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The Evaluation of Dyspnea in Elderly Patients with Advanced Non-Small-Cell-Lung Cancer Receiving Palliative Chemotherapy

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Abstract

Background: Therapeutic decisions in lung cancer patients are in great part based on ECOG performance status. Little is known, however, what is the relation between dyspnea and ECOG performance status. The aim of the study was to elucidate to what extent dyspnea influences ECOG performance status in the elderly patients with the with advanced Non-Small Cell Lung Cancer (NSCLC) and whether dyspnea may be considered as a factor influencing the results of palliative chemotherapy.

Material and Methods: Material of the study consisted of 27 patients aged over 65 years with advanced NSCLC scheduled for the first-line palliative chemotherapy. The following studies were performed: spirometry, Modified Medical Research Council (mMRC) questionnaire, Six Minutes Walk Test (6MWT), Borg dyspnea scale, and COPD Assessment Test (CAT). After removing from CAT 3 items not related to dyspnea (cough, phlegm and sleep), the remaining 5 questions were analyzed as modified CAT, i.e. mCAT.

Results: Dyspnea was a complaint of 78% of patients. The patients with ECOG 1/ECOG 2 performance status had higher mMRC and CAT scores than the patients with ECOG 0 performance status. mCAT score was almost 2.5 times higher in the patients with ECOG 1/ECOG 2 than in the patients with ECOG 0 performance status (13.0 ± 5.1 *vs.* 5.1 ± 5.1, $p < 0.001$). Score of mCAT positively correlated with the score in mMRC scale ($r = 0.68$, $p < 0.05$) and Borg scale at rest ($r = 0.390$, $p < 0.05$) and negatively correlated with the distance in the 6MWT ($r = -0.56$, $p < 0.05$). Non-completion of chemotherapy was associated with smaller FEV1 and FVC, shorter distance in 6MWT and more severe dyspnea in the Borg scale.

Conclusion: Dyspnea is a complaint of the majority of elderly patients with advanced NSCLC patients and is more severe in the patients with the performance status higher than ECOG 0. 6MWT and modified CAT are the best tools to evaluate dyspnea in the elderly patients with advanced NSCLC. The evaluation of dyspnea may help to assess the performance status in the elderly patients with advanced NSCLC. Objective measure of dyspnea, i.e. shortened distance in 6MWT, may allow to predict unfavorable course of the palliative chemotherapy in the elderly patients with advanced NSCLC.

Keywords: Lung cancer; Dyspnea; Performance status; CAT; mMRC; Six-minutes-test walk

Introduction

Dyspnea, important problem in the patients with lung cancer, may have multiple causes, including – among the other – atelectasis, multiple metastases, carcinomatous lymphangiosis, superior vena cava syndrome, infiltration of mediastinum and paresis of laryngeal and/or phrenic nerves, pleural or pericardial fluid, secondary pneumonia, thromboembolic lung disease. Dyspnea in the course of lung cancer, occurs regardless the age and sometimes may be very severe [1-3]. It strongly influences performance status of the patients.

Therapeutic decisions in lung cancer patients are in great part based on Eastern Cooperative Oncology Group (ECOG) performance status. ECOG scale includes grades from 0 to 5, where grade 0 (patient is fully active, able to carry on all pre-disease performance without restriction), grade 1 (patient is restricted in strenuous activity but able to carry out a light work), and grade 2 (patient is able of all selfcare, but unable to carry out any work activities and spends more than half of a day outside the bed) allow considering the eligibility of the patient to chemotherapy [4]. Little

Table 1: The comparison of age, TNM stage, coexistence of COPD and severe ischemic heart disease, nutritional status, number of received cycles of chemotherapy and number of patients who completed the scheduled at least three cycles of chemotherapy in the patients with advanced NSCLC according to the ECOG 0 or ECOG 1 and ECOG 2 performance status.

