Vomiting grade ≥2 occurred in 31 patients (72%). Diarrhea grade ≥2 was observed in 7 patients (16%). Grade 1 or 2 alopecia and edema were observed in 23 and 7 patients, respectively. In the first cycle, creatinine showed grade ≥2 in 2 patients, resulting in transient rises. In the following cycle, the creatinine level was kept at grade 1 by reducing the dosage of cisplatin. Grade 1 or 2 skin rash was observed in 3 patients. Finally, there were no treatment-related deaths.

Discussion

Cisplatin is one of the key drugs for the treatment of NSCLC. Its high response rate of 40% and safety when it was given alone by continuous infusion over 5 days [14] are confirmed.

Docetaxel is also an active agent to treat NSCLC, and docetaxel of 60 mg/m^2/day (day 1), a recommended dose in Japan, showed a response rate of 19% [7]. Docetaxel has no cross-resistance with cisplatin, and in clinical practice, docetaxel was effective in some patients who were resistant to cisplatin [19]. In addition, additive effects are confirmed between cisplatin and docetaxel, and major side effects of the two drugs are different.

This was a phase II study to determine the usefulness and safety of combination chemotherapy of cisplatin (5-day continuous infusion) and docetaxel for the treatment of advanced NSCLC. The response rate in this study was 49%, which is higher than with docetaxel alone. In comparison with other combination therapies, response rates were 39–42% for cisplatin (bolus) and docetaxel [20, 21], and 58.5% for cisplatin (infusion) and irinotecan with G-CSF. In combination with cisplatin (bolus) and newly developed anticancer agents, the response rates were 44% with paclitaxel [22], 31% with gemcitabine [23], and 26% with vinorelbine [24]. Although these studies differed as regards patients' backgrounds, generally, combination therapies showed better response rates than docetaxel alone.

In our study, side effects predominantly involved hematological toxicity (leukopenia, neutropenia, and anemia). Fever associated with neutropenia was observed in 8 (23%) of 43 patients, and they were treated by administering antibiotics. Hematological toxicities were similar to those in other combination therapies [20, 21]. Nonhematological toxicities were mild, with only 1 patient showing an increased creatinine level of grade 3. The increase was transient, and soon returned to normal. Peripheral edema was observed in only 16%, which was markedly lower than the 24–46% found in other studies [5, 25, 26]. When accumulated doses of docetaxel exceeded 500 mg/m^2, the incidence of edema increased, and at a dose of 85 mg/m^2 or less, eruption was not observed [27]. The dosage was 60 mg/m^2 in our study, and no patients received 500 mg/m^2. There were no side effects concerning hypersensitivity or treatment-related deaths.

We carried out a phase II study of combination treatment of cisplatin (5-day continuous infusion) and docetaxel in 43 patients with NSCLC. The response rate was 49%, and median survival time was 47 weeks. A major side effect was neutropenia. A combination treatment of infusional cisplatin and docetaxel is a tolerable and active regimen for patients with advanced NSCLC. It is to be recommended as a candidate regimen in planning a phase III clinical study in advanced NSCLC, and this regimen will ultimately be evaluated in a phase III clinical study.

Acknowledgement

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CLINICAL INVESTIGATION

A PHASE II STUDY OF HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) AFTER INDUCTION CISPLATIN (CDDP) AND VINORELBINE (VNR) FOR STAGE III NON–SMALL-CELL LUNG CANCER (NSCLC)

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Purpose: The purpose was to assess the feasibility and efficacy of hyperfractionated accelerated radiotherapy (HART) after induction chemotherapy for Stage III non–small-cell lung cancer.
Methods and Materials: Treatment consisted of 2 cycles of cisplatin 80 mg/m² on Day 1 and vinorelbine 25 mg/m² on Days 1 and 8 every 3 weeks followed by HART, 3 times a day (1.5, 1.8, 1.5 Gy, 4-h interval) for a total dose of 57.6 Gy.
Results: Thirty patients were eligible. Their median age was 64 years (range, 46–73 years), 24 were male, 6 were female, 8 had performance status (PS) 0, 22 had PS 1, 9 had Stage IIIA, and 21 had Stage IIIB. All but 1 patient completed the treatment. Common grade ≥3 toxicities during the treatment included neutropenia, 25; infection, 5; esophagitis, 5; and radiation pneumonitis, 3. The overall response rate was 83%. The median survival was 24 months (95% confidence interval [CI], 13–34 months), and the 2-year overall survival was 50% (95% CI, 32–68%). The median progression-free survival was 10 months (95% CI, 8–20 months).
Conclusion: Hyperfractionated accelerated radiotherapy after induction of cisplatin and vinorelbine was feasible and promising. Future investigation employing dose-intensified radiotherapy in combination with chemotherapy is needed. © 2005 Elsevier Inc.

