PATIENTS AND METHODS

Patient selection

Patients with histologically or cytologically confirmed NSCLC with unresectable stage III disease were assessed for eligibility. Unresectable stage IIIA disease was defined by the presence of multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT) which rendered in the opinion of the treating investigator, the patients unsuitable as candidates for surgical resection. Eligible patients also needed to meet the following criteria: measurable disease of 20 mm or more; no prior history of chemotherapy or TRT; Eastern Cooperative Oncology Group performance status (PS) ≤ 1; age ≤ 75 years; leukocytes ≥ 4,000/μL, platelets ≥ 100,000/μL, and hemoglobin ≥ 9.5 g/dL, serum creatinine ≤ institutional upper limit of normal [ULN], 24-hour creatinine clearance ≥ 60 mL/min, bilirubin ≤ 1.5 mg/dL, AST and ALT ≤ 2.0 x ULN and partial pressure of arterial oxygen ≥70 Torr .

Patients were excluded if they had pulmonary fibrosis, other active, invasive malignancies in the three years leading up to protocol entry, malignant effusion, pyrexia of 38°C or more at baseline, infections, significant cardiac disease, uncontrolled diabetes mellitus, paresis of the intestine ileus, or regular

use of steroids. The institutional ethics committee of each of the participating institutions approved the protocol and all patients provided written informed consent prior to the start of the study.

For staging, all patients underwent CT of the thorax including the upper abdomen, and either a brain CT or brain MRI. A radioisotopic bone scan was also performed for all the patients. PET was not obtained in any of the enrollees at baseline.

Treatment Schedules

Patients were randomly assigned to one of the three following treatment arms (Figure 2). Treatment was composed of concurrent chemoradiotherapy and subsequent consolidation chemotherapy.

In arm A, chemotherapy consisted of vindesine 3 mg/m^2 on days 1 and 8, cisplatin 80 mg/m^2 on day 1, and mitomycin C 8 mg/m^2 on day 1. This chemotherapy was repeated every 4 weeks and four courses were administered. On day 2 of chemotherapy, TRT was begun at the dose of 2 Gy/fraction given in 15 fractions over 3 weeks, followed by a rest period of 1 week. Subsequently, radiation was again resumed at the dose of 2 Gy /

fraction given in 15 fractions over 3 weeks. The total dose of radiation administered was 60 Gy.

In arm B and C, concurrent chemoradiotherapy was undertaken with the agents administered at reduced doses weekly for six weeks, followed by full-dose chemotherapy during the consolidation phase. The consolidation phase chemotherapy, initiated 3 to 4 weeks after the concurrent chemoradiotherapy, was administered in two cycles. TRT was initiated on day 1 at the dose of 2.0 Gy daily, five times per week. The total dose of 60 Gy dose was given in 30 fractions over a 6-week period.

The concurrent phase chemotherapy consisted of irinotecan 20 mg/m^2 followed by carboplatin area under the plasma concentration time curve (AUC) 2 mg/mL·min in arm B and paclitaxel 40 mg/m^2 followed by carboplatin AUC 2 mg/mL·min in arm C. The consolidation chemotherapy consisted of 3-week cycles of irinotecan (50 mg/m^2 on days 1 and 8) / carboplatin (AUC 5 mg/mL·min on day 1) in arm B, and paclitaxel (200 mg/m^2 administered over 3 hours), followed by carboplatin (AUC 5 mg/mL·min on day 1) in arm C.

Radiation Therapy

All patients were treated with a linear accelerator photon beam of 4-MV or more. The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over 6 weeks in arms B and C, and 7 weeks in arm A.

At the start of this multi-institutional study, three-dimensional (3D) treatment planning system using computed tomography was not available at all institutions. So, two-dimensional (2D) treatment planning techniques were allowed, and 3D dose constraints for both planning target volume (PTV) and normal risk organs were not determined in the protocol. Radiation doses were specified at the center of the target volume. In 2D treatment planning, doses were calculated assuming tissue homogeneity without correction for lung tissues, while lung inhomogeneity correction was performed in 3D treatment planning. Among 412 patients who received =>54Gy (arm A; 139, arm B; 137, and arm C; 136), 2D and 3D treatment planning were performed for 200 and 212 patients, respectively.

