Dose-escalation study of weekly irinotecan and daily carboplatin with concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

M Yamada*,1, S Kudoh1, H Fukuda2, K Nakagawa3, N Yamamoto1, Y Nishimura4, S Negoro5, K Takeda5, M Tanaka6 and M Fukuoka2

1First Department of Internal Medicine, Osaka City University Medical School, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan; 2Department of Radiology, Osaka University Medical School, Osaka, Japan; 3Fourth Department of Internal Medicine, Kinki University School of Medicine, Osaka, Japan; 4Department of Radiology, Kinki University School of Medicine, Osaka, Japan; 5Department of Pulmonary Medicine, Osaka City General Hospital, Osaka, Japan; 6Department of Radiology, Osaka City General Hospital, Osaka, Japan

Dose-escalation study was performed to evaluate the maximum tolerated dose, recommended dose and toxicity profile of weekly irinotecan in daily carboplatin and concurrent thoracic radiotherapy in patients with locally advanced non-small-cell lung cancer. Thirty-one previously untreated patients with unresectable stage III non-small-cell lung cancer were enrolled in this study. Patients received weekly irinotecan plus carboplatin (20 mg m$^{-2}$ daily for 5 days a week) for 4 weeks and thoracic radiotherapy (60 Gy in 30 fractions). The irinotecan dose was escalated from 30 mg m$^{-2}$ in increments of 10 mg m$^{-2}$. Four irinotecan dose levels were given and 30 patients were assessable. Their median age was 62 years (range: 52 – 72 years), 28 had a performance status of 0 – 1 and two had a performance status of 2. 12 had stage IIIA disease and 18 had IIIB disease. There were 19 squamous cell carcinomas, 10 adenocarcinomas, and one large cell carcinoma. The dose-limiting toxicities were pneumonia, esophagitis, thrombocytopenia and neutropenia. The maximum tolerated dose of irinotecan was 60 mg m$^{-2}$, with two patients developing grade 4 pulmonary toxicity and one patient died of pneumonia (grade 5). The recommended dose of irinotecan was 50 mg m$^{-2}$. Other grade 3 or 4 toxicities were nausea and vomiting. Three patients achieved complete remission and 15 had partial remission, for an objective response rate of 60.0%. The median survival time was 14.9 months, and the 1- and 2-year survival rates were 51.6% and 34.2%, respectively. The study concluded that the major toxicity of this regimen was pneumonia. This therapy may be active against unresectable non-small-cell lung cancer and a phase II study is warranted.