Non–small-cell lung cancer, Hyperfractionated accelerated radiation therapy, Chemoradiotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death for men and the second for women in Japan. During 2001, approximately 55,000 patients died of lung and bronchus cancer (1). Surgery is the standard of care for patients with Stage I–II non–small-cell lung cancer (NSCLC), but a combination of chemotherapy and thoracic radiotherapy with or without surgery is indicated for the majority of patients with Stage III disease. Cisplatin (CDDP) based chemotherapy with conventional radiotherapy improved survival compared to conventional radiotherapy alone (2–6) and was the standard of care in the 1990s. Recently, concurrent chemoradiotherapy has been revealed to be superior to sequential chemoradiotherapy (7, 8), but it is difficult to give full-dose chemotherapy using newer cytotoxic agents concurrently with radiotherapy, and the optimal combination has not yet been clarified. In the meantime, continuous hyperfractionated accelerated radiotherapy (CHART) with 3 daily fractions to intensify the local effect of

radiotherapy has been found to be superior to conventional radiotherapy (9). The survival benefit of CHART was encouraging, but the protocol including treatments on weekends and 6-h intervals between fractions had some difficulties in practicality. Mehta et al. introduced hyperfractionated accelerated radiotherapy (HART) (modified CHART) with 3 daily fractions and 4-h interfraction intervals with weekend breaks and also showed promising results similar to those using sequential chemoradiotherapy (10). After these results, we started a Phase II trial to evaluate the feasibility and efficacy of induction chemotherapy with HART for patients with Stage III NSCLC.

METHODS AND MATERIALS

Eligibility criteria

Eligibility criteria included previously untreated patients with pathologically proven NSCLC with clinical tumor-node-metastasis system Stage III, and pathologic N2 was also required for Stage

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IIIA; age, 20 to 74 years; performance status (PS) (based on Eastern Cooperative Oncology Group [ECOG] scale) 0 to 1; measurable disease; adequate hematologic (WBC count ≥4,000/mm³, platelet count ≥100,000/mm³, and hemoglobin ≥9.5 g/dL), hepatic (AST and ALT level ≤2 times the upper limit of normal and total bilirubin level ≤ the upper limit of normal), and renal (creatinine ≤1.2 mg/dL and creatinine clearance ≥60 mL/min) functions; PaO₂ ≥70 torr; no pleural and pericardial effusion; radiation field encompassed one-half or less of the ipsilateral lung; and no serious comorbidity. All patients signed written informed consent in accordance with our institutional review board.

Pretreatment evaluation included history and physical examination; serum chemistries (lactate dehydrogenase, alkaline phosphatase, AST, ALT, bilirubin, albumin, creatinine, and calcium); chest radiograph; CT scan of the chest; ultrasound of the abdomen; MRI or CT scan of the brain; and bone scintigraphy.

Treatment details

The treatment consisted of 2 cycles of CDDP 80 mg/m² on Day 1 and vinorelbine (VNR) 25 mg/m² on Days 1 and 8 every 3 weeks followed by HART; 3 times a day with minimal interval of 4 hours for a total dose of 57.6 Gy in 36 fractions over 2.5 weeks.

Radiation therapy was started after the patient recovered from the toxicity of chemotherapy and was delivered with megavoltage equipment. Lung heterogeneity corrections were not used. The first and third fraction of each day consisted of anterior-posterior opposed fields that encompassed the primary tumor, the metastatic lymph nodes, and the regional lymph nodes with a 1.5 to 2-cm margin. The fraction size was 1.5 Gy. Regional nodes excluding the contralateral hilar and supraclavicular nodes were included in these fractions. However, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The second fraction of each day consisted of bilateral oblique fields that encompassed the primary tumor and the metastatic lymph nodes with a 1.5 to 2-cm margin; the fraction size was 1.8 Gy. Attempts were made to design the field of the second fraction to minimize the irradiated volume of the esophagus without compromising the margin around the tumor or spinal cord.

