discontinued if clinical or radiological evidence of progression was present.

Statistical analysis

Event-free survival was measured from the first day of treatment until the observation of evidence of the first local, regional, or distant recurrence or progression of the tumor or the final day of follow-up without recurrence. Time to progression was measured from the first day of salvage treatment until disease progression or the final day of follow-up without disease progression, and the overall survival was measured from the first day of treatment until death or the final day of follow-up.

After excluding patients treated with local therapy only, pretreatment and treatment variables were investigated for their relation to event-free survival, and overall survival using both univariate and multivariate Cox regression analyses. The variables were selected after considering the possible effects on prognosis indicated by our experience and previous investigations (Bacci et al. 2000; Catterill et al. 2000; Obata et al. 2007; Rodriguez-Galindo et al. 2003; Sluga et al. 2001). The variables were followed as: gender (male versus female), age (<15 years vs. 15≤), Eastern Cooperative Oncology Group performance status (0 vs. 1≤), primary tumor type (bone versus soft-tissue), primary tumor site (non-pelvic as extremities or axial sites versus intra-thoracic or abdominal), primary tumor size (≤8 cm vs. 8<), disease type (localized versus metastatic), serum lactate dyhydrogenase level (elevated vs. normal or unknown), serum neuron-specific enolase level (elevated vs. normal or unknown). The median event-free survival, time to progression, and overall survival were estimated using the Kaplan–Meier method. We used univariate and multivariate logistic regression analysis to assess the relationship between pretreatment and treatment variables and the response to chemotherapy. A statistical analysis was also performed to identify factors associated with the time to progression in patients treated with salvage therapy. The statistical analyses were performed using SAS, version 9.1.3 (SAS Institute, Cary, NC, USA), and the significance level was set at $P = 0.05$ (two-sided).

Results

Patient characteristics

Fifty-five men and 39 women with a median age at the time of diagnosis of 22 years (range 2–70 years) were enrolled in this study. The median Eastern Cooperative Oncology Group performance status was 0 (range 0–2). Forty-nine patients (52%) had primary tumors in bone and the others had primary tumors in soft tissue. The primary tumor sites are listed in Table 1. Sixty-four primary tumors (68%) were located in the trunk, and the remaining 30 tumors were located in extremities. The median largest dimension of the primary tumor was 7 cm (range 1.5–29 cm). Twenty-two patients had metastasis at the time of diagnosis. The median number of sites involved in each of the 22 patients with metastases was 2 (range 1–4).

Treatment

Of the 94 patients, 79 had received chemotherapy as their first-line treatment and the remaining 15 patients had been treated without chemotherapy (2 patients had undergone a combination of surgery and radiation therapy, 11 patients had undergone surgery, and 2 patients had undergone radiation therapy). When grouped according to their chemotherapy regimen, 4 patients received group I treatments, 62 patients received group II treatments, and 13 patients received group III treatments. Twenty-two patients received high-dose chemotherapy as their first-line chemotherapy treatment (1 patient in group I, 20 patients in group II, and 1 patient in group III). Among the patients that received chemotherapy, 9 patients received chemotherapy in an adjuvant setting (7 patients in group II, including 2 patients who received high-dose chemotherapy; and 2 patients in group III). Among the 79 patients who received chemotherapy, 23 patients also underwent a combination of surgery and radiation therapy, 26 patients underwent surgery, 17 patients underwent radiation therapy, and 13 patients did not undergo local therapy.

Response to chemotherapy

The response rate of 70 patients whose response to chemotherapy was assessable was 61% [95% confidence interval

Table 1 Sites of primary tumors in 94 patients with EFT

Tumor location	N	%
Osseous	49	
Skull	3	3.2
Trunk	13	13.8
Pelvic	14	14.9
Upper extremities	8	8.5
Lower extremities	11	11.7
Extra-osseous	45	
Head and neck	4	4.2
Trunk	8	8.5
Intra-thoracic	5	5.3
Intra-abdominal	17	18
Upper extremities	3	3.2
Lower extremities	8	8.5

(CI): 50 to 73%; 6 complete responses (CR), 37 partial responses (PR), 17 no changes (NC) or NE, and 10 progressive diseases (PD)]. Performance status, primary tumor size, and primary tumor site were significantly associated with response in univariate analysis. A multivariate logistic regression analysis indicated that the only significant predictor of response was a non-pelvic primary tumor [hazard ratio (HR), 3.01; 95% CI, 1.02–8.91; $P = 0.04$).

Outcome

Of the 79 patients, the 5-year event-free rate and overall survival rate were 41 and 54%. The median event-free survival and overall survival were 2.0 and 6.1 years, respectively (Fig. 1). Among the 57 patients without metastasis, the 5-year event-free rate and overall survival rate were 47 and 68%, respectively. And the 22 patients with metastasis, the 5-year event-free rate and overall survival rate were 30 and 37%, respectively. Age, primary tumor size, primary tumor site, and disease type were significantly associated with event-free survival in univaliate analysis. And a multivariate Cox regression analysis disclosed that metastasis at the time of diagnosis was a significant adverse prognostic factor of event-free survival ($P = 0.02$, Table 2). Age, primary tumor size, performance status, and disease type were significantly associated with OS in univariate analysis. And Cox regression analysis disclosed significant adverse prognostic factors for OS were an age ≥ 15 years, a performance status ≥ 1, and metastasis at the time of diagnosis, respectively ($P < 0.01$, Table 2).

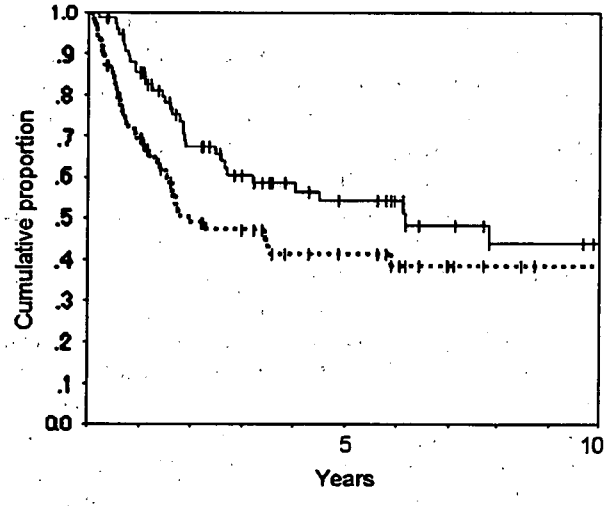

Fig. 1 Kaplan–Meier analysis of event-free survival (*dotted line*) and overall survival (*solid line*) in 79 patients who received chemotherapy. The *vertical bars* indicate censored cases

Salvage treatment

Of the 94 patients, 54 had received second line treatment for disease progression or recurrence. The median number of disease sites was 1 (range 1–3). The most common disease sites were the lung ($n = 24$), bone ($n = 15$), primary tumor site ($n = 11$), lymph node ($n = 7$), liver ($n = 5$), peritoneum ($n = 4$), soft-tissue ($n = 4$), and brain ($n = 2$). The majority of patients (85%) had received chemotherapy, and eight patients had received local therapy—including one patient who had undergone surgery. When grouped according to their chemotherapy regimen, 4 patients received group I treatments, 21 patients received group II treatments, and 21 patients received group III treatments, including 5 patients who received high-dose chemotherapy as a second line treatment (2 patients in group II, 3 patients in group III). The time to progression was 3.4 months after second line treatment. Progression during first-line treatment was significantly associated with time to progression after second line treatment (HR, 2.56; 95% CI, 1.21–.39; $P = 0.01$). The duration of the event-free survival was not significantly associated with the time to progression.

After second line treatment, 53 patients had developed progression. In these patients, 37 patients had received third line treatment including 20 patients had been treated by chemotherapy, 1 patients received group I treatments, 3 patients received group II treatments, and 16 patients received group III treatments. The other 17 patients had been treated by local therapy, 13 patients received radiation therapy, 4 patients received surgery. After third line treatment, 12 patients had been treated with chemotherapy and 7 patients had received local therapy in forth line treatment. Although 5 patients had received further treatment, all heavily treated patients had died.