Keywords: non-small cell lung cancer; irinotecan; carboplatin; chemoradiotherapy

In patients with unresectable stage III non-small-cell lung cancer (NSCLC), two or more cycles of cisplatin-based chemotherapy, with or followed by radiation, has been proven to enhance survival (American Society of Clinical Oncology, 1997). Chemotherapy is appropriate for selected patients who have a good performance status. In general, chemotherapy is either given first followed by radiation, or is administered concurrently with radiation. Concurrent chemoradiotherapy regimens employ chemotherapy agents as radiosensitisers. Most studies that have shown a benefit for chemoradiotherapy have used cisplatin- or carboplatin-based combinations (Dillman et al, 1990; Le Chevalier et al, 1991; Jeremic et al, 1995), and both drugs are known to be radiosensitizers (Schaake-Koning et al, 1992; Jeremic et al, 1996). New active agents, such as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan, have been introduced and clinical trials of these agents for NSCLC have yielded promising data. These agents have been compared with each other in a phase III study performed in patients with advanced NSCLC, and several studies have suggested the radiosensitising properties of these new agents (Tishler et al, 1992; Leonard et al, 1996; McGinn et al, 1996; Okishio et al, 1996). However, the phase I and II studies combining these agents with radiotherapy have mostly been preliminary (Choy et al, 1994; Greco et al, 1996; Gregor, 1997; Maurers et al, 1998; Herschel et al, 1998). Irinotecan has a mechanism of action targeting the nuclear enzyme topoisomerase I as radiosensitizer in vitro (Okishio et al, 1996). A response rate of 32% was observed in untreated patients with advanced NSCLC (Fukuoka et al, 1992) while a recent phase III study showed that irinotecan in combination with cisplatin achieved a significantly better survival compared with the combination of cisplatin and vindesine in patients with metastatic NSCLC (Fukuoka et al, 2000). We have already reported that a phase I/II study of weekly irinotecan with concurrent radiotherapy showed acceptable toxicity (esophagitis, diarrhea, and pneumonitis)(Takeda et al, 1999). Carboplatin has also been investigated as a radiosensitizer. Several studies (Groen et al, 1995; Kunitoh et al, 1997; Atagi et al, 2000) of concurrent daily carboplatin and radiotherapy have suggested that this combination is feasible and reasonably effective. Irinotecan and carboplatin have independently shown a synergistic effect with ionizing radiation in preclinical studies (Doupe et al, 1985; Okishio et al, 1996). Based on these findings, we conducted a phase I trial of daily carboplatin and weekly irinotecan with concurrent thoracic radiotherapy for the treatment of locally advanced...
NSCLC in order to find the optimum dose of irinotecan and to estimate the antitumor activity and toxicity profile of this therapy.

MATERIALS AND METHODS

Patients selection

Patients were eligible for this study if they had histologically or cytotologically documented and locally advanced stage III NSCLC that was deemed unresectable. Other eligibility requirements included an age of less than 75 years, an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, no previous chemotherapy or radiotherapy, ability to give written informed consent, as well as adequate pretreatment haematologic function (leucocyte count \( \geq 4000 \, \text{m}^{-3} \), haemoglobin \( \geq 9.5 \, \text{g d}^{-1} \), and platelet count \( \geq 100 \,000 \, \text{m}^{-3} \)), renal function (a normal serum creatinine concentration), hepatic function (transaminases \( \leq \) twice the normal range and serum bilirubin level \( \leq 1.5 \, \text{m}^{-3} \)), and pulmonary function (PaO\(_2\) \( \geq 70 \, \text{Torr} \), %DLco \( > 60\% \)). Patients were excluded if they had contralateral hilar lymph node metastasis, a serious pre-existing disease, or a radiation field that exceeded half of one lung. Patient’s informed consent and approval of the institutional ethics committee were mandatory for participation in the trial.

Treatment plan

Irinotecan was administered as a 90-min intravenous infusion once weekly, and carboplatin was given as a 30-min infusion (20 mg m\(^{-2}\)) prior to thoracic radiotherapy daily for 5 days each week. Irinotecan and carboplatin were both administered for 4 weeks.

Thoracic radiotherapy started on day 1 and was given to a total dose of 60 Gy in 2.0 Gy fractions, which were delivered five times a week for 6 weeks using a linear accelerator (\( \geq 4 \text{MV} \)). The treatment volumes consisted of original and boost volumes irradiated sequentially. The initial large-field target volume consisted of the primary tumour, mediastinum, and involved hilar of supraclavicular nodes (total dose, 40 Gy), and boost dose of 20 Gy was delivered to a volume that consisted of the primary tumour and involved nodes. A combination of parallel-opposed anterior and posterior and oblique fields was used. The maximal spinal cord dose did not exceed 40 Gy. The target volume of the primary tumour included the complete extent of the visible primary tumour as defined radiographically (by computed tomography) with a minimum 1.5 cm and a maximum 2.5 cm margin around the mass.

The following therapy is optional. If the patient became operable as a result of tumour regression, surgery was done within 1 month of the completion of chemoradiotherapy. If the patient remained inoperable, two cycles of cisplatin with vindesine (cisplatin 80 mg m\(^{-2}\) day 1 and vindesine 3 mg m\(^{-2}\) on days 1, 8, 15) were given as systemic chemotherapy.

