no feeling of happiness", "nothing to look forward in life", "daily life is not enjoyable", "loss of confidence", "reluctance to talk with others", "depressed", "a sense of uselessness", "shallow sleep", "difficulty falling asleep", "pessimism", "lapse of memory", "inability of concentrate", "inability to solve problems", "inability to readily make judgements", "inability to sleep because of worries", "a sense of tension", "feeling of anxiety for no special reason", and "a vague feeling of fear". The physical symptoms and mental symptoms were evaluated using a five-point scale (1 through 5).

To perform the second evaluation of the QOL scores using the five-point scale, we evaluated the transition of the QOL scores regarding each symptom before and after chemotherapy. We determined a significant change in the second evaluation of the QOL score, when the values changed more than 10% from the baseline score. We allocated the changed rates of each symptom before

and after chemotherapy, *i.e.*, as three types, that is improved ("↑"; increased more than 10%), unchanged ("→"; changed within ±10%), and worse ("↓"; decreased less than −10%).

2.6. Statistical Analysis

A statistical analysis of the results was performed using the paired t-test. A value of $p < 0.05$ was considered to indicate a statistically significant change. A statistical analysis of the results was performed using the paired t-test for comparison of the values between the level at the baseline and that after 8 weeks of administration in each group.

3. Results

3.1. Patient Characteristics

A total of 19 patients (13 males and 6 females) received chemotherapy in our department as summarized in Table 1. The majority of patients were males (13/19, 68.4%) with a median age of 66.2 ± 10.1 years (range 44 - 86). The ECOG performance status was 0 in the 19 patients (19/19, 100%). A lobectomy was performed in the 19 patients (19/19, 100%). Tumor histology included 17 patients with adenocarcinoma (89.5%), and 2 patients with squamous cell carcinoma (10.5%). There were 2 patients with stage IIA (10.5%), 9 patients with stage IIIA (47.4%), 3 patients with stage IIIB (15.8%), and 5 patients with stage IV (26.3%). The GEM + CBDCA regimen was performed for 13 patients (13/19, 68.4%), PTX + CBDCA was for 3 patients (3/19, 15.8%), DOC + CDDP for 2 patients (2/19, 10.5%), and DOC monotherapy for 1 patient (1/19, 5.3%). The toxicities of more than grade 3 and/or grade 4 were observed in 14 patients (14/19, 73.7%).

3.2. Treatment Background

A total of 57 chemotherapy cycles of the planned 2 (n = 8), 3 (n = 3), and 4 cycles (n = 8) were administered as listed in Table 1. Regarding the compliance, all patients (100%, 19/19) received the scheduled cycles. Five patients (26.3%, 5/19) received a dose reduction in the next course. One patient (5.3, 1/19%) delayed the course.

3.3. Treatment Response

Regarding the final effect of treatment, that is neo adjuvant therapy (n = 3) and intensive chemotherapy for recurring cases (n = 5), there were 3 partial responses for an overall response rate of 37.5% (3/8) as listed in Table 1. In addition, 5 patients (62.5%, 5/8) had stable diseases.

3.4. Toxicity

Table 2 shows the hematological toxicities. For the grade 4 toxicities, there were 7 neutropenia (7/19, 36.8%) and 3 thorambocytopenia (3/19, 15.8%). For the

grade 3/4 toxicities, there were 12 neutropenia (12/19, 63.2%) and 9 thorambocytopenia (9/19, 47.4%). For the grade 3 febrile neutropenia, there were 5 cases (5/19, 26.3%).

Table 3 shows the non-hematological toxicities. There were no grade 3 and grade 4 toxicities. For the grade 2 toxicities, there were 2 anorexia (2/19, 10.5%), 2 fatigue (2/19, 10.5%), 5 alopecia (5/19, 26.3%), 1 fever (1/19, 5.3%), and 1 other (healing) (1/19, 5.3%).

