before paclitaxel infusion on both days 1 and 8. The treatment was repeated every 3 weeks. In the second cycle, the reversed sequence of drug administration, preceding administration of paclitaxel followed by irinotecan, was conducted on days 1 and 8. From the third cycle onwards the same schedule as that in the first cycle was planned, but repeating the sequence of the second cycle was accepted, if the toxicities experienced in the second cycle were milder than those in the first cycle. Five dose levels were planned. The starting dose of both irinotecan and paclitaxel was 40 mg/m$^2$, which was then increased in 10 mg/m$^2$ increments alternately.

Administration of irinotecan and paclitaxel on day 8 was cancelled if either hematological toxicities of grade 3 or greater, or non-hematological toxicities of grade 2 or greater were observed on the same day. Patients were treated with at least two cycles of chemotherapy unless there was disease progression, unacceptable toxicity in the first cycle, or withdrawal of their consent. Initiation of the next cycle of chemotherapy was delayed until recovery of a WBC count to $\geq$3000/$\mu$l, a neutrophil count to $\geq$1500/$\mu$l, a platelet count to $\geq 10 \times 10^4/\mu$l, and resolution of non-hematologic toxicities to $\leq$grade 1.

## 2.3. Assessment of toxicity and dose escalation

Toxicity was graded according to modified version of the National Cancer Institute-Common Toxicity Criteria [11]. Dose-limiting toxicity (DLT) was defined as development of at least one of the following adverse events: any non-hematologic toxicities $\geq$grade 3 except for alopecia, nausea, vomiting, and hyponatremia; platelet count $\leq 2 \times 10^4/\mu$l; grade 4 leukopenia; persistence of grade 4 neutropenia for more than 5 days; grade 3 or greater neutropenia with fever $\geq$38 °C or with infection; the cancellation of irinotecan and paclitaxel on day 8; and failure to recover from toxicities enough to begin a next cycle of treatment by day 29.

Six patients were scheduled to enter the study at each dose level. If fewer than three of six patients experienced DLT, then the next group of patients was treated at the next higher dose level. The MTD was defined as a dose level that produced any of the DLTs developed in three or more patients among a maximum of six patients, and further dose escalation was not permitted. All treatment cycles were analyzed to determine the DLT and MTD, although the decision to increase to the next higher dose level was based on the toxicities in the first cycle. Dose escalation above starting doses in the individual patient was not allowed. The recommended dose was defined as the dose level below the MTD. If grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia was noted, the use of granulocyte colony-stimulating factor was permitted. The dose could be reduced in the subsequent cycles if patients experienced DLT in the previous cycle, but this decision was left to the discretion of the physician.

## 2.4. Assessment of antitumor activity

Standard Response Evaluation Criteria in Solid Tumors [12] was used to evaluate responses. The best overall response was defined as the best response recorded from the start of the treatment until disease progression or recurrence. The smallest measurement recorded during the treatment was used as a reference to assess the case as the disease progressed. A radiologist reviewed all response assessments.

## 2.5. Pharmacokinetic analysis

Blood samples for pharmacokinetic analysis were obtained during the first day of the first and the second cycles, from an indwelling venous catheter placed in the arm contralateral to that used for drug infusion. For kinetic analyses of paclitaxel, irinotecan, and 7-ethyl-10-hydroxy-camptothecin (SN-38), 10 ml of blood was collected in heparinized tubes before drug administration, at 0.5 and 1 h during the infusion of irinotecan, and 0.5, 1, 2, 5, 8 and 23 h after the end of the infusion in the first cycle. In the second cycle, blood was collected at the same points before, during and after the infusion of paclitaxel. After centrifugation, the plasma was obtained and stored at −80 °C until assay. The plasma concentrations of paclitaxel, irinotecan, and SN-38 were measured by high-performance liquid chromatography (HPLC), as previously described [13]. The area under the plasma concentration–time curve (AUC) was calculated using WINNONLIN Standard Edition Version 1.5. Differences in the AUCs between dose level 1 and dose level 2, or the first cycle and the second cycle were evaluated by the unpaired *t*-test. The correlations between pharmacokinetic parameters and clinical toxicities such as leukopenia, neutropenia, diarrhea, and hepatic toxicity, were assessed with Pearson's correlation coefficient. Statistical analyses were performed using the STATVIEW 5.0 program (Brainpower, Calabasas, CA). A *P* value of less than 0.05 was considered statistically significant.

