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Phase I study of docetaxel and irinotecan in patients with advanced non-small-cell lung cancer

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Summary The role of non-platinum combination chemotherapy in the treatment of advanced non-small-cell lung cancer (NSCLC) has not yet been clarified. In this phase I study, the dose-limiting toxicity (DLT), the maximum tolerable dose (MTD) and the antitumor activity of a two-drug combination of docetaxel (DCT) and irinotecan (CPT) in patients with advanced NSCLC were evaluated. Previously untreated patients with NSCLC in stage IIIB with malignant pleural effusion or stage IV were eligible. Both drugs were administered by 1-h intravenous infusion on day 1, and repeated every 3 weeks. DCT was given before CPT administration. Five escalating dose levels of DCT/CPT (40/135, 50/135, 50/150, 60/150, and 60/165 mg/m^2) were studied. Eighteen patients received 44 courses. The DLT was considered to be neutropenia, because grade 4 neutropenia lasting for 3 days or more was observed in three patients, which was accompanied with three episodes of febrile neutropenia. As a non-hematological toxicity, grade 3 diarrhea occurred in three patients. Since all the three patients treated at the fifth dose level (DCT at 60 mg/m^2 and CPT at 165 mg/m^2) experienced DLT (grade 4 neutropenia in two patients and grade 3 hepatic toxicity in one), this dose level was determined to be the MTD. The objective response rate was 33.3%, and the median survival time was 13.6 months. To confirm the effectiveness of this combination for advanced NSCLC which was suggested in the present study, a phase II study with the recommended doses (150 mg/m^2 for CPT and 50–60 mg/m^2 for DCT) is warranted.

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1. Introduction

A meta-analysis of 52 randomized clinical studies comparing cisplatin (CDDP)-containing chemotherapy plus best supportive care with best supportive care alone in patients with advanced non-small-cell lung cancer (NSCLC) demonstrated the survival benefit of CDDP-containing chemotherapy [1]. Since then, CDDP has been considered to be a key drug in the treatment of advanced NSCLC. However, the prolongation of survival by CDDP-containing chemotherapy was very limited [1]. Several new agents, such as paclitaxel (PCT), docetaxel (DCT), vinorelbine, gemcitabine, and irinotecan (CPT), were recently tested in clinical trials [2]. These agents were shown to have survival benefit for advanced NSCLC as single agents [3–5]. Furthermore, a few randomized trials comparing one of these new agents with an existing drug such as vindesine or etoposide in two-drug CDDP-containing regimens showed that the new agents were superior to the conventional drugs even though the survival advantage was also minimal [6–8]. These results were confirmed by a meta-analysis [9]. Afterwards, many researchers expected that non-platinum regimens consisting of only new agents might be equally effective and less toxic compared with CDDP-containing regimens.

DCT, a semi-synthetic taxane, exerts its cytotoxicity through binding to beta-tubulin, promotion of polymerization and inhibition of microtubule dissembly, and causes cell cycle arrest at the G2/M phase. DCT was shown to be more active than PCT in vitro, which has been explained by its higher achievable intracellular concentrations, greater affinity for microtubules and slower cellular efflux [10]. The effectiveness of DCT in patients with advanced NSCLC, both as a single agent and in combination with CDDP, has already been confirmed [4,11]. CPT is a semi-synthetic, water-soluble derivative of camptothecin. CPT inhibits topoisomerase I, an enzyme that relaxes DNA torsional strain by inducing single-strand DNA breaks [12]. Recent studies have shown that CPT is also active for NSCLC both as a single agent and in combination with CDDP [13–15]. Furthermore, the antitumor spectrum of DCT was completely different from that of CPT in an in vitro study using 24 human lung cancer cell lines [16].

On the basis of these results, we planned a phase I study of combination chemotherapy consisting of DCT and CPT to investigate the safety and effectiveness of this non-platinum combination in patients with advanced NSCLC. The primary objective of this study was to determine the dose-limiting toxicity (DLT) and the maximum tolerable dose (MTD) of the combination. The secondary objectives included evaluation of the response rate and survival, and determination of the recommended dose (RD) for a subsequent phase II study.

2. Patients and methods

2.1. Patient selection

The present study was scientifically and ethically examined by the Protocol Committee of the Okayama Lung Cancer Study Group (OLCSG); the Committee members were independent on the OLCSG. Eligibility requirements for entry into the study were as follows: (1) histologically or cytologically proven NSCLC; (2) stage IV or stage IIIB disease with malignant pleural effusion; (3) no prior chemotherapy, radiotherapy or surgery; (4) age of 75 years or less; (5) performance status (PS) of 0–1 on the Eastern Cooperative Oncology Group (ECOG) scale [17]; (6) presence of measurable disease; (7) adequate functional reserves of the kidney (creatinine clearance$\geqq$60 ml/min), liver (ALT, AST is less than twice the upper limit of normal) and bone marrow (a leukocyte count$\geqq$3000 μl^{-1}; neutrophil count$\geqq$2000 μl^{-1}; and a platelet count$\geqq$100 000 μl^{-1}); (8) no concomitant malignancies; and (9) acquisition of a written form of informed consent.

2.2. Evaluation

Staging procedures included a complete history and physical examination, a complete blood cell count (CBC), standard blood chemistry profile, 24-h urine creatinine clearance (Ccr), a chest radiograph, computerized tomographic (CT) scans of the chest and abdomen, magnetic resonance imaging of the brain, a radionuclide bone scan, and fiberoptic bronchoscopy.

The CBC was repeated two or three times a week. Blood chemistry, Ccr, and chest radiography were repeated at least once a week during treatment. CT scans of the chest were repeated once per treatment cycle. After completion of the chemotherapy, each patient was restaged on the basis of all the tests used during the initial work-up and followed up at the outpatient clinic with monthly chest radiographs. CT scans of the chest were repeated every 3 months.

2.3. Treatment plan

Both DCT and CPT were given by 1-h intravenous infusion on day 1 and repeated every 3

weeks. DCT dissolved in 500 ml of 5% dextrose was infused first, followed by administration of CPT-11 diluted in 500 ml of physiological saline. In this study, the starting doses of DCT and CPT were decided as 40 and 135 mg/m^2, respectively, which were 60–70% of the recommended doses of each drug in the previous phase II studies [2]. The dose level of DCT/CPT was escalated as follows: 40/135, 50/135, 50/150, 60/150, and 60/165 mg/m^2.