3.5. Patient-Centered Outcomes of Quality of Life

3.5.1. Patient-Reported Outcomes of QOL-ACD

Table 4 shows the assessment results of the factors of "daily-life activities", "physical condition", "psychology condition", "social attitude", "face scale", and "overall QOL". The four items ("daily-life activities", "physical condition", "face scale", and "overall QOL") at post-chemotherapy significantly resulted in a worse QOL compared to the values at pre-chemotherapy (the baseline). The scale of "daily-life activities" significantly decreased, which changed from 25.3 ±5.1 at the baseline to 20.7 ± 6.8 at post-chemotherapy ($p = 0.013$). The scale of

Table 2. Outcomes for hematological toxicities.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)	
Leukopenia	8	5	0	0	0	
Neutropenia	3	3	5	7	12	(63.2)
Anemia	3	4	0	0	0	
Thrombocytopenia	0	3	6	3	9	(47.4)
Febrile neutropenia	0	0	5	0	5	(26.3)

Table 3. Outcomes for non-hematological toxicities.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	16	0	0	0
Vomiting	1	0	0	0
Anorexia	13	2	0	0
Fatigue	13	2	0	0
Diarrhea	2	0	0	0
Constipation	2	0	0	0
ALT/AST	0	0	0	0
Creatinine	0	0	0	0
Neuropathy	0	0	0	0
Pain, joint	1	0	0	0
Pain, muscle	1	0	0	0
Skin rash	1	0	0	0
Alopecia	1	5	0	0
Infection	0	0	0	0
Fever	5	1	0	0
Others (hearing)	0	1	0	0

Table 4. Outcomes for QOL-ACD.

Scale	Items*	Pre-chemotherapy (Scores at baseline)	Post-chemotherapy (Scores at 2 weeks)	p value
Daily-life activities	1 - 6	25.3 ± 5.1	20.7 ± 6.8	0.013
Physical condition	7 - 11	21.5 ± 3.2	16.4 ± 4.5	< 0.001
Psychological condition	12 - 16	18.6 ± 4.1	16.8 ± 4.3	0.091
Social attitude	17 - 21	13.9 ± 3.8	13.2 ± 5.0	0.306
Face scale	22	3.8 ± 0.9	2.9 ± 0.9	0.003
Overall QOL		83.1 ± 12.1	69.9 ± 17.2	0.005

*Numbers correspond to item numbers on the 22-item questionnaire (QOL-ACD).

"physical condition" significantly decreased, which changed from 21.5 ± 3.2 at the baseline to 16.4 ± 4.5 at post-chemotherapy ($p < 0.001$). The scale of "face scale" significantly became worse, which changed from 3.8 ± 0.9 at the baseline to 2.9 ± 0.9 at post-chemotherapy ($p = 0.003$). The scale of "overall QOL" significantly showed a worse change, which changed from 83.1 ± 12.1 at the baseline to 69.9 ± 17.2 at post-chemotherapy ($p = 0.005$). For the other scales of "psychology condition" and "social attitude", the values at post-chemotherapy appeared to undergo a similar change compared to the values at the baseline, however, there were no significant changes.

3.5.2. Patient-Reported Outcomes of AA-QOL

Table 5 shows the values of 30 items of the physical symptoms. Seven symptom items ("lethargy", "thirst", "anorexia", "early satiety", "liable to catch colds", "diarrhea", and "constipation") became significantly worse compared to those at pre-chemotherapy.

The symptom of "lethargy" changed from 2.2 ± 1.1 at pre-chemotherapy (at the baseline) to 3.2 ± 1.2 at post-chemotherapy ($p = 0.004$) (an increase of 1.5-fold magnitude). The symptom of "thirst" changed from 1.7 ± 0.8 at the baseline to 2.5 ± 1.2 at post-chemotherapy ($p = 0.006$) (an increase of 1.5-fold magnitude). The symptom of "anorexia" changed from 2.1 ± 1.0 at the baseline to 3.5 ± 1.4 at post-chemotherapy ($p = 0.001$) (increase of 1.7-fold magnitude). The symptom of "early satiety" changed from 1.6 ± 0.8 at the baseline to 2.6 ± 1.3 at post-chemotherapy ($p = 0.001$) (increase of 1.6-fold magnitude). The symptom of "liable to catch colds" changed from 1.8 ± 0.9 at the baseline to 2.3 ± 1.2 at post-chemotherapy ($p = 0.035$) (increase of 1.3-fold magnitude). The symptom of "diarrhea" changed from 1.5 ± 0.9 at the baseline to 2.1 ± 1.4 at post-chemotherapy ($p = 0.049$) (increase of 1.4-fold magnitude). The symptom of "constipation" changed from 2.2 ± 1.3 at the baseline to 3.2 ± 1.4 at post-chemotherapy ($p = 0.005$) (increase of 1.5-fold magnitude). Regarding the second evaluation of the anti-aging QOL, 19 items were evaluated and became worse (63.3%, 19/30). These symptoms become worse due to the chemotherapy, while the other 11 items were evaluated to be unchanged (36.7%, 11/30). There were no symptoms that became better after the chemotherapy.