**Table 1** Hematological toxicity of grade 2 or greater (all cycles)

| Toxicity | Grade | No. of cycles (%) | |
|---|---|---|---|
| | | Dose level 1 (nine cycles) | Dose level 2 (three cycles) |
| Leukopenia | 2 | 1 (11%) | 0 (0%) |
| | 3 | 0 (0%) | 2 (67%) |
| | 4 | 0 (0%) | 0 (0%) |
| Neutropenia | 2 | 0 (0%) | 0 (0%) |
| | 3 | 0 (0%) | 2 (67%) |
| | 4 | 1 (11%) | 0 (0%) |
| Anemia | 2 | 1 (11%) | 1 (33%) |
| | 3 | 0 (0%) | 0 (0%) |
| | 4 | 0 (0%) | 0 (0%) |

## 3. Results

### 3.1. Patients' characteristics

Nine patients with advanced NSCLC were enrolled in this trial between October 2001 and September 2002. There were five men and four women with a median age of 70 ranging from 55 to 75. All patients had ECOG performance status of 1. Six patients were treated at dose level 1 and three at dose level 2. Eight patients had adenocarcinoma and one non-classified non-small cell carcinoma. Clinical stage was IV in eight patients and postoperative recurrence in one. Five dose levels (irinotecan/paclitaxel) were planned as follows: 40/40, 40/50, 50/50, 50/60 and 60/60 mg/m$^2$. A total of 12 chemotherapy cycles were administered, with a median number of one cycle per patient (range, 1–2). Six patients (67%) received only one cycle of chemotherapy, because of unacceptable toxicity in five patients and the patient's refusal in one. All patients and cycles were assessable for safety.

### 3.2. Hematological toxicity

The main toxicity of this combination was myelosuppression (Table 1). Both grade 3 or 4 neutropenia and leukopenia were observed in 67% of cycles at dose level 2, whereas they developed in 11 and 0% of cycles at dose level 1, respectively. Two patients, one each in dose levels 1 and 2, were unable to receive irinotecan and paclitaxel on day 8 of the first cycle, because they developed grade 3 neutropenia and leukopenia on day 8, respectively. These toxicities were, therefore, considered to be DLT. Anemia and thrombocytopenia were relatively mild, and no transfusions were required.

**Table 2** Non-hematologic toxicity of grade 2 or greater (all cycles)

| Toxicity | Grade | No. of cycles (%) | |
|---|---|---|---|
| | | Dose level 1 (nine cycles) | Dose level 2 (three cycles) |
| Nausea/ vomiting | 2 | 0 (0%) | 0 (0%) |
| | 3 | 2(22%) | 1 (33%) |
| Febrile neutropenia | 2 | 0 (0%) | 0 (0%) |
| | 3 | 0 (0%) | 1 (33%) |
| Arrhythmia | 2 | 0 (0%) | 0 (0%) |
| | 3 | 0 (0%) | 1 (33%) |
| Hepatotoxicity | 2 | 1 (11%) | 1 (33%) |
| | 3 | 0 (0%) | 0 (0%) |
| Hyponatremia | 2 | 0 (0%) | 0 (33%) |
| | 3 | 1 (11%) | 0 (0%) |
| Peripheral neuropathy | 2 | 1 (11%) | 0 (0%) |
| | 3 | 0 (0%) | 0 (0%) |

No grade 4 non-hematologic toxicity was noted.

### 3.3. Non-hematological toxicity

Febrile neutropenia occurred in one patient (11%) receiving a level 2 dose in the first cycle (Table 2), however, it was reversible with appropriate supportive care. One patient who was treated at dose level 1 was unable to receive irinotecan and paclitaxel on day 8 because of grade 2 hepatic dysfunction, which was also considered to be DLT. Another patient receiving a level 2 dose experienced paroxysmal supraventricular tachycardia (grade 3) soon after the administration of paclitaxel on day 8 of the first cycle. He had a past history of artrial premature beat, and the condition improved with the administration of digoxin. Grade 3 hyponatremia during the first cycle at dose level 1 and grade 3 nausea at both dose levels were reversible toxicities. Diarrhea, arthralgia, myalgia, and peripheral neuropathy were mild, and no intensive management was required.