Toxicities were graded according to the National Cancer Institute common toxicity criteria (Version 2.0). The DLT was defined as grade 4 hematological toxicity lasting for 3 days or more, and grade 3 or 4 non-hematological toxicity other than nausea, vomiting and alopecia. At least three patients were enrolled at each dose level. If all the three patients developed the DLT, the dose level was determined to be the MTD. If two of the three patients experienced the DLT, three additional patients were subjected to the same dose level. When the DLT developed in more than half of the patients, the dose was also defined as the MTD. The patients who experienced the DLT in the previous course were treated with the lower dose level in the next course. Before the next course was started, leukocyte and platelet counts had to be at least 3500 mm^{-3} or more and 100 000 mm^{-3} or more, respectively. When grade 3 or higher leukopenia or neutropenia occurred, administration of recombinant human granulocyte colony stimulating factor (rhG-CSF) was permitted. The response was evaluated according to the ECOG criteria [17]. The time to progression and overall survival time were calculated from the date of initiation of chemotherapy until the first documentation of disease progression and death, respectively, using the Kaplan–Meier method. Intrapatient dose escalation was not permitted. Statistical analyses were performed using SPSS Base System™ and Advanced Statistics™ Program (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Determination of MTD

Eighteen patients were enrolled in this study and received 44 assessable courses of chemotherapy. There were 13 men and 5 women, and the median age was 71 years ranging from 48 to 75. All patients had a good PS (PS 0 in 7 patients and PS 1 in 11). Thirteen (72%) patients had adenocarcinoma, four (22%) squamous cell carcinoma, and one (6%) unclassified non-small-cell carcinoma. The clinical stage was IIIB in 2 (11%) patients and IV in 16 (89%).

Table 1 Dose escalation scheme

Dose level	Dose (mg/m^2) of		No. of patients	
	Docetaxel	Irinotecan	Evaluated	With DLT
1	40	135	3	1
2	50	135	3	0
3	50	150	3	0
4	60	150	6	3
5	60	165	3	3

DLT: dose-limiting toxicity.

Dose escalation was conducted as shown in Table 1. At the first dose level, one of the three patients developed grade 3 diarrhea, which recovered on day 6. At the second and third dose levels, no patients developed a DLT. At the fourth dose level, two patients developed grade 3 diarrhea and one of them had grade 4 neutropenia. Three additional patients were then treated at the same dose level, and one patient developed grade 3 liver damage. Thus, three of the six patients treated at the fourth dose level experienced a DLT. At the fifth dose level, all the three patients experienced a DLT (grade 4 neutropenia in two and grade 3 liver damage in one). Therefore, the fifth dose level was determined to be the MTD, and the RD for the phase II study was considered to be the third or fourth dose level.

3.2. Toxicity

All patients were assessable for toxicity. No treatment-related deaths were experienced. Table 2 lists the toxicities observed during the first cycle of the chemotherapy. Neutropenia was the

Table 2 Toxicity (grade 3 or 4)

	Dose level				
	1	2	3	4	5
No. of patients evaluated	3	3	3	6	3
Leukopenia	1	0	1	5 (1)	3 (2)
Neutropenia	2 (1)	2 (1)	2	5 (4)	2 (2)
Thrombocytopenia	0	0	1	0	0
Anemia	0	0	1	0	0
Diarrhea	1	0	0	2	0
Nausea and vomiting	1	0	0	2	0
Liver damage	0	0	0	1	1

Number in parenthesis is number of patients encountered grade 4 toxicity.

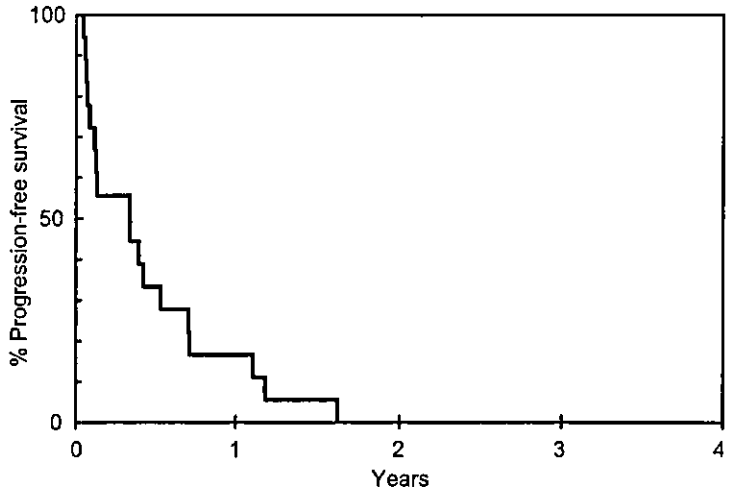

Fig. 1 Kaplan–Meier analysis of progression-free survival.

principal toxicity, and the majority of patients developed grade 3 or 4 neutropenia. At the fourth dose level, grade 4 neutropenia occurred in four of the six patients, but a DLT (grade 4 neutropenia lasting for 3 days) occurred in only one patient. At the fifth dose level, two of the three patients experienced grade 4 neutropenia lasting for 4 days, which were considered to be the DLT. Five patients treated at the fourth dose level and all the three patients at the fifth dose level received rhG-CSF. Thrombocytopenia and anemia were rarely observed. None of the patients received platelet or RBC transfusions.

The non-hematological toxicities were generally mild except for diarrhea. One patient at the first dose level and two at the fourth dose level experienced grade 3 diarrhea. The diarrhea occurred on day 1 in two patients and on day 3 in one, and lasted for 1, 3 and 8 days, respectively, although it was successfully managed with loperamide hydrochloride. Three patients (one at the first dose level and two at the fourth dose level) had grade 3 nausea and vomiting, but recovered within 24 h by conventional antiemetic therapy. Two patients developed transient hepatotoxicity lasting for 4 and 7 days, respectively. No patients experienced a hypersensitivity reaction, fluid retention or peripheral neuropathy.

3.3. Response

All patients were assessable for response (Table 3). One patient at the first dose level achieved a

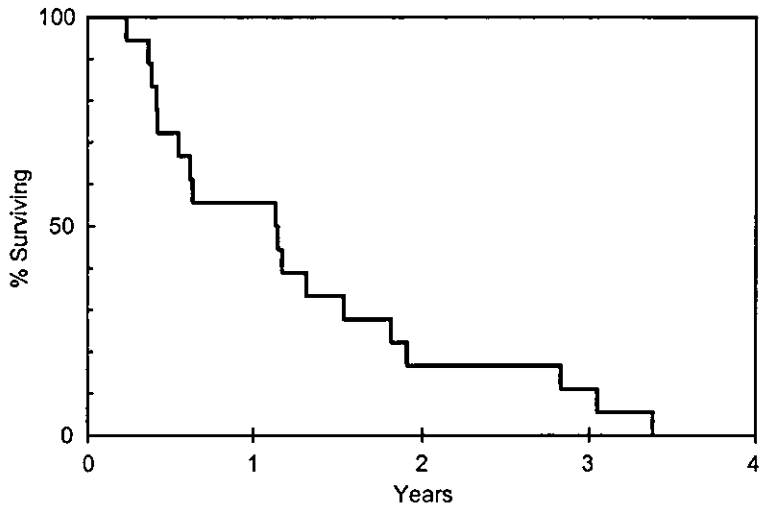

Fig. 2 Kaplan–Meier analysis of overall survival.

