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**Kazuto Nishio · Tokuzo Arao · Tatsu Shimoyama · Yasuhiro Fujiwara · Tomohide Tamura · Nagahiro Saijo**

# Translational studies for target-based drugs

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**Abstract** The biological background for the clinical and prognostic heterogeneity among tumors within the same histological subgroup is due to individual variations in the biology of tumors. The number of investigations looking at the application of novel technologies within the setting of clinical trials is increasing. The most promising way to improve cancer treatment is to build clinical research strategies on intricate biological evidence. New genomic technologies have been developed over recent years. These techniques are able to analyze thousands of genes and their expression profiles simultaneously. The purpose of this approach is to discover new cancer biomarkers, to improve diagnosis, predict clinical outcomes of disease and response to treatment, and to select new targets for novel agents with innovative mechanisms of action. Gene expression profiles are also used to assist in selecting biomarkers of pharmacodynamic effects of drugs in the clinical setting. Biomarker monitoring in surrogate tissues may allow researchers to assess "proof of principle" of new treatments. Clinical studies of biomarkers monitoring toxicity profiles have also been done. Such pharmacodynamic markers usually respond to treatment earlier than clinical response, and as such may be useful predictors of efficacy. Epidermal growth factor receptor (EGFR) mutation in lung cancer tissues is a strong predictive biomarker for EGFR-targeted protein tyrosine kinase inhibitors. Monitoring of EGFR mutation has been broadly performed in retrospective and prospective clinical studies. However, global standardization for the assay system is essential for such molecular correlative studies. A more sensitive assay for EGFR mutation is now under evaluation for small biopsy samples. Microdissection for tumor samples is also useful for the sensitive detection of EGFR mutation. Novel approaches for the detection of EGFR mutation in other clinical samples such as cytology, pleural effusion and circulating tumor cells are ongoing.

**Keywords** Biomarker · Proof of principle · Pharmacodynamic marker · EGFR mutation

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K. Nishio (✉) · T. Arao · T. Shimoyama
Shien Lab, National Cancer Center Hospital,
Tsukiji 5–1–1, Chuo-ku, 104–0045 Tokyo, Japan
E-mail: knishio@gan2.res.ncc.go.jp
Tel.: +81-3-35422511
Fax: +81-3-35475185

T. Shimoyama · Y. Fujiwara · T. Tamura · N. Saijo
Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

K. Nishio (✉) · T. Arao
Pharmacology Division,
National Cancer Center Research Institute, Tokyo, Japan

## Correlative studies at the National Cancer Center Hospital

Molecular correlative studies are essential for the development of anticancer molecular-targeted drugs. One of the major purposes of a correlative study is "proof of principle" (POP). However, clinical POP studies for small molecules are often more difficult to complete than those for antibodies.

Since 2001, the National Cancer Center Hospital (Tokyo, Japan) has been operating as a laboratory for translational studies to develop molecular correlative studies. The laboratory members include medical oncologists, basic researchers, CRC research fellows, invited researchers from abroad, technicians and statisticians. The laboratory is located next to the phase I wards in the hospital, enabling more than ten molecular correlative studies to be simultaneously performed. New clinical samples can be quickly obtained from patients (including outpatients), prepared for storage and stored in the laboratory. The medical doctors

**Table 1** Classification of biomarkers and their goals

| Biomarker | Goal |
|---|---|
| Diagnostic markers | |
| Prognostic markers | |
| Predictive markers (patient selection) | Selection of patients most likely to benefit from given treatment |
| Pharmacodynamic markers | Dose finding and schedule |
| Response and efficacy markers | To measure or infer patient benefit/relate patient benefit to target inhibition |
| Toxicity prediction markers | |

working in the laboratory are often research fellows supported by government grants as these individuals are often interested in this kind of research.

The location of the laboratory also gives frequent opportunities to medical oncologists to communicate with researchers. The significance of study endpoints, study design, technical and statistical information and feasibility are often discussed, especially among young medical oncologists and researchers. As a result, young oncologists and researchers often collaborate in the proposal of new molecular correlative studies.

The major activities of the laboratory are pharmacokinetics and pharmacodynamics studies for early clinical trials (phase I–II) and reverse translational studies. Essentially, "biomarker monitoring" using various biological technologies in these clinical studies are preformed. The selection and validation of biomarkers is a major endpoint for molecular correlative studies. Biomarkers are defined as described in Table 1. Tissue banking and quality control are two of the most important activities. Part of clinical sample testing is performed in collaboration with the Contract Research Organization (CRO) (Fig. 1).

## Gene expression profiles

Gene expression array (DNA chips) has been widely used in clinical studies to predict response and in POP studies [3]. Many kinds of DNA chip are now available. Oligonucleotide arrays containing >40,000 genes have recently become popular. These chips can be used differentially depending on the requirements. Before the clinical use, however, an array's quality (linearity and reproducibility) should be determined in preclinical studies. At the National Cancer Center Hospital, the quality of each array is evaluated and expressed as the Pearson's product-moment coefficient of correlation. Based on the validated quality of the cDNA, protocols based on "experienced designs" are then established.

In clinical settings, sample quality and protocol feasibility are often major limitations in the design of new studies. To maintain the quality of clinical samples, a system for sample flow has been established. First, purity of the nucleotides must be carefully examined. Purification methods largely depend on the tumor types. For example, brain tumors contain large amounts of carbohydrate chains, lung cancer samples are sometimes very hard, and breast cancer biopsy samples are lipid rich. These sample characteristics influence the purification quality and efficiency.

After the gene expression profiles have been obtained for each sample, the data are analyzed by standardization, clustering, statistical analysis and validation methods. Statistical and biological validation are essential. Ideally, clinical cross-validation studies should be performed for independent clinical studies. On the other

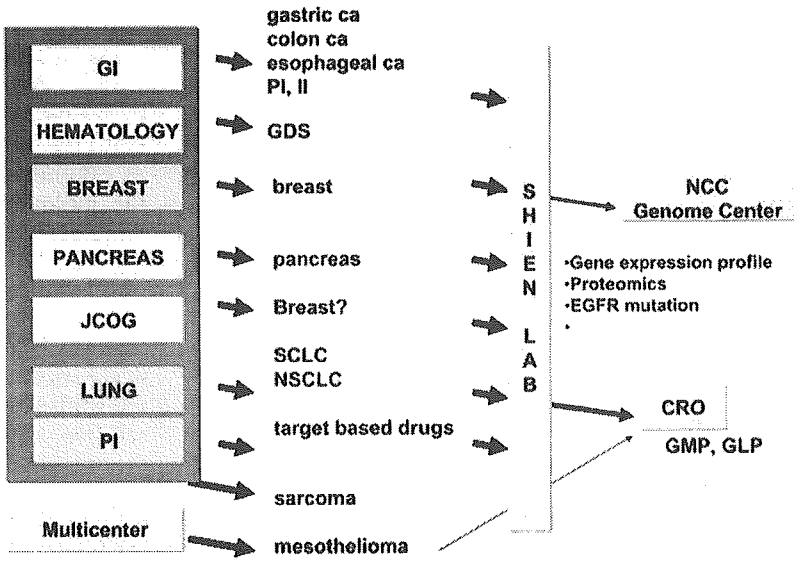


**Fig. 1** Flow of clinical samples in molecular correlative studies at the National Cancer Center Hospital. (*GI* gastrointestinal, *JCOG* Japan Clinical Oncology Group, *PI* clinical phase I study, *PII* clinical phase II study, *GDS* gene delivery system, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *NCC* National Cancer Center, *CRO* Contact Research Organization, *GMP* Good Manufacturing Practice)

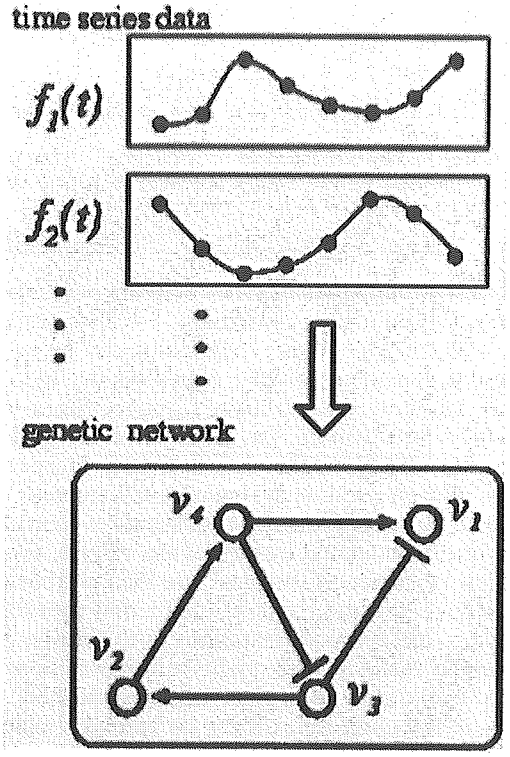


**Fig. 2** Network analysis to determine transcriptional pathway and signal transduction pathway modulated by transcriptional regulators and multitarget tyrosine kinase inhibitors using gene expression profiling dataset

hand, biomarkers can be validated in the same clinical study by the "leave-one-out" method. The endpoint of these correlative studies is usually the selection of biomarkers for predicting response or toxicity. For such endpoints, the quality of the clinical study itself is also very important.