Table 5. Outcomes for anti-aging quality of life assessment (30 items, physical symptoms).

Physical symptoms (30 items)	Post-chemotherapy (Scores at 2 weeks)		p value	change (%)	2nd evaluation of QOL
Tired eyes	2.3 ± 1.1	2.7 ± 1.2	0.131	16.1	↑
Blurry eyes	2.2 ± 1.0	2.3 ± 1.2	0.346	5.8	→
Eye pain	1.3 ± 0.6	1.5 ± 0.8	0.145	16.1	↑
Stiff shoulders	2.5 ± 1.1	2.6 ± 1.2	0.353	4.8	→
Muscular pain/stiffness	2.0 ± 1.1	2.5 ± 1.3	0.079	24.5	↑
Palpitations	1.6 ± 0.7	1.7 ± 0.8	0.353	5.1	→
Dyspnea	1.9 ± 1.0	2.1 ± 1.1	0.247	11.1	↑
Tendency to gain weight	1.7 ± 1.0	1.7 ± 1.0	0.483	−0.7	→
Weight loss; thin	2.3 ± 1.1	2.6 ± 1.4	0.163	15.8	↑
Lethargy	2.2 ± 1.1	3.2 ± 1.2	0.004	41.4	↑
No feeling of good health	2.5 ± 1.1	3.0 ± 1.4	0.105	18.0	↑
Thirst	1.7 ± 0.8	2.5 ± 1.2	0.006	43.9	↑
Skin problems	2.1 ± 1.0	2.6 ± 1.3	0.061	26.0	↑
Anorexia	2.1 ± 1.0	3.5 ± 1.4	0.001	67.0	↑
Early satiety	1.6 ± 0.8	2.6 ± 1.3	0.001	65.8	↑
Epigastralgia	1.6 ± 0.7	2.0 ± 1.1	0.083	23.1	↑
Liable to catch colds	1.8 ± 0.9	2.3 ± 1.2	0.035	31.0	↑
Coughing and sputum	2.5 ± 1.2	2.7 ± 1.0	0.307	6.3	→
Diarrhea	1.5 ± 0.9	2.1 ± 1.4	0.049	38.9	↑
Constipation	2.2 ± 1.3	3.2 ± 1.4	0.005	48.1	↑
Headaches	2.7 ± 1.4	2.7 ± 1.4	0.500	0.0	→
Dizziness	2.0 ± 1.4	2.0 ± 1.4	0.500	0.0	→
Tinnitus	1.9 ± 0.9	2.1 ± 1.0	0.188	13.3	↑
Lumbago	1.7 ± 1.0	1.8 ± 1.0	0.280	10.0	↑
Arthralgia	2.0 ± 1.2	2.1 ± 1.0	0.450	2.0	→
Edematous	2.0 ± 1.1	2.6 ± 1.3	0.063	25.5	↑
Easily breaking into a sweat	1.7 ± 0.7	2.1 ± 1.3	0.114	21.1	↑
Frequent urination	1.5 ± 0.7	1.4 ± 0.5	0.311	−5.7	→
Hot flash	2.5 ± 1.4	2.4 ± 1.3	0.337	−6.3	→
Cold skin	1.9 ± 0.7	2.0 ± 0.8	0.283	7.0	→

A five-point scale (1-point: absolutely none; 2-point: almost not; 3-point: mild, 4-point: moderate; 5-point: severe). Mean ± SD, Wilcoxo's signed rank test.

Table 6 shows the values of 21 items regarding the mental symptoms. Three symptom items ("nothing to look forward in life", "a sense of uselessness", and "shallow sleep") became significantly worse compared to those at pre-chemotherapy (at the baseline). The symptom of the "nothing to look forward in life" changed from 2.1 ± 0.8 at the baseline to 2.6 ± 1.2 at post-chemotherapy (p =

Table 6. Outcomes for anti-aging quality of life assessment (21 items, mental symptoms).