	ECOG 0	ECOG 1/ECOG 2	p
	N=18	N=9	
Age (years)	71.8±4.6	70.4±5.6	NS
Stage III A and III B (number of patients)	10	5	NS
Stage IV (number of patients)	8	4	NS
COPD (number of patients)	8	4	NS
Heart infarct in the past (number of patients)	6	3	NS
BMI (kg/m²)	27.6±4.2	23.3±3.6	<0.05
Overweight or obese patients (number)	14	1	<0.001
Number of received cycles of chemotherapy	3.1±1.1	3.6±1.2	NS
Completion of at least 3 cycles of chemotherapy (number of patients)	14	8	NS

is known, however, about the relation between dyspnea and ECOG performance status. Dyspnea is also important factor influencing quality of life of the patients with lung cancer, and changes in quality of life significantly influence the results of chemotherapy and survival [5].

Thus the aim of the study was to evaluate the dyspnea in the elderly patients with the advanced Non-Small Cell Lung Cancer (NSCLC) and to answer the question to what extent subjectively and objectively measured dyspnea influences the patients' ECOG performance status and whether dyspnea may be considered as a factor influencing the results of palliative chemotherapy.

Material and Methods

Material of the study consisted of 27 patients (19 men) aged over 65 years with advanced NSCLC, diagnosed and treated at the Lower Silesian Center of Lung Diseases in Wroclaw, Poland, in the years 2015-16. Based on the TNM classification there were nine patients in the stage IIIA, six patients in the stage IIIB and 12 patients in the stage IV. The patients with clinical or radiological signs of brain metastases were excluded from the study. There were nine patients who previously underwent heart infarct and 12 patients were diagnosed with Chronic Obstructive Pulmonary Disease (COPD). There were 17 patients who had either COPD or underwent ischemic heart disease. There were 18 patients with ECOG 0, four patients with ECOG 1 and five patients with ECOG 2 performance status. All the patients were scheduled for the first-line palliative chemotherapy.

The patients underwent spirometric studies, fulfilled the Modified Medical Research Council (mMRC) questionnaire, performed Six Minutes Walk Test (6MWT) with Borg dyspnea scale, and fulfilled COPD Assessment Test (CAT).

Spirometric study included the measurements of Forced Vital Capacity (FVC), Forced Expiratory Volume in first second (FEV_1) and FEV_1/FVC ratio calculation.

The mMRC was used to measure the grade of breathlessness on a five-point scale, ranging from 0 to 4. Grade 0 indicates breathlessness only with strenuous exercise, grade 1 – short of breath when hurrying on level ground or walking up a slight hill, grade 2 – need to walking slower than people of the same age on a level plane because of breathlessness, grade 3 – need to stop for breath after walking about 100 meters or after a few minutes on level ground, and grade 4 – breathlessness when dressing [6].

In the 6MWT the patients were asked to walk as far as possible along a flat course during six minutes, instructed and encouraged according to standard rules [7]. During 6MWT walking distance was the primary outcome and the following measures were taken twice, i.e. before and at the end of the test: oxygen saturation of hemoglobin (SaO_2) based on pulsoximetry recordings, heart rate and arterial blood pressure measurements, and dyspnea score based on modified Borg dyspnea scale.

The modified Borg scale allows to assess the dyspnea based on 10-items' scale, describing the dyspnea as none, extremely mild, very mild, mild, moderate, intense, rather intense, very intense, almost unbearable or unbearable [8-10].

CAT is a questionnaire, containing the items regarding coughing (from never to coughing all the time), feeling of having no phlegm (mucus) in the chest or feeling that the chest is completely full of phlegm, sensation that the chest does not feel tight at all to sensation that the chest feels very tight, breathlessness or not while walking up a hill or one flight of stairs, limitations doing activities at home (from no limitations to being very limited), feeling confident/unconfident leaving home despite/because of lung condition, sleeping soundly or not sleeping soundly because of lung condition, having lots of energy or having no energy at all [11]. In the eight-items CAT the answers are scored from 0 to 5, thus the total score range is 0-40, with the lowest values indicating better, and higher scores indicating worse state of health [12]. As in the CAT questionnaire there are four items that may be indirectly related to dyspnea (tightness in the chest, limitations during activities at home, feeling unconfident leaving home, lack of energy) and one item directly indicating dyspnea (breathlessness while walking up a hill or upstairs) the scores in these items were summed and analyzed separately. The score of these five items derived from CAT was called modified CAT (mCAT). This scale might vary from 0 to 25.

Informed consent has been obtained from all the patients participating in the study.