Table 3 Response

	Dose level					Total
	1	2	3	4	5	
No. of patients evaluated	3	3	3	6	3	18
Complete response	1	0	0	0	0	1 (5.6%)
Partial response	1	1	1	1	1	5 (27.8%)
No change	1	2	0	4	2	9 (50.0%)
Progressive disease	0	0	2	1	0	3 (16.7%)

complete response lasting for 9 months, and five patients achieved a partial response with a median duration of 4.5 months ranging from 2 to 8.5 months. The objective response rate was 33.3% with a 95% confidence interval (95% CI) of 22.2–44.4%. There was no clear relationship between the dose level and the response. As second-line therapy, eight patients received platinum-based regimens and one non-platinum-based regimen. However, no patients achieved objective response. The median progression-free survival time was 4.0 months (95% CI, 0.0–9.1 months, Fig. 1). The median survival time and 1-year survival rate were 13.6 months (95% CI, 6.7–26.6 months) and 55.6%, respectively (Fig. 2).

4. Discussion

CDDP is a key drug in the treatment advanced NSCLC, and the current standard chemotherapy for advanced NSCLC is considered to be a two-drug combination consisting of cisplatin and one of the new agents [9]. However, some patients are unable to tolerate CDDP-containing chemotherapy because of CDDP-induced severe toxicities such as neuropathy, fatigue and renal toxicity. Therefore, many researchers have been investigating the effectiveness of non-platinum regimens for advanced NSCLC, since the development of a several new agents in the 1990s. Georgoulias et al. [18] and Kosmidis et al. [19] have already reported that non-platinum regimens were equally effective with CDDP- or carboplatin-containing regimens. On the other hand, Gridelli et al. [20] and Van Meerbeeck et al. [21] found that non-platinum regimens were less effective, although they were also less toxic. Thus, the role of non-platinum regimen in the treatment of advanced NSCLC has not yet been determined. We designed the present study to evaluate the usefulness of a non-platinum regimen for advanced NSCLC. The objective of this study was to evaluate the safety and effectiveness of a two-drug non-platinum combination consisting of DCT and CPT in patients with advanced NSCLC.

The principal toxicity of this regimen was neutropenia, and a majority of the patients developed grade 3 or 4 neutropenia. Particularly, four of the six patients at the fourth dose level developed grade 4 neutropenia and five patients received G-CSF administration. However, since the neutropenia promptly resolved (duration: 1–3 days) and no life-threatening complications occurred, we considered that this dose level was tolerable and administration of G-CSF might have been unnecessary in majority of the patients. We considered that G-CSF administration should be determined cautiously. As non-hematological toxicities, diarrhea and liver damage occurred, which were easily managed with standard treatment. Thus, this regimen was considered to be tolerable. The RDs for the phase II study were suggested to be 50–60 mg/m^2 for DCT and 150 mg/m^2 for CPT.

Couteau et al. [22] have already completed a phase I study of the same combination using same sequence of administration. The DLT in their study was neutropenia, which was the same as in the present study. However, their recommended doses for a phase II study, 60 mg/m^2 for DCT and 275 mg/m^2 for CPT, were substantially higher than those concluded on the basis of the present study. The only difference between two studies was that CPT was given for 90 min in the Couteau's study, while it was given for 60 min in the present study. The short administration time in the present study may have produced severe toxicities. In the present study, the two drugs were administered in rapid succession without any time interval between the infusions. Because both DCT and CPT are considered to be substrates for CYP3A, competition of DCT and CPT for this enzyme might have resulted in a decrease in DCT clearance when the intravenous infusions of both drugs were conducted sequentially on the same day. Masuda et al. [23] also reported a phase I study of this combination with fractionated administration of CPT on days 1, 8 and 15, and a single infusion of DCT on day 2, thus avoiding the days of CPT administration. In their study, in spite of the fact that the days of CPT administration were different from the day of DCT administration, the recommended doses per course were 50 mg/m^2 of DCT and 150 mg/m^2 of CPT, which are close to the doses recommended in our study. Furthermore, the actually delivered dose of CPT was only 76% of the planned dose in their study, because CPT administration was fre-

quently omitted on day 8 or day 15 due to diarrhea and leukopenia. Based on these results, we consider that the single administration of CPT used in our regimen may be better than fractionated administration.

Regarding the effectiveness, the objective response rate of 33% in this study was comparable with the rates reported in other studies investigating the effectiveness of non-platinum regimens [18,19] and in Masuda et al.'s study (37%) [23]. However, the median survival time of 13.6 months and 1-year survival rate of 55.6% were quite good, and superior to those of the previous reports [18,19,23]. It is of note that there was no relationship between the dose level and the objective response rate in this study, and an objective response was observed even in some of the patients treated at the RD levels or lower level. Furthermore, it was recently reported that determination of the UDP-glucuronosyltransferase (UGT) 1A1 enzyme might be useful for predicting severe toxicity of irinotecan [24]. Therefore, we will be able to prevent the development of severe toxicity with this regimen by determination of the UGT1A1 enzyme in each patient or using a lower dose.

In conclusion, this two-drug regimen consisting of DCT and CPT at the RD level is feasible and effective in patients with advanced NSCLC. These results warrant further testing in a phase II study.