Mental symptoms (21 items)	Pre-chemotherapy (Scores at baseline)	Post-chemotherapy (Scores at 2 weeks)	p value	change (%)	2nd evaluation of QOL
Irritability	1.4 ± 0.5	1.5 ± 0.6	0.299	6.1	→
Easily angered	1.9 ± 1.1	1.8 ± 1.2	0.402	−4.3	→
Loss of motivation	2.0 ± 0.8	2.3 ± 1.0	0.193	11.4	↑
No feeling of happiness	2.0 ± 0.9	2.1 ± 0.9	0.367	4.5	→
Nothing to look forward in life	2.1 ± 0.8	2.6 ± 1.2	0.049	23.3	↑
Daily life is not enjoyable	2.1 ± 1.0	2.5 ± 1.2	0.089	21.2	↑
Loss of confidence	1.8 ± 0.9	2.2 ± 1.1	0.102	20.5	↑
Reluctance to talk with others	2.0 ± 1.0	2.2 ± 1.3	0.218	13.1	↑
Depressed	2.1 ± 1.0	2.3 ± 1.1	0.222	10.7	↑
A sense of uselessness	1.9 ± 0.9	2.4 ± 1.2	0.038	29.9	↑
Shallow sleep	1.8 ± 0.7	2.4 ± 1.3	0.031	31.9	↑
Difficulty falling asleep	2.2 ± 1.0	2.4 ± 1.0	0.254	8.7	→
Pessimism	2.3 ± 1.1	2.7 ± 1.2	0.101	18.1	↑
Lapse of memory	2.3 ± 1.1	2.7 ± 1.2	0.097	19.0	↑
Inability of concentrate	1.8 ± 0.9	2.2 ± 1.2	0.104	20.8	↑
Inability to solve problems	2.4 ± 1.2	2.2 ± 1.0	0.325	−6.0	→
Inability to make judgements readily	2.1 ± 0.9	2.5 ± 1.2	0.098	18.7	↑
Inability to sleep because of worries	2.1 ± 1.1	2.1 ± 0.8	0.495	0.2	→
A sense of tension	2.0 ± 0.9	2.2 ± 1.0	0.327	6.4	→
Feeling of anxiety for no special reason	2.3 ± 1.1	2.5 ± 1.1	0.339	5.8	→
A vague feeling of fear	2.4 ± 0.9	2.3 ± 1.1	0.404	-3.0	→

A five-point scale (1-point: absolutely none; 2-point: almost not; 3-point: mild, 4-point: moderate; 5-point: severe), Mean ± SD, Wilcoxo's signed rank test.

0.049) (increase of 1.2-fold magnitude). The symptom of "a sense of uselessness" changed from1.9 ± 0.9 at the baseline to 2.4 ± 1.2 at post-chemotherapy (p = 0.038) (increase of 1.3-fold magnitude). The symptom of "shallow sleep" changed from 1.8 ± 0.7 at the baseline to 2.4 ± 1.3 at post-chemotherapy (p = 0.031) (increase of 1.3-fold magnitude). Regarding the second evaluation of the anti-aging QOL, 12 items were evaluated that became worse (57.1%, 12/21), and 9 items were evaluated to be unchanged (42.9%, 9/21). There was no symptoms that became better after the chemotherapy.

4. Discussion

NSCLC is the leading cause of cancer mortality [3] [33] [34]. The last decade has seen significant improvement in the first- and second-line treatments of NSCLC.

Chemotherapy prolongs survival, alleviates disease-related symptoms and can improve the QOL in the patient population compared to best supportive care [20] [21] [35] [36]. A superiority in efficacy, toxicity and QOL has been demonstrated for the new platinum-containing regimens compared to the older regimens [19] [37] [38] [40] [41] [42] [43] [44]. Non-platinum-containing regimens have also demonstrated equivalence in efficacy with differing toxicities [45] [46] [47] [48] [49]. Studies suggest that the efficacy benefits of chemotherapy are reached after 3 - 4 cycles, and further treatment beyond this may only increase the toxicity and reduce the QOL [50] [51] [52].

In contrast, adjuvant therapy for early-stage NSCLC has been the focus of many studies in the hope of reducing the relapse risk and improving survival from the 40% to 60% achieved with surgery alone [34]. Adjuvant chemotherapy for early stage NSCLC is now the standard of care, but there is little information regarding its impact on the quality of life (QOL). Bezjak A *et al*. [53] reported the QOL results of JBR.10, a North American, intergroup, randomized trial of adjuvant cisplatin and vinorelbine compared with observation in patients who had complete resections, stages IB to II NSCLC. The findings of this trial indicated that the negative effects of adjuvant chemotherapy on the QOL appear to be temporary, and that improvements (with a return to baseline function) are likely in most patients [53].