### 3.4. Maximum-tolerated dose

DLT was observed in two of six patients at dose level 1 (cancellation of irinotecan and paclitaxel on day 8 because of myelosuppression and hepatic dysfuntion), and in all three patients at dose level 2 (febrile neutropenia, supraventricular arrhythmia, and cancellation of irinotecan and

paclitaxel on day 8 because of myelosuppression). There were no treatment-related deaths. We determined the MTD of irinotecan and paclitaxel to be 40 and 50 mg/m$^2$, respectively.

### 3.5. Antitumor activity

All patients were assessable for response. Objective tumor response was not observed, although eight patients (88.9%) achieved a stable disease. The one remaining patient developed a progressing disease (11.1%).

### 3.6. Pharmacokinetic analysis

Pharamacokinetic parameters were obtained during the first day of the first cycle in nine patients and the first day of the second cycle in three patients. The maximum concentration ($C_{max}$) of paclitaxel at dose level 2 was higher than that at dose level 1 (1753.3 ± 270.0 versus 1041.8 ± 94.1 ng/ml, $P = 0.016$), whereas the other parameters of the two drugs were comparable between dose levels 1 and 2 (Table 3). We also evaluated differences of several parameters between cycles 1 and 2 in order to investigate a sequence-dependent effect on the pharmacokinetics of irinotecan and paclitaxel. As listed in Table 4, there was a tendency for the AUC of irinotecan to be relatively high in cycle 2 (paclitaxel followed by irinotecan) compared with that in cycle 1 (irinotecan followed by paclitaxel), while the AUC of paclitaxel in cycle 1 was slightly higher than that in cycle 2.

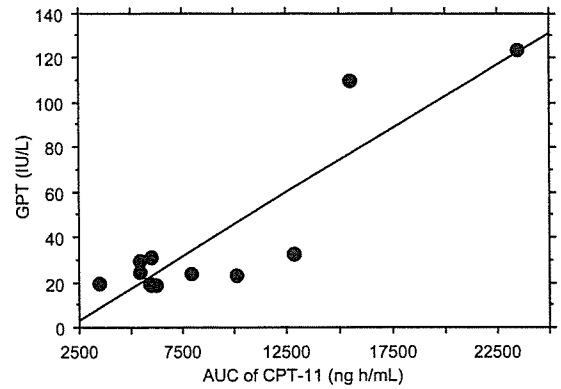


**Fig. 1** The correlation between the maximum levels of GPT and the area under the plasma concentration–time curve of irinotecan. Pearson's correlation coefficient was 0.894 with 95% confidential interval of 0.656–0.970 ($P < 0.0001$). AUC: area under the plasma concentration–time curve; CPT-11: irinotecan.

### 3.7. Pharmacodynamic analysis

The correlation of several toxicity profiles with the pharmacokinetic parameters of the drugs was analyzed. The AUC of irinotecan was strongly correlated to the elevation of GPT after treatment (Pearson's $r = 0.894$, $P < 0.0001$) (Fig. 1). Maximal hepatic toxicity was observed early after the drug administration (median: day 8, range: day 2–day

**Table 3** Various pharmacokinetic parameters of the drugs at dose levels 1 and 2

| | Level 1 (PTX 40 mg/m$^2$) (no. of patients: 6) | Level 2 (PTX 50 mg/m$^2$) (no. of patients: 3) | *P* |
|---|---|---|---|
| CPT-11 | | | |
| $T_{max}$ (h) | 1 | 1 | |
| $C_{max}$ (ng/ml) | 779.4 ± 119.4 | 775.2 ± 37.5 | 0.981 |
| AUC (ng h/ml) | 8588.1 ± 3030.7 | 9950.3 ± 2873.1 | 0.582 |
| CL (l/h) | 6.7 ± 1.3 | 4.2 ± 1.3 | 0.284 |
| SN-38 | | | |
| $T_{max}$ (h) | 3 | 2 | |
| $C_{max}$ (ng/ml) | 46.6 ± 14.1 | 54.4 ± 5.2 | 0.718 |
| AUC (ng h/ml) | 334.7 ± 80.6 | 458.2 ± 52.5 | 0.348 |
| CL (l/h) | 182.6 ± 57.5 | 89.5 ± 9.7 | 0.306 |
| PTX | | | |
| $T_{max}$ (h) | 1 | 1 | |
| $C_{max}$ (ng/ml) | 1041.8 ± 94.1 | 1753.3 ± 270.0 | 0.016 |
| AUC (ng h/ml) | 1786.4 ± 342.7 | 2454.3 ± 509.6 | 0.304 |
| CL (l/h) | 26.2 ± 4.5 | 22.9 ± 6.0 | 0.677 |

Each data represents the mean values and standard errors. CPT-11: irinotecan; PTX: paclitaxel; AUC: area under the plasma concentration–time curve; CL: clearance.