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REVIEW

An overview of 48 elderly-specific clinical trials of systemic chemotherapy for advanced non-small cell lung cancer

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KEYWORDS
Elderly patient;
Clinical trial;
Non-small cell lung cancer;
Calendar age;
Chemotherapy;
Vinorelbine

Summary *Purpose:* The aim of the present study was to identify elderly-specific clinical trials for advanced non-small cell lung cancer (NSCLC) and to clarify the study design and patient characteristics entered of each of these trials. *Methods:* We used the MEDLINE database to select prospective clinical trials evaluating the efficacy of chemotherapy in elderly patients with advanced NSCLC. *Results:* Our literature search yielded 48 prospective clinical trials between 1990 and 2003, involving a total of 2648 elderly patients with advanced NSCLC. The median number of patients treated per trial was 36. In 23 (48%) of the 48 trials, only the abstract was available. In 44 trials (92%), elderly patients were defined using their calendar age, and the age of 70 years was the most frequently used lower limit for inclusion. Vinorelbine was the most widely studied chemotherapy agent in elderly patients. *Conclusions:* Our review revealed that (i) the definition of "elderly" varied from trial to trial, and elderly patients were simply defined using calender age in the clinical trials; (ii) the quality of elderly-specific trials were generally poor, mainly because of their small sample size.

1. Introduction

The peak incidence of lung cancer, the leading cause of death from cancer in the industrial countries, is currently between 60 and 65 years of age. More than 60% of patients are over 65 years old [1,2], and approximately 30% are 70 years or older [3]. Furthermore, since the proportion of the population over the age of 65 years, which was 12.8% in 1995, is expected to increase up to 20.1% by 2030 [2], the number of elderly lung cancer patients is expected to rapidly increase. Therefore, the management of elderly lung cancer patients is becoming a major challenge in the field of medical oncology.

Chemotherapy plays a critical role in improving the survival of patients with advanced non-small cell lung cancer (NSCLC). The results of a meta-analysis suggested that cisplatin-based chemotherapy regimen prolong survival, compared with best supportive care alone, in patients with advanced NSCLC [4]. In addition, a community-based analysis of 6232 elderly patients from the National

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Cancer Institute Surveillance Epidemiology End Results (SEER) tumor registry showed that chemotherapy for metastatic NSCLC in this large population seemed to be equally effective, as that shown in a meta-analysis, which included only small number of elderly patients [5]. Therefore, all suitable patients with advanced NSCLC should be given the opportunity to receive systemic chemotherapy.

However, many elderly patients may not be receiving sufficient treatment, as revealed very clearly in a recent analysis of clinical trial data from the Southwest Oncology Group (SWOG) [6]. In the USA, 66% of patients with lung cancer were 65 years old or older, whereas the proportion of patients aged 65 years or older in the SWOG-sponsored studies on lung cancer was only 39%. Similarly, elderly patients are less frequently treated with chemotherapy in clinical practice. A retrospective analysis of insurance claims revealed that only 5.1% of patients with advanced lung cancer who were older than 64 years of age received chemotherapy, whereas this value increased to 18.8% in insured patients of a younger age group [7]. Physicians may assume that elderly lung cancer patients have a poor prognosis or are at a high risk for toxicity, such explanations have been cited as possible reasons for the limited enrollment of elderly patients in clinical trials and the limited use of chemotherapy in elderly patients.

Recently, several new agents with novel mechanisms of action have been developed and shown to have consistent activity and improved tolerability in non-elderly patients with advanced NSCLC [8]. Elderly-specific clinical trials for advanced NSCLC have also extensively investigated these new agents. However, since the definition of "elderly" remains unclear, the ages of patients registered in elderly-specific trials may vary. To clarify these issues, we identified recent elderly-specific clinical trials and evaluated patient characteristics and study designs of each trial. In addition, to determine the role of chemotherapy in elderly patients with NSCLC, we also reviewed data regarding the impact of chemotherapy on efficacy.

2. Patients and methods

2.1. Search for trials

To avoid publication bias, both published and unpublished trials reported between January 1990 and December 2003 were identified through a computer-based search of the MEDLINE database and a manual search of abstracts from the past conferences of the American Society of Clinical Oncology and the International Association for the Study of Lung Cancer held between 1995 and 2003. We searched using the following concepts: *lung cancer, elderly, clinical trial, and human.* Only references published in English were included. The search was also guided by a thorough examination of the reference lists of published reports of trials, review articles, relevant books, and the Physician Data Query registry of clinical trials.

2.2. Selection of trials

Prospective trials that were designed to evaluate the efficacy and toxicity of chemotherapy in elderly lung cancer patients were eligible for inclusion in this study. Within the definition of "elderly", both physiologically old patients and patients with an advanced calendar year were allowed, and a cut-off was not set. We also included trials comparing elderly patients with non-elderly counterparts if the trials were designed to accrue and evaluate the two populations independently. Subset analyses of treatment efficacy for elderly patients and retrospective analyses comparing elderly patients with non-elderly counterparts were excluded from the current study. Trials that evaluated combined modality therapy were also excluded.

2.3. Data extraction

To avoid bias in the data extraction process, all data were checked for internal consistency by group consensus. The following information was obtained from each trial: the period of enrollment, the country in which the trial was performed, the number of patients, the primary endpoint, patient characteristics (gender, age, comorbid conditions, performance status, histology), treatment regimens, response rate, median survival time, toxicities, the number of treatment-related deaths, and quality-of-life assessments. According to the type of trials, reports were separately compiled as phase I trials, phase II trials and phase III trials, whereas trials whose types were not clearly documented were classified as phase II trials.

3. Results

3.1. Identification of elderly-specific clinical trials

The computer-based search of the MEDLINE database, the manual search of the abstracts from

major international conferences, and the reference lists of relevant articles yielded 3147, 20, and 4 reports, respectively. These included at least 72 prospective clinical trials for elderly patients with NSCLC. The other 3099 reports consisted of trials for small cell lung cancer (SCLC) or combined modalities with curative surgery or radiotherapy for NSCLC, review articles, and retrospective subgroup analyses for elderly patients; all of these trials were excluded from the present study. Since one of the 72 trials did not define the term "elderly" and did not provide the age distribution of the accrued patients, it was also excluded [9]. An additional 20 trials were deemed to be inappropriate for our study because these trials included non-elderly patients with a poor performance status or evaluated treatment efficacy in a single group of patients with distinctive characteristics that were considered to affect the results [10–29]. Furthermore, three trials including both NSCLC and SCLC patients were also excluded [30–32]. Accordingly, data from 48 trials involving 2648 elderly patients with advanced NSCLC was included in the final analysis (Tables 1–5) [33–80]. Of 2648 patients, 2539 elderly patients received anti-cancer agents, whereas the remaining 109 patients were treated with best supportive care alone as a control arm in two phase III trials [33,36].

3.2. Characteristics of elderly-specific clinical trials

In 23 trials (48%), only abstracts were obtained. Of the 48 trials, 26 trials were initiated in the 1990s, and seven trials were initiated in the 2000s. In the remaining 15 trials, the time of the initial patient accrual was not provided. The median number of accrued patients per trial was 12 for the phase I trials and 35 for the phase II trials. The median number of patients per arm in the phase III trials was 60. A statement regarding written informed consent was not included in 26 of the 48 trials and, surprisingly, in 19% of the 26 trials that were published as a full text.