In 2010, the NSCLC Meta-analysis Collaborative Group [54] showed a benefit of adjuvant chemotherapy after surgery from the results that the meta-analysis of surgery plus chemotherapy versus surgery alone was based on 34 trial comparisons and 8447 patients (3323 deaths). The NSCLC Meta-analyses Collaborative Group [54] recorded a benefit of adding chemotherapy after surgery (hazard ratio [HR] 0.86, 95%CI 0.81 - 0.92, $p < 0.0001$) with an absolute increase in survival of 4% (95%CI 3 - 6) at 5 years (from 60% to 64%).There were phase III trials using four cycles of vinorelbine and cisplatin, namely the JBR.10 [55] and ANITA trials [56]. In the JBR.10 trial, 77% of the patients required at least a one-dose reduction [55]. In the ANITA trial, the median percentage of the planned doses of vinorelbine and cisplatin were 56.3% and 76.1%, respectively, because of adverse events [56]. Treatment compliance has thus to date been low in the platinum-based adjuvant chemotherapy in oversea postsurgical resection patients. In the Japanese patients, the UFT trial has only been a phase III trial to demonstrate survival benefits for patients whose NSCLCs were completely resected.

The evidence reports about the carboplatin plus gemcitabine regimen in Japan are few compared to those of carboplatin plus paclitaxel, almost all being reported from overseas [57] [58]. The gemcitabine plus carboplatin regimen was allowed to be administered in a outpatients setting due to the short drip infusion time and mild non hematological toxicities such as alopecia and gastroenterological symptoms, however, thrombocytopenia should require attention. On the other hand, carboplatin plus paclitaxel was one of the standard treatments based on significant evidence reported around the world, and was appropriate to ad-

minister in an outpatients setting due to the mild toxicities. However, during the long-term administration, its neuropathy was frequently recognized [39]. For these reasons and the inconvenience of prolonged infusion, the weekly administration of paclitaxel was evaluated in several cancer patients, yielding a beneficial activity and reduced toxicity [59].

We previously reported the result of chemotherapy (gemcitabine plus carboplatin versus paclitaxel plus carboplatin) in elderly patients with non-small cell lung cancer [60] and that the gemcitabine plus carboplatin and paclitaxel plus carboplatin combination chemotherapies are efficacious and feasible regimens for lung cancer therapy, especially, both regimens should be considered as one of the standard therapies for elderly patients during lung cancer therapy. We also previously reported the result of adjuvant chemotherapy (gemcitabine plus carboplatin versus paclitaxel plus carboplatin), and these results demonstrated that the gemcitabine plus carboplatin and paclitaxel plus carboplatin combination chemotherapies are efficacious and feasible regimens, which should be considered as one of the standard therapies for adjuvant therapy [61].

The past decade has seen a significant interest in QOL research within oncology and palliative medicine. It is now widely accepted that some consideration of a patient's QOL must be an integral part of the optimal medical care. More recently, the term PROs or patient-reported outcome measurement (PROM) was introduced by regulatory authorities [62] as a term encompassing any measures directly obtained from the patient and including areas of HR-QOL, but also broader concepts such as patient satisfaction with care. Patient-reported HR-QOL has also been found to predict the response to treatment and survival in a number of advanced solid cancers [63] [64].

The outcomes of a clinical intervention obtained by the patient, i.e., PROs, seemed to be of more importance in the future than any other outcomes like the clinical, physiological or caregiver-reported [65]. As past studies, the enhanced treatment adherence and outcomes can be obtained by paying attention to patient feedback on healthcare outcomes and patient behavior changes [65]. A PRO is any report about the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by clinicians or anyone else [65].

The outcomes are broadly classified into clinical (e.g., cure, survival), humanistic (e.g., role performance, emotional status) and economical (e.g., expenses, savings) [66]. In the clinical scenario, the outcomes can be clinician-reported (e.g., performance of the patient), caregiver-reported (e.g., functional status), physiologic (e.g., tumor size by MRI) or patient-reported (e.g., symptoms). If the patient is observed for the outcomes by clinicians, researcher or caregiver, then the outcomes become observer-reported outcomes. If the patient has revealed in the written questionnaire that he/she is experiencing morning stiffness, it is PRO, but if the clinician is asking to describe the morning stiffness, *i.e.*, the severity and nature are considered to be observer-reported outcomes [65].