Dose escalation schedule

The starting dose of irinotecan was 30 mg m\(^{-2}\) and this was escalated by 10 mg m\(^{-2}\) increments in every three patients. There was no interpatient escalation. The next scheduled dose of irinotecan was omitted when grade 3 leukenopia, thrombocytopenia, or grade 2 diarrhoea was observed.

Both thoracic radiotherapy and intravenous carboplatin were withheld if grade 3 leukenopia, neutropenia, thrombocytopenia, or grade 4 esophagitis was observed and restarted as soon as possible after recovery to grade 3 esophagitis and grade 2 haematological toxicity.

Dose-limiting toxicity

Dose-limiting toxicity was defined as grade 3 or 4 nonhaematologic toxicity, excluding nausea, vomiting, and alopecia, as neutropenic fever (grade 3 neutropenia and \( > 38^\circ \text{C} \)) or as grade 4 haematologic toxicity according to the WHO criteria (World Health Organization, 1979). If irinotecan was omitted two times or more due to any toxicity or radiotherapy and daily carboplatin was postponed for more than one week because of grade 3 haematological toxicity or grade 4 oesophagitis, we decided this was dose-limiting toxicity. If dose-limiting toxicity was observed in one or two out of three patients, an additional three patients were scheduled to be treated at the same dose level, and dose escalation could then continue if the toxicity was only observed in one or two out of six patients. If the dose-limiting toxicity was observed in all three patients or in more than three out of six patients, that dose was defined as the maximum tolerated dose. Recommended dose was defined the previous dose level.

Response and toxicity evaluation

Responses were evaluated according to the World Health Organization (WHO) criteria and toxicity was assessed prior to any further non-protocol therapy according to the WHO criteria (World Health Organization, 1979). Pulmonary toxicity was recorded as Grade 0–5 according to late Radiation Therapy Oncology Group (RTOG) criteria (Robert et al, 1999) as follows: 0; none; 1, asymptomatic or mild symptoms, slight radiographic changes; 2, moderate symptomatic fibrosis or pneumonitis, low-grade fever, patchy radiographic appearances; 3, severe symptomatic fibrosis or pneumonitis, dense radiographic changes; 4, severe respiratory insufficiency, continuous oxygen, assisted ventilation; and 5, fatal. All reported responses and toxicities were confirmed by independent extramural review. Survival was measured from the initiation of chemoradiotherapy to death, and survival curves were estimated using the Kaplan–Meier method (Kaplan and Meier, 1958).

RESULTS

Patient characteristics

Between May 1996 and July 1998, 31 patients with histologically or cytologically confirmed stage III NSCLC were enrolled in this dose escalation study. Their clinical characteristics are summarised in Table 1. Four dose levels of irinotecan were administered (Table 2), and 30 patients were assessable for toxicity and efficacy. The

| Table 1 | Patient characteristics |
|---------|------------------------|
| No. of patients enrolled | 31 |
| Evaluability | Not evaluable 1* |
| Performance status (ECOG) | 0 10 (33%) |
| Age, median (range) years | 62 (52–72) |
| Sex | Male 24 (80%) Female 6 (20%) |
| Histology | Squamous cell carcinoma 19 (63%) Adenocarcinoma 10 (33%) Large cell carcinoma 1 (3%) |
| Stage | IIIA 12 (40%) IIIB 18 (60%) |

Abbreviation: ECOG, Eastern Cooperative Oncology Group. *A brain metastasis was discovered on day 7 of treatment, and this patient was removed from the study.
remaining one patient who enrolled into irinotecan dose level of 50 mg m$^{-2}$ was ineligible because brain metastasis was confirmed after enrollment. For these 30 patients, the median age was 62 years (range: 52–72 years). The performance status was 0–1 in 28 patients, while it was 2 in two patients. Twelve patients were in stage IIIA and 18 were in stage IIIB. Their tumours included 19 squamous cell carcinomas, 10 adenocarcinomas, and one large cell carcinoma.