Table 2 Multivariate analyses in 79 patients treated with chemotherapy

Variables	Event-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Metastasis at the time of diagnosis	2.34	1.16–4.72	0.02	2.71	1.31–5.65	<0.01
Age ≥ 15	–	–	–	4.76	1.60–14.2	<0.01
PS ≥ 1	–	–	–	2.91	1.55–5.43	<0.01

HR Hazard ratio, 95% CI, 95% confidence interval, *PS* ECOG performance status

Patients treated without chemotherapy in first-line treatment

In this study, 15 patients did not receive chemotherapy as part of their first-line treatments. The median age of these patients was 39 years (range 20–53 years). None of these patients had metastasis, and most of the patients (87%) had extra-osseous primary tumors. Two-thirds of the patients had a primary tumor size ≤80 mm. Nine patients had pelvic primary tumors, and only two patients had primary tumors in their extremities. A univariate analysis indicated that age, percentage of extra-osseous primary tumor sites, and percentage of pelvic primary tumor sites were significantly different among these 15 patients, compared with the other 79 patients. Two-thirds of these cases were admitted during the last 5 years of the study period. Regrettably, all patients had recurred, 13 patients had developed systemic recurrence and the other had local recurrence. The median time to recurrence was 9.4 months. The most common systemic disease sites was lung ($n = 6$), liver ($n = 5$), bone ($n = 4$), lymph nodes ($n = 3$), and miscellaneous ($n = 2$). In 13 patients with systemic recurrence, all patients had received group II treatment, including 5 patients had received additional local therapy (3 patients in radiation therapy and 2 patients in surgery). Despite chemotherapy in group II was performed for systemic recurrence, 12 of 13 patients had died and only 1 patient survived over 2 years after systemic recurrence. In patients with local recurrence (intra-thoracic and lower extremities in each patient), they had received group II treatment. Although patient with intra-thoracic tumor had progression again, the patient treated with group III treatment and survives over 2 years after local recurrence. The other patient survives over 1 year without recurrence. The median overall survival of these patients was 2.9 years, significantly shorter than that of the other 79 patients ($P = 0.03$, log-rank test).

Discussion

This retrospective study revealed that predictive factor of response in first-line chemotherapy and the progressive disease in first line chemotherapy was associated with outcome of second line treatment. The prognostic factors and prognosis in EFTs patients with low incidence may be similar to that of patients in previous reports. This study suggested that appropriate timing of systemic chemotherapy was important to achieve good prognosis, even if local therapy as surgery had successful in patients with localized disease of EFTs.

The incidence of EFTs in Asian countries is generally lower than that of Caucasian populations (Guo et al. 1999). Previous studies have described the background characteristics and treatment results in Japanese populations, which have a low incidence of EFTs (Obata et al. 2007; Ozaki et al. 2002; Yamada et al. 2006). Two studies of EFTs were small sample size less than 20 patients, and the largest study of EFTs of bone included 243 patients. Recent study suggested the there was no considerable differences in clinical background in patients with EFTs of bone. (Obata et al. 2007) When comparing the present study with reports from Western countries, the present study showed a higher frequency of soft-tissue primary tumors. Our hospital is a specialist orthopedic cancer referral center, and the present study describes no small sample to be reported in an Asian population. Differences among populations are difficult to judge because of selection biases. Previous studies reporting different frequencies of genetic aberrations may explain the different incidences and prognoses among populations (de Alava et al. 1998; Ozaki et al. 2002). We had insufficient material for statistical analyses of any possible relation between genetic alteration in our patients' tumors and their prognosis.

Limitations of this study were retrospective nature and the considerable heterogeneity of the treatment regimens. However, the majority of the patients had received multidrug-chemotherapy regimens consisting of VAIAdr or VAdrC/IE. Thus, the treatment outcome among the patients who received chemotherapy, adjusted for the presence of metastasis, was probably representative.

Advances in systemic chemotherapy have generally contributed to the improvement of treatment results (Sluga et al. 2001). In the present study, some of the patients were treated without chemotherapy, within the last 5 years. These patients were relatively older and had higher incidences of soft-tissue and pelvic primary tumors. Although none of these patients had metastatic disease at the time of their diagnosis, the prognosis of the patients without chemotherapy was clearly poorer. Present study demonstrates that even in patients with small primary tumors had been completely extirpated with sufficient margin, appropriate timing of systemic chemotherapy has an important role for cure. Population with low incidence leads to less experienced physicians. However, EFTs arouses from various site and adult patients with atypical primary tumors have a particularly poor prognosis. Therefore, promoting of multimodality treatment strategy and education for physicians will improve clinical outcome.

Although it is not a true prognostic factor that can be assessed at the time of diagnosis, the radiologic response to initial chemotherapy appeared to be a strong predictor of overall survival. (Sluga et al. 2001) The present study indicated that patients with non-pelvic primary tumors responded well to chemotherapy. Thus, this favorable subset of patients with EFTs may have a better prognosis. Previous report attributed the poor prognosis in pelvic primary

tumors to difficulties in local therapy, especially surgical resection (Catterill et al. 2000). This problem associated with primary site will not be solved easily. Biological and molecular characteristics may be explored among patients with pelvic primary tumors, and new molecular targeted therapy should be developed to prolong survival in this group.

The prognosis of patients with relapsed disease is poor. Many reports have investigated chemotherapy regimens that can be effective in producing temporary disease control in second line settings (El Weshi et al. 2004; Shankar et al. 2003) In addition, high-dose chemotherapy and peripheral blood stem cell transplantation have been studied as second line treatments for patients with relapsed EFTs (Burdach et al. 1993; Stewart et al. 1996). Although a subgroup of patients benefit from these treatments, both the role and indications for second line treatment remain uncertain. A previous study reported that patients with a short first remission derived little benefit from second line therapy. (Shankar et al. 2003) Although the duration of remission was not associated with the time to progression in the present study, the patients who had progressive diseases during their first-line treatments were significantly associated with a poor outcome after second line treatment. Therefore, patients with these poor prognostic factors should receive palliative therapy, rather than aggressive second line treatment.

Previous reports mostly including EFTs of bone have analyzed prognostic factors such as metastatic disease, patient age, tumor size, and pelvic primary tumor location (Bacci et al. 2000; Catterill et al. 2000; Obata et al. 2007; Rodriguez-Galindo et al. 2003; Sluga et al. 2001). Although the outcome of treatment in the present study was slightly worse than that reported in Western populations, the prognostic factors for event-free and overall survival identified in the present report were similar to those mentioned in previous reports. The current staging system (localized or metastatic) is clearly important for categorizing patients. In addition, risk-adapted strategies using prognostic factors should help to clarify the best treatment strategy in each risk group.

Much remains to be done to improve the outcome of patients with EFTs, especially in countries with low incidences. Because of the difficulty of conducting clinical trials in populations with low incidences, joining nationwide treatment study or international study group would be important to develop a common staging system and common treatment guideline in worldwide.

Acknowledgments This study was supported by grants from the Ministry of Health, Labour and Welfare and Takeda Science Foundation. The authors thank Eisuke Kobayashi, Makoto Endo, Yoshiyuki Suehara, (Orthopedic Division, National Cancer Center Hospital), Naoko Tsuji, and Hiroshi Kawamoto, (Pediatric Division, National Cancer Center Hospital), Kunihiko Seki (Clinical Laboratory Division, National Cancer Center Hospital) for their assistance in the present study.

References

de Alava E, Kawai A, Healey JH, Fligman I, Meyers PA, Huvos AG, Gerald WL, Jhanwar SC, Argani P, Antonescu CR, Pardo-Mindan FJ, Ginsberg J, Womer R, Lawlor ER, Wunder J, Andrulis I, Sorensen PH, Barr FG, Ladanyi M (1998) EWS-FL1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. J Clin Oncol 16:1248–1255

Bacci G, Ferrari S, Bertoni F, Rimondini S, Longhi A, Bacchini P, Forni C, Manfrini M, Donati D, Picci P (2000) Prognostic factors in nonmetastatic Ewing's sarcoma adjuvant chemotherapy: analysis of 359 patients at the Instituto Ostopedico Rizzoli. J Clin Oncol 18:4–11

Burdach S, Jurgens H, Peters C, Nurnberger W, Mauz-Korholz C, Korholz D, Paulussen M, Pape H, Diloo D, Kascielniak E, Gadner H, Gobel U (1993) Myeloablative radiochemotherapy and hematopoietic stem-cell rescue in poor-prognosis Ewing's sarcoma. J Clin Oncol 11:1482–1488

Burgert EO Jr, Nesbit ME, Garnsey LA, Gehan EA, Herrmann J, Vietti TJ, Cangir A, Tefft M, Evans E, Thomas P, Askin FB, Kissane JM, Prichard DJ, Neff J, Makley T, Giula L (1990) Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: Intergroup study IESS-II. J Clin Oncol 8:1514–1524

Cardenas-Cardos R, Rivera-Luna R, Lopez-Facundo NA, Leal-leal C, Gomez-Martinez R, Catellanos-Toled A (1999) Ewing's sarcoma: prognosis and survival in Mexican children from a single institution. Pediatr Hematol Oncol 16:519–523

Catterill SJ, Ahrens S, Paulussen M, Jurgens HF, Voute PA, Gadner H, Craft AW (2000) Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European intergroup cooperative Ewing's sarcoma study group. J Clin Oncol 18:3108–3114