A statistical software was used for all the measures (Statistica for Windows, version 12). For descriptive data mean values with Standard Deviation (SD) were used. In comparisons between the groups non-parametric U Mann-Whitney test was used for data with distributions of values different from normal and t-test for data with normal distribution. A p value < 0.05 was considered significant.

Table 2: The results of spirometric studies, mMRC dyspnea scale, 6MWT, and CAT score in the whole group of patients with advanced NSCLC and in the subgroups with ECOG 0 and ECOG 1+ECOG 2 performance scale.

		1	2	3	
		All	ECOG 0	ECOG 1 and 2	p
			n=18	n=9	
		mean±SD	mean±SD	mean±SD	
spirometry	FEV_1 (l)	1.7±0.6	1.6±0.5	1.8±0.8	NS
	FEV_1 (%)	68.8±22.5	68.6±23.3	69.3±22.4	NS
	FVC (l)	2.7±0.8	2.6±0.8	2.9±0.9	NS
	FVC (%)	84.3±22.7	83.3±22.2	86.7±25.8	NS
	FEV_1/FVC (%)	63.2±10.2	63.6±10.8	62.1±9.7	NS
mMRC (score 0-4)		1.2±1.2	0.5 ±0.5	2.3±1.2	<0.001
6MWT	distance (m)	306.7±93.8	326.7±73.0	266.7±120.8	NS
	BORG scale pre- test (0-10)	0.9±1.4	0.83±1.5	1.0±1.2	NS
	Borg scale post-test (0-10)	2.2±2.1	1.88±1.9	2.8±2.2	NS
	SaO_2 pre-test (%)	97.2±0.75	97.3±0.8	97.1±0.6	NS
	SaO_2 post-test (%)	95.6±2.1	95.6±2.5	95.5±1.1	NS
	blood pressure systolic pre-test (mmHg)	126.8±9.1	129.16±7.9	122.0±9.9	NS
	blood pressure diastolic post-test(mmHg)	73.8±8.3	75.55 ±6.4	70.33±10.7	NS
	blood pressure systolic pre-test (mmHg)	137.0±8.8	138.05±6.9	135.0±12.0	NS
	blood pressure diastolic post-test (mmHg)	80.2±6.8	81.38±4.8	77.8±9.4	NS
	heart rate pre-test (n/min)	76.7±7.1	77.1±5.93	75.9±9.4	NS
	heart rate post-test (n/min)	89.1±10.1	88.5±10.2	90.2±10.4	NS
CAT	total score (0-40)	15.3±8.8	12.6±7.7	20.8±8.7	<0.05
	coughing (0-5)	2.7±1.8	2.8±1.8	2.3±1.80	NS
	phlegm in the chest (0-5)	1.9±1.7	1.9±1.8	1.8±1.71	NS
	feeling tight in the chest (0-5)	0.9±1.5	0.9±1.5	1.0±1.7	NS
	dyspnea at one flight of stairs (0-5)	2.9±2.0	2.3±1.9	4.2±1.3	<0.05
	limitations doing activities at home (0-5)	1.3±1.9	0.4±1.0	3.1±2.0	<0.001
	unconfident leaving home (0-5)	1.4±1.9	0.8±1.5	2.7±2.1	<0.05
	not sleeping soundly (0-5)	2.4±1.9	2.3±2.0	2.7±1.6	NS
	lack of energy (0-5)	1.6±1.8	0.8±1.4	3.0±1.7	<0.01
	mCAT score (0-25)	7.7±6.3	5.1±5.1	13.0±5.1	<0.001

Results

Dyspnea, as evaluated in the subjective scales, such as mMRC, Borg scale at rest, i.e. before 6MWT and in one item of CAT, was a complaint of 21 patients (78%) before chemotherapy and only five patients did not have dyspnea in any scale.

There were 16 patients who had dyspnea, as scored in the mMRC scale: 13 patients – when hurrying on level ground or walking up a slight hill (mMRC 1), two patients – enabling to walk as quickly as people of the same age on a level plane (mMRC 2), two patients – after walking about 100 meters or after a few minutes on level ground (mMRC 3) and two patients – when dressing (mMRC 4).

There were nine patients who had dyspnea at rest, as scored in the Borg scale before 6MWT: one patient described dyspnea as very mild, four patients – as mild, three patients – as moderate, and one patient – as rather intense.