**Actual doses of chemotherapy and radiotherapy**

The planned individual drug doses, the actual delivered doses and dose intensity are listed in Table 2. Fourteen patients were treated with 30 mg m$^{-2}$ of irinotecan. Although six patients should have been the maximum number in one step in our protocol, we added eight patients in first step to carry out this protocol safely because grade 4 pulmonary toxicity was observed in one patient, in the former study (Takeda et al, 1999) of weekly irinotecan combined with concurrent thoracic radiation therapy we experienced the treatment related death of pneumonitis and the Monitoring Committee of this protocol decided to add more patients in initial step. Administration of irinotecan was withheld due to neutropenia in three patients, disease progression in two patients, and diarrhea and localized erythema in one patient. Three patients did not complete the intravenous carboplatin schedule, one due to disease progression and the other due to a mistake about administration times. Dose intensities of irinotecan and carboplatin are listed in Table 2. The percentage of actually delivered dose-intensity of irinotecan and carboplatin was range from 91.1% to 100%. Twenty-five out of the 30 patients (83.3%) completed their radiotherapy as scheduled. The reason for not completing radiotherapy was disease progression in two patients and thrombocytopenia in one patient. Also, the first patient who received 60 mg m$^{-2}$ of irinotecan suffered treatment-related death from pneumonitis and thrombocytopenia, so the other two patients treated at this dose level discontinued radiotherapy after 50 Gy.

**Haematologic toxicity**

Thirty patients were assessable for haematologic toxicity, and the results summarised in Table 3. Haematologic toxicities were mild. The only grade 4 leucopenia and neutropenia were seen in one patient (grade 4 neutropenia) given 30 mg m$^{-2}$ of irinotecan. G-CSF was administered to five of 14 patients on 30 mg m$^{-2}$ of irinotecan, three of six on 40 mg m$^{-2}$, four of seven on 50 mg m$^{-2}$, and all three on 60 mg m$^{-2}$ dose of irinotecan. Grade 4 thrombocytopenia occurred in two patients (one at the 50 mg m$^{-2}$ and one at 60 mg m$^{-2}$ doses of irinotecan) and this was dose-limiting toxicity. These two patients required platelet transfusions.

**Nonhaematologic toxicity**

The nonhaematologic toxicities are summarised in Table 4. One patient suffered from grade 3 esophagitis at an irinotecan dose of 40 mg m$^{-2}$, and two patients had grade 3 nausea with vomiting at 30 mg m$^{-2}$ of irinotecan. No patient suffered from either grade 3 or 4 diarrhea. Grade 4 pneumonitis was observed in two patients treated with 60 mg m$^{-2}$ of irinotecan, as well as in one patient each at both 30 mg m$^{-2}$ and 40 mg m$^{-2}$. Grade 5 pneumonitis was observed in one patient with 60 mg m$^{-2}$ of irinotecan. Grade 4–5 pneumonitis was dose-limiting toxicity and was observed in all three patients at the 60 mg m$^{-2}$ of irinotecan dose. Therefore we decided that this dose was defined as the maximum tolerated dose. Of these five patients who had grade 4–5 pneumonitis, all were treated with steroids and three required mechanical ventilation. Four patients eventually recovered, however one patient given 60 mg m$^{-2}$ of irinotecan suffered treatment-related death. Pneumonitis seemed to be a principal toxicity of this combined modality.

**Response**

The response to treatment is summarised in Table 5. Three patients achieved complete remission and 15 patients achieved partial remission, for an overall objective response rate of 60.0% (95% confidence interval 41.4–78.6%). Among the 18 responders, five patients underwent surgical resection of their residual disease and five received systemic chemotherapy with cisplatin and vindesine. Among the 11 patients with stable disease, four also received systemic chemotherapy.