Half of the trials were conducted in Italy (56%), with all four phase III trials conducted there. Response rate was usually used as the primary endpoint in the phase II trials, while overall survival was used in the phase III trials; quality-of-life was assessed as the primary endpoint in one phase III trial [33]. In 10 trials (21%), a quality-of-life assessment was used as a secondary endpoint. A pharmacokinetic analysis was also conducted in one trial (2%) [54]. None of the published report assessed the economical issues of chemotherapy.

3.3. Definition of "elderly" and other patient characteristics

In the 44 trials, "elderly" was defined using the patient's calendar age. The age of 70 years was the most frequently used lower limit (70%), followed by the age of 65 (23%). None of the trials used physiological factors to define the term "elderly". Four trials did not clearly state their working definition of an elderly patient [55,62,67,71]. However, the lowest ages of the patients were 65 years in three of the four trials and 64 years in the remaining one trial, indicating that their definition was based on calendar age. Majority of the trials only evaluated patients with a performance status of 0, 1 or 2, whereas patients with a performance status 3 were included in six trials (13%) [38,41,45,54,55,58]. The median percentage of women in the trials was 17%, ranging from 4 to 41%; these figures are comparable with that of a European community-based studies (19.0%) [81,82]. The proportion of stage IV disease varied from 19 to 92%, with a median value of 62%. Only 13 trials (27%) documented comorbid conditions, with a median prevalence of 65%, ranging from 24 to 100%.

3.4. Efficacy of chemotherapy in elderly patients with NSCLC

Half (50%) of the 48 trials evaluated the efficacy of single-agent chemotherapy, while the remaining reports examined multidrug chemotherapy regimens. Vinorelbine, which was used either alone or in combination with other agents, was the most widely studied chemotherapy agent (38% of the 48 trials). The objective response rate was reported in all of these trials, with a median value of 21%, ranging from 0 to 65%, while survival data was included in 35 trials (73%).

As a single-agent chemotherapy regimen, vinorelbine was reported to be active with a response rate of 3–39% and a median survival time of 18–43 weeks, involving 654 patients in 11 trials. One phase III trial demonstrated a significant survival benefit from vinorelbine over best supportive care alone [33]. Additionally, gemcitabine was also extensively studied as a single-agent chemotherapy regimen for elderly patients with advanced NSCLC, involving 531 patients in eight trials. In one phase III trial, gemcitabine was shown to be almost as effective as vinorelbine in elderly patients with NSCLC, although a direct comparison of these drugs was not performed [35]. Two trials examining docetaxel and one examining paclitaxel regimen in elderly patients with advanced NSCLC were also reported

Table 1 Phase III trials for elderly patients with advanced non-small cell lung cancer

Author	Study period	Form of report	Country	Chemotherapy regimen	No. of assessable pts	Eligibility criteria regarding age (years)	RR (%)	No. of pts with early death (%)	Median survival (weeks)	1-Year survival (%)	Assessment of QOL	Ref.
ELVIS	1996–1997	F	Italy	VNR 30 mg/m² d1,8 q3w	76	>69	20	0	28	32	Yes	[33]
				Best supportive care	78				21	14		
Frasci	1997–1999	F	Italy	VNR 30 mg/m² d1,8 q3w	60	>69	15	1 (2)	18	13	Yes	[34]
				VNR 30 mg/m² d1,8 q3w + GEM 1200 mg/m² d1,8 q3w	60		22	2 (3)	29	30		
Gridelli	1997–2000	F	Italy	VNR 30 mg/m² d1,8 q3w	233	>69	18	NR	36	38	Yes	[35]
				GEM 1200 mg/m² d1,8 q3w + VNR 25 mg/m² d1,8 GEM 1000 mg/m² d1,8 q3w	233		16	NR	28	28		
					232		21	NR	30	30		
Marinis	1990–1992	F	Italy	VDS 3 mg/m² weekly	30	>70	3	12 (10)[a]	24[a]	20[a]	No	[36]
				LND 450 mg daily	32		0					
				VDS 3 mg/m² weekly + LND 450 mg daily	33		6					
				Best supportive care	31							

[a] Data from all patients entered in the trial. *Abbreviations:* pts: patients; RR: response rate; QOL: quality-of-life; ref.: references; ELVIS: The Elderly Lung Cancer Vinorelbine Italian Study Group; A: abstract only; F: full text; VNR: vinorelbine; GEM: gemcitabine; VDS: vindesine; LND: lonidamine; NR: not recorded.

Table 2 Phase II and relevant trials for elderly patients with advanced non-small cell lung cancer (single-agent therapy)

Author	Study period	Form of report	Country	Chemotherapy regimen	No. of assessable pts	Eligibility criteria regarding age (years)	RR (%)	No. of pts with early death (%)	Median survival (weeks)	1-Year survival (%)	Assessment of QOL	Ref.
Colleoni	1992–1994	F	Italy	VNR 25 mg/m^2 weekly	25	>64	16	0	21	NR	No	[37]
Veronesi	1992–1994	F	Italy	VNR 25 mg/m^2 weekly	23	>69	39	0	39	NR	No	[38]
Tononi	1993–1996	F	Italy	VNR 25 mg/m^2 weekly	25	>64	12	0	43	NR	No	[39]
Gridelli	1994–1995	F	Italy	VNR 30 mg/m^2 weekly	43	>69	23	0	36	36	No	[40]
Buccheri	1995–1998	F	Italy	VNR 25 mg/m^2 weekly	40	>69	4	0	34	NR	Yes	[41]
Mattioli	1996–	A	Italy	VNR 30 mg/m^2 d1,8 q3w	15	>70	20	1 (7)	NR	NR	Yes	[42]
Schulz	NR	A	USA	VNR 60 mg/m^2 weekly (oral)	58	>64	3	2 (3)	31	NR	No	[43]
Gridelli	2001–2002	A	Italy	VNR 60 mg/m^2 weekly (oral)	56	>70	13	NR	NR	NR	No	[44]
Quoix[a]	NR	A	France	GEM 1000 mg/m^2 d1,8,15 q4w	42	>69	14	0	22	NR	No	[45]
				GEM 1125 mg/m^2 d1,8 q3w	39		26	0	29	NR		
Bianco	1996–1999	F	Italy	GEM 1000 mg/m^2 d1,8,15 q4w	52	>64	39	0	34	46	Yes	[46]
Ricci	1997–1998	F	Italy	GEM 1000 mg/m^2 d1,8,15 q4w	46	>70	22	2 (4)	29	27	No	[47]
Altavilla	1997–1998	F	Italy	GEM 1250 mg/m^2 d1,8 q3w	21	>70	33	0	32	NR	Yes	[48]
Martoni	1997–1999	F	Italy	GEM 1000 mg/m^2 d1,8,15 q4w	46	>69	22	4 (9)	39	44	No	[49]
Wilson	NR	A	Canada	GEM 1250 mg/m^2 d1,8,15 q4w	35	>64	16	NR	19	NR	No	[50]
Pasquini	NR	A	Italy	GEM 1250 mg/m^2 d1,8,15 q4w	17	>65	42	NR	NR	NR	No	[51]
Yoshimura	1997–1999	A	Japan	DOC 60 mg/m^2 d1 q4w	30	>69	18	1 (3)	NR	48	No	[52]
Tibaldi	NR	A	Italy	DOC 37.5 mg/m^2 d1,8 q3w	17	>70	10	NR	NR	NR	No	[53]
Fidias	1998–2000	F	USA	PTX 90 mg/m^2 1h weekly	35	>69	23	2 (6)	44	45	No	[54]
Gallotti	1990–1992	A	Italy	VDS 2 mg/m^2 d1–3, q3w	22	NR	20	0	NR	NR	No	[55]
Baldini	NR	F	Italy	DXF 2250 mg d1–4 weekly	33	>69	13	0	20	NR	No	[56]