We have also used other endpoints in early clinical studies, such as comparing clinical samples obtained before and after the treatment. Analysis of gene alterations after treatment can be utilized to reveal pharmacodynamic effects. We have completed such correlative studies as part of a clinical assessment of multitarget tyrosine kinase inhibitors (TKI), farnesyl transferase inhibitor, and cytotoxic drugs [7].

For biological confirmation, we usually perform real-time RT-PCR and immunostaining. However, we recently discovered that "pathway analysis" is a powerful method for improving our understanding of the alteration of genes related to biological signal transduction pathways. To analyze transcription factors, "network analysis" can be used to identify their signaling pathways (Fig. 2).

## Toxicogenomic project for breast cancer

As an approach of gene expression profiling in clinical samples, we monitored gene expression in breast cancer

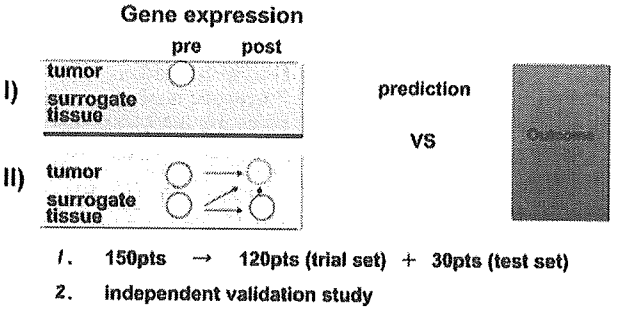


**Fig. 3** Gene expression monitoring to distinguish the outcome of treatment for breast cancer patients

patients during treatment with FEC followed by weekly paclitaxel ± trastuzumab in the adjuvant setting. The purpose of this approach was to predict outcomes as well as to study the pharmacodynamic effects of each treatment. Gene expression profiles of peripheral blood mononuclear cells obtained pre- and posttreatment and of tumor biopsy samples obtained pretreatment were determined (Fig. 3). An algorithm to distinguish outcomes using the dataset of these three sampling points was created and expected to be more powerful than conventional outcome assessment techniques.

It seems quite an unusual approach to use normal cells in gene expression profiling in oncology; however, this has proved to be a useful way to monitor drug pharmacodynamic effects and to select biomarkers. Using this approach, we selected biomarkers to capture adverse effects of the treatments. Such "biomarker monitoring" is a rapidly growing field of research.

## Biomarker monitoring for tyrosine kinase inhibitors

Recently, EGFR mutation has become an exciting topic in research on TKI [4, 6]. Mutation analysis is now essential for any correlative studies for TKI. Patients with tumors containing the EGFR mutation in different exons are thought to have different responses to TKI. A short, in-frame deletional mutant (E746-A750del) is one of the major mutant forms of EGFR in Japanese populations, and a determinant for EGFR-specific TKI such as gefitinib and ZD6474 (Fig. 4) [1, 8]. We investigated the biological and pharmacological functions of this mutated EGFR to determine whether tumors with deletional-EGFR status are responsive to ligand stimulation, whether mutated EGFR is constitutively active, and whether the downstream intracellular signaling pathway is altered. We concluded that deletional EGFR is constitutively active and that its downstream events are shifted to the AKT pathway (Fig. 5). In addition, a cell-free kinetic assay using mutant EGFR proteins demonstrated differential affinity to TKI among different EGFR mutants. Additional mutations after treatment are also generating interest with regard to their role in acquired resistance to TKI [2]. Thus, the mutation

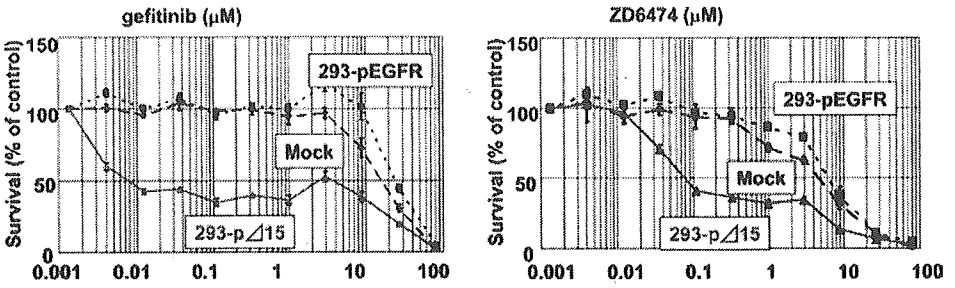


**Fig. 4** In vitro sensitivity of 293 cells transfected with a deletional epidermal growth factor receptor (*EGFR*) gene (E746-A750) to tyrosine kinase inhibitors (gefitinib and ZD6474) determined by MTT assay. EGFR mutation (E746-A750 type deletion) increases sensitivity to tyrosine kinase inhibitors (gefitinib and ZD6474). HEK293 cells were transfected with empty vector (293-mock), wild-type EGFR (293 p-EGFR), and deletional EGFR (293-pΔ15). Reprinted with permission of the American Association for Cancer Research Inc., from Arao et al. [1]

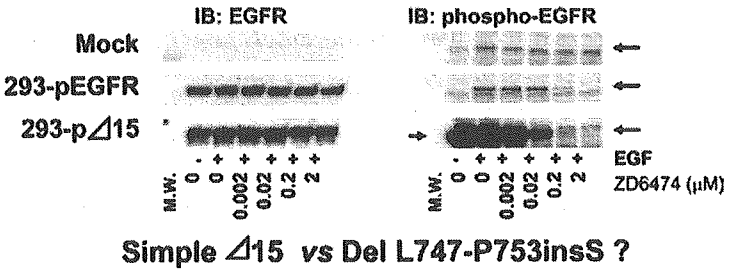


**Fig. 5** Constitutive phosphorylation of mutant EGFR. Phosphorylation of EGFR was determined by immunoblotting in 293 cells transfected with Mock, wild-type EGFR, and deletional EGFR cDNA. Increased phosphorylation was observed in the 293-pΔ15 cells under no ligand stimulation. Reprinted with permission of the American Association for Cancer Research Inc., from Arao et al. [1]. (*EGF* epidermal growth factor receptor, *IB* immunoblotting)

status of EGFR is one of the determinants for the prediction of tumor response to EGFR-targeted TKI. On the other hand, the clinical impact of EGFR mutation on survival in patients treated with these TKI remains unclear. Therefore, molecular correlative study including EGFR mutation analysis is quite important for prospective studies. Various technologies for EGFR mutation assay have been developed and some of these assays have been validated in the clinical situation [5]. Gene mutation analysis in prospective studies of TKI using standardized technologies is very important.

## Protein arrays

Proteomics technology has been developed and successfully used to identify biomarkers for target-based drugs in a few clinical studies. Additional approaches such as antibody arrays and "PowerBlots®", especially those using phospho-specific antibodies, should enable us to perform "kinome" analyses. Hence, these protein analysis technologies are now powerful tools for research on TKI.

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# Chemoradiotherapy for lung cancer

Yuichiro Ohe
*Department of Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

Chemoradiotherapy is a standard treatment for both unresectable locally advanced non-small cell lung cancer and limited-stage small cell lung cancer. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of ~ 15% for patients with unresectable locally advanced non-small cell lung cancer. The state-of-the-art treatment for limited-stage small cell lung cancer is four cycles of chemotherapy with cisplatin plus etoposide combined with early concurrent twice-daily thoracic irradiation and prophylactic cranial irradiation after complete remission. A 5-year survival rate of ~ 25% is expected among patients treated for limited-stage small cell lung cancer. The incorporation of new agents, including target-based drugs, is one of the most promising strategies for improving the survival of patients.

**Keywords:** chemoradiotherapy, fractionation, non-small cell lung cancer, small cell lung cancer, target-based drug

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## 1. Introduction

Lung cancer has been the most common cancer worldwide since 1985; as of 2002, 1.35 million new cases have been reported, representing 12.4% of all new cancers. It was also the most common cause of death from cancer with 1.18 million deaths: 17.6% of the world total [1]. Lung cancer remains a highly lethal disease. Survival at 5 years measured by the Surveillance Epidemiology and End Results (SEER) programme in the US was 15%: the best recorded rate at the population level. Average survival in Europe is 10%, which is not much better than the 8.9% observed in developing countries [1]. Lung cancer in both men and women continues to be the most common fatal cancer in the US. In 2005 lung cancer is expected to account for 31 and 27% of all deaths from cancer in men and women, respectively, in the US [2]. Nearly 60,000 patients died of lung cancer in 2004, and mortality continues to rise in Japan. In particular, the number of elderly lung cancer patients in Japan is increasing. Lung cancer is the leading cause of cancer death in men and is anticipated to become the leading cause of cancer deaths in women in Japan.