El Weshi A, Memon M, Raja M, Bazarbashi S, Rahal M, El Foudeh M, Pai C, Allam A, El Hassan I, Ezzat A (2004) VIP (etoposide, ifosfamide, cisplatin) in adult patients with recurrent or refractory Ewing sarcoma family of tumors. Am J Clin Oncol 27:529–534

Grier H, Krailo M, Tarbell N, Link MP, Fryer CJ, Prichard DJ, Gebhardt MC, Dickman PS, Perlman EJ, Meyers PA, Donaldson SS, Moore S, Rausen AR, Vietti TJ, Miser JS (2003) Addition of ifosfamide and etoposide to standard chemotherapy for Ewing 's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 348:694–701

Guo W, Xu W, Huvos AG, Healey JH, Feng C (1999) Comparative frequency of bone sarcomas among different racial group. Chin Med J 112:1101–1104

Jenkin DR, Al-Fawaz I, Al-Shabanah M, Allam A, Ayas M, Khafaga Y, Memon M, Rifai S, Shultz H, Younge D (2002) Localised Ewing sarcoma/PNET of bone prognostic factors and international data comparison. Med Pediatr Oncol 39:586–593

Jurgens H, Exner U, Gadner H, Harms D, Michaelis J, Sauer R, Treuner J, Voute T, Winkelmann W, Winkler K, Gobel U (1988) Multidisciplinary treatment of primary Ewing's sarcoma of bone. A 6-year experience of a European Cooperative Trial. Cancer 61:23–32

Meyers PA, Wunder J, Healey J, Paulian G, Huvos A (1995) Ewing's sarcoma/primitive neurolectodermal tumor of bone: histological response to pre-operative chemotherapy predicts event free survival. Proc Meet Am Soc Clin Oncol 14:A1407

Meyers PA, Gorlick R, Heller G, Casper E, Lane J, Huvos AG, Healey JH (1998) Intensification of preoperative chemotherapy for

Lung Cancer (2007) 56, 357–362

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/lungcan

Postoperative radiotherapy for non-small-cell lung cancer: Results of the 1999–2001 patterns of care study nationwide process survey in Japan

Takashi Uno[a,*], Minako Sumi[b], Ayaka Kihara[c], Hodaka Numasaki[c], Hiroyuki Kawakami[a], Hiroshi Ikeda[b], Michihide Mitsumori[d], Teruki Teshima[c],

Japanese PCS Working Subgroup of Lung Cancer

[a] *Department of Radiology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuou-ku, Chiba City, Chiba 260-8670, Japan*
[b] *Division of Radiation Oncology, National Cancer Center, Tokyo, Japan*
[c] *Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, Suita, Osaka, Japan*
[d] *Department of Therapeutic Radiology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

Received 29 November 2006; received in revised form 4 January 2007; accepted 17 January 2007

KEYWORDS
Non-small-cell lung cancer;
Postoperative radiation therapy;
Patterns of care study;
Practice;
Survey;
PORT meta-analysis

Summary To investigate the practice process of postoperative radiation therapy for non-small-cell lung cancer (NSCLC) in Japan. Between April 2002 and March 2004, the Patterns of Care Study conducted an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data on treatment process of 627 patients with NSCLC who received radiation therapy were collected. Ninety-nine (16%) patients received postoperative radiation therapy between 1999 and 2001 (median age, 65 years). Pathological stage was stage I in 8%, II in 17%, IIIA in 44%, and IIIB in 20%. The median field size was 9 cm × 11 cm, and median total dose was 50 Gy. Photon energies of 6 MV or higher were used for 64 patients, whereas a cobalt-60 unit was used for five patients. Three-dimensional conformal treatment was used infrequently. Institutional stratification influenced several radiotherapy parameters such as photon energy and planning target volume. Smaller non-academic institutions provided worse quality of care. The study confirmed continuing variation in the practice of radiotherapy according to stratified institutions. Outdated equipment such as Cobalt-60 units was used, especially in non-academic institutions treating only a small number of patients per year.

Corresponding author. Tel.: +81 43 226 2100; fax: +81 43 226 2101.
E-mail address: unotakas@faculty.chiba-u.jp (T. Uno).

0169-5002/$ – see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2007.01.017

1. Introduction

Postoperative radiation therapy (PORT) decreases the risk of local–regional recurrence in patients with resected non-small-cell lung cancer (NSCLC) [1–3]. However, reduction in the frequency of local recurrence has not translated into a survival benefit in most studies. In 1998, the impact of PORT for NSCLC was analyzed in a meta-analysis of phase III trials [4]. After publication of the PORT meta-analysis, which emphasized deleterious effects in patients receiving PORT for completely resected N0-1 cases, much of the clinical focus on adjuvant therapy shifted to chemotherapy [5,6]. Thus, the role of PORT for patients at high risk for locoregional failure such as those with N2 disease remains unclear. Adjuvant chemotherapy trials have often permitted use of PORT as an option for patients with N2 disease [5,7]. One clinical study reported promising results for combined PORT and chemotherapy for patients with pathologic stage II or IIIA disease [8]. The results of these trials imply that PORT delivered using modern radiotherapy techniques may potentially provide a survival advantage for selected high-risk patients.

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice for cancer patients during a specific period [9,10]. In April 2002, the PCS started a nationwide survey for patients with NSCLC treated with radiation therapy in Japan. In the present report, we provide results of analyses focused on patients who received PORT for NSCLC during the study period. The objectives of this study were to reveal clinical practice patterns regarding PORT after publication of the PORT meta-analysis and to assess variation in clinical practice according to stratified institutions.

2. Materials and methods

Between April 2002 and March 2004, the PCS conducted a national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format and performed an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data collection consisted of two steps of random sampling. Prior to random sampling, all institutions were classified into one of four groups. Criteria for stratification have been described elsewhere [10]. Briefly, the PCS stratified Japanese institutions as follows: A1, academic institutions such as university hospitals or national/regional cancer center hospitals treating $\geqq 430$ patients per year; A2, academic institutions treating <430 patients; B1, non-academic institutions treating $\geqq 130$ patients per year; and B2, <130 patients. The cut-off values in number of patients treated per year between A1 and A2 institutions and B1 and B2 institutions, respectively, were increased from those used in the previous PCS study because of the increase in the number of patients treated by radiation therapy in Japan [10]. Eligible patients had 1997 International Union Against Cancer (UICC) stage I–III NSCLC that was treated with PORT between 1999 and 2001, a Karnofsky Performance Status (KPS) >50 prior to start of treatment, and no evidence of other malignancies within 5 years. The current PCS collected specific information on 627 patients (A1:157, A2:117, B1:214, B2:139) who were treated with radiation therapy between 1999 and 2001. Of those, 99 (16%) patients (A1:15, A2:17, B1:45, B2:22) who received PORT constitute the subjects of the present analysis. The practice of PORT was investigated by reviewing items in each medical chart such as demographics, symptoms, history, work-up examinations, pathology, clinical stage, treatment course including radiation therapy, surgery and chemotherapy, and radiotherapy parameters. In addition, simulation films and linacgraphy of each patient were also reviewed by surveyors.

The PCS surveyors consisted of 20 board-certified radiation oncologists. For each institution, one radiation oncologist visited and surveyed data by reviewing patient charts. In order to validate the quality of collected data, the PCS utilized an internet mailing-list among all surveyors. In situ real-time check and adjustment of data input were available between each surveyor and the PCS committee. In tables, "missing" indicates that the item in the data format was left empty, whereas "unknown" means that the item in the format was completed with data "unknown". We combined "missing" and "unknown" in tables because their meanings were the same in most cases; no valid data were obtained in the given resources. Cases with missing or unknown values were included when both the percentage and significance value were calculated. Statistical significance was tested by the χ^2 test. A p-value less than 0.05 was considered statistically significant. Overall survival was assessed from the day of surgery and was estimated by the Kaplan–Meier product limit method using the Statistical Analysis System, Version 6.12.