Toxicity assessment

Patients were observed weekly during treatment to monitor toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity was graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Late toxicity was defined as that occurring more than 90 days after treatment initiation.

Follow-up evaluation

The following evaluations were performed until disease progression every 2 months for the first year, every 3 months for the second year, and every 6 months thereafter: physical examination, toxicity assessment, and chest radiograph. CT scan of the chest was performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. Restaging at 6 months after the treatment was also performed with ultrasound of the abdomen, MRI or CT scan of the brain, and bone scintigraphy.

Response assessment

Complete response (CR) was defined as complete disappearance of all measurable and assessable lesions for ≥4 weeks, partial response (PR) was defined as a decrease of 50% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions for ≥4 weeks, and progressive disease (PD) was defined as an increase of 25% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions or the appearance of any new lesion. Stable disease was defined as the remainder of evaluable patients without CR, PR, or PD.

Pattern of failure

Patterns of failure were defined as first site of failure. Local/regional failure included the primary tumor and regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

Statistics

A Simon's two-stage optimal design was used for this study with the assumption that a protocol compliance rate of less than 60% would not be feasible, and protocol compliance rate of 80% or greater with α error of 0.10 and β error of 0.10 would warrant further investigation of this regimen. In the first stage, 11 assessable patients were entered. If fewer than 7 patients completed the treatment, accrual would be stopped with the conclusion that the regimen was not feasible for further investigation. If 7 or more patients completed the treatment, an additional 27 patients would be accrued in the second study. According to this design, this study would be determined to be feasible and be proceeded to a multicenter Phase II study if 27 patients completed the treatment. The actuarial median survival time and 2-year survival were estimated by the Kaplan–Meier method (11).

RESULTS

Patient population

Between July 1999 and March 2001, 30 patients were enrolled in the study. The accrual was stopped, because 29 of 30 patients completed the treatment, and conclusions could be drawn at that time. The patients' median age was 64 years (range, 46–73 years), 24 were male, and 6 were female. The patient and tumor characteristics are summarized in Table 1.

Treatment compliance and toxicity

All patients completed 2 cycles of induction chemotherapy. Six of 30 patients required dose modification, and 13 patients had treatment delay. The median time to start of HART from start of chemotherapy was 49 days (range, 41–62 days). Twenty-nine of 30 patients completed HART, and the median overall treatment time of HART was 17 days (range, 16–22 days). In total, 29 of 30 patients (97%; 95% confidence interval [CI], 83–100%) completed this combined treatment.

The toxicity profile of the treatment is shown in Tables 2 and 3. Common Grade 3 or greater acute toxicities were neutropenia, 25 (83%); infection, 5 (17%); esophagitis, 5 (17%); and radiation pneumonitis, 3 (19%). There were 2 cases of treatment-related death due to radiation pneumonitis. As of the date of this analysis, 2 cases with Grade

Table 1. Patient and tumor characteristics

Number of patients	30
Age	
Median	64
Range	46–73
Gender	
Male	24
Female	6
Performance status	
0	8
1	22
Weight loss	
<5%	25
≥5%	5
Tumor and lymph nodes	
T1N2	3
T1N3	1
T2N2	5
T2N3	5
T3N2	1
T4N0	1
T4N1	4
T4N2	9
T4N3	1
Stage	
IIIA	9
IIIB	21
Histology	
Squamous	13
Nonsquamous	17

Table 2. Hematologic toxicities ($n = 30$)*

	Grade					
	0	1	2	3	4	≥Grade 3 (%)
Leukopenia	1	3	8	16	2	18 (60)
Neutropenia	3	0	2	6	19	25 (83)
Thrombocytopenia	20	7	1	2	0	2 (7)
Anemia	1	10	16	3	0	3 (10)

* National Cancer Institute–Common Toxicity Criteria version 2.

3 s.c. tissue fibrosis and 1 case with spontaneous rib fracture were observed as late toxicities.