[a] Randomized phase II trial. *Abbreviations:* pts: patients; RR: response rate; QOL: quality-of-life; A: abstract only; F: full text; ref.: references; VNR: vinorelbine; GEM: gemcitabine; DOC: docetaxel; PTX: paclitaxel; VDS: vindesine; DXF: doxifluridine; NR: not recorded.

Table 3 Phase II and relevant prospective trials for elderly patients with advanced non-small cell lung cancer (combination therapy)

Author	Study period	Form of report	Country	Chemotherapy regimen	No. of assessable pts	Eligibility criteria regarding age (years)	RR (%)	No. of pts with early death (%)	Median survival (weeks)	1-Year survival (%)	Assessment of QOL	Ref.
Martins	1996–1998	A	Brazil	CDDP 60–90 mg/m^2 d1 q3w VNR 25 mg/m^2 d1,8	44	>70	54	2 (5)	31	37	No	[57]
Lippe	1999–2000	A	Italy	CDDP 25 mg/m^2 d1,8,15 q3w VNR 30 mg/m^2 d1,8,15	13	>64	31	1 (8)	30	NR	No	[58]
Feliu	1999–2001	F	Spain	CDDP 50 mg/m^2 d1 q3w GEM 1000 mg/m^2 d1,8	46	>69	35	0	44	35	Yes	[59]
Lippe	NR	F	Italy	CDDP 35 mg/m^2 d1,8,15 q4w GEM 1000 mg/m^2 d1,8,15	29	>65	48	2 (9)	43	NR	Yes	[60]
Berardi	NR	F	Italy	CDDP 35 mg/m^2 d1,8,15 q4w GEM 1000 mg/m^2 d1,8,15	48	>69	24	1 (2)	39	34	No	[61]
Moscetti	2000–2002	A	Italy	CDDP 60–100 mg/m^2 d2 q3ws GEM 1000–1250 mg/m^2 d1,8	34	NR	44	1 (3)	NR	74	No	[62]
Niho	2000–2002	A	Japan	CDDP 20 mg/m^2 d1,8,15 q4w DOC 25 mg/m^2 d1,8,15	33	>74	52	0	68	64	No	[63]
Kanat	NR	F	Turkey	CDDP 60 mg/m^2 d1 q4w ETP 120 mg/m^2 d1–3	24	>69	13	0	49	38	No	[64]
Souquet	1995–	A	France	CDDP 50 mg/m^2 d1 q3w IFO 3g/m^2 d1 + MMC 6 mg/m^2 d1	16	>70	38	NR	NR	NR	No	[65]
LeCaer	NR	A	France	CBDCA AUC = 5, d1 q4w VNR 25 mg/m^2, d1,8	40	>69	20	1 (3)	NR	NR	No	[66]
Maestu	1998–2000	A	Spain	CBDCA AUC 4 d1 q3w GEM 1250 mg/m^2 d1,8	79	NR	39	NR	42	NR	No	[67]
Molinier	2002–	A	France	CBDCA AUC 6 d1 4w PTX 90 mg/m^2 d1,8,15	43	>69	36	NR	NR	NR	No	[68]
Jatoi	2000–2001	F	USA	CBDCA AUC 2 d1 4w PTX 50 mg/m^2 d1,8,15	49	>64	14	1 (2)	30	31	No	[69]
Gridelli	NR	F	Italy	CBDCA 300 mg/m^2 d1 q4w ETP 100 mg d1–7	14	>69	0	0	26	NR	No	[70]
Cuzzoni	NR	A	Italy	CBDCA 100 mg/m^2 d1–3 q3w ETP 100 mg/m^2 d1–3	42	NR	31	NR	45	NR	No	[71]

Santomaggio[a]	2000–	A	Italy	GEM 1600 mg/m² d1,8 q4w VNR 25 mg/m² d1,8	30	>70	NR	NR	NR	NR	No	[72]
				GEM 1600 mg/m² d1,8 q4w VDS 3 mg/m² d1,8	29							
Maestu	2001–2003	A	Spain	GEM 1750 mg/m² d1,15 VNR 30 mg/m² d1,15	43	>69	30	NR	NR	NR	Yes	[73]
Baron	1999	A	Spain	GEM 1250 mg/m² d1,8 q3w VNR 30 mg/m² d1,8	30	>70	15	1 (6)	17	NR	No	[74]
Chen	1998–2001	F	Taiwan	GEM 800 mg/m² d1,8,15 q4w VNR 20 mg/m² d1,8,15	20	>79	65	2 (10)	43	38	No	[75]
Salvati	1990–1991	F	Italy	LND 450 mg daily CPA 600 mg/m² q3w	35	>69	15	NR	39	NR	No	[76]
Malarme	NR	A	Belgium	IFO 1.5g/m² d1–5 q4w VDS 3 mg/m² d1	20	>65	15	1 (5)	NR	NR	No	[77]

[a] Randomized phase II trial. *Abbreviations:* pts: patients; RR: response rate; QOL: quality-of-life; A: abstract only; F: full text; ref.: references; CDDP: cisplatin; VNR: vinorelbine; GEM: gemcitabine; DOC: docetaxel; ETP: etoposide; IFO: ifosphamide; MMC: mitomycin C; CBDCA: carboplatin; PTX: paclitaxel; LND: lonidamine; CPA: cyclophosphamide; VDS: vindesine; NR: not recorded.