3. Results

3.1. Patient and tumor characteristics

Patient and clinical tumor characteristics are shown in Table 1. Of the 99 patients who received PORT, 32 were treated at academic institutions and 67 at non-academic institutions. The proportion of patients with NSCLC who received PORT was significantly higher in non-academic institutions than in academic institutions (19% versus 12%, $p=0.013$). Overall, median age was 65 years (range, 39–82), and the male to female ratio was 4:1. Ninety-three percent of patients had a KPS greater than or equal to 80%. Preoperative examinations included chest computed tomography (CT) in 97% of patients, bronchoscopy in 87%, brain CT or magnetic resonance imaging (MRI) in 75%, abdominal CT in 75%, bone scintigraphy in 83%, and mediastinoscopy in 4%. The primary tumor site was the upper lobe in 62 patients, middle lobe in 7, and lower lobe in 27. The remaining 2 patients had a primary tumor near the border of the upper and middle lobes that involved both lobes, and they were allocated to "others". Peripheral tumors were twice as common as central tumors. When tumors were analyzed by laterality, the ratio of right to left side primary site was 1.5. Clinical T- and N-classifications were T1 in 28 patients, T2 in 35, T3 in 24, T4 in 11, and N0 in 33, N1 in 19, N2 in 40, and N3 in 6, resulting in clinical stage I in 27 patients, II in 14, IIIA in 41, and IIIB in 16. The numbers less than 99 are due to missing or unknown data.

Table 1 Patient and tumor characteristics

No. of patients	99
Men	79
Women	20
Age (years)	
Median	65
Range	32–89
% KPS ≥ 80	93
Preoperative work-up (%)	
Chest CT	97
Bronchoscopy	87
Brain CT or MRI	75
Abdominal CT	75
Bone scan	83
Mediastinoscopy	4
Primary tumor site	
Upper lobe	62
Middle lobe	7
Lower lobe	27
Other	2
Missing	1
Tumor location	
Central	30
Peripheral	60
Missing	9
Laterality	
Left lung	38
Right lung	59
Missing	2
Clinical T factor	
TX	1
T1	28
T2	35
T3	24
T4	11
Clinical N factor	
NX	1
N0	33
N1	19
N2	40
N3	6
Clinical stage	
IA	14
IB	13
IIA	7
IIB	7
IIIA	41
IIIB	16
Missing	1

KPS, Karnofsky performance status score.

3.2. Surgery and tumor pathology characteristics (Table 2)

The primary surgical procedure was a lobectomy in 78 patients, pneumonectomy in 12, and segmentectomy in 9.

Table 2 Surgical procedure and tumor pathology characteristics

Type of surgery	
Lobectomy	78
Pneumonectomy	12
Segmentectomy	9
Histopathology	
Squamous cell carcinoma	47
Adenocarcinoma	43
Large cell carcinoma	7
Adenosquamous carcinoma	2
Surgical margin status	
Negative	55
Positive	31
Missing	13
Pathological T factor	
T1	22
T2	35
T3	23
T4	18
Missing	1
Pathological N factor	
N0	15
N1	19
N2	56
N3	4
Missing	5
Pathologically involved mediastinal nodes (%)[a]	
No. 1	16
No. 2	23
No. 3	26
No. 4	34
No. 5	28
No. 6	5
No. 7	34
No. 8	12
Pathological stage	
IA	4
IB	5
IIA	9
IIB	8
IIIA	45
IIIB	20
Missing/unknown	8

[a] Nearly half of the data for this item were "missing/unknown".

Among all 99 patients, complete resection was accomplished for 55 patients. Surgical margin status was positive in 31 patients. Histopathology was squamous cell carcinoma in 47 patients, adenocarcinoma in 43, large cell carcinoma in 7, and adenosquamous carcinoma in 2. Predominantly involved mediastinal nodes confirmed pathologically to contain tumor were No. 7 (34%), No. 4 (34%), No. 5 (28%), and No. 3 (26%) according to the lymph node mapping system of the Japan Lung Cancer Society [11], although nearly half of the data for this item were "missing/unknown." The pathological T-

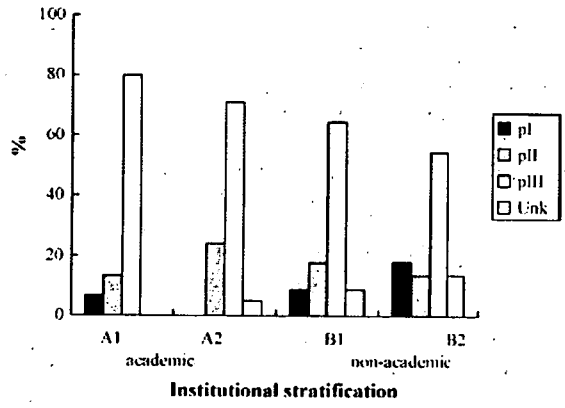

Fig. 1 Proportion of patients with pathologic stage III disease tended to be higher in large academic institutions ($p = 0.13$).

Table 3 Pathological stage in patients with complete surgery according to the stratified institution

Pathological stage	Institutional stratification				Total
	A1	A2	B1	B2	
I–II	2	4	8	4	18
III	5	6	18	8	37
Total	7	10	26	12	55

and N-classifications were pT1 in 22 patients, pT2 in 35, pT3 in 23, and pT4 in 18, and pN0 in 15 patients, pN1 in 19, pN2 in 56, and pN3 in 4. Pathological stage was stage I in 9 patients, II in 17, IIIA in 45, and IIIB in 20, respectively. The proportion of pathological stage III patients tended to be higher in large academic institutions (Fig. 1, $p = 0.13$). Breakdown of pathological stage in 55 patients who underwent complete surgery according to the stratified institution group was shown in Table 3. As for the proportion of pathological stage III patients, no significant difference was observed between institutions.

3.3. Radiotherapy parameters (Table 4)

A CT-simulator was used for planning for 26 patients. Ninety-one patients were treated with opposed AP-PA fields, and field reduction during the course of radiotherapy was done for 48%. Three-dimensional treatment was used in only 2 patients. Photon energies of less than 6 MV were used for 34 patients (34%). Dose prescription by isodose line technique was performed for only 8 patients (8%). The median field size was 9 cm × 11 cm, and the median total dose was 50 Gy. The planning target volume included the ipsilateral hilus in 80%, ipsilateral mediastinum in 86%, contralateral mediastinum in 68%, contralateral hilus in 9%, ipsilateral supraclavicular region in 30%, and contralateral supraclavicular region in 22%. Institutional stratification was found to influence several radiotherapy parameters. A photon energy of 6 MV or higher was used for 73% of patients in A1, 77% in A2, and 80% in B1 institutions, whereas it was used for only 23% of patients in B2 institutions (Fig. 2, $p < 0.0001$). A Cobalt-60 unit was used only in 5 B2 institutions. The planning target volume included the contralateral mediastinum for more than 70% of patients in A1 to B1 institutions, whereas it was included in only 46% of patients treated in B2 institutions ($p = 0.011$).

Table 4 Radiotherapy parameters

Simulation method	
CT-simulator	26
X-ray simulator	38
X-ray simulator + CT	26
Missing	7
Treatment technique	
AP-PA	91
Oblique	2
Three-field	1
Three-dimensional conformal	2
Other	2
Missing	1
Photon energy	
60 Co	5
<6 MV	29
≥6 MV	64
Missing	1
Dose prescription	
Isodose line	8
Point	91
Total dose	
≤3000 cGy	1
3001–4000 cGy	6
4001–5000 cGy	49
5001–6000 cGy	37
6001–7000 cGy	6
Missing	1
Median total dose (cGy)	5000
All fields treated each day (%)	83
Median field size (cm)	
Left-right	9 (range, 5–23)
Cranio-caudal	11 (range, 5–20)
Field reduction during radiotherapy (%)	48
Field included (%)	
Ipsilateral hilus	80
Ipsilateral mediastinum	86
Contralateral mediastinum	68
Contralateral hilus	9
Ipsilateral supraclavicula	30
Contralateral supraclavicula	22

3.4. Use of chemotherapy

Thirty patients (31%) received systemic chemotherapy. For 21 patients, chemotherapy and PORT were administered concurrently, mainly using a platinum-based, two-drug combination. For 9 of the 30 patients, platinum-based chemotherapy was used as induction therapy. Oral fluorouracil was used for 9 patients.

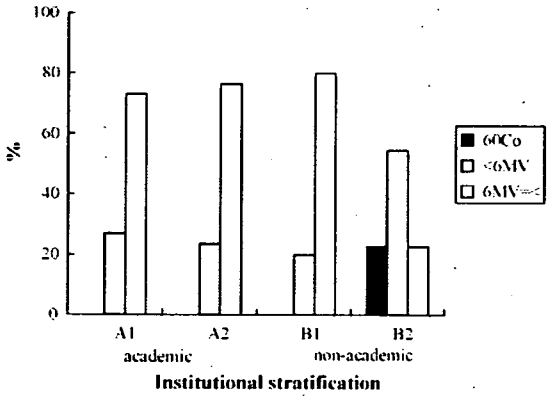

Fig. 2 A photon energy of 6 MV or higher was used for 73% of patients in A1 institutions, 77% in A2, and 80% in B1, whereas only 23% in B2 institutions ($p < 0.0001$). A Cobalt-60 unit was used only in B2 institutions.