The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (#2) to subcarinal lymph nodes

(#7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. For the primary tumors and the involved lymph nodes of 1 cm in the shortest diameter, a margin of 1.5 to 2 cm was added. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5 to 1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods such as the oblique opposing method. Appropriate PTV margin and leaf margin were added for CTV1 and CTV2. When grade 4 hematologic toxicity, grade 3/4 esophagitis or dermatitis, pyrexia of 38°C or more or a PaO2 of less than 60 torr occurred, the TRT was interrupted.

Evaluation of Response and Toxicity

All eligible patients who received any treatment at all were considered as assessable for response and toxicity. Chest X-rays, complete blood counts and blood chemistry studies were repeated once a week during the treatment period. Thoracic CT was performed once a month during the treatment period. After the treatment, thoracic CT was obtained every 3 months, and other

imaging examinations were obtained when recurrence was suspected. The response was evaluated in accordance with the RECIST. In the evaluation of the antitumor effects, extramural review was conducted. Overall survival (OS) was defined as the time from registration until death from any cause. Progression-free survival (PFS) was defined as the time between randomization and disease progression, death, or last known follow-up. OS and PFS were estimated by the Kaplan-Meier method.

Statistical Analysis

The primary endpoint of this study was comparison of the OS between the control group (arm A) and each of the treatment groups (arm B or C). It was projected that the control group would achieve a median OS time of 16.5 months[5], whereas the treatment group would show an increase in the median OS to 20.5 months, based on previously published data[14]. When the upper limit of the adjusted confidence interval (CI) of the hazard ratio of the control group to each treatment group was low 1.176 (1/0.85), the results were recognized as demonstrating non-inferiority of the experimental treatment to the control treatment. The sample size was calculated assuming a 2.5% one-

sided type I error, and 80% power. The patient accumulation period was 4.5 years, and the follow-up period was 3 years. In view of the possibility of variance inflation due to censoring, the sample size was set at 450.

Baseline characteristics were compared among the treatment groups using the Kruskal-Wallis test for continuous variables and Fisher's exact test for discrete variables. Rates of occurrence of specific toxicities and treatment delivery were compared among the groups using Fisher's exact test.

RESULTS

Patient characteristics

From September 2001 to September 2005, a total of 456 patients were registered for the study and 153, 152 and 151 were allocated to arm A, B, and C, respectively. Of the total, 16 patients (arm A 7, B 5 and C 4) did not receive the protocol treatment, because they were deemed ineligible for the study before the start of treatment after registration in 5 patients (2: large irradiation area, 1: stage IIB, 2: stage IV), worsening of the underlying disease in 4, worsening of complications in 5, patient refusal in 1, and unknown reason in 1 patient. The safety and antitumor effects of the treatments were eventually assessed based on the data of 440 patients after exclusion of these 16 patients from the total of 456 patients enrolled. After the start of the treatment, 3 patients were found to be ineligible due to stage IV disease, but the data of these patients were included in all the analyses.

The patient characteristics were no statistically significant differences among the three arms (Table 1).

Treatment Administered

Table 2 shows the status of implementation of chemotherapy. During the concurrent phase, 40.8% of patients in arm B and 58.5% of patients in arm C received 6 weekly cycles of chemotherapy (p=0.003); 67.3% of patients in arm B and 87.8% patients in arm C completed at least 5 cycles (p<0.001). In regard to the consolidation phase, 41.1%, 29.3%, and 49.7% in arms A, B, and C, respectively, received the 2 scheduled courses of therapy (p=0.002). Chemotherapy interruptions were more common in arm B than in arm A and C in both the concurrent and consolidation phases.

In most of the patients, TRT at 60 Gy was completed, and 6.8%, 8.2%, and 8.8% of patients in arms A, B, and C, respectively, received a radiation dose of less than 60 Gy. The reason for the reduced radiation dose was toxicity in two-third of the patients (3 cases from arm A, 6 cases from arm B, including 2 cases of esophagitis and 2 cases of pneumonitis, and 7 cases from arm C, including one case of esophagitis and 2 cases of pneumonitis).