**Table 4** Various pharmacokinetic parameters of the drugs on cycles 1 and 2

| | Cycle 1 (CPT-PTX) (no. of patients: 3) | Cycle 2 (PTX-CPT) (no. of patients: 3) | *P* |
|---|---|---|---|
| CPT-11 | | | |
| $T_{max}$ (h) | 1 | 1 | |
| $C_{max}$ (ng/ml) | 615.1 ± 109.0 | 742.4 ± 100.0 | 0.438 |
| AUC (ng h/ml) | 5761.6 ± 1293.9 | 7399.0 ± 1354.3 | 0.431 |
| CL (l/h) | 7.8 ± 2.0 | 5.7 ± 0.9 | 0.390 |
| SN-38 | | | |
| $T_{max}$ (h) | 3 | 1 | |
| $C_{max}$ (ng/ml) | 46.3 ± 25.3 | 38.6 ± 8.6 | 0.788 |
| AUC (ng h/ml) | 336.3 ± 133.4 | 214.4 ± 41.6 | 0.433 |
| CL (l/h) | 165.7 ± 63.8 | 205.7 ± 49.3 | 0.647 |
| PTX | | | |
| $T_{max}$ (h) | 1 | 1 | |
| $C_{max}$ (ng/ml) | 937.0 ± 178.5 | 1020.3 ± 135.4 | 0.729 |
| AUC (ng h/ml) | 1417.3 ± 288.0 | 1315.1 ± 214.0 | 0.790 |
| CL (l/h) | 31.2 ± 7.5 | 32.5 ± 6.3 | 0.905 |

Each data represents the mean values and standard errors. CPT-11: irinotecan; PTX: paclitaxel; AUC: area under the plasma concentration–time curve; CL: clearance.

26). Two of nine patients had hepatic metastasis; however, they did not encounter any hepatic toxicity. No significant correlation was observed between the other pharmacokinetic parameters and the degree of leukopenia, neutropenia, or diarrhea.

## 4. Discussion

The present study demonstrated that the combination of irinotecan and paclitaxel in this schedule had considerable toxicities despite no promising activity for advanced NSCLC. Several toxicity profiles in this combination have been previously reported. Yamamoto et al. documented that all patients receiving this combination at the initial dose level (irinotecan 50 mg/m$^2$: days 1, 8 and 15; and paxlitaxel 135 mg/m$^2$: day 2) had severe dose-limiting myelotoxicity [9]. Rosen et al. also reported that dose escalation of the two drugs above the starting dose (irinotecan 225 mg/m$^2$ and paxlitaxel 100 mg/m$^2$, once every 3 weeks) was impossible because of neutropenic fever or severe diarrhea [14]. On the other hand, Murren et al. investigated the combination of the two drugs in a weekly schedule for patients with advanced various cancers, and concluded that this combination was well tolerated, although they experienced several adverse events in the patients treated with the recommended dose [15]. These results suggest that the combination of irinotecan and paclitaxel produces relatively severe toxicities, compared with other regimens containing irinotecan or paclitaxel such as cisplatin plus irinotecan or carboplatin plus paclitaxel [5,16]. However, we considered that fractionated schedule of the two drugs might be less toxic and promising, and we planned the current study.

In the previous dose escalation studies, a range of MTDs was reported, however, this may be attributable to differences in the definition of DLT. In our study, the MTD was determined to be dose level 2, which was much lower than that in the previous reports. The major cause may be our strict criteria for DLT, especially assessing the cancellation on day 8 as DLT, which was encountered in three patients because of grade 3 neutropenia, grade 2 hepatic dysfunction, or grade 3 leukopenia.

In the previous pharmacokinetic analysis, Kasai et al. [8] showed the elevation of the AUC of irinotecan by the preceding administration of a relatively high dose of paclitaxel, and speculated that the competitive inhibition of metabolism was the possible mechanism, since both drugs were metabolized by cytochrome P450 (CYP) 3A4 [17,18]. However, no pharmacokinetic analysis of paclitaxel was investigated in their study. Our study revealed the possibility that the preceding administration of paclitaxel increased the AUC of irinotecan, and the preceding irinotecan also increased the AUC of paclitaxel, which suggests that irinotecan and paclitaxel might have affected each others'

metabolic pathways, possibly by the consumption of CYP3A4. However, the results in the present study were not statistically significant, which might result from the following reasons. Firstly, the doses of irinotecan and paclitaxel in the present study were relatively low, and secondly, both drugs are metabolized not only by CYP3A4 but also by other enzymes such as carboxylesterase or CYP2C8 [19,20].