3.5. Failure pattern and preliminary clinical outcome

The site of first failure was local in 6, regional in 5, and distant in 31. Of the patients who developed failure, the median time to first failure was 7 months. Although the current PCS has limitations in terms of outcome analysis due to a short follow-up period and significant variations in follow-up information according to institutional stratification [10,12], overall survival for the entire group was 88% at 1 year and 63% at 3 years, with a median follow-up period after PORT of 1.7 years.

4. Discussion

The results of the present PCS reflect national practices for PORT for NSCLC in Japan. However, when interpreting our data, it is important to note that they were limited to patients who received radiation therapy. We have no information about patients who did not receive radiation therapy after surgery. Thus, we have no data concerning the percentage of patients who underwent radiation therapy after surgery. Analysis of the national practice process for all patients with NSCLC in the adjuvant setting is beyond the scope of this study.

All eligible patients in this study received radiation therapy after publication of the PORT meta-analysis that emphasized deleterious effects in patients receiving PORT, especially for patients with completely resected N0-1 disease [4]. Since then, the clinical focus on adjuvant treatment has largely shifted to chemotherapy, which has become part of the postoperative standard of care for patients with NSCLC [5,6,8]. In the United States, use of PORT has substantially declined due to the lack of proven survival benefit [13]. However, PORT was still incorporated as an option in recent clinical trials that recruited patients with pathological N2 disease [5,7]. The recent analysis of Surveillance, Epidemiology, and End Results (SEER) data in the United States demonstrated that PORT was associated with improved survival for patients with N2 disease [14,15]. In addition, a recent clinical study has reported promising results for combined PORT and chemotherapy using modern radiotherapy techniques [7,8]. Thus, the current clinical question is whether adjuvant chemotherapy combined with PORT improves survival for patients at high risk for locoregional failure compared with adjuvant chemotherapy alone. Taking all of the evidence together, we conclude that PORT still plays an important role in the adjuvant setting. We believe that this PCS study provides basic data of current practice regarding PORT in Japan.

Results of the present study demonstrated that patients who received PORT accounted for 16% of all patients with NSCLC who received radiation therapy in Japan between 1999 and 2001. Of all 99 patients, 65 had pathological stage III disease (45, stage IIIA; 20, stage IIIB). Using a median field size of 9 cm × 11 cm, a median total dose of 50 Gy was delivered mainly through opposed AP-PA fields. Three-dimensional conformal treatment was infrequently used. Field size reduction during the course of radiotherapy was done for almost half of the patients. A dedicated CT-simulator was used for 26 patients. The PORT meta-analysis was criticized because the authors included several old studies in which a cobalt machine was used for radiotherapy. It was pointed out that suboptimal administration of PORT using outdated techniques counterbalanced the beneficial locoregional effects of PORT treatment in the meta-analysis [16]. Because of potential pulmonary/cardiac toxic effects of mediastinal radiotherapy, PORT should be delivered with modern radiotherapy techniques using CT-based three-dimensional conformal treatment planning, a technique with which target volumes and normal tissue constraints are precisely defined. Although the patients included in this PCS survey were treated between 1999 and 2001, the modern radiotherapy era, 34% of all patients were treated using photon energies <6 MV, including five patients who were treated using a cobalt machine. Institutional stratification influenced several radiotherapy parameters in PORT for NSCLC. As shown in the previous report for small-cell lung cancer in Japan [17], smaller non-academic institutions (B2) provided a lower quality of care for their patients. Planning target volume typically included the ipsilateral hilus, ipsilateral mediastinum, and contralateral mediastinum in A1 to B1 institutions, whereas the contralateral mediastinum was included for only 46% of patients treated in B2 institutions. Although there is controversy concerning prophylactic nodal irradiation in the setting of definitive radiation therapy, PORT for patients with pN2 NSCLC should include the contralateral mediastinum. Proportion of patients with pathological stage I–II who underwent complete surgery did not differ between stratified institution groups. Thus, it was considered that omission of treating the contralateral mediastinum in B2 institutions was not caused by unbalance in stage distribution. We speculate that this discrepancy in care was due mainly to the extremely small number of radiation oncologists in B2 institutions. We also found that obsolete equipment such as Cobalt-60 units were still used, especially in non-academic institutions treating only a small number of patients per year. The proportion of patients treated with 6 MV or higher photon energies was significantly higher in A1 to B1 institutions than in B2 institutions. A Cobalt-60 unit was used only in B2 institutions. The present study again confirms differences in the practice of radiotherapy according to institutional stratification status.

We consider that the structure of radiation oncology is a domestic problem specific to each country. The results represent intrinsic problems with the structure of radiation therapy in Japan. Considering the current immaturity of the Japanese structure of radiation oncology, PCS still perform an important role in monitoring structure and process, as well as providing essential information not only to medical staff and their patients but also to administrative policy makers.

5. Conclusions

Through the audit survey and subsequent data analyses, the PCS established nationwide basic information on the practice of PORT for NSCLC in Japan. Even after the publication of the PORT meta-analysis, PORT was used for a considerable proportion of patients receiving radiotherapy. However, this PCS documented that outdated modalities such as cobalt-60 units were still used in small non-academic institutions during the study time frame. Thus, the current PCS confirmed the continuing existence of variation in the practice of radiotherapy according to institution stratification.

Conflict of interest

We have no conflict of interest in connection with this paper.

Acknowledgments

This study was presented in part at the Second USA/Japan PCS Workshop, in Tokyo, Japan, on February 17–19, 2003 and in part at the 13th European Cancer Conference, in Paris, France, on October 30–November 3. The authors thank all radiation oncologists and staff who participated in this study for their support and cooperation. This study was supported by the following grants: Ministry of Health, Labor and Welfare (Grants-in-Aid for Cancer Research nos. 10-17 and 14-6); Japan Society for Promotion of Sciences; and the Research Fund in 1999 and 2000 from the Japan Society of Therapeutic Radiology and Oncology.

References

[1] The Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. N Engl J Med 1986;315:1377–81.

[2] Mayers R, Smolle-Juettner FM, Szolar D, Stuecklschweiger GF, Quehenberger F, Friehs G, et al. Postoperative radiotherapy in radically resected non-small-cell lung cancer. Chest 1997;112:954–9.

[3] Feng QF, Wang M, Wang LJ, Yang ZY, Zhang YG, Zhang DW, et al. A study of postoperative radiotherapy in patients with non-small cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys 2000;47:925–9.

[4] PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systemic review and meta-analysis of individual patient data from nine randomized controlled trials. Lancet 1998;352:257–63.

[5] The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351–60.

[6] Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–97.

[7] Douillard J-Y, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomized controlled trial. Lancet Oncol 2006;7:719–27.

[8] Bradley JD, Paulus R, Graham MV, Ettinger DS, Johnstone DW, Pilepich MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group—RTOG 9705. J Clin Oncol 2005;23:3480–7.

[9] Hanks GE, Cola LR, Curry J. Patterns of care studies. Past, present and future. Semin Radiat Oncol 1997;7:97–100.

[10] Teshima T. Japanese PCS Working Group. Patterns of Care Study in Japan. Jpn J Clin Oncol 2005;35:497–506.

[11] Naruke T, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. J Thorac Cardiovasc Surg 1978;76:832–9.

[12] Sugiyama H, Teshima T, Ohno Y, Inoue T, Takahashi Y, Oshima A, et al. The patterns of care study and regional cancer registry for non-small-cell lung cancer in Japan. Int J Radiat Oncol Biol Phys 2003;56:1005–12.

[13] Bekelman J, Rosenzweig KE, Bach PB, Schrag D. Trends in the use of postoperative radiotherapy for resected non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;66:492–9.

[14] Rescigno J. Use of postoperative radiotherapy for node-positive non-small-cell lung cancer. Clin Lung Cancer 2002;4:35–44.

[15] Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the Surveillance, Epidemiology, and End Results database. J Clin Oncol 2006;24:2998–3006.

[16] Bogart JA, Aronowitz JN. Localized non-small cell lung cancer: adjuvant radiotherapy in the era of effective systemic therapy. Clin Cancer Res 2005;11(Suppl. 13):5004s–10s.

[17] Uno T, Sumi M, Ikeda H, Teshima T, Yamashita M, Inoue T, et al. Radiation therapy for small-cell lung cancer: results of the 1995–1997 patterns of care process survey in Japan. Lung Cancer 2002;35:279–85.