Toxicity

Table 3 lists the grade 3 or more severe toxicities. There were a total of 11 treatment-related deaths. The cause of death was radiation pneumonitis

in 1 and sepsis in 1 of the 2 patients in arm A, meningitis in 1, pneumonia in 1, radiation pneumonitis in 2, and mycosis in 1 of the 5 patients in arm B, and radiation pneumonitis in 3 and death from other cause in 1 of the 4 patients in arm C. The clinical course of the patients who died of radiation pneumonitis are presented below. One case from arm A developed pneumonitis on day 2 of the 4th course of treatment. In this case, the pneumonitis subsided temporarily in response to steroid therapy, but it aggravated again subsequently, resulting in death. In arm B, one case developed pneumonitis after 54Gy of TRT and died despite mechanical ventilation, and another case developed pneumonitis at the end of the concurrent phase. In the latter case, the pneumonitis subsided temporarily in response to pulsed steroid therapy, but it aggravated again, resulting in death. In arm C, 2 cases developed pneumonitis at the end of the concurrent phase. Another case from arm C developed pneumonitis on day 16 of the concurrent phase.

The incidences of grade 3 or more severe hematologic toxicity, infection, febrile neutropenia and gastrointestinal toxicity were significantly higher in arm A than in arm B or C. The incidence of grade 3 or more severe neurogenic toxicity was significantly higher in arm C as compared with that in the other two

arms. There were no statistically significant differences in the incidences of esophagitis, dyspnea, or pneumonitis, which are manifestations of radiation-related toxicity, among the three groups. The incidence of Grade 2 or more severe esophagitis was significantly higher in Arm C (20.5%, 23.1% and 33.3% from Arm A, B and C, respectively; p = 0.003).

Efficacy

The objective response rate was 66.4%, 56.5% and 63.3% in arm A, B and C, respectively (Table 4). The response rates in arm B and C were not statistically significantly different from the rate in arm A.

The OS and PFS are shown in Figures 3. Most of the patients had been followed up for >3 years, and 343 patients had died. The median survival time (MST), 3-year and 5-year survival rates in arm A were 20.5 months, 35.3%, 17.5%, respectively. The corresponding values were 19.8 months, 24.2% and 17.8% in arm B, and 22.0 months, 26.4% and 19.5% in arm C. There was no statistically significant difference in the OS between arm B or C and arm A (arm A vs. B; p = 0.392, arm A vs.C; p = 0.876). The upper limits of the adjusted CI of the hazard ratio between arm A and B (1.402) or C (1.204) exceeded

1.176. Thus, the results did not show non-inferiority of the three experimental regimens (arm B and C) as compared with the reference treatment (arm A). The OS is no significant difference by gender (male, female), stage (IIIA, IIIB) and weight loss (<5%, ≥5%) in among three arms. The causes of death after the third year are disease progression (15, 6 and 9 in arm A, B and C, respectively) and other disease (3, 1 and 0 in arm A, B and C, respectively).

The median PFS was 8.2, 8.0 and 9.5 months in arm A, B and C, respectively. There was also no statistically difference of the PFS between arm B or C, and A (arm A vs. B; p = 0.466, arm A vs. C; p = 0.621).

Discussion

This is the first phase III trial designed for direct comparison between second generation and third generation regimens applied in combination with concurrent TRT in patients with locally advanced lung carcinoma. This study was additionally aimed at comparing a cisplatin-based regimen with a carboplatin-based regimen, and also more frequent radiosensitizing doses during TRT with systemic doses of chemotherapy during RT. In regard to chemotherapy for advanced lung cancer, a previous meta-analysis demonstrated that cisplatin-based regimen is superior to carboplatin-based regimen in terms of the OS. In the present study, however, the OS in arm A (cisplatin-based regimen) was not significantly longer than that in arm B or C (carboplatin-based regimen). The observed inter-group differences possibly reflect the differences between the 2nd and 3rd generation regimens, or between more frequent radiosensitizing doses and systemic doses of chemotherapy. In any event, the results of this study suggest that the 3rd generation carboplatin regimen (particularly carboplatin + paclitaxel) was at least comparable to the 2nd generation cisplatin regimen, which is the

conventionally used therapeutic regimen, in terms of the survival-prolonging effect when applied in combination with concurrent thoracic radiotherapy.