In the present study, we did not use the famous and most world-widely-used

EORTC QLQ questionnaire survey, however, we used the two patient-reported questionnaire surveys of the QOL. One is the quality of life questionnaire for cancer patients treated with anticancer drugs (QOL-ACD), which consists of four domains (functional, physical, mental, and psychosocial) and a global face scale, which was developed as a generic questionnaire for Japanese cancer patients undergoing chemotherapy [26]. The other is the anti-aging QOL assessment (AA-QOL), which is specified for 30 physical and 21 mental symptoms for the Japanese elderly population [27].

Based on the outcomes of the QOL-ACD, the three items ("physical condition", "social attitude", and "overall QOL") at post-chemotherapy significantly showed worse results compared to the values at pre-chemotherapy (at the baseline). For the other scales of "daily-life activities", "psychology condition", and "social attitude", the values at post-chemotherapy became worse compared to the values at the baseline, however, there was no significant changes. For the outcomes of AA-QOL, 4 items of physical symptoms ("thirst", "anorexia", "early satiety", and "diarrhea") were significantly worse compared to that of baseline. For the second evaluation of AA-QOL, 19 items were observed with increased changes (63.3%, 19/30), while 11 items were unchanged (36.7%, 11/30). For the mental symptoms, 2 items (nothing to look forward in life and a sense of uselessness) were significantly worse compared to those at the baseline. For the second analysis of AA-QOL, 12 items were observed with increased changes (57.1%, 12/21), while 9 items were unchanged (42.9%, 9/21).Based on the outcomes on the symptomatic changes of the QOL after chemotherapy, both the physical and mental symptoms became worse during the chemotherapy term.

Regarding the relationship between the self-reported outcomes based on the questionnaires (QOL-ACD and AA-QOL) and clinical ones used for our four chemotherapeitc regimens, the hematological toxicities showed moderate to severe toxicities(grade 3/4 toxicities were highly observed (14/1, 73.7%). However, in contrast, the non-hematological ones mostly displayed mild toxicities (grade 1/2 toxicities were highly observed). For the mild non-hematological toxicities, the adverse event could not be correctly expressed by the patient's individual sense and its degrees were a small difference in the QOL, because they were mostly ambiguous and diverse. On the other hand, the self-reported outcomes should be able to express subtle individual sense and changes in the QOL, and its physical and mental symptoms should be able to be accurately indicated as a variable of the QOL change, which information should be useful in the multidisciplinary.

Previously, we reported the PRO of the surgery of lung cancer by the evaluation based on the questionnaires of AA-QOL and EORTC-C30 QLQ [25]. Based on our results of the PRO of the surgical treatment [25], the healthy changes suggested that the physical symptoms became worse compared to the menal symptoms. However, in the present study, for the chemotherapeutic modality, the healthy changes suggested that the both physical and mental symptoms became worse.

Based on the research of the difference between the symptoms and HR-QOL [65], although the symptoms of the patient and HR-QOL are similar, they are two different concepts. Symptom is a one-dimensional property while HR-QOL is multidimensional. Symptoms are often the main objective of treatment, mirror clinician-patient discourse and vary dynamically with time. However, for the HR-QOL, all of these items are rare. Symptoms are directly related to disease and the treatment effect, while there is an indirect relation of them with the HR-QOL. For the PRO concepts, symptoms are often considered for behavioral objective measures, but seldom for the HR-QOL. The complexity of the concepts is high for the HR-QOL, but simple in the case of symptoms.

To clarify the healthy changes of the QOL reported by a patient in chemotherapy due to lung cancers is very important for doctors and nurses, which should play a role in providing the appropriate care and treatment in order to realize a satisfaction by the patients and their support. For a patient receiving chemotherapy due to lung cancer, and for multidisciplinary teamwork, the PROs should provide very helpful information and very convenient to obtain informed consent in making a decision of receiving chemotherapy, which encourages future chemotherapeuic patients to use as a reference in considering the symptomatic and healthy changes during chemotherapeuic treatment.

5. Conclusion

To clarify the changes of the QOL in chemotherapy reported by a patient with lung cancers is very important for multidisciplinary teamwork, which should play a role in providing the appropriate care and treatment in order to realize a satisfactory patient-support.

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Abbreviation

GEM: Gemcitabine, CBDCA: Carboplatin, PTX: Paclitaxel, CDDP: Cisplatin, DOC: Docetaxel, QOL-ACD: the quality of life questionnaire for cancer patients treated with anticancer drugs, Anti-aging quality of life assessment: AA-QOL.