Response and survival

Of 30 patients, 2 achieved CR, and 23 achieved PR with a response rate of 83% (95% CI, 65–94%). Five patients remained in a stable disease state, and there were no PD patients. With a median follow-up period of 40 months for surviving patients, the median survival and the 2-year and 3-year survivals (Fig. 1) were 24 months (95% CI, 13–34 months), 50% (95% CI, 32–68%), and 32% (95% CI, 15–49%), respectively. The median progression-free survival and the 1-year progression-free survival (Fig. 2) were 10 months (95% CI, 8–20 months) and 47% (95% CI, 29–65%), respectively.

Pattern of failure

At the time of this analysis, 22 of 30 patients (73%) showed tumor progression, 2 patients (7%) had died as a result of treatment, and 6 patients (20%) were alive without disease progression. The patterns of first failure were as follows: local/regional only, 13 (43%); local/regional and distant, 4 (13%); distant only, 5 (17%).

DISCUSSION

In the 1970s, treatment of locally advanced NSCLC was by conventional radiotherapy alone. In the 1980s, sequential chemotherapy and conventional radiotherapy were revealed to be superior to conventional radiotherapy alone. In the 1990s, optimal sequences of chemoradiotherapy and radiation fractionation were investigated. The West Japan Lung Cancer Group compared sequential vs. concurrent radiotherapy with induction CDDP, vindesine, and mitomycin (7). In an RTOG 9410 trial, induction CDDP and vinblastine plus sequential standard radiotherapy, CDDP and vinblastine plus concurrent standard radiotherapy, and CDDP and etoposide plus concurrent twice-daily hyperfractionated radiotherapy were compared (8). Both trials showed similar results; concurrent chemoradiotherapy was superior to the sequential approach and achieved 5-year survivals for concurrent and sequential approach of approximately 20% and 10%, respectively. However, twice-daily hyperfractionated radiotherapy, which seemed to be promising in a preceding RTOG 9015 trial (12), failed to show a survival advantage over standard once-daily radiotherapy, and concurrent chemotherapy and once-daily radiotherapy is the standard of care today. Recently, a Czech randomized Phase II trial (13) suggested a similar advantage of the concurrent approach using CDDP and VNR, a newer cytotoxic agent. However, there remains some argument that newer cytotoxic agents cannot be delivered as full-dose chemotherapy with concurrent radiotherapy, and the survival advantage of newer cytotoxic agents over old ones has not yet been demonstrated in Stage III NSCLC patients. The optimal schedule and fractionation of thoracic radiotherapy in combination with chemotherapy also remains to be determined.

Another promising regimen was altered fractionation of radiotherapy such as CHART or HART, 3 times a day with a fraction interval of 4 to 6 hours over 2.5 weeks or less. CHART was developed at Mount Vernon Hospital, United Kingdom, in the 1980s. It was designed to combine both a shortening of the overall treatment time of radiotherapy, which is analogous to the concept of dose intensification of cytotoxic chemotherapy, and a reduction in dose per fraction. The rationale was to overcome accelerated repopulation of the tumor during the course of radiotherapy, which may lead to local failure, and to reduce normal tissue toxicities that depend on the dose per fraction. After the results of a randomized trial that showed survival benefits of CHART over conventional

Table 3. Nonhematologic toxicities (n = 30)*

	Grade						
	0	1	2	3	4	5	≥Grade 3 (%)
Acute toxicity							
Nausea	7	16	4	3	0	0	3 (10)
Vomiting	23	3	4	0	0	0	0
Infection	20	3	2	5	0	0	5 (17)
Esophagitis	1	11	13	4	1	0	5 (17)
Pneumonitis	18	4	5	1	0	2	3 (10)
Late radiation morbidity[†]							
Esophagus	26	1	0	0	0	0	0
Heart	26	0	1	0	0	0	0
Lung	9	13	5	0	0	0	0
Subcutaneous tissue	17	6	2	2	0	0	2 (7)
Bone	26	0	0	0	1	0	1 (3)

* National Cancer Institute–Common Toxicity Criteria version 2.
† Three patients died within 90 days of the beginning of radiotherapy.