Of lung cancer patients ~ 15 – 20% have small cell lung cancer (SCLC); the remaining patients typically have non-small cell lung cancer (NSCLC), such as adenocarcinoma, squamous cell carcinoma or large cell carcinoma. Surgery is the most effective curative treatment for early-stage NSCLC; however, only 30% of patients with NSCLC receive a curative resection [3]. Platinum-based chemotherapy offers a survival benefit and symptom relief for patients with metastatic NSCLC, and the combination of cisplatin-containing chemotherapy with thoracic radiotherapy is presently the standard treatment for patients with unresectable locally advanced NSCLC [4]. Of patients with unresectable locally advanced NSCLC ~ 15% could be cured by concurrent chemoradiotherapy [5]. Most patients with SCLC are not considered to be candidates for surgery. Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 5-year survival rate of ~ 25% in limited-stage (LD) patients [6-8]. Chemoradiotherapy plays a very important

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**Table 1. Survival after concurrent chemoradiotherapy for unresectable locally advanced NSCLC and resectable pN2 NSCLC after surgery.**

| Study | JCOG 9202 [11] | JCOG 9209 [12] |
|---|---|---|
| Objective | Unresectable | Resectable, pN2 |
| Treatment | Cisplatin + vindesine + mitomycin Concurrent RT | Surgery with/ without induction cisplatin + vindesine |
| No. of patients | 160 | 62 |
| No. of institutions | 27 | 18 |
| ***c-stage*** | | |
| IIIA/IIIB (%) | 29/71 | 98/2 |
| N0-1/N2/N3 (%) | 12/54/34 | 0/98/2 |
| ***Survival rate*** | | |
| 2 year (%) | 35 | 36 |
| 3 year (%) | 22 | 25 |
| 5 year (%) | 16 | 17 |

JCOG: Japan Clinical Oncology Group; NSCLC: Non-small cell lung cancer.

role in the treatment of both patients with unresectable locally advanced NSCLC and patients with LD-SCLC.

## 2. Chemoradiotherapy for non-small cell lung cancer

### 2.1 Patient selection

Patients with stage IIIA or IIIB NSCLC without pleural effusion, pericardiac effusion and/or pleural dissemination are candidates for chemoradiotherapy. Only selected patients with stage IIIA NSCLC are candidates for surgery [9]. Surgery after induction chemotherapy for cytologically proven N2 NSCLC did not improve either overall survival or progression-free survival compared with thoracic radiotherapy [10]. Chemoradiotherapy for unresectable locally advanced NSCLC has achieved a long-term survival rate comparable to that of resectable N2 NSCLC after surgery (**Table 1**) [11,12]. Patients receiving chemoradiotherapy should have a good performance status and adequate organ function. Only few data exist about the feasibility of chemoradiotherapy in patients with poor performance status. If a patient receives radiotherapy with a radiation field including the contralateral hilum and > 50% of the lung, the patient should be excluded from radiotherapy. Pre-existing pulmonary fibrosis as identified on plain chest X-ray films is a very strong risk factor for treatment-related death after thoracic radiotherapy because of pneumonitis [13,14]. Thus, patients with pulmonary fibrosis identified on plain chest X-ray films should be excluded from radiotherapy.

### 2.2 Chemoradiotherapy versus radiotherapy alone or chemotherapy alone

A meta-analysis of 1780 cases in 11 randomised trials showed that cisplatin-containing chemoradiotherapy was significantly superior to radiotherapy alone in terms of survival [4]. Other meta-analyses have also demonstrated the survival superiority of chemoradiotherapy compared with radiotherapy alone, for patients with unresectable locally advanced NSCLC [15,16]. On the other hand, Kubota *et al.* reported that the addition of radiotherapy to chemotherapy for locally advanced NSCLC significantly improved the 2- and 3-year survival rates compared with chemotherapy alone [17]. Sculier *et al.* reported the results of a randomised Phase III trial that compared further chemotherapy and chest irradiation as a consolidation treatment after the achievement of a response to induction chemotherapy in patients with non-metastatic unresectable NSCLC [18]. No significant difference in survival or response duration was seen, but chest irradiation was associated with a significantly greater duration of local control than chemotherapy. Thus, the combination of cisplatin-containing chemotherapy with thoracic radiotherapy has been considered the standard treatment for patients with unresectable locally advanced NSCLC.

### 2.3 Timing of chemotherapy and radiotherapy

Randomised Phase III trials to compare the sequence schedule of chemoradiotherapy with concurrent chemoradiotherapy have been conducted by the Japan Clinical Oncology Group (JCOG) and by the Radiation Therapy Oncology Group (RTOG) (**Table 2**) [11,19]. In the JCOG trial, 320 patients with unresectable locally advanced NSCLC were randomised and received chemotherapy with cisplatin, vindesine and mitomycin followed by radiotherapy (sequential arm) or concurrent chemoradiotherapy (concurrent arm). The response rate for the concurrent arm was significantly higher (84%) than that of the sequential arm (66%) ($p = 0.0002$). The median survival duration was significantly longer in patients receiving concurrent therapy (16.5 months) compared with those receiving sequential therapy (13.3 months; $p = 0.03998$). The 2-, 3-, 4- and 5-year survival rates in the concurrent group (34.6, 22.3, 16.9 and 15.8%, respectively) were better than those in the sequential group (27.4, 14.7, 10.1 and 8.9%, respectively). The concurrent approach yielded a significantly higher response rate and enhanced survival duration compared with the sequential approach [11]. Similar results were reported by the RTOG trial. Survival was significantly superior in the concurrent arm, with a median survival time (MST) of 17 months and a 4-year survival rate of 21%, than in the sequential arm, with 14.6 months and 12%, respectively ($p = 0.046$). This report also demonstrated a long-term survival benefit of the concurrent delivery of cisplatin-based chemotherapy with thoracic radiotherapy, compared with the sequential delivery of these therapies [19]. In these trials, acute toxicities such as myelosuppression and oesophagitis were greater among patients in the concurrent arm than in the sequential arm. Based on these Phase III trials, concurrent chemoradiotherapy seems to result in a better survival than sequential therapy.

There are some limitations to the generalisation of the results of these trials because old-generation cisplatin-based

**Table 2. Randomised trials of sequential versus concurrent chemoradiotherapy.**

| Author | Treatment | N | MST (months) | 2-year survival | 4-year survival | p value |
|---|---|---|---|---|---|---|
| Furuse [11] | CDDP + VDS + MMC sequential TRT | 158 | 13.3 | 27.4 | 8.9 (5 years) | |
| | CDDP + VDS + MMC concurrent TRT | 156 | 16.6 | 34.6 | 15.8 (5 years) | 0.3998 |
| Curran [19] | CDDP + VBL sequential TRT | | 14.6 | 32 | 12 | - |
| | CDDP + VBL concurrent TRT | 610 (total) | 17.0 | 35 | 21 | 0.046 |
| | CDDP + ETOP concurrent TRT (twice daily) | | 15.2 | 34 | 17 | 0.296 |
| Fournel [29] | CDDP + VNR sequential TRT | 101 | 14.5 | 26 | 14 | |
| | CDDP + ETOP concurrent TRT followed by CDDP + VNR | 100 | 16.3 | 39 | 21 | 0.24 |
| Zatloukal [30] | CDDP + VNR sequential TRT | 50 | 12.9 | 14.3 | 9.5 (3 years) | |
| | CDDP + VNR concurrent TRT | 52 | 16.6 | 34.2 | 18.6 (3 years) | 0.023 |

CDDP: Cisplatin; ETOP: Etoposide; MMC: Mitomycin; MST: Mean survival time; TRT: Thoracic radiotherapy; VBL: Vinblastine; VDS: Vindesine; VNR: Vinorelbine.

combination chemotherapies were used in these trials: cisplatin, vindesine plus mitomycin or cisplatin plus vinblastine [11,19]. These old-generation cisplatin-based chemotherapies could be combined with concurrent radiotherapy using a full dose. Several new anticancer agents were developed in the 1990s, such as irinotecan, paclitaxel, docetaxel, gemcitabine and vinorelbine [20-24]. The combination of platinum and these new agents is more effective than the old-generation combination chemotherapy for metastatic NSCLC [23,24]; however, these new agents cannot be combined with concurrent radiotherapy at the full dose [25-28]. A French cooperative group conducted a Phase III trial to compare sequential versus concurrent chemoradiotherapy for unresectable NSCLC [29]. The sequential arm consisted of three cycles of cisplatin plus vinorelbine followed by thoracic radiotherapy. The concurrent arm consisted of two cycles of cisplatin plus etoposide with concurrent thoracic radiotherapy followed by two cycles of cisplatin plus vinorelbine. A total of 205 patients were enrolled in this trial. The MST was 14.5 months for the sequential arm and 16.3 months for the concurrent arm. The 2-year survival rates were 26 and 39%, respectively [29]. Whereas concurrent therapy tended to be more favourable, the difference was not statistically significant ($p = 0.24$). Zatloukal *et al.* reported the results of a randomised study of concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced NSCLC [30]. The concurrent chemoradiotherapy arm demonstrated significant benefits in terms of response rate, overall survival and time to progression over the sequential chemoradiotherapy arm. However, they used a reduced dose of vinorelbine in both the concurrent and sequential arms. No data from Phase III trials comparing sequential full-dose, new-generation chemotherapy with concurrent reduced-dose, new-generation chemotherapy are available.