Unfortunately, an objective response was not obtained in the present study. Kasai et al. previously documented the favorable antitumor effect (response rate of 31%) for advanced NSCLC. The difference in the antitumor activity between Kasai's study and ours might be partly attributable to the insufficient doses of the two drugs in our study. As another possible explanation, the difference in the schedule of administration should be considered. Kano et al. reported the antagonistic effect of the two drugs when exposed to human lung cancer cell lines simultaneously, whereas sequential exposure produced an additive effect [21]. Debernardis et al. also demonstrated the antagonistic effect with simultaneous exposure of the two drugs [22]. Kasai et al. administered paclitaxel on day 1, and irinotecan on days 1, 8 and 15. Furthermore, irinotecan was infused following a 2 h rest period after completion of paclitaxel administration on day 1 [8], while we gave both drugs sequentially on the same days without a rest period, which was much closer to the simultaneous exposure of the two drugs than Kasai's study. This difference in the treatment schedules might have produced different antitumor effects.

In the pharmacodynamic analysis, we demonstrated that the AUC of irinotecan was strongly associated with the elevated serum levels of GPT. To our knowledge, this relationship has never been reported, though the pharmacokinetic/pharmacodynamic relationship between irinotecan AUC and myelosuppression, and between SN-38 pharmacokinetic variables and diarrhea has been identified in the previous studies [23]. Accordingly, monitoring of the AUC of irinotecan may be useful for the early prediction of hepatic toxicity in our treatment schedule. Further investigation is warranted to confirm the role of monitoring the AUC of irinotecan.

In conclusion, this phase I study was able to show neither feasibility nor effectiveness of this two-drug combination consisting of irinotecan and paclitaxel for patients with advanced NSCLC. Other drug administration schedules or different combinations should be investigated to establish more optimal combination chemotherapy in patients with advanced NSCLC.

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

Naoyuki Nogami[a], Shingo Harita[b], Hiroshi Ueoka[a,*], Toshiro Yonei[c], Katsuyuki Kiura[a], Haruhito Kamei[d], Masahiro Tabata[a], Yoshihiko Segawa[e], Kenichi Gemba[f], Mitsune Tanimoto[a]

[a] *Department of Internal Medicine II, Okayama University Medical School, 2-5-1 Shikatacho, Okayama, Okayama Prefecture 700-8558, Japan*
[b] *Department of Internal Medicine, Chugoku Central Hospital, 6-3-1 Nishifukazucho, Fukuyama, Hiroshima Prefecture 721-8581, Japan*
[c] *Department of Respiratory Medicine, National Okayama Medical Center, 1711-1 Tamasu, Okayama, Okayama Prefecture 701-1192, Japan*
[d] *Department of Internal Medicine, Sumitomobesshi Hospital, 3-1 Ojicho, Niihama, Ehime Prefecture 792-8543, Japan*
[e] *Department of Respiratory Medicine, National Shikoku Cancer Center, 13 Horinouchi, Matsuyama, Ehime Prefecture 790-0007, Japan*
[f] *Respiratory Disease Center for Workers, Okayama Rousai Hospital, 1-10-25 Chikkoumidorimachi, Okayama, Okayama Prefecture 702-8055, Japan*

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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.


*Corresponding author. Tel.: +81-86-235-7225; fax: +81-86-232-8226.
*E-mail address:* hueoka@md.okayama-u.ac.jp (H. Ueoka).

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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 $\mu l^{-1}$; neutrophil count$\geqq$2000 $\mu l^{-1}$; and a platelet count$\geqq$100 000 $\mu l^{-1}$); (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.