Table 4 Phase I trials for elderly patients with advanced non-small cell lung cancer

Author	Study period	Form of report	Country	Chemotherapy regimen (MTD)	No. of assessable pts	Eligibility criteria regarding age (years)	Main dose-limiting toxicity	No. of pts with early death (%)	RR (%)	Ref.
Inoue	2000–2001	F	Japan	DOC 30 mg/m^2 d1,8,15 q4w	11	>69	Neutropenia, diarrhea	0	18	[78]
Yamamoto	NR	A	Japan	254-S 100 mg/m^2 d1,8,15	36	>69	Neutropenia	NR	33	[79]
Ohe	1998–1999	F	Japan	CDDP 25 mg/m^2 d1,8,15 q4w DOC 25 mg/m^2 d1,8,15	12	>74	Infection	0	58	[80]

Abbreviations: MTD: maximum-tolerated dose; pts: patients; RR: response rate; ref.: references; F: full text; A: abstract only; DOC: docetaxel; 254-S: nedaplatin; CDDP: cisplatin; DOC: docetaxel; NR: not recorded.

Table 5 Characteristics of patients enrolled in elderly-specific clinical trials

Author	Study Period	Chemotherapy regimen	No. of assessable pts	Median age (range) (years)	%Female	%PS 0/1	%Ad	%Stage IV	%Comorbidities	Ref.
ELVIS	1996–1997	VNR	76	74 (70–85)	15	76	34	74	49	[33]
		BSC	78	74 (70–86)	12	76	38	72	65	
Frasci	1997–1999	VNR	60	74 (71–81)	8	78	40	58	25	[34]
		VNR + GEM	60	75 (71–83)	12	73	38	60	23	
Gridelli	1997–2000	VNR	233	74 (63–83)	12	81	35	71	90	[35]
		GEM	233	74 (70–86)	17	82	33	70	89	
		VNR + GEM	232	74 (69–84)	21	81	33	69	87	
Marinis	1990–1992	VDS	30	75 (65–88)	15	65	NR	40	NR	[36]
		LND	32							
		VDS + LND	33							
		BSC	31							
Colleoni	1992–1994	VNR	25	70 (65–80)	20	64	76	68	NR	[37]
Veronesi	1992–1994	VNR	23	72 (70–80)	4	NR[a]	35	48	NR	[38]
Tononi	1993–1996	VNR	25	71 (65–77)	16	NR[b]	60	52	NR	[39]
Gridelli	1994–1995	VNR	43	73 (70–80)	12	49	26	56	65	[40]
Buccheri	1995–1998	VNR	40	75 (70–83)	13	23	50	45	NR	[41]
Mattioli	1996–	VNR	15	70 (65–84)	7	NR	NR	53	100	[42]
Schulz	NR	VNR[c]	58	73 (65–87)	NR	88	NR	NR	NR	[43]
Gridelli	2001–2002	VNR[c]	56	74 (70–82)	25	52	NR	77	88	[44]
Quoix	NR	GEM(q4w)	42	75 (71–90)	14	81	29	62	NR	[45]
		GEM(q3w)	39	75 (70–89)	21	72	39	72		
Bianco	1996–1999	GEM	52	70 (65–82)	21	85	29	19	60	[46]
Ricci	1997–1998	GEM	46	75 (70–81)	11	80	48	65	NR	[47]
Altavilla	1997–1998	GEM	21	74 (70–81)	14	52	33	67	NR	[48]
Martoni	1997–1999	GEM	46	73 (70–82)	17	NR[b]	43	39	52	[49]
Wilson	NR	GEM	35	74 (66–89)	41	NR	65	73	NR	[50]
Pasquini	NR	GEM	22	NR	NR	NR	NR	NR	NR	[51]
Yoshimura	1997–1999	DOC	30	76 (70–83)	27	70	53	73	NR	[52]
Tibaldi	NR	DOC	17	73 (70–80)	18	18	29	NR	NR	[53]
Fidias	1998–2000	PTX	35	76 (70–85)	32	80	71	86	NR	[54]
Gallotti	1990–1992	VDS	22	72 (64–74)	NR	0	NR	NR	NR	[55]
Baldini	NR	DXF	33	74 (70–80)	9	84	52	67	NR	[56]

Table 5 (*Continued*)

Author	Study Period	Chemotherapy regimen	No. of assessable pts	Median age (range) (years)	%Female	%PS 0/1	%Ad	%Stage IV	%Comorbidities	Ref.
Martins	1996–1998	CDDP + VNR	44	74 (71–85)	NR	50	NR	43	NR	[57]
Lippe	1999–2000	CDDP + VNR	13	70 (65–80)	23	69	NR	92	NR	[58]
Feliu	1999–	CDDP + GEM	46	74 (70–81)	9	65	24	57	74	[59]
Lippe	NR	CDDP + GEM	29	70 (66–77)	7	86	41	55	NR	[60]
Berardi	NR	CDDP + GEM	48	74 (70–78)	23	50	44	69	NR	[61]
Moscetti	2000–	CDDP + GEM	34	71 (65–77)	NR	82	47	50	NR	[62]
Niho	2000–2002	CDDP + DOC	33	77 (75–86)	21	100	61	52	NR	[63]
Kanat	NR	CDDP + ETP	24	72 (70–77)	8	38	21	71	NR	[64]
Souquet	1995–	CDDP + IFO + MMC	16	NR	NR	NR	NR	NR	NR	[65]
LeCaer	NR	CBDCA + VNR	40	72 (70–82)	23	100	30	80	NR	[66]
Maestu	1998–2000	CBDCA + GEM	79	74 (65–81)	NR	67	17	53	62	[67]
Molinier	2002–	CBDCA + PTX	43	74 (70–88)	26	89	58	84	NR	[68]
Jatoi	2000–2001	CBDCA + PTX	49	73 (65–85)	41	77	NR	86	NR	[69]
Gridelli	NR	CBDCA + ETP	14	73 (70–77)	7	71	36	64	43	[70]
Cuzzoni	NR	CBDCA + ETP	42	68 (65–75)	29	NR[b]	83	57	NR	[71]