### 2.4 Fractionation

Radical radiotherapy for NSCLC is most commonly given in daily fractions, Monday to Friday, for a total dose of 60 – 70 Gy over 6 – 8 weeks [31,32]. Novel fractionation schedules have been explored, with the aim of improving local tumour control and survival without increasing late morbidity (Table 3). In hyperfractionated radiotherapy, the dose per fraction is reduced and the total dose is increased to give improved tumour control without increased late morbidity. The clinical trials of RTOG used hyperfractionated radiotherapy, 1.2 Gy/fraction b.i.d. for a total of 69.6 Gy [33]. However, this hyperfractionation schedule did not offer significant benefits when compared with conventional radiotherapy plus chemotherapy [34,35]. Schild *et al.* reported the results of a Phase III study that compared split-course accelerated hyperfractionated radiotherapy (AHFRT), at 1.5 Gy/fraction b.i.d. (60 Gy), with standard radiotherapy (STDRT) at 2 Gy/fraction/day (60 Gy) combined with concurrent chemotherapy

**Table 3. Once-daily versus multiple-daily radiotherapy for unresectable NSCLC.**

| Author | Chemotherapy | Radiotherapy | N | MST (months) | 2-year survival (%) | 5-year survival (%) | p values |
|---|---|---|---|---|---|---|---|
| Sause [34,35] | None | 2 Gy/day; 60 Gy 5 days/week continuous | 163 | 11.4 | 21 | 5 | - |
| | CDDP + VBL induction | 2 Gy/day; 60 Gy 5 days/week, continuous | 164 | 13.2 | 32 | 8 | 0.04 |
| | None | 1.2 Gy b.i.d.; 69.6 Gy 5 days/week continuous (HFRT) | 163 | 12.0 | 24 | 6 | NR |
| Schild [36] | CDDP + ETOP concurrent | 2 Gy/day; 60 Gy 5 days/week continuous | 117 | 14 | 37 | 13 | |
| | | | | | | | 0.4 |
| | CDDP + ETOP concurrent | 1.5 Gy b.i.d.; 60 Gy 5 days/week split (AHFRT) | 117 | 15 | 40 | 20 | |
| Saunders [37,38] | None | 2 Gy/day; 60 Gy 5 days/week continuous | 225 | NR | 20 | NR | |
| | | | | | | | 0.004 |
| | None | 1.5 Gy t.i.d., 54 Gy 7 days/week continuous (CHART) | 338 | NR | 29 | NR | |
| Belani [42] | CBDCA + PTX induction | 2 Gy/day; 64 Gy 5 days/week continuous | 56 | 14.9 | 34 | NR | |
| | | | | | | | 0.28 |
| | CBDCA + PTX induction | 1.5 – 1.8 – 1.5 Gy/day; 57.6 Gy 5 days/week continuous (HART) | 56 | 20.3 | 44 | NR | |

AHFRT: Accelerated hyperfractionated radiotherapy; CBDCA: Carboplatin; CDDP: Cisplatin; CHART: Continuous hyperfractionated accelerated radiotherapy; ETOP: Etoposide; HART: Hyperfractionated accelerated radiation therapy; HFRT: Hyperfractionated radiotherapy; MST: Median survival time; NR: Not reported; NSCLC: Non-small cell lung cancer; PTX: Paclitaxel; VBL: Vinblastine; VNR: Vinorelbine.

[36]. The toxicity, tumour control and survival rates were similar with AHFRT and STDRT. JCOG retrospectively compared STDRT and AHFRT using data from six JCOG clinical trials [5]. AHFRT did not show a clear tendency to improve the survival of the patients with locally advanced NSCLC. Twice-daily fractionations at doses of 1.2 or 1.5 Gy/fraction were not superior, compared with standard once-daily fractionation, in patients with locally advanced NSCLC.

More recently, continuous hyperfractionated accelerated radiotherapy (CHART) and hyperfractionated accelerated radiation therapy (HART) have been investigated [37-43]. CHART consisted of 36 small fractions of 1.5 Gy given three-times daily, yielding 54 Gy administered on only 12 consecutive days, including the weekend. CHART, compared with conventional radiotherapy, provided a significant improvement in the survival of patients with NSCLC [37,38]; however, this result was obtained from randomised Phase III trials of radiotherapy alone. No randomised trials of chemoradiotherapy using CHART have been reported. HART consisted of a total dose of 57.6 Gy in 36 fractions delivered over 15 days using three-times daily fractions with a 4-h interval between fractions and an 8-h interval between on-cord fields [40-43]. Patients were not treated on weekends. The results of a Phase III study comparing standard thoracic radiotherapy with HART after induction chemotherapy for patients with unresectable NSCLC were reported by the Eastern Cooperative Oncology Group (ECOG) [42]; however, the study was closed prematurely because of poor patient accrual. Nevertheless, induction chemotherapy of carboplatin plus paclitaxel followed by HART resulted in an acceptable toxicity profile and a provocative efficacy, with a median survival of 20.3 months, in contrast to a median survival of 14.9 months in the standard thoracic radiotherapy arm [42]. Ishikura *et al.* reported the results of a pilot study of HART following induction cisplatin and vinorelbine for stage III NSCLC [43]. A total of 30 patients were enrolled in the study. The overall objective response rate was 83%, and the MST was 24 months. The 2- and 3-year survival rates were 50 and 32%, respectively [43]. Further investigations of CHART or HART with chemotherapy are warranted.

### 2.5 Selection of anticancer agents

In the 1980s to early 1990s, old-generation cisplatin-based chemotherapy, such as cisplatin plus etoposide, cisplatin plus vindesine, cisplatin plus vinblastin or cisplatin, vindesine plus

**Table 4. Randomised Phase II study of chemoradiotherapy for unresectable NSCLC (CALGB94 31) [26].**

| No. of patients | Induction CT | RT (66Gy) + CT | CR (%) | RR (%) | MST (months) | 3-year survival (%) |
|---|---|---|---|---|---|---|
| 62 | Gem 1250 mg/m$^2$ on days 1, 8, 22 and 29; CDDP 80 mg/m$^2$ on days 1 and 22 | Gem 600 mg/m$^2$ on days 43, 50, 64 and 71; CDDP 80 mg/m$^2$ on days 43 and 64 | 13 | 74 | 18.3 | 28 |
| 58 | PTX 225 mg/m$^2$ on days 1 and 22; CDDP 80 mg/m$^2$ on days 1 and 22 | PTX 135 mg/m$^2$ on days 43 and 64; CDDP 80 mg/m$^2$ on days 43 and 64 | 33 | 67 | 14.8 | 19 |
| 55 | VNR 25 mg/m$^2$ on days 1, 8, 15, 22 and 29; CDDP 80 mg/m$^2$ on days 1 and 22 | VNR 15 mg/m$^2$ on days 43, 50, 64 and 71; CDDP 80 mg/m$^2$ on days 43 and 64 | 29 | 73 | 17.7 | 23 |

CDDP: Cisplatin; CR: Complete response; CT: Chemotherapy; Gem: Gemcitabine; MST: Median survival time; PTX: Paclitaxel; RR: Response rate; RT: Radiotherapy; VNR: Vinorelbine.

mitomycin, were commonly used in chemoradiotherapy according to sequential or concurrent schedules for the treatment of locally advanced NSCLC [5,11,19]. In the 1990s, several new anticancer agents were developed, including irinotecan, paclitaxel, docetaxel, gemcitabine and vinorelbine [20-24]. Most of these new agents have different mechanisms of action from those of the old-generation agents. A full dose of the old-generation combination chemotherapy could be combined with concurrent radiotherapy [11,19]. When combining new-generation chemotherapy and thoracic radiotherapy, however, either reduced-dose chemotherapy with concurrent thoracic radiotherapy or full-dose chemotherapy followed by sequential radiotherapy must be used [25-28]. Full-dose, old-generation combination chemotherapy combined with concurrent radiotherapy and reduced-dose, new-generation chemotherapy combined with concurrent thoracic radiotherapy have not yet been compared. Very few reports have compared chemotherapy regimens with concurrent thoracic radiotherapy. To evaluate the use of the new drugs, gemcitabine, paclitaxel and vinorelbine, in combination with cisplatin in patients with unresectable locally advanced NSCLC, the Cancer and Leukaemia Group B (CALGB) conducted a randomised Phase II study of two cycles of induction chemotherapy followed by two additional cycles of the same drugs with concomitant radiotherapy (**Table 4**) [26]. A total of 175 patients received four cycles of cisplatin 80 mg/m$^2$ on days 1, 22, 43 and 64 with gemcitabine 1250 mg/m$^2$ on days 1, 8, 22 and 29 and 600 mg/m$^2$ on days 43, 50, 64 and 71, or paclitaxel 225 mg/m$^2$ for 3 h on days 1 and 22 and 135 mg/m$^2$ on days 43 and 64, or vinorelbine at 25 mg/m$^2$ on days 1, 8, 15, 22 and 29 and at 15 mg/m$^2$ on days 43, 50, 64 and 71. Radiotherapy was initiated on day 43 at 2 Gy/day for a total dose of 66 Gy. The response rates after completion of radiotherapy were 74, 67 and 73% for the gemcitabine, paclitaxel and vinorelbine arms, respectively. The MSTs were 18.3 (95% confidence interval [CI] 13.8 – 23.6), 14.8 (95% CI 12 – 19.5) and 17.7 months (95% CI 12.4 – 24.7) for the gemcitabine, paclitaxel and vinorelbine arms, respectively [26]. No consistent standard chemotherapy regimens for chemoradiotherapy have been established.