**Survival and duration of response**

The overall median survival time (MST) was 14.9 months, while the 1-year and 2-year survival rates were 51.6% and 34.2%, respectively. In the responding patients (i.e., those who achieved either complete

---

**Table 2** Dose levels of irinotecan, dose actually delivered and dose intensity

| Irinotecan (mg m$^{-2}$ dose level) | No. of evaluable patients | Administration of irinotecan | DI (mg m$^{-2}$ per week) (% of ADDI) | Administration of carboplatin | DI (mg m$^{-2}$ per day) (% of ADDI) | Treatment of radiotherapy |
|----------------------------------|--------------------------|----------------------------|--------------------------------------|-------------------------------|-------------------------------------|--------------------------|
| 30                              | 14                       | complete                   | 10                                   | 27.3 (91.1%)                  | 13                                   | complete 12              |
|                                  |                          | one dose missed             |                                       | 6 doses 1 b (95.0%)           | complete 12                         |
|                                  |                          | two doses missed            |                                       | 6 doses 1 b (95.0%)           | complete 12                         |
| 40                              | 6                        | complete                   | 5                                    | 38.1 (93.6%)                  | 5                                    | complete 6               |
|                                  |                          | one dose missed             |                                       | 19 doses 1 e (99.2%)          | complete 6                           |
| 50                              | 7                        | complete                   | 6                                    | 48.2 (96.4%)                  | 6                                    | complete 6               |
|                                  |                          | one dose missed             |                                       | 19 doses 1 e (99.3%)          | complete 6                           |
| 60                              | 3                        | complete                   | 2                                    | 55                            | 3                                    | complete 1               |
|                                  |                          | one dose missed             |                                       | 55                            | 1                                   | complete 1               |

Abbreviation: DI, dose-intensity, ADDI, actually delivered dose intensity. *Myelosuppression, b disease progression, c skin rash, d diarrhea, *mistake.

**Table 3** Haematologic toxicity

| Irinotecan (mg m$^{-2}$) | No. of patients | Haemoglobin | Neutrophils | Platelets |
|-------------------------|----------------|-------------|-------------|-----------|
| 30                      | 14             | 1           | 0           | 2         |
| 40                      | 6              | 1           | 0           | 2         |
| 50                      | 7              | 0           | 0           | 2         |
| 60                      | 3              | 0           | 0           | 3         |

**Nonhaematologic toxicity**

The nonhaematologic toxicities are summarised in Table 4. One patient suffered from grade 3 esophagitis at an irinotecan dose of 40 mg m$^{-2}$, and two patients had grade 3 nausea with vomiting at 30 mg m$^{-2}$ of irinotecan. No patient suffered from either grade 3 or 4 diarrhea. Grade 4 pneumonitis was observed in two patients treated with 60 mg m$^{-2}$ of irinotecan, as well as in one patient each at both 30 mg m$^{-2}$ and 40 mg m$^{-2}$. Grade 5 pneumonitis was observed in one patient with 60 mg m$^{-2}$ of irinotecan. Grade 4–5 pneumonitis was dose-limiting toxicity and was observed in all three patients at the 60 mg m$^{-2}$ of irinotecan dose. Therefore we decided that this dose was defined as the maximum tolerated dose. Of these five patients who had grade 4–5 pneumonitis, all were treated with steroids and three required mechanical ventilation. Four patients eventually recovered, however one patient given 60 mg m$^{-2}$ of irinotecan suffered treatment-related death. Pneumonitis seemed to be a principal toxicity of this combined modality.

**Response**

The response to treatment is summarised in Table 5. Three patients achieved complete remission and 15 patients achieved partial remission, for an overall objective response rate of 60.0% (95% confidence interval 41.4–78.6%). Among the 18 responders, five patients underwent surgical resection of their residual disease and five received systemic chemotherapy with cisplatin and vindesine. Among the 11 patients with stable disease, four also received systemic chemotherapy.