Jpn J Clin Oncol 2007;37(3)175–180
doi:10.1093/jjco/hym008

Phase I Study of Cisplatin Analogue Nedaplatin, Paclitaxel, and Thoracic Radiotherapy for Unresectable Stage III Non-Small Cell Lung Cancer

Ikuo Sekine[1], Minako Sumi[2], Yoshinori Ito[2], Terufumi Kato[1], Yasuhito Fujisaka[1], Hiroshi Nokihara[1], Noboru Yamamoto[1], Hideo Kunitoh[1], Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Divisions of Internal Medicine and Thoracic Oncology and [2]Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Received September 6, 2006; accepted November 1, 2006; published online April 23, 2007

Background: The standard treatment of unresectable stage III non-small cell lung cancer is concurrent chemoradiotherapy in patients in good general condition, but where the optimal chemotherapeutic regimen has not been determined.
Methods: Patients with unresectable stage III non-small cell lung cancer received nedaplatin (80 mg/m^2) and paclitaxel on day 1 every 4 weeks for 3–4 cycles and concurrent thoracic radiotherapy (60 Gy/30 fractions for 6 weeks) starting on day 1. The dose of paclitaxel was escalated from 120 mg/m^2 in level 1, 135 mg/m^2 in level 2 to 150 mg/m^2 in level 3.
Results: A total of 18 patients (14 males and 4 females, with a median age of 62.5 years) were evaluated in this study. Full cycles of chemotherapy were administered in 83% of patients in level 1, and in 50% of patients in levels 2 and 3. No more than 50% of patients developed grade 4 neutropenia. Transient grade 3 esophagitis and infection were noted in one patient, and unacceptable pneumonitis was noted in three (17%) patients, two of whom died of the toxicity. Dose-limiting toxicity (DLT), evaluated in 15 patients, noted in one of the six patients in level 1, three of the six patients in level 2 and one of the three patients in level 3. One DLT at level 2 developed later as radiation pneumonitis. Thus, the maximum tolerated dose was determined to be level 1. The overall response rate (95% confidence interval) was 67% (41–87%) with 12 partial responses.
Conclusion: The doses of paclitaxel and nedaplatin could not be escalated as a result of severe pulmonary toxicity.

Key words: non-small cell lung cancer – chemoradiotherapy – paclitaxel – nedaplatin – pneumonitis

INTRODUCTION

Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA disease with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions, and/or involvement of the mediastinal or supraclavicular lymph nodes, and occult systemic micrometastases (1). Concurrent chemoradiotherapy, recently shown to be superior to the sequential approach in phase III trials, is the standard medical care for this disease (2–4). Chemotherapy regimens used concurrently with thoracic radiotherapy in these randomized trials were second-generation platinum-based chemotherapy, such as combinations of cisplatin, vindesine and mitomycin, cisplatin and vinblastine, and cisplatin and etoposide. The third-generation cytotoxic agents including vinorelbine and paclitaxel, which provided a better survival rate in patients with disseminated disease than second-generation agents, must be reduced when administered concurrently with thoracic radiotherapy (5–7). Thus, the optimal chemotherapy for concurrent chemoradiotherapy has not been established.

Nedaplatin (*cis*-diammine-glycolate-O,O′-platinum II, 254-S) is a second-generation platinum derivative that has an

For reprints and all correspondence: Ikuo Sekine, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

antitumor activity comparable to that of cisplatin but is less toxic to the kidney as shown in preclinical experiments (8). Nedaplatin produced a promising response rate for NSCLC, especially for squamous cell lung cancer (9,10). In addition, this drug can be safely administered with full-dose thoracic radiation, as shown in patients with esophageal cancer (11). Paclitaxel is another promising drug for the treatment of stage III NSCLC, as shown by the favorable response rate and survival in phase II trials in combination with platinum and thoracic radiation (6,7).

Our previous study of the nedaplatin and paclitaxel combination in patients with systemic disease showed that the recommended dose of these drugs was 80 mg/m^2 and 180 mg/m^2, respectively, repeated every 3–4 weeks. A promising response rate of 55% was achieved in patients with squamous cell lung cancer (12). The objectives of the present study were primarily to evaluate the toxicity of nedaplatin, paclitaxel and concurrent thoracic radiotherapy and determine the recommended dose of these two drugs for a phase II trial, and secondarily to observe the antitumor effect of this regimen in patients with stage III NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease indicated for curative radiotherapy; no previous treatment; measurable disease; the percentage of the normal lung volume receiving 20 Gy or more (V_{20}) (13) expected to be 30% or less; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status (14) 0 or 1; adequate bone marrow function (12.0 $\times$ 10^9/L $\geq$ white blood cell (WBC) count $\geq$ 4.0 $\times$ 10^9/L, neutrophil count $\geq$ 2.0 $\times$ 10^9/L, hemoglobin $\geq$ 10.0 g/dL and platelet count $\geq$ 100 $\times$ 10^9/L), liver function (total bilirubin $\leq$ 1.5 mg/dL and transaminase $\leq$ twice the upper limit of the normal value), and renal function (serum creatinine $\leq$ 1.5 mg/dL and creatinine clearance $\geq$ 60 mL/min); and a PaO_2 of 70 torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan, and radionuclide bone scan.

Treatment Schedule

Paclitaxel and nedaplatin were administered as previously described (12). Briefly, paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication consisting of dexamethasone, ranitidine and diphenhydramine. Nedaplatin diluted in 250 ml of normal saline was administered in a 1-h intravenous infusion. This treatment was repeated every 4 weeks for 3–4 cycles. The dose of paclitaxel was escalated as follows: 120 mg/m^2 (level 1), 135 mg/m^2 (level 2), and 150 mg/m^2 (level 2). The dose of nedaplatin was 80 mg/m^2 through the levels 1–3.

Thoracic radiation therapy was given with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV. The total dose of 60 Gy was delivered at a single dose of 2 Gy once daily Monday through Friday for 6 weeks without interruption beginning on day 1 of the chemotherapy. Three-dimensional conformal radiotherapy technique was used in all patients. The gross target volume (GTV) included the primary lesion (GTV1) and involved lymph nodes whose short diameter was 1 cm or larger (GTV2) based on conventional chest X-ray and CT scans. The clinical target volume (CTV) consisted of CTV1 and CTV2, identical to GTV1 and GTV2, respectively, and CTV3, the ipsilateral hilum and bilateral mediastinum area. The contralateral hilum was excluded from the CTV. The supraclavicular fossa was also excluded unless it was involved. The planning target volume (PTV) for the initial dose up to 40 Gy consisted of CTV1-3 with the superior and inferior field margins extended to 1–2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The PTV for the boost 20 Gy included only CTV1-2 based on the second CT scans with the same margins. The spinal cord dose was limited to 44 Gy by using oblique parallel opposed fields.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations and a chest X-ray were performed once a week during the course of treatment. Toxicity was graded according to the NCI Common Toxicity Criteria version 2.0. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<$3.0 $\times$ 10^9/L, neutrophil count $<$1.5 $\times$ 10^9/L, platelet count $<$100 $\times$ 10^9/L, serum creatinine level $\geq$1.6 mg/dL, infection $\geq$ grade 2, elevated hepatic transaminase level or total serum bilirubin $\geq$ grade 2, pneumonitis $\geq$ grade 2, peripheral neuropathy, musculoskeletal pain $\geq$ grade 3, fever $\geq$ 38°C, or performance status $\geq$ 2. Chemotherapy was terminated if the toxicities did not

recover within 2 weeks. The doses of nedaplatin and paclitaxel were reduced by 25% in all subsequent cycles if any of the dose-limiting toxicities (DLTs) defined below were noted. The dose of nedaplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: fever $\geq$ 38C, infection $\geq$ grade 2, esophagitis of grade 3, performance status $\geq$ 3, or radiation pneumonitis was suspected. Thoracic radiotherapy was terminated if radiation pneumonitis that required corticosteroid administration was noted, or radiotherapy was not completed within 60 days. Both chemotherapy and thoracic radiotherapy were terminated if any of the following was noted: disease progression, any of the grade 4 non-hematological toxicities except abnormal electrolytes, performance status of 4, patient refusal to receive subsequent treatment, protocol violation, or patient death of any cause. Granulocyte colony-stimulating factor and antibiotics were administered if febrile neutropenia was noted.

DLT, Maximum Tolerated Dose (MTD), and Recommended Dose For Phase II Trials

The DLT was defined as a grade 4 leukopenia, grade 4 neutropenia lasting 7 days or longer, febrile neutropenia, platelet count $<20 \times 10^9$/L, grade 3 or a more severe non-hematological toxicity other than nausea, vomiting and transient electrolyte abnormality, and treatment termination before two cycles of chemotherapy and thoracic radiotherapy were completed. Dose levels were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If none to two of the six patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15).