Concomitant low-dose daily or weekly chemotherapies are also used for chemoradiotherapy as a radiosensitiser. Cisplatin or carboplatin have been commonly used in studies to investigate sensitising effects [44-47]. Of the numerous single-platinum studies, only one Phase III study demonstrated a survival benefit for the daily administration of cisplatin with thoracic radiotherapy [44]. Two studies demonstrated prolonged survival with concomitant, platinum-based, multidrug chemotherapy and hyperfractionated radiotherapy [48,49]. No data from large Phase III studies comparing full-dose chemotherapy with low-dose sensitising chemotherapy combined with concurrent radiotherapy for the treatment of locally advanced NSCLC have been reported. CALGB conducted a Phase III study to compare low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy (arm 1) and induction chemotherapy with full-dose carboplatin plus paclitaxel followed by the same concomitant chemoradiotherapy (arm 2) for stage III NSCLC [50]. A total of 366 patients were entered in the study. The median survival in arm 1 was 11.4 versus 14.0 months in arm 2, and the 1-year survival rates were 48 and 54%, respectively ($p = 0.154$). The median survival achieved in each of the treatment groups was low compared with other recent trials. This result indicated that low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy may be insufficient for the treatment of stage III NSCLC. Induction chemotherapy with full-dose carboplatin plus paclitaxel, followed by radiotherapy with concomitant low-dose weekly chemotherapy with carboplatin plus paclitaxel, was not superior in terms of survival compared with the same induction chemotherapy followed by radiotherapy alone [51]. Not only do the systemic effect of low-dose weekly or daily chemotherapy, such as carboplatin plus paclitaxel, remain unclear, but so do the radiosensitising effects.

The Southwest Oncology Group (SWOG) conducted a Phase II study of concurrent chemoradiotherapy with cisplatin

plus etoposide followed by consolidation docetaxel in patients with stage IIIB NSCLC [52]. Treatment consisted of cisplatin 50 mg/m$^2$ on days 1, 8, 29 and 36, etoposide 50 mg/m$^2$ on days 1 – 5 and 29 – 33, and concurrent thoracic radiotherapy, with a total dose of 61 Gy. Consolidation docetaxel was started 4 – 6 weeks after chemoradiotherapy at an initial dose of 75 mg/m$^2$. A total of 83 eligible patients were entered in this study. The median survival was 26 months, and the 1-, 2- and 3-year survival rates were 76, 54 and 37%, respectively [52]. Recently, long-term follow-up data revealing a 5-year survival rate of 29% was reported [53]. These results are much better than the results of the previous SWOG trial. To evaluate the feasibility and efficacy of docetaxel consolidation therapy following cisplatin, vinorelbine and concurrent thoracic radiotherapy in patients with unresectable stage III NSCLC, the authors conducted a feasibility study [54]. Among 97 patients the response rate was 82%, the median progression-free survival period was 12.8 months, and the MST was 30.8 months. Although this regimen was effective, the docetaxel consolidation compliance was very poor, with only one third of the patients completing all three cycles of consolidation docetaxel [54]. Phase III trials evaluating docetaxel consolidation have been initiated to validate these results.

### 2.6 Incorporation of target-based drugs

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors such as gefitinib, erlotinib and cetuximab are one of the most promising kinds of target-based agents for NSCLC [55,56]. Strong preclinical evidence indicates that EGFR inhibition is additive or synergistic with radiotherapy in NSCLC [57-61]. A large, randomised, Phase III trial comparing definitive dose radiotherapy with or without cetuximab in locally advanced head and neck cancer has been completed and reported [62]. The addition of cetuximab to radiotherapy improved locoregional control. More importantly, the MST was prolonged from 28 to 54 months, and the 3-year survival rate was increased from 44 to 57% in the treatment arm receiving radiation plus cetuximab [62]. CALGB 30106 and a multi-institutional Australian Phase I trial have shown that gefitinib can be added to concurrent chemoradiotherapy for stage III NSCLC without excessive toxicity [63,64]. A Phase I trial at the University of Chicago evaluated erlotinib with concurrent chemoradiotherapy in patients with stage III NSCLC [65]. Thus, the combination of gefitinib or erlotinib with chemoradiotherapy is a candidate strategy for improving the survival of patients with unresectable locally advanced NSCLC. JCOG has started a safety and efficacy trial of induction chemotherapy with cisplatin and vinorelbine followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced NSCLC (JCOG 0402-MF). SWOG 0023 is a large, Phase III, randomised trial comparing concurrent chemoradiotherapy and consolidation docetaxel with or without maintenance small-molecule therapy with gefitinib [66]. Unfortunately, SWOG 0023 was closed based on the interim analysis, which showed that the continuation of SWOG 0023 would not have shown a survival benefit for gefitinib. These results may indicate that the maintenance use of gefitinib after induction chemoradiotherapy does not improve the survival of patients with locally advanced NSCLC; however, the incorporation of EGFR tyrosine kinase inhibitors in chemoradiotherapy is still an attractive strategy for locally advanced NSCLC.

The combination of antiangiogenic agents and radiotherapy is also an attractive strategy. *In vivo* and *in vitro* studies supported that the combination of radiation with an antiangiogenic agent, angiostatin, improved tumour eradication without increasing deleterious effects [67]. Recent Phase III studies demonstrated the survival benefits of the anti-vascular endothelial growth factor antibody bevacizumab in addition to chemotherapy for several kinds of cancer including NSCLC [68]. Thus, a combination of chemoradiotherapy with bevacizumab is also a candidate strategy for improving the survival of patients with unresectable locally advanced NSCLC. Thalidomide is also well known as an antiangiogenic agent. ECOG is conducting a Phase III study of carboplatin, paclitaxel and radiotherapy with or without thalidomide in treating patients with stage III NSCLC (ECOG 3598) based on their pilot study [69].

COX-2 overexpression in lung cancer is a poor prognostic factor and COX-2 inhibitors add to the efficacy of both chemotherapy and radiotherapy. A pilot study has shown the feasibility of celecoxib with docetaxel plus radiation, and consolidation docetaxel plus cisplatin in inoperable stage IIIa and IIIb NSCLC [70]. Celecoxib (400 mg b.i.d.) administration continued as a maintenance therapy over 6 months for patients.

## 3. Chemoradiotherapy for small cell lung cancer

### 3.1 Patient selection

SCLC is generally classified into a two-stage system, LD and extensive disease (ED) [71,72]. In the consensus reports of the International Association of Lung Cancer, LD is defined as disease involvement of one haemithorax including ipsilateral pleural effusion and regional lymph nodes including ipsilateral hilar, bilateral mediastinal and bilateral supraclavicular [71,72]. Patients with LD-SCLC, except for those with ipsilateral malignant pleural effusion and ipsilateral pulmonary metastasis, are considered to be candidates for chemoradiotherapy. Patients requiring radiotherapy with a radiation field of > 50% of the lung, or those with pre-existent pulmonary fibrosis identified on plain chest X-ray films, should be excluded from chemoradiotherapy [6,13,14].

### 3.2 Standard chemoradiotherapy for small cell lung cancer

A meta-analysis including 13 trials and 2140 patients with LD-SCLC demonstrated a survival benefit of chemoradiotherapy, compared with chemotherapy alone [73]. The relative risk of

**Table 5. Twice- versus once-daily radiotherapy for limited-stage small cell lung cancer.**

| Author | Chemotherapy | Radiotherapy | N | MST (months) | 5-year survival (%) | p values |
|---|---|---|---|---|---|---|
| Turrisi [8] | CDDP + ETOP x four cycles | 1.5 Gy b.i.d.; 45 Gy, 1st cycle continuous | 211 | 23 | 26 | |
| | | | | | | 0.04 |
| | CDDP + ETOP x four cycles | 1.8 Gy/day; 45 Gy, 1st – 2nd cycle continuous | 206 | 19 | 16 | |
| Bonner [75] Schild [76] | CDDP + ETOP x six cycles | 1.5 Gy b.i.d.; 48 Gy, 4th – 5th cycles split | 130 | 20.6 | 22 | |
| | | | | | | 0.68 |
| | CDDP + ETOP x six cycles | 1.8 Gy/day; 50.4 Gy, 4th – 5th cycles continuous | 132 | 20.6 | 21 | |

CDDP: Cisplatin; ETOP: Etoposide; MST: Median survival time.

death in the chemoradiotherapy group, compared with the chemotherapy group, was 0.86 (95% CI 0.78 – 0.94; p = 0.001), corresponding to a 14% reduction in the mortality rate. The benefit in terms of overall survival at 3 years was 5.4%. Based on this meta-analysis, chemoradiotherapy is presently regarded as the standard treatment for LD-SCLC. In this meta-analysis, non-platinum-based combination chemotherapies were commonly used, and only a few trials used platinum-based modern chemotherapy. Recently, cisplatin plus etoposide has become widely regarded as a standard chemotherapy for LD-SCLC, particularly because this regimen can be integrated with concurrent thoracic irradiation with acceptable toxicity [74]. Early thoracic irradiation with concurrent cisplatin plus etoposide chemotherapy is the state-of-the-art treatment for LD-SCLC.

A US intergroup trial demonstrated a survival benefit of twice-daily accelerated thoracic radiotherapy over once-daily radiotherapy with cisplatin plus etoposide for LD-SCLC (Table 5) [8]. A total of 417 LD-SCLC patients were randomised to receive a total of 45 Gy of concurrent thoracic radiotherapy, given either twice daily over a 3-week period or once daily over a period of 5 weeks. The median survival was 19 months for the once-daily group and 23 months for the twice-daily group. The 2- and 5-year survival rates were 41 and 16%, respectively, for patients receiving once-daily radiotherapy, and 47 and 26%, respectively, for the twice-daily group (p = 0.04 by the log-rank test) [8]. In contrast, another Phase III trial using split-course twice-daily radiotherapy failed to demonstrate a survival benefit of twice-daily radiotherapy with cisplatin plus etoposide [75,76]. A split radiotherapy schedule seems to diminish the benefit of twice-daily radiotherapy (Table 4).