There were 21 patients who had dyspnea while walking up a hill or upstairs, as indicated in the item of CAT: four patients scored dyspnea

as very mild (score 1- two patients) or mild (score 2- two patients), two patients – as medium (score 3), 15 patients – as submaximal (score 4- eight patients) or maximal (score 5- seven patients). The scores in mCAT ranged from 0 to 19.

There was no correlation between mMRC and Borg scale at rest. Score of mCAT positively correlated with the score in mMRC scale (r = 0.68, p <0.05) and Borg scale at rest (r = 0.390, p <0.05).

Borg scale score increased significantly after 6MWT (Table 2), both in the patients with ECOG 0 performance status (p <0.01) and in the patients with ECOG 1 or ECOG 2 performance status (p <0.001).

The objective evaluation of dyspnea with 6MWT revealed the distance ranging from 120 m to 430 m, mean 306.7 ± 93.8 m.

There was a negative correlation between the distance in the 6MWT with subjective score of dyspnea as evaluated in the Borg scale at rest (r = -0.689, p <0.05) and with mCAT (r = -0.56, p <0.05), but not with the total CAT score and not with the item of CAT directly indicating dyspnea. There was no correlation between 6MWT

Table 3: The comparison of the results of age, BMI, spirometric studies, CAT score mMRC dyspnea scale, and 6MWT in the patients with advanced NSCLC who completed and non-completed the scheduled of at least three cycles of chemotherapy.

		Completion of at least 3 cycles of chemotherapy	Non-completion of at least 3 cycles of chemotherapy	p
		n=23	n=5	
Age (years)		71.1±5.0	72.6±4.4	NS
BMI (kg/m²)		26.2±4.7	26.0±4.1	NS
spirometry	FEV₁ (ml)	1.8±0.6	1.04±0.1	<0.05
	FEV₁ (%)	72.6±22.1	47.0±6.5	NS
	FVC	2.8±0.8	1.81±0.4	<0.05
	FVC%	88.1±22.3	62.7±9.5	NS
	FEV₁/FVC	63.9±10.4	58.7±9.7	NS
CAT total score (0-40)		15.1±9.2	16.0±7.4	NS
mCAT score (0-25)		8.4±5.9	7.6±6.5	NS
mMRC (score 0-4)		1.3±1.2	0.6±0.6	NS
6MWT	distance (m)	324.1±83.2	230.0±109.1	<0.05
	BORG scale pre-test (0-10)	0.6±1.1	2.0±1.9	<0.05
	Borg scale post-test (0-10)	1.97±2.0	3.1±2.4	NS
	SaO₂ pre-test (%)	97.3±0.6	97.0±1.2	NS
	SaO₂ post- test(%)	95.6±2.2	95.4±1.7	NS
	blood pressure systolic pre-test (mmHg)	135.7±7.9	143.0±10.9	NS
	blood pressure diastolic post-test (mmHg)	80.0±7.4	81.00±2.2	NS
	blood pressure systolic pre-test (mmHg)	125.4±9.1	133.0±6.7	NS
	blood pressure diastolic post-test (mmHg)	73.5±8.9	75.0±5.0	NS
	heart rate pre-test (n/min)	76.6±7. 6	77.20±5.4	NS
	heart rate post-test (n/min)	90.0±10.6	85.0±7.1	NS

distance and mMRC score.

Because both COPD and ischemic heart disease may cause dyspnea the result were compared in the groups of 17 patients with either COPD or heart infarct in anamnesis and in the group of remaining 10 patients without any of these diseases. Dyspnea, evaluated both subjectively (mMRC scale, Borg scale at rest, CAT scores) or objectively (as 6MWT distance) was of similar intensity in both groups.

In order to reveal possible relation between dyspnea and the patients' performance status, the groups of patients with ECOG 0 performance status were compared with the patients with ECOG 1 or ECOG 2 performance status (Table 1 and 2). The patients in both groups were of similar age, with similarly advanced disease and with similar frequency of concomitant diseases, such as COPD or heart infarct in anamnesis. The patients in the ECOG 0 group had higher BMI and more frequently were overweight or obese. The results of spirometric studies were similar in both groups. In all the patients there was a normal SaO₂ at rest, similar in both groups and exceeding 94%.