Study Design, Data Management and Statistical Analyses

This study was designed as a phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 2 years and a follow-up period of 3 years were planned. Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method (16). Overall survival time was measured from the date of registration to the date of death from any cause or last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression or death from any cause or last follow-up. Patients who were lost to follow-up without event were censored at the date of their most known follow-up. A confidence interval for the response rate was calculated using methods for exact binomial confidence intervals. Response rates among patients with squamous cell carcinoma and those with non-squamous carcinoma were assessed with the χ^2 test. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of The Patients

From October 2003 to July 2004, six patients were registered at dose level 1, eight patients at dose level 2 and five patients at dose level 3. Two patients at dose level 2 were excluded from the DLT evaluation, because they discontinued receiving the treatment early because of disease progression and anaphylactic shock, respectively. Initially, DLT was noted in only two of the six patients at dose level 2, and therefore, patient registration at dose level 3 was started. However, severe radiation pneumonitis developed 5 weeks after the end of radiotherapy in another patient at dose level 2 and this pneumonitis was counted as DLT. Thus, because DLT was finally noted in three of the six patients at dose level 2, patient registration at dose level 3 was stopped. One patient at dose level 3 was found to be ineligible because the radiation treatment planning showed that the V_{20} exceeded 30%. The patient did not receive the current treatment and was excluded from the analysis. Thus, a total of 18 patients were subjects of this study and their detailed demographic characteristics are listed in Table 1.

Treatment Delivery

The planned three to four cycles of chemotherapy were administered in 83% of patients in level 1 and in 50% of patients in levels 2 and 3. Radiation delivery was generally well maintained and it did not differ among the three dose levels (Table 2).

Toxicity, DLT and MTD

Hematological toxicity was generally mild. No more than 50% of patients developed grade 4 neutropenia, and no one developed grade 2 or higher thrombocytopenia (Table 3). Non-hematological toxicity other than lung toxicity was also well tolerated. One patient developed transient grade 3 esophagitis and grade 3 infection not associated with neutropenia, which were considered DLTs. Another patient developed grade 4 anaphylactic shock 1 min after the second cycle infusion of paclitaxel, but soon recovered with fluid

Table 1. Patient characteristics

	n	(%)
Number of patients	18	
Gender		
male	14	(78)
female	4	(22)
Age		
median (range), years	62.5	(46–69)
PS		
0	11	(61)
1	7	(39)
Body weight loss		
< 5%	15	(83)
5–9%	2	(11)
≥ 10%	1	(6)
Clinical stage		
IIIA	10	(56)
IIIB	8	(44)
Histology		
adenocarcinoma	8	(44)
squamous cell carcinoma	6	(33)
non-small cell, not specified	4	(22)

PS, performance status.

replacement and oxygen therapy. This patient was excluded from DLT evaluation. One patient in level 1 and another patient in level 2 developed grade 4 pneumonitis after completion of two cycles of chemotherapy and thoracic radiotherapy and they died of the pneumonitis. The V_{20} and mean lung dose (MLD) of these patients were 23% and 30%, and 1341 cGy and 1675 cGy, respectively.

Table 2. Treatment delivery

Dose level	Level 1	Level 2	Level 3
	(*n* = 6)	(*n* = 8)	(*n* = 4)
Number of chemotherapy cycles			
3–4	5	4	2
2	1	3	1
1	0	1	1
Total radiation dose (Gy)			
60	6	7	3
50–59	0	1	0
NE	0	0	1
Radiotherapy delay (days)			
0–4	5	7	2
5–9	1	0	1
NE	0	1	1

NE, not evaluable.

Table 3. Toxicity in all patients

Dose level	Level 1 (*n* = 6)			Level 2 (*n* = 8)			Level 3 (*n* = 4)		
Toxicity grade	2	3	4	2	3	4	2	3	4
Leukopenia	2	3	0	3	3	0	1	2	1
Neutropenia	0	4	1	2	3	1	0	2	2
Anemia	0	0	0	2	0	0	2	0	0
GPT elevation	1	0	0	2	0	0	0	0	0
Total bilirubin elevation	1	0	0	1	0	0	1	0	0
Infection	0	0	0	1	1	0	0	0	0
Allergic reaction	1	0	0	2	0	1	0	0	0
Anorexia	1	0	0	2	0	0	0	0	0
Nausea	0	0	0	1	0	0	0	0	0
Constipation	0	0	0	2	0	0	0	0	0
Esophagitis	1	0	0	2	1	0	0	0	0
Pneumonitis	0	0	1*	1	0	1*	0	0	0
Musculoskeletal pain	1	0	0	1	0	0	1	0	0
Alopecia	4	0	0	4	0	0	0	0	0

GPT, glutamic pyruvic transaminase.
*Pneumonitis was fatal in these patients.

Both patients were former heavy smokers with a smoking index of 520 and 1680, respectively. The chest CT scan of the former patient disclosed mild emphysematous, but no interstitial changes. A spirometry analysis showed a vital capacity (VC) of 3480 ml (104% of predicted), and a forced expiratory volume one second percent (FEV1.0%) of 82%. The lung diffusing capacity measurement using carbon monoxide (DL_{CO}) was not done in this patient. The PaO_2 was 93.3 torr. The serum LDH level before treatment was 241 IU/l (the upper limit of the normal value was 229 IU/l). The chest CT scan of the latter patient disclosed slight changes in the dorsal portion of the both lungs, which were considered the gravitation effect, or fibrotic changes. The VC was 3810 ml (107% of predicted), % DL_{CO} was 111%, and PaO_2 was 99.7 torr. The serum LDH level before treatment was 147 IU/l. Another patient in level 2, whose V_{20} and MLD were 15% and 822 cGy, respectively, developed grade 2 pneumonitis when he received 52 Gy of radiotherapy and the subsequent protocol treatment was stopped. The chest CT scan of this patient before treatment showed no abnormal findings except for lung cancer. Pulmonary function test values were all within normal limits. The serum LDH level before treatment was 178 IU/l. Thus, in total three (17%) of 18 patients developed unacceptable severe pneumonitis induced by the current treatment, which was counted as DLT.

To sum up, DLT was noted in one of six patients in level 1, three of six patients in level 2, and one of three patients in level 3. The DLTs were pneumonitis in three patients, grade 4 leukopenia in one patient, and grade 3 esophagitis and grade 3 infection in one patient. Thus, the MTD was determined to be level 1.

Objective Response and Survival

All patients were included in the analyses of tumor response and survival. No CR, 12 PRs, and 3 SD were noted among the 18 patients and the overall response rate (95% confidence interval) was 67% (41–87%). The response rate in patients having squamous cell carcinoma was 100%, while that for non-squamous histology was 58%. The median progression-free survival time was 9.7 months. The median overall survival time has not yet been reached and the 1-year survival rate was 78%.

DISCUSSION

The feasible doses of anticancer agents in this study were paclitaxel 120 mg/m^2 and nedaplatin 80 mg/m^2 every 4 weeks. These figures are lower than those in a randomized phase II trial for stage III NSCLC conducted in the USA, where paclitaxel 135 mg/m^2 and cisplatin 80 mg/m^2 were administered every 3 weeks concurrently with thoracic radiotherapy (6). The occurrence of severe pneumonitis hampered the dose escalation of the anticancer agents in this study. A Japanese phase I/II study of weekly paclitaxel, nedaplatin and concurrent thoracic radiotherapy for stage III NSCLC showed that the DLT was also pneumonitis and that the response rate was 75% and progression-free survival was 5.6 months, similar to the outcome of this study (17). The reasons for the frequent pneumonitis in this study remain unknown. Paclitaxel was the most frequently used anticancer agent together with thoracic radiotherapy in patients with NSCLC outside Japan. A randomized phase II study of induction chemotherapy followed by concurrent chemoradiation therapy in patients with stage III NSCLC (CALGB study 9431) showed that grade 3–4 pneumonitis during chemoradiation was noted in 14% of patients treated with gemcitabine and cisplatin, 20% of patients treated with paclitaxel and cisplatin, and 20% of patients treated with vinorelbine and cisplatin. One patient died of pneumonitis in the vinorelbine and cisplatin arm (6). Thus, incidence of pneumonitis in patients receiving paclitaxel was reported to be the same as that for other agents in this setting. Nedaplatin was a new agent but one of the platinum that has been repeatedly shown to be safely administered with radiation (1). A case series of 24 esophageal cancer patients treated with radiation therapy (60–70 Gy) combined with Nedaplatin (80–120 mg) and 5-fluorouracil (500–1000 mg for 5 days) showed that toxicity was mainly hematological and no grade 3 or higher non-hematological toxicity was observed (18). Treatment-related pneumonitis may be more readily developed among Japanese patients, because gefitinib-induced pneumonitis is more common in Japan than in other countries (19–21). Similarly, a relatively high incidence of drug-induced pneumonitis was noted among Japanese patients in association with the use of weekly docetaxel (20) and leflunomide, a newly developed disease-modifying antirheumatic drug that exhibits anti-inflammatory, antiproliferative and immunosuppressive effects (22). Further studies are needed to define ethnic or geographic variation of treatment-related pneumonitis.