The brain is one of the most common relapse sites of SCLC. However, the CNS is protected from anticancer drugs by the blood–brain barrier. Several Phase III trials have demonstrated that prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis in patients with SCLC, but no Phase III trials have demonstrated a survival benefit of PCI for patients with SCLC [77-79]. A meta-analysis using individual data for 987 patients with SCLC in complete remission (CR) who took part in seven trials comparing PCI with no PCI demonstrated a survival benefit [80]. The relative risk of death in the PCI group, compared with the no PCI group, was 0.84 (95% CI 0.73 – 0.97; p = 0.01), corresponding to a 5.4% increase in the rate of survival at 3 years (15.3% in no PCI group versus 20.7% in PCI group). This absolute improvement in 3-year survival (5.4%) was the same as that shown in the meta-analysis comparing chemotherapy with chemoradiotherapy for SCLC [73,80]. Thus, PCI for SCLC, in patients who achieved a CR, has similar power to improve survival as that of thoracic radiotherapy for LD-SCLC.

The state-of-the-art treatment for LD-SCLC is four cycles of combination chemotherapy with cisplatin plus etoposide, combined with early concurrent twice-daily thoracic irradiation 45 Gy. If patients achieve a CR, PCI should be administered. A 5-year survival rate of ~ 25% is expected using this state-of-the-art treatment for LD-SCLC.

### 3.3 Incorporation of new drugs

JCOG conducted a randomised, multi-centre Phase III study of irinotecan plus cisplatin versus etoposide plus cisplatin for previously untreated ED-SCLC (JCOG 9511) [81]. A total of 154 patients were randomised, 77 into each arm. The MST was 12.8 months in the irinotecan plus cisplatin arm and 9.4 months in the etoposide plus cisplatin arm. The irinotecan plus cisplatin arm showed a significantly better survival, compared with the standard treatment with etoposide plus cisplatin (p = 0.002; unadjusted one-sided log-rank test). Treatment with four cycles of irinotecan plus cisplatin every 4 weeks yielded a highly significant improvement in survival, with less myelosuppression in ED-SCLC patients, over the standard etoposide plus cisplatin treatment [81]. Thus, the incorporation of irinotecan into the treatment of LD-SCLC is considered to be one of the most important strategies for improving the survival of LD-SCLC patients. Concurrent twice-daily thoracic

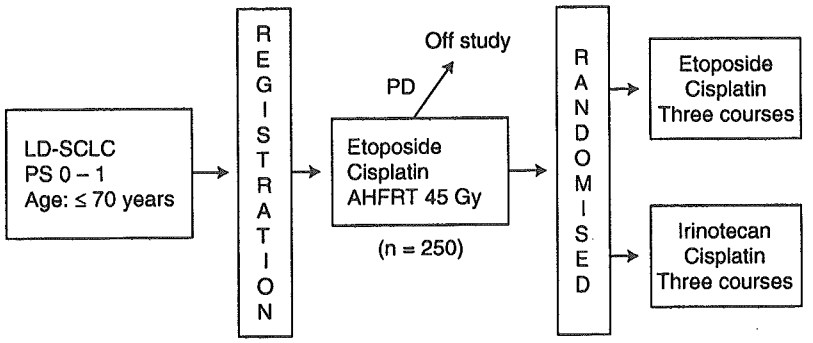


**Figure 1. On-going randomised Phase III trial for LD-SCLC in JCOG (JCOG 0202-MF).**
AHFRT: Accelerated hyperfractionated radiotherapy; JCOG: Japan Clinical Oncology Group; LD-SCLC: Limited-stage small cell lung cancer; PD: Progressive disease; PS: Performance status.

radiotherapy with combination chemotherapy consisting of irinotecan and cisplatin may be the most powerful treatment for LD-SCLC patients, if the full dose of irinotecan can be used with acceptable toxicity. Previously, JCOG conducted a dose-finding study of irinotecan and cisplatin plus concurrent radiotherapy for patients with unresectable stage III NSCLC (JCOG 9405) [82]. The dose intensity of irinotecan in the study was low because of the need to omit irinotecan administration on days 8 and/or 15 as a result of leukopoenia or diarrhoea, and the radiotherapy completion rate was also low. This was a very small study, however, and chemotherapy with full-dose irinotecan and cisplatin plus concurrent radiotherapy was deemed unacceptable based on the results of JCOG 9405. Full-dose chemotherapy consisting of etoposide and cisplatin can even be used in combination with concurrent radiotherapy; however, when irinotecan is used as a single agent with concurrent radiotherapy, the dose of irinotecan must be reduced from 100 to 60 mg/m$^2$ in a weekly schedule [82]. This dose reduction is likely to reduce the efficacy of irinotecan in the treatment of LD-SCLC patients. JCOG is conducting a Phase III study (JCOG 0202-MF) of concurrent twice-daily thoracic radiotherapy with four cycles of etoposide and cisplatin as a standard arm versus concurrent twice-daily thoracic radiotherapy with etoposide and cisplatin followed by three cycles of chemotherapy with the standard dose of irinotecan and cisplatin (**Figure 1**).

Amrubicin (SM-5887) is a totally synthetic anthracycline and a potent topoisomerase II inhibitor. In a Phase II study of amrubicin using a schedule of 45 mg/m$^2$ on days 1 – 3 every 3 weeks in 33 previously untreated ED-SCLC patients, an overall response rate of 76% and a 9% complete response rate were reported; moreover, the MST was 11.7 months in the single-agent Phase II study of amrubicin [83]. In a combination Phase I/II study of cisplatin plus amrubicin for untreated ED-SCLC, the MST was 13.6 months and the 1-year survival rate was 56.1% [84]. Amrubicin is one of the most active new agents for SCLC. Further clinical development of amrubicin, including chemotherapy for both LD and ED-SCLC, is warranted.

## 4. Conclusion

Chemoradiotherapy is considered to be the standard treatment for both unresectable locally advanced NSCLC and LD-SCLC [4,73]. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of ~ 15% for patients with unresectable locally advanced NSCLC [5,11,19]. Cisplatin plus etoposide with concurrent twice-daily thoracic radiotherapy also yields a 5-year survival rate of ~ 25% for patients with LD-SCLC [7,8]. Several new strategies are currently underway in an attempt to improve the survival of these patients. The incorporation of target-based drugs such as gefitinib, erlotinib, cetuximab and bevacizumab is considered to be the most promising strategy for unresectable locally advanced NSCLC. The incorporation of irinotecan is also a promising strategy for improving the survival of patients with LD-SCLC. JCOG is presently conducting clinical trials to develop new treatment strategies for both unresectable locally advanced NSCLC and LD-SCLC.

## 5. Expert opinion

The state-of-the-art treatment for LD-SCLC is four cycles of chemotherapy with cisplatin plus etoposide combined with early concurrent twice-daily thoracic irradiation and PCI after CR [74]. In contrast, no standard treatments for locally advanced NSCLC have been established. Concurrent chemoradiotherapy may be superior to other sequences of chemotherapy and radiotherapy [11,19]. Full-dose, old-generation chemotherapy; reduced-dose, new-generation chemotherapy; and daily or weekly low-dose chemotherapy may be used for concurrent chemoradiotherapy for the treatment of locally advanced NSCLC. No Phase III studies have directly compared chemotherapy with concurrent radiotherapy. The systemic effect of low-dose weekly or daily chemotherapy and also the radiosensitising effects are still unclear. Recent results of a Phase III study indicate that weekly low-dose chemotherapy with radiotherapy may be

inferior to full-dose, old-generation chemotherapy or reduced-dose, new-generation chemotherapy [50]. The role of consolidation docetaxel is still under evaluation in a Phase III study; however, very promising survival data has been reported by a recent clinical trial using new-generation chemotherapy [52-54]. A Phase III study to establish a standard chemoradiotherapy for locally advanced NSCLC may be warranted.

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## Affiliation

Yuichiro Ohe MD, PhD
Department of Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel: +81 3 3542 2511; Fax: +81 3 3542 7006;
E-mail: yohe@ncc.go.jp

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# Phase I–II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer

Y. Ohe[1]*, S. Negoro[2], K. Matsui[3], K. Nakagawa[4], T. Sugiura[5], Y. Takada[6], Y. Nishiwaki[7], S. Yokota[8], M. Kawahara[9], N. Saijo[7], M. Fukuoka[4] & Y. Ariyoshi[10]
On behalf of the Amrubicin SCLC Study Group

[1]*Department of Internal Medicine, National Cancer Center Hospital, Tokyo;* [2]*Department of Clinical Oncology, Osaka City General Hospital, Osaka;* [3]*Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Osaka;* [4]*Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Osaka;* [5]*Department of Internal Medicine, Aichi Cancer Center Hospital, Nagoya, Aichi,* [6]*Department of Radiology, Hyogo Medical Center for Adults, Akashi, Hyogo;* [7]*Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba;* [8]*Department of Internal Medicine, National Hospital Organization Toneyama National Hospital, Toyonaka, Osaka;* [9]*Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Osaka;* [10]*Aichi Prefectural Hospital, Okazaki, Aichi, Japan*

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**Background:** Amrubicin, a totally synthetic 9-amino-anthracycline, demonstrated excellent single-agent activity for extensive-stage small-cell lung cancer (ED-SCLC). The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy with amrubicin and cisplatin, and to assess the efficacy and safety at their recommended doses (RD).