radiotherapy (9), the Department of Health in the United Kingdom recommended CHART as the radiotherapy schedule of choice in inoperable NSCLC, and a CHART implementation group was formed to facilitate its introduction throughout the United Kingdom (14). There were difficulties in changing departmental working hours and a lack of sufficient financial support in UK hospitals to introduce CHART into routine practice (15), although it was suggested that CHART gave more benefit than any sequential combination of conventional radiotherapy and chemotherapy with minimally increased toxicity. To make the accelerated regimen more widely applicable, Continuous Hyperfractionated Accelerated Radiotherapy Week-End Less (CHARTWEL) and HART were introduced and were found to be as effective as CHART. Both CHARTWEL and HART showed improved survival over conventional radiotherapy, but the local tumor control was still unsatisfactory. Radiation dose escalation and

use of chemotherapy combined with CHARTWEL/ HART were also investigated to improve the local control and survival. Saunders et al. (16) reported on CHARTWEL combined with induction chemotherapy (17). In that study, 113 patients were enrolled, and dose escalation from 54 Gy to 60 Gy with or without chemotherapy was successfully achieved. Locoregional control at 2 years was 37% and 55% for CHARTWEL 54 Gy and 60 Gy alone, respectively, compared with 72% in those treated with 60 Gy and induction chemotherapy. These results suggested that chemotherapy improved locoregional control, but unfortunately they failed to show a statistically significant survival advantage, because of the relatively small number of patients and imbalanced tumor characteristics enrolled in each arm. The advantage of dose-escalated CHARTWEL against conventional radiotherapy is currently being investigated in a German Phase
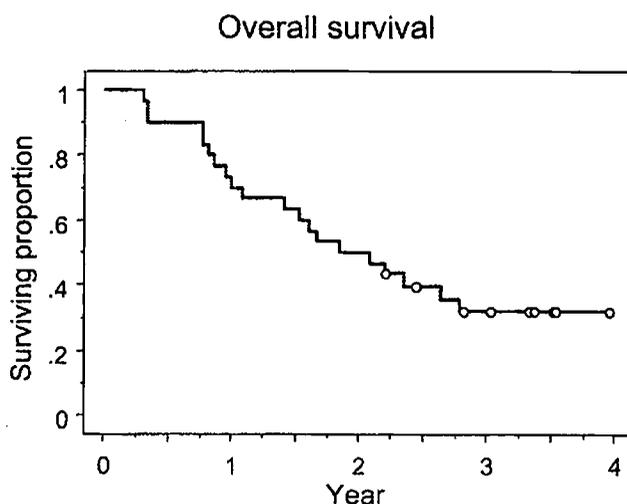
Overall survival

Fig. 1. Overall survival for all patients enrolled in this study.
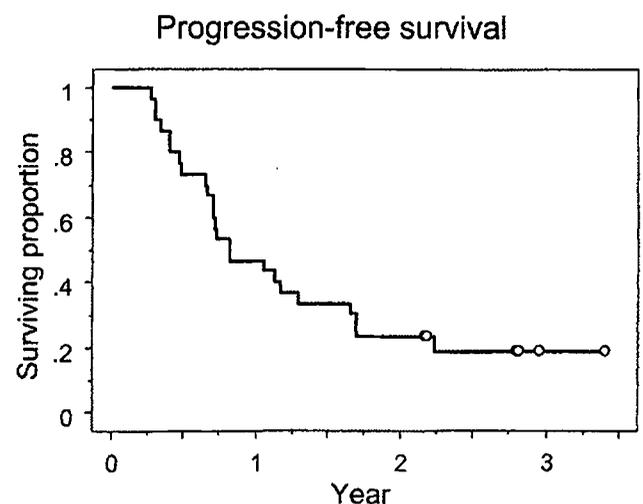
Progression-free survival

Fig. 2. Progression-free survival for all patients enrolled in this study.

III trial (18). Belani *et al.* reported the results of a randomized Phase III trial (19) that compared conventional radiotherapy with HART after induction chemotherapy (ECOG 2597). This study randomized 119 patients and unfortunately was closed because of slow accrual, but the results were provocative: The median survival time and the 2-year survivals for conventional radiotherapy and HART were 13.7 months and 33% vs. 22.2 months and 48%, respectively. These results seemed to be reliable despite the modest number of patients, because the median survival time of 13.7 months for the conventional radiotherapy arm was similar to that of a sequential chemoradiotherapy trial (2). The optimum chemotherapy regimen in combination with radiotherapy has not yet been determined, and we used a CDDP/VNR regimen instead of the carboplatin/paclitaxel regimen used in the ECOG 2597 trial. Both regimens are standards for advanced-stage NSCLC (20, 21). The compliance and toxicity profiles of chemotherapy in our study were acceptable, the incidence of esophagitis after HART was less than we expected, and the survival figure was nearly identical to that of the ECOG 2597 trial. This suggests that HART after induction CDDP/VNR or carboplatin/paclitaxel can achieve reproducible and promising results.