**Survival and duration of response**

The overall median survival time (MST) was 14.9 months, while the 1-year and 2-year survival rates were 51.6% and 34.2%, respectively. In the responding patients (i.e., those who achieved either complete
or partial remission), the median duration of response was 11.0 months. In the patients who had either surgery or adjuvant chemotherapy, the MST was 21.9 months (range: 7.8 to 33.0 months) and 24.3 months (range: 5.4 to 32.4 months), respectively. In the other patients, the MST was 10.6 months (range: 1.1 to 36.9 months). The overall survival of all the patients is plotted in Figure 1.

**Pattern of failure**

The sites of initial relapse are shown in Table 6. There were 22 sites of relapse in 29 patients who had partial remission or stable disease. The primary tumour inside the radiation field was the site of initial relapse in eight patients (seven without and one with distant metastasis), while distant metastasis was in ten patients and pleural effusion in four patients. Of five patients who underwent surgery, three patients had no relapse, one died of another disease, and one had pulmonary metastasis.

**DISCUSSION**

Our present study showed that the combination of daily low-dose carboplatin and weekly irinotecan with concurrent thoracic radiotherapy is feasible. All three patients who received 60 mg m\(^{-2}\) of irinotecan developed grade 4–5 pneumonitis, although grade 4–5 pneumonitis was not observed at the 50 mg m\(^{-2}\) dose. In our former study of a phase I/II study (Takeda et al., 1999) of weekly irinotecan alone and concurrent thoracic radiotherapy in patients with stage III NSCLC, radiation therapy (2 Gy daily to a total dose of 60 Gy) was performed concurrently with administration of irinotecan done once weekly for 6 weeks. Twenty-seven patients were enrolled at three irinotecan dose levels (30, 45 and 60 mg m\(^{-2}\)). In that phase I study, grade 4 pneumonitis occurred in one patient at a dose of 60 mg m\(^{-2}\), while in the phase II study using 45 mg m\(^{-2}\), one out of 10 patients developed severe toxicity (grade 4 pneumonitis plus grade 3 diarrhea) and died. In our study, the irinotecan administration period was reduced from 6 to 4 weeks because in our former study (Takeda et al., 1999) the number of patients increased who experienced the skip of the 5th and/or 6th administration of irinotecan. On the former study we added the daily carboplatin as another radiosensitizer.

Development of pulmonary toxicity is generally thought to be related to radiation dose, method of fractionation, and volume of the lung irradiated (Ginsberg et al., 1993). In patients receiving combined chemoradiotherapy, other confounding factors, such as the type of chemotherapeutic agent, also may play an important role in determining the risk of this toxicity. New chemotherapeutic agents, such as paclitaxel, have also been reported to show pulmonary toxicity (Choy et al., 1998). Therefore, the mechanism of pneumonitis seemed to be an interaction between all three parts of the treatment.
Recent studies suggest that analysis of the three-dimensional dose distribution gives useful data for the prediction of pulmonary toxicity (Martel et al., 1994; Marks et al., 1997; Graham, 1997). We could not calculate radiotherapy volume data since three-dimensional (3D) radiation therapy were not available with our study. So we calculated radiation portal size by two-dimensional treatment planning data. Radiation portal size was range from 105 m² to 322 m² (mean ± SD; 179.7 ± 48.0 m²). For five patients with grade 4 or 5 pulmonary toxicity, radiation field size was range from 168 m² to 304 m² (mean ± SD; 208.8 ± 54.4 m²). There was no significant relationship between radiation field size and pulmonary toxicity. It is very difficult to interpret the toxicity without more information about radiation volume data. This study thinks it is also worth reporting the premorbid lung function data, so we collected the individual data of pulmonary function tests (PFTs) before radiotherapy. Premorbid lung function data (including spirometry, volume measurements, and diffusion capacity) as follows (mean ± SD): the per cent predicted vital capacity (%VC) 89.4 ± 19.2%; the forced expiratory volume in 1 sec (FEV1) 1.88 ± 0.58 L; the per cent predicted diffusion capacity to carbon monoxide (%DLCO) 90.1 ± 21.7%. For five patients with grade 4 or 5 pulmonary toxicity, lung function data as follows (mean ± SD): %VC 93.6 ± 15.9%; FEV1.0 1.91 ± 0.67L; %DLCO 78.0 ± 23.5%. There was no relationship between PFT parameters and pulmonary toxicities. According these limited information, we suggest that pulmonary toxicity may be drug related rather than field size or baseline PFTs. In our study, radiation volume was not estimated, so we have to plan further study to reveal whether a dose and radiation volume are related to the occurrence of pulmonary toxicity.