Santomaggio	2000 onwards	GEM + VNR GEM + VDS	30 29	75	NR	49	NR	42	NR	[72]
Maestu	2001–2003	GEM VNR	43	74 (70–82)	NR	56	NR	65	79	[73]
Baron	1999–1999	GEM VNR	40	75 (70–84)	20	73	NR	43	NR	[74]
Chen	1998–2001	GEM VNR	40	83 (80–88)	20	20	50	50	100	[75]
Salvati	1990–1991	LND CPA	35	73 (71–79)	9	100	34	19	NR	[76]
Malarme	NR	IFO VDS	20	72 (66–79)	20	NR	NR	75	NR	[77]
Inoue	2000–2001	DOC	11	73 (70–78)	18	100	55	27	NR	[78]
Yamamoto	NR	254-S	36	76 (70–82)	11	97	NR	58	NR	[79]
Ohe	1998–1999	CDDP DOC	12	76 (75–80)	8	100	6	67	NR	[80]

Abbreviations: pts: patients; PS: performance status; Ad: adenocarcinoma; ref.: references; ELVIS: The Elderly Lung Cancer Vinorelbine Italian Study Group; VNR: vinorelbine; GEM: gemcitabine; VDS: vindesine; LND: lonidamine; DOC: docetaxel; PTX: paclitaxel; DXF: doxifluridine; CDDP: cisplatin; IFO: ifosphamide; MMC: mitomycin C; CBDCA: carboplatin; ETP: etoposide; CPA: cyclophosphamide; 254-S: nedaplatin; NR: not recorded.

[a] Median performance status was 1 (range, 0–3).

[b] Median performance status was 1 (range, 0–2).

[c] Oral vinorelbine. Median performance status was 2 (range, 1–3).

[52–54]. The efficacy of these agents appeared to be comparable with that of vinorelbine or gemcitabine.

Regarding combination chemotherapy regimens, platinum-based chemotherapy was performed in 16 trials, with a response rate ranging from 0 to 58% and a median survival time ranging from 27 to 74 weeks. The efficacy of non-platinum combination regimens was evaluated in nine trials, including six reports examining gemcitabine plus vinorelbine in a total of 425 patients [34,35,72–75]. The response rates and median survival times ranged from 3 to 65% and from 17 to 43 weeks, respectively. The efficacy of multidrug chemotherapy seemed to be comparable with that of single-agent chemotherapy, a finding that was confirmed in one phase III trial [35].

Quality-of-life was used in 10 trials (21%) as one of the endpoints. Of note, systemic chemotherapy improved the quality-of-life in the majority of the trials. In particular, the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) phase III trial evaluated quality-of-life as the primary endpoint and clearly demonstrated that vinorelbine improved not only overall survival, but also quality-of-life, when compared with best supportive care alone [33].

4. Discussion

Most trials identified in this study included only a small number of patients, and a statistically accurate estimation of the required sample size was often lacking. Of the 48 trials, the sample size was properly calculated in only 16 trials (33%). In addition, since several trials were reported only as an abstract, the details of the trials were difficult to obtain. Such missing data made some information unreliable, resulting in a limitation of the current study.

The term "elderly patient" was simply defined based on calendar age in all the trials, and an arbitrary age of 70 or 65 years was frequently used as the cut-off value. Aging is a very individualized process that involves changes in physical, cognitive, emotional, social and economic domains and these changes in an individual person cannot be predicted by only one's calendar age. Recently, several reports remarked on the issue of comprehensive geriatric assessment (CGA) and the possibility to include such instrument in study designs for elderly patients [83]. Although CGA has not been standardized, several screening tests were proposed for CGA, assessing mental status, emotional status, depression, activities of daily living, instrumental activities of daily living, home environment, social support, comorbidity, nutrition, and polypharmacy.

Our study revealed that only 27% of the authors reported comorbid conditions, indicating that physicians seldom recognize their importance. Frasci et al. demonstrated in a phase III trial that a high Charlson comorbidity score was strongly associated with a high risk of early treatment suspension [34]. Comorbidity is also reported to be a prognostic factor for overall survival [84,85] and the number of comorbidities increases with advancing age in cancer patients [2]. Thus, the assessment of comorbid status is one of the important issues especially in clinical trials of elderly patients.

The median prevalence of comorbidity in the trials we analyzed was at most 65%, whereas community-based studies have shown that approximately 80% of elderly cancer patients have one or more comorbidity [2,85,86]. This difference might not be attributed to exclusion of patients with a performance status of 3 or 4 in most trials we identified, since comorbidity and performance status have been reported to exhibit a low level of correlation [84,85,87]. It might simply suggest that elderly patients without any comorbidity were predominantly selected for enrollment in the trials.

We found several trials that included not only elderly patients but also non-elderly patients with a poor performance status [10–29], where the treatment efficacy for both groups was evaluated as a single group. Of these trials, Frasci et al. performed a subset analysis comparing elderly patients with non-elderly patients with a poor performance status in a phase II study of carboplatin and etoposide and concluded that the tumor responses and overall survival times for the two populations were clearly different [27]. Edelman et al. has also documented different toxicity and efficacy profiles for these two groups [28]. Thus, elderly patients and non-elderly patients with a poor performance status seem to compose distinct populations and should be accrued separately in clinical trials, even if the primary endpoint for each population is identical.

Quality-of-life is an extremely important issue in elderly patients with advanced NSCLC; however, formal quality-of-life assessments were only performed in a few elderly-specific clinical trials. Of these, the ELVIS trial demonstrated that single-agent chemotherapy with vinorelbine clearly improved quality-of-life [33]. Another phase III trial revealed that the baseline assessment of quality-of-life was a prognostic factor [88]. Quality-of-life assessments are particularly important when the difference in survival between two treatment strategies is very small and quality-of-life becomes one of the major determinants of treatment choice. Thus, the results obtained from the two phase III trials indicate that

an assessment of quality-of-life is necessary for identifying elderly patients with advanced NSCLC who are candidates for systemic chemotherapy.

5. Conclusion

Our review revealed that (i) the definition of "elderly" varied from trial to trial, and "elderly" patients were usually defined using their calendar age in most of the elderly-specific trials; (ii) the quality of the elderly-specific clinical trials was generally poor because most trials included only a small number of patients, often did not include a statement of written informed consent, were reported in abstract-form only and the enrolled patients were unlikely to have comorbidities suggesting the presence of a study bias; and (iii) single-agent chemotherapy with new drugs is promising for the treatment of elderly patients with advanced NSCLC. Well-designed prospective trials with a sufficient patient sample size are needed to elucidate many unanswered questions regarding the optimal and most effective treatments for elderly patients.

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