The pattern of failure in our study showed that local failure was still high (17 of 30, 57%) compared with distant metastasis (9 of 30, 30%), and further improvement of local control is needed. Future directions may include further dose intensification of radiotherapy and introduction of molecular-targeted agents. Recent innovation of information technology has made it possible to use sophisticated three-dimensional conformal radiotherapy (3DCRT). This can deliver intensified radiation doses to the tumor while minimizing the doses to the normal tissues that prevented further dose escalation using conventional two-dimensional radiotherapy. There have been several reports evaluating dose-intensified 3DCRT (22–25), and the technique is now under investigation in combination with cytotoxic chemotherapy in the Radiation Therapy Oncology Group trial (RTOG L-0117). Currently, molecular-targeted agents are being investigated most enthusiastically in Phase II and Phase III trials (26–29). It will be determined in the near future whether or not the combination of these agents has a survival impact. However, the optimal combination of these agents, newer cytotoxic agents, radiation fractionation, and 3DCRT will still need to be determined. Further investigation employing dose-intensified radiotherapy will be necessary to make a great leap in the treatment of locally advanced NSCLC.

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Expert Opinion

Monthly Focus: Oncologic

Chemoradiotherapy for lung cancer

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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.

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 adeno-carcinoma, 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

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

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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/m² on days 1, 8, 22 and 29; CDDP 80 mg/m² on days 1 and 22	Gem 600 mg/m² on days 43, 50, 64 and 71; CDDP 80 mg/m² on days 43 and 64	13	74	18.3	28
58	PTX 225 mg/m² on days 1 and 22; CDDP 80 mg/m² on days 1 and 22	PTX 135 mg/m² on days 43 and 64; CDDP 80 mg/m² on days 43 and 64	33	67	14.8	19
55	VNR 25 mg/m² on days 1, 8, 15, 22 and 29; CDDP 80 mg/m² on days 1 and 22	VNR 15 mg/m² on days 43, 50, 64 and 71; CDDP 80 mg/m² 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/m² on days 1, 22, 43 and 64 with gemcitabine 1250 mg/m² on days 1, 8, 22 and 29 and 600 mg/m² on days 43, 50, 64 and 71, or paclitaxel 225 mg/m² for 3 h on days 1 and 22 and 135 mg/m² on days 43 and 64, or vinorelbine at 25 mg/m² on days 1, 8, 15, 22 and 29 and at 15 mg/m² 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

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plus etoposide followed by consolidation docetaxel in patients with stage IIIB NSCLC [52]. Treatment consisted of cisplatin 50 mg/m² on days 1, 8, 29 and 36, etoposide 50 mg/m² 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/m². 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

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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

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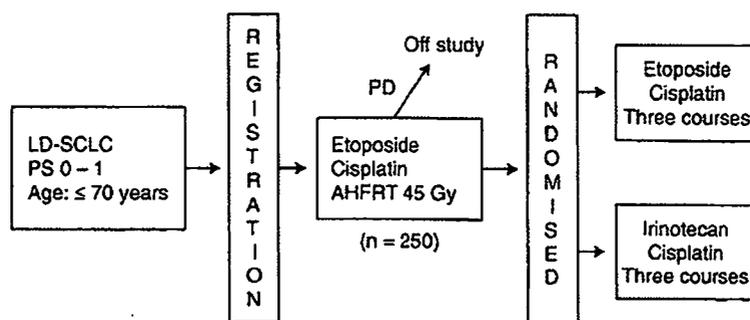
Figure 1. On-going randomised Phase III trial for LD-SCLC in JCOG (JCOG 0202-MF).
AHFRT: Accelerated hyperfractionated radiotherapy; JCOG: Japan Clinical Oncology Group; LD-SCLC: Limited-stage small cell lung cancer; PD: Progressive disease; PS: Performance status.

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/m² 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/m² 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

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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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