In the subjective evaluation of dyspnea, the patients in the ECOG1/ECOG2 group had higher scores in the mMRC and in some items in CAT, i.e. in the item indicating dyspnea at one flight of stairs, limitations doing activities at home, unconfident feeling leaving home and lack of energy – leading to higher total score of CAT. The sum of the item directly indicating dyspnea climbing the stairs or walking up the hill and four items in CAT indirectly related to dyspnea (i.e. mCAT) revealed higher score in the patients with ECOG

1 and ECOG 2 group. There were no differences in the subjective evaluation of dyspnea in the Borg scale – both before or after 6MWT. The objective measure of the distance in 6MWT revealed slightly, not significantly, shorter distance in the patients in the ECOG 1/ECOG 2 group. Heart rate and arterial blood pressure in 6MWT did not differ between the groups.

The comparison of the groups of patients who completed or not-completed the scheduled at least three cycles of chemotherapy revealed that non-completion of chemotherapy was associated with smaller lung volumes and capacities (FEV₁ and FVC) and more severe dyspnea in objective measure of a distance in 6MWT, as well in subjective measure in the Borg test before 6MWT (Table 3).

Discussion

In the elderly patients with advanced NSCLC dyspnea differentiated the groups with ECOG 0 or ECOG 1/ECOG 2 performance status. The patients with ECOG 0 had lower mMRC scores and lower scores of CAT.

mMRC is a scale of breathlessness recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) to assess the symptoms of the patients with COPD [13]. It can be also used in the lung cancer patients [14,15].

In our elderly patients with advanced NSCLC the mean score was slightly above 1 in the five-level mMRC scale (1.2 ± 1.2). In the COPD patients mMRC score <2 is considered as a mark of slight symptoms [13]. In our group of patients mMRC score was above 2 in the patients with ECOG 1/ECOG 2 performance status and almost five

times higher than in the patients with ECOG 0 performance status (2.3 ± 1.2 vs. 0.5 ± 0.5, p <0.001). As mMRC allows to assess dyspnea during daily activities, higher score of mMRC in the patients with poorer performance status mirrored limited physical possibilities of these patients.

The CAT was developed to measure dyspnea and other components of quality of life in the COPD patients [11] and is also recommended by GOLD to assess the symptoms of the COPD patients [13]. The CAT serve not only to evaluate COPD patients [12], but recently – also to evaluate the patients with interstitial lung diseases [16]. To the best of our knowledge CAT was not used to assess the symptoms of the patients with lung cancer.

In our elderly patients with NSCLC the mean CAT score was 15.3 ± 8.8 and was significantly higher in the patients with ECOG1 and ECOG 2 performance status that in the patients with ECOG 0 performance status (20.8 ± 8.7 vs. 12.6 ± 7.7, p <0.05). In the COPD patients total CAT score of >10 indicates more severe symptoms [13]. Thus high score of CAT in our elderly patients with NSCLC, especially in ECOG 1/ECOG2 group, indicated severely impaired health status.

In the eight-item CAT one question directly regards dyspnea, i.e.– while climbing one flight of stairs or walking up the hill – and in the scale from 0 to 5 our elderly patients with NSCLC reached the mean value of 2.9 ± 2.0, that clearly indicated dyspnea on effort. The dyspnea was much more severe in the patients with ECOG1/ECOG2 that in the ECOG 0 performance status patients (4.2 ± 1.3 vs. 2.3 ± 1.9).

After removing from CAT three items obviously not related to dyspnea (describing cough, phlegm and sleep), the remaining five questions were analyzed and called by the authors modified CAT, i.e. mCAT. mCAT score was significantly (p <0.001), i.e. almost 2.5 times, higher in the patients with ECOG1/ECOG2 (13.0 ± 5.1) than in the patients with ECOG 0 performance status (5.1 ± 5.1), indicating more severe complaints related to dyspnea either directly (the question about breathlessness while walking up a hill or upstairs) or indirectly (the questions about tightness in the chest, limitations during activities at home, feeling unconfident leaving home, and lack of energy) in this group of patients.

The value of mCAT was confirmed by its positive correlation with other subjective scales of dyspnea, such as mMRC and Borg scales, and – especially – by its negative correlation with objective measure of dyspnea, i.e. with the distance in the 6MWT. Thus our modification of CAT, i.e. selection of five items directly or indirectly related to dyspnea from CAT, allowed to find a tool clearly differentiating ECOG 0 and ECOG1/ECOG 2 patients.