**Patients and methods:** Eligibility criteria were patients having histologically or cytologically proven measurable ED-SCLC, no previous systemic therapy, an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function. Amrubicin was administered on days 1–3 and cisplatin on day 1, every 3 weeks.

**Results:** Four patients were enrolled at dose level 1 (amrubicin 40 mg/m$^2$/day and cisplatin 60 mg/m$^2$) and three patients at level 2 (amrubicin 45 mg/m$^2$/day and cisplatin 60 mg/m$^2$). Consequently, the MTD and RD were determined to be at level 2 and level 1, respectively. The response rate at the RD was 87.8% (36/41). The median survival time (MST) was 13.6 months and the 1-year survival rate was 56.1%. Grade 3/4 neutropenia and leukopenia occurred in 95.1% and 65.9% of patients, respectively.

**Conclusions:** The combination of amrubicin and cisplatin has demonstrated an impressive response rate and MST in patients with previously untreated ED-SCLC.

**Key words:** anthracycline, cisplatin, phase I–II, small-cell lung cancer

## Introduction

Small-cell lung cancer (SCLC) is one of the most chemosensitive solid tumors, and the outcome of SCLC patients is slowly but surely improving. Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 26% 5-year survival rate in limited-stage (LD) patients [1]. Despite the high response rate to combination chemotherapy, however, local and distant failure is very common, especially in extensive-stage (ED) patients. Moreover, resistance to chemotherapeutic agents develops easily after failure of initial treatment. Thus, long-term survivors are still very rare among patients with ED-SCLC. To improve the outcome of SCLC patients, several strategies, such as high-dose chemotherapy, dose-intensive chemotherapy, alternating chemotherapy and introduction of new drugs, have been investigated [2–6]. However, only the introduction of new agents has improved the outcome of SCLC patients. Combination chemotherapy with etoposide plus cisplatin or etoposide plus cisplatin alternating cyclophosphamide, doxorubicin and vincristine had been mainly used for SCLC in North America. Recently, a Japanese trial [Japan Clinical Oncology Group (JCOG) 9511] demonstrated the superiority of the combination of irinotecan and cisplatin for ED-SCLC patients over the combination of etoposide and cisplatin [6]. The development of more active chemotherapy, and especially the introduction of effective new drugs, is therefore essential to improve the survival of SCLC patients.

Amrubicin (SM-5887) is a totally synthetic anthracycline and a potent topoisomerase II inhibitor [7–14]. It has antitumor activity, and is more potent than doxorubicin against various mouse experimental tumors and human tumor

*Correspondence to*: Dr Y. Ohe, Department of Internal Medicine, National Cancer Center Hospital 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3542-7006; E-mail: yohe@ncc.go.jp

xenografts. Amrubicin and its 13-hydroxy metabolite, amrubicinol, inhibit purified human DNA topoisomerase II [11]. Amrubicinol is 10–100 times more cytotoxic than amrubicin [9]. The potent therapeutic activity of amrubicin is caused by the selective distribution of its highly active metabolite, amrubicinol, in tumors [9]. In an experimental animal model, amrubicin did not exhibit any chronic cardiotoxicity potential, and no deleterious effects on doxorubicin-induced cardiotoxicity in dogs was observed [14]. In a phase II study of amrubicin using a schedule of 45 mg/m$^2$ on days 1–3 every 3 weeks, in 33 previously untreated ED-SCLC patients, an overall response rate of 76% and a complete response (CR) rate of 9% were reported [15]. Moreover, median survival time (MST) was 11.7 months in the single-agent phase II study of amrubicin. Amrubicin is one of the most active new agents for SCLC. Thus, we conducted a phase I/II study of amrubicin plus cisplatin for untreated ED-SCLC, because cisplatin is considered as one of the most important drugs in the treatment of SCLC. The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy of amrubicin with cisplatin, to assess the efficacy and safety for ED-SCLC at their recommended doses (RD), and to examine the pharmacokinetics of the drug combination.

## Patients and methods

### Patient selection

Patients with histologically and/or cytologically documented SCLC were eligible for this study. Each patient was required to meet the following criteria: extensive-stage disease [16]; no prior therapy for primary lesion; measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; expected survival time >2 months; age 20–74 years; adequate hematological function [white blood cell (WBC) count 4000–12 000/mm$^3$, neutrophils ≥2000/mm$^3$, platelets ≥100 000/mm$^3$, hemoglobin ≥10 g/dl]; adequate hepatic function [total bilirubin within 1.5× the upper limit of normal; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5× the upper limit of normal]; adequate renal function (creatinine within the upper limit of normal); partial pressure of arterial oxygen 60 torr; no abnormality requiring treatment on electrocardiogram; left ventricle ejection fraction >60%; written informed consent. Patients with symptomatic brain metastasis, pleural effusion that required drainage, non-steroidal anti-inflammatory drug or glucocorticoid use for >50 days, pericarditis carcinomatous, active infection, varicella, superior vena cava syndrome, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), gastric and/or duodenal ulcer, severe heart disease, severe renal disease, active concomitant malignancy, symptomatic pneumonitis and/or pulmonary fibrosis and pregnant/nursing women were excluded. This study was approved by the Institutional Review Board at each hospital.

### Patient evaluation

Pretreatment evaluation consisted of complete blood cell counts, differential, routine chemistry measurements, progastrin-releasing peptide (ProGRP), neuron-specific enolase, electrocardiogram, echocardiography, chest radiograph, chest and abdominal computed tomography (CT) scan, whole-brain magnetic resonance imaging (MRI) or CT scan, and isotope bone scan. Complete blood cell counts, differential and routine chemistry measurements were performed at least once a week during the chemotherapy.

### Treatment schedule

At level 1, chemotherapy consisted of cisplatin 60 mg/m$^2$ on day 1 and amrubicin 40 mg/m$^2$ on days 1–3. Amrubicin was administered as an intravenous injection over 5 min and cisplatin was administered as a drip infusion over 60–120 min with adequate hydration. At level 2 the dose of amrubicin was increased to 45 mg/m$^2$ on days 1–3. Level 3 was planned with cisplatin 80 mg/m$^2$ on day 1 and amrubicin 45 mg/m$^2$ on days 1–3. The chemotherapy was repeated every 3 weeks for four to six courses. Intrapatient dose escalation was not allowed. Administration of granulocyte colony-stimulating factor (G-CSF) was permitted prophylactically for patients expected to experience grade 3 neutropenia during the first course. Prophylactic administration of G-CSF was only permitted at second or later courses.

The administrations of both cisplatin and amrubicin were postponed if patients met the following criteria: WBC <3000/mm$^3$; neutrophils <1500/mm$^3$; platelets <100 000/mm$^3$; AST and ALT >5× the upper limit of normal; total bilirubin >1.5× the upper limit of normal; creatinine >1.3× the upper limit of normal; ECOG PS 3 or 4; active infection; grade 2 or worse non-hematological toxicity, except for alopecia, anorexia, nausea, vomiting or fatigue.

The administrations of both cisplatin and amrubicin were withdrawn if patients met the following criteria: tumor regression <15% after first course or <30% after second course; WBC <3000/mm$^3$; neutrophils <1500/mm$^3$; platelets <100 000/mm$^3$; no recovery from grade 3 or 4 non-hematological toxicity at 6 weeks after the start of previous chemotherapy; abnormality of electrocardiogram requiring treatment for more than 6 weeks; left ventricle ejection fraction <48%; treatment delay of >4 weeks.

The dose of amrubicin was decreased 5 mg/m$^2$/day if patients met the following criteria: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 neutropenia with fever; platelets <20 000/mm$^3$ during the previous course. The dose of cisplatin was decreased to 75% if creatinine increased to >1.5× the upper limit of normal during the previous course.

The dose-limiting toxicity (DLT) was defined as follows: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 febrile neutropenia; platelets <20 000/mm$^3$; grade 3 or worse non-hematological toxicity except for nausea, vomiting, anorexia, fatigue, hyponatremia and infection. Initially, three patients were treated at each dose level. If DLT was not observed in any of the three patients, dose escalation was carried out. If DLT was observed in one of three patients, an additional three patients were entered at the same dose level. If DLT was observed in three or more of six patients, or two or three of the initial three patients, we considered that dose to be the MTD. If DLT was observed in one or two of six patients, dose escalation was also carried out. Dose escalation was determined based only on the data from the first course of chemotherapy.

### Response and toxicity evaluation

Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) and tumor markers were excluded from the criteria [17]. CR was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks and no new lesions. Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameters of target lesion, taking as reference the baseline sum longest diameter, the required non-progression in non-target lesions and no new lesions for at least 4 weeks. Stable disease (SD) included: regression of target lesions insufficient to meet the criteria for PR, a <20% increase in the sum of the longest diameter of target lesion, taking as reference the smallest sum longest diameters recorded since the treatment started, the required non-progression in non-target lesions and no new lesions for at least 6 weeks. Progressive disease (PD) indicated a >20% increase in the sum of the longest diameters of target lesion, taking as reference the smallest sum longest diameter recorded since the treatment started

and/or unequivocal progression of existing non-target lesions and/or appearance of new lesions. The evaluation of objective tumor response for all patients was performed by an external review committee.