REFERENCES

American Society of Clinical Oncology (1997) Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997. J Clin Oncol 15: 2996–3003

Atagi S, Kawahara M, Ogawara M, Matsui K, Masuda N, Kudoh S, Negoro S, Furuse K (2000) Phase II trial of daily low-dose carboplatin and thoracic radiotherapy in elderly patients with locally advanced non-small cell lung cancer. Jpn J Clin Oncol 30: 59–64

Choy H, Akerley W, Safran H, Akerley W, Graziano SL, Bogart JA, Cole BF (1998) Phase II trial of weekly paclitaxel and concurrent radiotherapy for advanced non-small cell lung cancer. J Clin Oncol 16: 2682–2686

Choy H, Safran H, Akerley W, Graziano SL, Bogart JA, Cole BF (1998) Phase II trial of weekly paclitaxel and concurrent radiotherapy for locally advanced non-small-cell lung cancer. Clin Cancer Res 4: 1931–1936

Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, Carey RW, Frei IIEF, Green MR (1990) A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 323: 940–945

Douple EB, Richmond RC, O’Hara JA, Coughlin CT (1985) Carboplatin as potentiator of radiation therapy. Cancer Treat Rev 12: 111–114

Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Aiyoshi Y, Negoro S, Masuda N (1992) A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 10: 16–20

Fukuoka M, Nagao K, Ohashi H, Niitani H (2000) Impact of irinotecan (CPT-11) and cisplatin (CDDP) on survival in previously untreated metastatic non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 19: 495a

Ginsberg RJ, Kris MG, Armstrong JG (1993) Cancer of the lung: Non-small cell lung cancer. In: Cancer: Principles and Practice of Oncology, 4th edn., DeVita VT, Hellman S, Rosenberg S (eds) pp 676–723 Philadelphia: Lippincott

Graham MV (1997) Predicting radiation response. Int J Radiat Oncol Biol Phys 39: 561–562

Greco FA, Stroup SL, Gray JR, Hainsworth JD (1996) Paclitaxel in combination chemotherapy with radiotherapy in patients with unresectable stage III non-small cell lung cancer. J Clin Oncol 14: 1642–1648

Gregor A. (1997) Gemcitabine plus radiotherapy for non-small cell lung cancer. Semin Oncol 24: 39–41

Groen HI, van der Leest AH, de Vries EG (1995) Continuous carboplatin infusion during 6 weeks’ radiotherapy in locally inoperable non-small-cell lung cancer. Br J Cancer 72: 992–997

Herschler LL, Hahn SM, Kroog F, Fass H, Tembeck B, Goldspiel B, Cook J, Mitchell JB, Liebmann J (1998) Phase I study of paclitaxel as radiation sensitizer in the treatment of mesothelioma and non-small-cell lung cancer. J Clin Oncol 16: 635–641

Jeremic B, Shibamoto Y, Acimovic L, Djuric I. (1995) Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. J Clin Oncol 13: 452–458

Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. (1996) Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small cell lung cancer: a randomized study. J Clin Oncol 14: 1065–1070

Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481

Kunitoh H, Watanabe K, Nagatomo A, Okamoto H, Kimbara K (1997) Concurrent daily carboplatin and accelerated hyperfractionated thoracic radiotherapy in locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1: 103–109

Le Chevalier T, Arriagada R, Quiss E, Ruffie P, Martin M, Tarayre M, Lacombe-Terrier MJ, Douillard JY, Laplanche A (1991) Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst 83: 417–423

Leonard CE, Chan DC, Chou TC, Kumar R, Bunn PA. (1996) Paclitaxel enhances in vitro radiosensitivity of squamous carcinoma cell lines of the head and neck. Cancer Res 56: 5198–5204
Marks LB, Munley MT, Bentel GC, Zhou SM, Hollis D, Scarfone C, Sibley GS, Kong FM, Jirtle R, Jaszcak R, Coleman RE, Tapson V, Anscher M (1997) Physical and biological predictors of changes in whole-lung function following thoracic irradiation. *Int J Radiat Oncol Biol Phys* 39: 563–570

Martel MK, Ten Haken RK, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS (1994) Dose-volume histogram and 3-D treatment planning evaluation of patients with pneumonitis. *Int J Radiat Oncol Biol Phys* 28: 575–581

Mattson K, Holsti LR, Holsti P, Jakobsson M, Kajanti M, Liippo K, Mantyla M, Niittamo-Korhonen S, Nikkanen V, Nordman E (1988) Inoperable non-small-cell lung cancer: radiation with or without chemotherapy. *Eur J Cancer Clin Oncol* 24: 477–482

Mauers AM, Masters G, Haraf DJ, Hoffman PC, Watson SM, Golomb HM, Yokes EE (1998) Phase I study of docetaxel with concomitant thoracic radiation therapy. *J Clin Oncol* 16: 159–164

McGinn CJ, Sherwach DS, Lawrence TS (1996) Radiosensitizing nucleosides. *J Natl Cancer Inst* 88: 1193–1203

Morton RF, Jett JR, McGinnis WL, Eafle JD, Therneau TM, Krook JE, Elliott TE, Mabillard JA, Nelmark RA, Maksymiuk AW (1991) Thoracic radiation therapy alone compared with combined chemoradiotherapy for locally unresectable non-small cell lung cancer: a randomized, phase III trial. *Ann Intern Med* 115: 681–686

Okishio K, Kudoh S, Kurihara N, Hirata K, Yoshikawa J (1996) Irinotecan (CPT-11) enhances the radiosensitivity of lung cancer cells in vitro. *Cell Pharmacol* 3: 247–252

Robert F, Childs HA, Spencer SA, Redden DT, Hawkins MM (1999) Phase I/II Study of Concurrent Paclitaxel and Cisplatin With Radiation Therapy in Locally Advanced Non-Small Cell Lung Cancer: Analysis of Early and Late Pulmonary Morbidity. *Semin Radiat Oncol* 2(Suppl 1): 136–147

Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, Emami B, Curran WJ, Byhardt RW, Turrisi AT (1995) Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4558: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 87: 198–205

Schaaake-Koning C, van den Vogtaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, Kirkpatrick A, Koolen M, Maat B, Nijs A (1992) Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 326: 524–530

Takeda K, Negoro S, Kudoh S, Masuda N, Takada M, Tanaka M, Nakajima T, Tada T, Fukuoka M (1999) Phase I/II study of weekly irinotecan and concurrent radiation therapy for locally advanced non-small cell lung cancer. *Br J Cancer* 79: 1462–1467

Tishler RB, Geard CR, Hall EJ, Schiff PB (1992) Taxol sensitizes human astrocytoma cells to radiation. *Cancer Res* 52: 3495–3497

World Health Organization (1979) WHO Handbook for Reporting Results of Cancer Treatment, WHO Publication No.48. Geneva, Switzerland: World Health Organization