In contrast to mMRC and CAT, another subjective measure of breathlessness, i.e. Borg scale, describes the sensation of dyspnea at the moment of assessment. Borg scale might be used to evaluate cancer patients [17]. In our elderly patients with advanced NSCLC, evaluated at rest, the values of the Borg scale were very low (mean 0.9±1.4), with no differences related to ECOG performance status. However, after an effort, i.e. after 6MWT, the scoring in the Borg scale increased significantly in all the patients, and especially – almost three times – in the patients with ECOG 1/ECOG 2 group (1.0 ± 1.2 to 2.8 ± 2.2, p <0.001).

In contrast to subjective scales of dyspnea, there were no differences in the objective measurement of distance in the 6MWT in the patients with different ECOG performance status groups.

It should be also underlined that the objective measurements of lung volumes were similar in the groups of patients with different performance status, despite clear differences in subjectively perceived dyspnea in mMRC scale and CAT. Similarly, the patients were not hypoxemic, as indicated by normal SaO_2 – both at rest and after 6MWT – and had similar SaO_2 in ECOG 0 and in ECOG1/ECOG2 groups.

Interestingly, the nutritional status differentiated the groups with ECOG 0 or ECOG 1/ECOG 2 patients. Most of the patients with ECOG 0 performance status were overweight or obese, as compared with only one obese patient with the ECOG 1 and no overweight or obese patients with ECOG 2 performance status. Malnutrition is a factor associated with low health-related quality of life in advanced NSCLC [18].

The usefulness of the evaluation of dyspnea in the patients with advanced NSCLC as a prognostic factor related to completion or not-completion of chemotherapy should be interpreted with caution and regarded only as a preliminary data, as a group of our patients was very small. However, it has been found that the objective measure of dyspnea, i.e. markedly decreased distance in the 6MWT, and one subjective measure, i.e. Borg scale at rest, were associated with non-completion of the scheduled chemotherapy. Although the patients who not completed chemotherapy had also lower FEV_1 and FVC , the measurements of dyspnea are also of importance, as spirometric values may not correlate with 6MWT [19]. Small FEV_1 was found to be a strong predictor of mortality of the patients with advanced NSCLC [20]. In our patients FEV_1 in the patients who have not completed chemotherapy was as low as 1.04 ± 0.1.

ECOG performance status remains one of the most important factors related to prognosis in the patients with NSCLC receiving chemotherapy [21,22]. This is especially important in the elderly patients with advanced NSCLC [23]. Multiple co-morbidities and decreased physiologic reserves of organ function, may result in higher risk of toxicity of chemotherapy [24]. The problem of lung cancer in elderly is important from epidemiological and clinical point of view as about half of the patients is over 70 years old and the tendency of incidence of lung cancer in the patients over 75 years is increasing [25]. Both currently and in the past, however, underrepresentation of elderly patients with lung cancer in clinical trials persists [26,27]. This may cause difficulties for physicians to make decisions regarding starting chemotherapy in elderly. Thus comprehensive geriatric assessment, encompassing several items in five domains, related to medical problems, mental health, functional capacity, social circumstances and environment [28] emerged in the assessment of the elderly patients with lung cancer [29]. However, it appeared to be not quite sufficient tool in the assessment of cancer patients because of multiple problems related to its use and numerous alternative instruments have been developed [30]. However, the problems of dyspnea remains underrepresented in those instruments. Our study added some information on the relations between both subjectively perceived and objectively measured dyspnea and ECOG performance status and the chances of completion of chemotherapy in elderly patients with advanced NSCLC.

Conclusion

Dyspnea is a complaint of the majority of the elderly patients with advanced NSCLC patients and is more severe in the patients

with performance status higher than ECOG 0. 6MWT and modified CAT are the best tools to evaluate dyspnea in the elderly patients with advanced NSCLC starting palliative chemotherapy. The evaluation of dyspnea may help to assess the performance status in the elderly patients with advanced NSCLC.

Objective measurement of dyspnea, indicating shortened distance in 6MWT may allow to predict unfavorable course of the scheduled palliative chemotherapy in the elderly patients with advanced NSCLC.

Acknowledgment

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