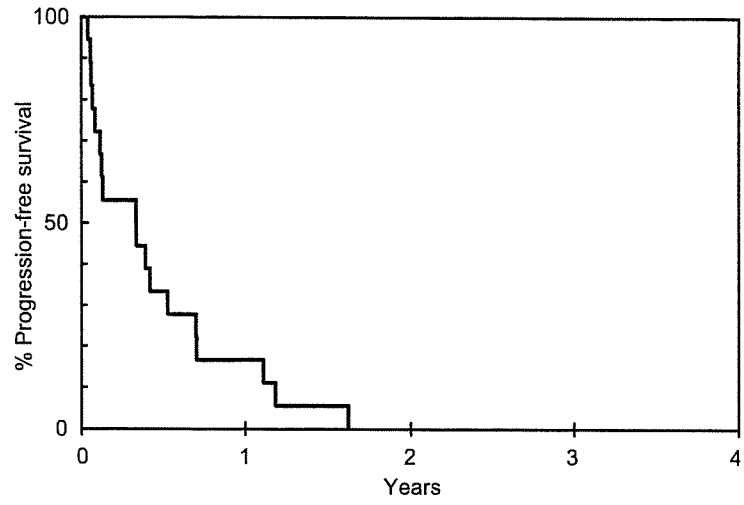


**Fig. 1** Kaplan–Meier analysis of progression-free survival.

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

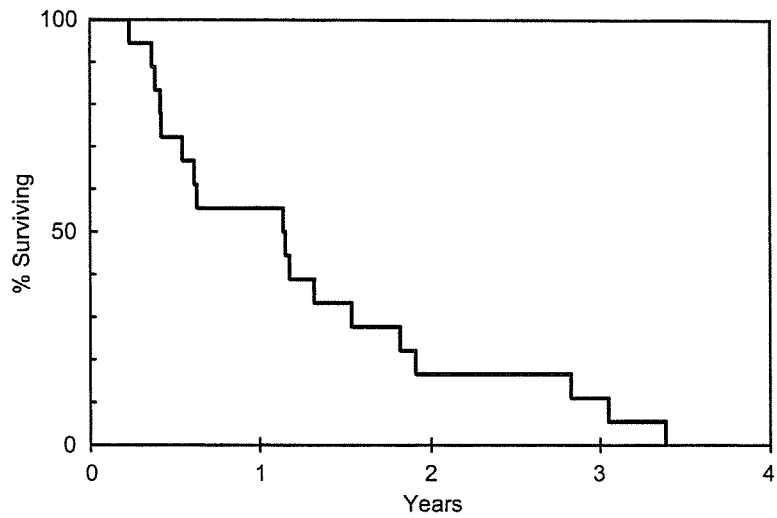


**Fig. 2** Kaplan–Meier analysis of overall survival.

**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

Katsuyuki Hotta*, Hiroshi Ueoka, Katsuyuki Kiura, Masahiro Tabata, Mitsune Tanimoto

*Department of Medicine II, Okayama University Medical School, 2-5-1, Shikata-cho, Okayama 700-8558, Japan*

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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

*Corresponding author. Tel.: +81-86-235-7227; fax: +81-86-232-8226.
*E-mail address:* khotta@md.okayama-u.ac.jp (K. Hotta).

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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/m$^2$ 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/m$^2$ d1,8 q3w | 60 | >69 | 15 | 1 (2) | 18 | 13 | Yes | [34] |
| | | | | VNR 30 mg/m$^2$ d1,8 q3w + GEM 1200 mg/m$^2$ d1,8 q3w | 60 | | 22 | 2 (3) | 29 | 30 | | |
| Gridelli | 1997–2000 | F | Italy | VNR 30 mg/m$^2$ d1,8 q3w | 233 | >69 | 18 | NR | 36 | 38 | Yes | [35] |
| | | | | GEM 1200 mg/m$^2$ d1,8 q3w | 233 | | 16 | NR | 28 | 28 | | |
| | | | | VNR 25 mg/m$^2$ d1,8 + GEM 1000 mg/m$^2$ d1,8 q3w | 232 | | 21 | NR | 30 | 30 | | |
| Marinis | 1990–1992 | F | Italy | VDS 3 mg/m$^2$ weekly | 30 | >70 | 3 | 12 (10)[a] | 24[a] | 20[a] | No | [36] |
| | | | | LND 450 mg daily | 32 | | 0 | | | | | |
| | | | | VDS 3 mg/m$^2$ 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<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>GEM 1250 mg/m$^2$ d1,8 | 79 | NR | 39 | NR | 42 | NR | No | [67] |
| Molinier | 2002– | A | France | CBDCA AUC 6 d1 4w<br>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<br>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<br>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<br>ETP 100 mg/m$^2$ d1–3 | 42 | NR | 31 | NR | 45 | NR | No | [71] |

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