Unfortunately, non-inferiority of OS was not demonstrated in the present study, probably because the number of the patients in this study resulted in a deficiency of power, since the therapeutic outcome in the reference arm was more favorable than that in conventional reports. The therapeutic outcome in the reference arm in recent phase III studies of chemoradiotherapy was more favorable than the estimated numerical data [16]. The favorable data may be attributable to bias due to the patient inclusion criteria or the development of radiotherapy, but no distinct cause could be identified.

Although non-inferiority in terms of OS was not demonstrated in this study, the survival curves themselves mostly coincided among the three groups, as shown in Figure 2. The hematologic and gastrointestinal toxicities noted in arm A were significantly serious as compared with those in the experimental arms. Although the incidence of grade 3 or more severe neurotoxicity was significantly higher, most of the other toxicities were the mildest in group C among the three groups. Between the experimental arms,

the rate of implementation of chemotherapy tended to be lower for arm C than for arm B. It was considered from the viewpoint of feasibility, that arm C may be superior to arm B.

From these data on the efficacy and toxicity, we judged that concurrent chemoradiotherapy involving the combined use of carboplatin + paclitaxel and TRT yielded the best results among the three groups, and we, the WJOG, are going to select this treatment method as the reference arm for phase III studies in the future.

Reference

1. Jemal A Sr, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics CCJC, 66., 2007

2. van Meerbeeck JP: Staging of non-small cell lung cancer: consensus, controversies and challenges. Lung Cancer 34:S95-107, 2001 (suppl 2)

3. Dillman RO, Seagren SL, Propert KJ, et al: 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, 1990

4. Sause W, Kolesar P, Taylor SIV, et al: Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. Chest 117:358-364, 2000

5. Furuse K, Fukuoka M, Kawahara M, et al: Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17:2692-2699, 1999

6. Curran D SC, Langer C et al.: Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with

unresected stage III NSCLC: RTOG 9410. Proc Am Soc Clin Oncol 22: 2499a., 2003

7. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 346: 92-98, 2002

8. Bunn PA, Jr., Kelly K: New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: A review of the literature and future directions. Clin Cancer Res 4:1087-1100, 1998

9. Hoffman PC, Mauer AM, Vokes EE: Lung cancer. Lancet 355:479-485, 2000

10. Movsas B, Hudes RS, Schol J, Induction and concurrent paclitaxel/carboplatin every 3 weeks with thoracic radiotherapy in locally advanced non-small-cell lung cancer: an interim report. Clin Lung Cancer. 3(2):125-32; discussion 133, 2001.

11. Govindan G, Bogart J, Wang X, et al: Phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small cell lung cancer: CALGB 30407. Proc Am Soc Clin Oncol 27 (15S): 383s, 2009

12. Vokes EE, Herndon JE 2nd, Crawford J, et al: Randomized phase II study

of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and leukemia group B study 9431. J Clin Oncol 20:4191-4198, 2002

13. Belani CP, Choy H, Bonomi P, et al: Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23:5883-5891, 2005

14. Choy H, Akerley W, Safran H,et al: Multiinstitutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small-cell lung cancer. J Clin Oncol 16::3316-3322, 1998

15. Vokes EE, Herndon JE II, Kelley MJ, et al: Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non–small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 25:1698-1704, 2007

16. Uejima H.: Dose-finding study of weekly irinotecan (CPT-11) and carboplatin (CBDCA) with concurrent thoracic radiotherapy (TRT) in locally advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 21:

220b, 2002

17. Endo M, Takada Y, Obayashi K, et al:Weekly paclitaxel and carboplatin with concurrent radiation therapy in locally advanced non-small cell lung cancer: Phase I study. Radiat Med 23: 331-335, 2005

18. Hanna N, Neubauer M, Yiannoutsos C, et al: Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non–small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 26: 5755-5760, 2008

Figure legends

Figure 1. CONSORT diagram

Figure 2. Treatment schema

Figure 3a. Comparison of the overall survival among the three randomly assigned arms.

Figure 3b. Comparison of the progression-free survival among the three randomly assigned arms