Toxicity grading criteria of the National Cancer Institute Common Toxicity Criteria (version 2.0) was used for evaluation of toxicity.

### Statistical analysis

This study was designed to reject response rates of 70% (P0) at a significance level of 0.05 (one-tailed) with a statistical power of 80% to assess the activity of the regimen as a 85% response rate (P1) at the recommended dose. The upper limit of rejection was 29 responses (CR + PR) among 37 evaluable patients. Overall survival was defined as the interval between the first administration of the drugs in this study and death or the last follow-up visit. Median overall survival was estimated using the Kaplan–Meier method [18].

**Table 1.** Characteristics of treated patients

| | Phase I | Phase II | Total |
|---|---|---|---|
| Number of patients | 7 | 37 | 44 |
| Gender | | | |
| Male | 5 | 31 | 36 |
| Female | 2 | 6 | 8 |
| Age (years) | | | |
| Median | 65 | 64 | 64.5 |
| Range | 54–73 | 50–74 | 50–74 |
| ECOG PS | | | |
| 0 | 0 | 5 | 5 |
| 1 | 7 | 32 | 39 |
| 2 | 0 | 0 | 0 |
| Stage | | | |
| IIIB | 0 | 2 | 2 |
| IV | 7 | 35 | 42 |
| Prior therapy | | | |
| Yes | 0 | 1 | 1 |
| No | 7 | 36 | 43 |
| Serum ALP | | | |
| Normal | 7 | 29 | 36 |
| Elevated | 0 | 7 | 7 |
| Serum LDH | | | |
| Normal | 3 | 14 | 17 |
| Elevated | 4 | 23 | 27 |
| Na | | | |
| Normal | 6 | 35 | 41 |
| Decreased | 1 | 2 | 3 |
| Number of metastases | | | |
| 0 | 0 | 2 | 2 |
| 1 | 4 | 27 | 31 |
| 2 | 3 | 6 | 9 |
| 3 | 0 | 1 | 1 |
| 4 or more | 0 | 1 | 1 |

In one patient, serum ALP level could not be measured.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

### Pharmacokinetic analysis

Pharmocokinetic analysis was performed in patients entering the phase I section of this study. One milliliter of the blood was taken from the patients before administration of amrubicin, and at 0 min, 15 min, 1, 2, 3, 4, 8 and 24 h after administration on days 1 and 3 in the first course of chemotherapy. Concentrations of amrubicin and its active metabolite, amrubicinol, in plasma and red blood cells were measured as reported elsewhere [9].

## Results

### Patient characteristics

Between April 2001 and December 2002, 45 patients with ED-SCLC were enrolled and 44 were treated in this study (Table 1). One patient did not receive the protocol treatment because atrial fibrillation was observed just before administration on day 1 of the first course. All treated patients were assessed for response, survival and toxicity. The median age of the treated patients was 64.5 years (range 50–74). There were 36 males and eight females. Five patients had an ECOG PS 0 and 39 patients had PS 1. Only one patient received surgery for brain metastasis as a prior therapy.

### MTD and DLT in the phase I study

Four patients were enrolled at dose level 1 (amrubicin 40 mg/m$^2$ on days 1–3 and cisplatin 60 mg/m$^2$ on day 1) and three patients at level 2 (amrubicin 45 mg/m$^2$ on days 1–3 and cisplatin 60 mg/m$^2$ on day 1). Toxicities in the phase I study are listed in Table 2. No DLT were observed during the first course of level 1. At level 2, grade 4 neutropenia for ≥4 days and febrile neutropenia occurred in one patient, and febrile neutropenia and grade 3 constipation occurred in another patient. Consequently, the MTD and RD were determined to be level 2 and level 1, respectively.

### Pharmacokinetics of amrubicin and its active metabolite, amrubicinol

Pharmacokinetic parameters of amrubicin in plasma were almost identical on days 1 and 3 at the two dose levels (Table 3). No clear dose relationship in the area under the concentration–time curve (AUC) of amrubicin in the plasma was observed. The AUC of amrubicinol in red blood cells tended to increase on day 3 at both doses (Table 4). No clear dose relationship in the AUC of amrubicinol in red blood cells was observed. Combination with cisplatin did not alter the pharmacokinetics of amrubicin and amrubicinol (data not shown).

### Treatment received in patients treated at the RD

Forty-one patients were treated at the RD: amrubicin 40 mg/m$^2$ on days 1–3 and cisplatin 60 mg/m$^2$ on day 1. Of 41 patients, 32 (78%) patients received more than three

**Table 2.** Toxicities during the first course in the phase I study

| | Level 1 ($n=4$) | | | | | Level 2 ($n=3$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Amrubicin | 40 mg/m$^2$ days 1–3 | | | | | 45 mg/m$^2$ days 1–3 | | | | |
| Cisplatin | 60 mg/m$^2$ day 1 | | | | | 60 mg/m$^2$ day 1 | | | | |
| | Grade (NCI CTC) | | | | | Grade (NCI CTC) | | | | |
| | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| Leukopenia | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 1 | 1 | 1 |
| Neutropenia | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 3 |
| Febrile neutropenia | 4 | – | – | 0 | 0 | 1 | – | – | 2 | 0 |
| Hemoglobin | 1 | 1 | 2 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |
| Thrombocytopenia | 1 | 2 | 0 | 1 | 0 | 0 | 2 | 0 | 1 | 0 |
| Stomatitis | 3 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| Nausea | 1 | 1 | 2 | 0 | – | 1 | 1 | 0 | 1 | – |
| Constipation | 3 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 |
| Hyponatremia | 2 | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 0 | 0 |
| Hypocalcemia | 3 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |

Dose limiting toxicity at level 2: febrile neutropenia, two patients; grade 4 neutropenia ≥4 days, one patient; grade 3 constipation, one patient.
NCI CTC, National Cancer Institute Common Toxicity Criteria.

**Table 3.** Pharmacokinetics of amrubicin in plasma

| Dose | $n$ | Day | $T_{1/2\alpha}$ (h) | $T_{1/2\beta}$ (h) | $V_d$ (l) | CL (l/h) | $AUC_{0-24\,h}$ (ng h/ml) |
|---|---|---|---|---|---|---|---|
| 40 mg/m$^2$ | 4 | 1 | 0.11±0.04 | 2.29±0.31 | 46.6±11.0 | 13.6±1.8 | 2995±434 |
| | 4 | 3 | 0.08±0.01 | 2.89±0.34 | 50.0±10.6 | 11.6±1.9 | 3511±514 |
| 45 mg/m$^2$ | 3 | 1 | 0.13±0.05 | 2.39±0.34 | 56.3±10.6 | 14.9±1.8 | 3052±402 |
| | 3 | 3 | 0.09±0.03 | 2.27±0.18 | 51.9±3.7 | 14.2±2.3 | 3217±479 |

$T_{1/2\alpha}$, half-life at distribution phase; $T_{1/2\beta}$, half-life at elimination phase; $V_d$, volume of distribution; CL, clearance; AUC, area under the concentration–time curve.

courses of chemotherapy, and 10 (31%) of these 32 patients needed dose reduction of amrubicin at the fourth course (Table 5). Of 41 patients, 22 (54%) patients completed four courses of chemotherapy without dose modification. The main cause of dose reduction was myelosuppression, especially leukopenia and neutropenia.

## Objective tumor response and overall survival

The objective tumor responses are given in Table 6. Four CRs and 32 PRs occurred, for an objective response rate of 87.8% [95% confidence interval (CI) 73.8% to 95.9%] in 41 patients treated at the RD. The objective response rate for all 44 patients was 88.6% (95% CI 75.4% to 96.2%). The overall survival times of the 41 patients treated at the RD are shown in Figure 1. The MST of the 41 patients was 13.6 months (95% CI 11.1–16.6), with a median follow-up time for eight censored patients of 16.4 months (95% CI 14.2–18.8). The 1- and 2-year survival rates were 56.1% and 17.6%, respectively. The MST of all 44 patients was 13.8 months (95% CI 11.1–16.6). The 1- and 2-year survival rates of all 44 patients were 56.8% and 21.4%, respectively.

**Table 4.** Pharmacokinetics of amrubicinol in red blood cells

| Dose | $n$ | Day | $T_{1/2}$ (h) | $AUC_{0-24\,h}$ (ng·h/ml) |
|---|---|---|---|---|
| 40 mg/m$^2$ | 4 | 1 | 21.0±3.1 | 1412±314 |
| | 4 | 3 | 20.7±4.8 | 2159±622 |
| 45 mg/m$^2$ | 3 | 1 | 19.6±6.1 | 1098±277 |
| | 3 | 3 | 18.1±5.7 | 2027±332 |

$T_{1/2}$, elimination half-life; AUC, area under the concentration–time curve.

**Table 5.** Treatment received in patients treated at the recommended dose

| Cycle | $n$ | Amrubicin (mg/m$^2$) | | | Cisplatin (mg/m$^2$) | |
|---|---|---|---|---|---|---|
| | | 40 | 35 | 30 | 60 | 45 |
| 1 | 41 | 41 | | | 41 | |
| 2 | 36 | 30 | 6 | | 36 | |
| 3 | 33 | 26 | 5 | 2 | 33 | |
| 4 | 32 | 22 | 8 | 2 | 32 | |
| 5 | 18 | 9 | 5 | 4 | 18 | |
| 6 | 13 | 6 | 3 | 4 | 12 | 1 |