Recent dose–volume histogram studies showed that the volume–dose parameters such as the V20 and MLD were significantly associated with development of severe radiation pneumonitis (23). The V_{20} and MLD in the three patients who developed unacceptable pneumonitis in this study (15–30% and 822–1675 cGy, respectively) were not so large, and therefore, the severe pneumonitis in these patients could not be fully explained by their irradiation volume alone. Patient characteristics such as age, sex, smoking habit, location of the primary tumor and pre-existing lung diseases may be associated with the development of radiation pneumonitis, but their contribution was inconclusive (24).

Radiation pneumonitis is the most common dose-limiting complication of thoracic radiation. Its incidence varies greatly from one report to another: the incidence of grade 2 radiation pneumonitis was between 2% and 33% and that of grade 3 was between 0% and 20% (25). This inconsistency among reports can be explained by the different radiation pneumonitis scoring system and follow-up duration in each study. No scoring system for radiation pneumonitis is perfect. The distinction between grade 2 and grade 3 toxicity is highly subjective. In addition, these scoring systems do not account for intercurrent symptoms from tumor, infection and chronic lung illnesses such as chronic obstructive pulmonary diseases (25).

For future trials, it is an important strategy to reduce the lung volume receiving radiation without an increase in the local recurrence rate. Elective nodal regions with potential subclinical micrometastases (CTV3 in this study) have been included in the standard irradiation volume. The advent of three-dimensional conformal treatment techniques, however, has allowed for a more precise definition of target volume and may allow the possibility of reduced toxicity and increased radiation dose delivery by the omission of elective nodal irradiation (26). We are conducting a phase I study of high-dose thoracic three-dimensional conformal radiotherapy without elective nodal irradiation concurrently combined with cisplatin and vinorelbine in patients with inoperable stage III non-small cell lung cancer.

In conclusion, the doses of paclitaxel and nedaplatin combined with thoracic radiotherapy could not be escalated owing to severe pulmonary toxicity. We do not recommend a phase II study of this chemoradiotherapy regimen.

Acknowledgements

We thank Yuko Yabe and Mika Nagai for preparation of the manuscript. This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest statement

None declared.

References

1. Vokes EE, Crawford J, Bogart J, Socinski MA, Clamon G, Green MR. Concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer. *Clin Cancer Res* 2005;11:5045s–50s.
2. Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H, Vergnenegre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2005;23:5910–7.
3. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, 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* 1999;17:2692–9.
4. Curran W, Scott CJ, Langer C, Komaki R, Lee J, Hauser S, 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* 2003;22:p621 (abstr 2499).
5. Sekine I, Noda K, Oshita F, Yamada K, Tanaka M, Yamashita K, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–5.
6. Vokes EE, Herndon JE, 2nd, Crawford J, Leopold KA, Perry MC, Miller AA, 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* 2002;20:4191–8.
7. Choy H, Akerley W, Safran H, Graziano S, Chung C, Williams T, et al. Multiinstitutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small-cell lung cancer. *J Clin Oncol* 1998;16:3316–22.
8. Kameyama Y, Okazaki N, Nakagawa M, Koshida H, Nakamura M, Gemba M. Nephrotoxicity of a new platinum compound, 254-S, evaluated with rat kidney cortical slices. *Toxicol Lett* 1990;52:15–24.
9. Furuse K, Fukuoka M, Kurita Y, Ariyoshi Y, Niitani H, Yoneda S, et al. A phase II clinical study of cis-diammine glycolato platinum, 254-S, for primary lung cancer. *Gan To Kagaku Ryoho* 1992;19:879–84.
10. Yamamoto N, Tamura T, Kurata T, Yamamoto N, Sekine I, Kunitoh H, et al. Phase I and pharmacokinetic (PK) study of (Glycolate-O, O')-diammine platinum (II) (Nedaplatin: 254-S) in elderly patients with non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2000;19:203a (abstr 792).
11. Nemoto K, Matsushita H, Ogawa Y, Takeda K, Takahashi C, Britton KR, et al. Radiation therapy combined with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. *Am J Clin Oncol* 2003;26:46–9.
12. Sekine I, Nokihara H, Horiike A, Yamamoto N, Kunitoh H, Ohe Y, et al. Phase I study of cisplatin analogue nedaplatin (254-S) and paclitaxel in patients with unresectable squamous cell carcinoma. *Br J Cancer* 2004;90:1125–8.
13. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, et al. Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45:323–9.
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
16. Armitage P, Berry G, Matthews J. Survival analysis. In: Armitage P, Berry G, Matthews J editors. Statistical Methods in Medical Research, 4th edn. Oxford: Blackwell Science 2002; 568–90.
17. Hasegawa Y, Takanashi S, Okudera K, Aoki M, Basaki K, Kondo H, et al. Weekly paclitaxel and nedaplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a phase I/II study. *Jpn J Clin Oncol* 2004;34:647–53.
18. Nemoto K, Matsushita H, Ogawa Y, Takeda K, Takahashi C, Britton KR, et al. Radiation therapy combined with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. *Am J Clin Oncol* 2003;26:46–9.
19. Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD, Jr, Morse D, et al. United States Food and Drug Administration drug approval summary: Gefitinib (ZD1839; Iressa) tablets. *Clin Cancer Res* 2004;10:1212–8.
20. Edelman MJ, Sekine I, Tamura T, Saijo N. Geographic variation in the second-line treatment of non-small cell lung cancer. *Semin Oncol* 2006;33(1 Suppl 1):39–44.
21. Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–56.
22. Sekine I, Takada M, Nokihara H, Yamamoto S, Tamura T. Knowledge of efficacy of treatments in lung cancer is not enough, their clinical effectiveness should also be known. *J Thorac Oncol* 2006;1:398–402.
23. Rodrigues G, Lock M, D'Souza D, Yu E, Van Dyk J. Prediction of radiation pneumonitis by dose – volume histogram parameters in lung cancer – a systematic review. *Radiother Oncol* 2004;71:127–38.
24. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys* 2005;63:5–24.
25. Machtay M. Pulmonary complications of anticancer treatment. In Abeloff MD, Armitage JO, Niederhuber JE, Kastran MB, McKenna WG editors. *Clinical Oncology*, 3rd edn. Philadelphia, PA: Elsevier Churchill Livingstone 2004; 1237–50.
26. Grills IS, Yan D, Martinez AA, Vicini FA, Wong JW, Kestin LL. Potential for reduced toxicity and dose escalation in the treatment of inoperable non-small-cell lung cancer: a comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. *Int J Radiat Oncol Biol Phys* 2003; 57:875–90.

Jpn J Clin Oncol 2007;37(3)181–185
doi:10.1093/jjco/hym005

Concurrent Chemoradiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients Aged 75 Years or Older

Toshio Shimizu[1,3], Ikuo Sekine[1], Minako Sumi[2], Yoshinori Ito[2], Kazuhiko Yamada[1], Hiroshi Nokihara[1], Noboru Yamamoto[1], Hideo Kunitoh[1], Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Divisions of Internal Medicine and Thoracic Oncology and [2]Radiation Oncology, National Cancer Center Hospital, Tokyo and [3]Department of Medical Oncology, Kinki University Nara Hospital, Ikoma, Nara, Japan

Received July 19, 2006; accepted November 8, 2006; published online April 10, 2007

Background: The optimal treatment for limited-disease small cell lung cancer (LD-SCLC) in patients aged 75 years or older remains unknown.
Methods: Elderly patients with LD-SCLC who were treated with chemoradiotherapy were retrospectively reviewed to evaluate their demographic characteristics and the treatment delivery, drug toxicities and antitumor efficacy.
Results: Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older. All of the seven patients were in good general condition, with a performance status of 0 or 1. Five and two patients were treated with early and late concurrent chemoradiotherapy, respectively. While the four cycles of chemotherapy could be completed in only four patients, the full dose of radiotherapy was completed in all of the patients. Grade 4 neutropenia and thrombocytopenia were noted in seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. Grade 3 or more severe esophagitis, pneumonitis and neutropenic fever developed in one, two and three patients, respectively, and one patient died of radiation pneumonitis. Complete response was achieved in six patients and partial response in one patient. The median survival time was 24.7 months, with three disease-free survivors for more than 5 years.
Conclusion: Concurrent chemoradiotherapy promises to provide long-term benefit with acceptable toxicity for selected patients of LD-SCLC aged 75 years or older.

Key words: elderly – small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 20% of all pulmonary neoplasms and 25–40% of patients with this disease are 70 years of age or older. The number of elderly patients with such disease are expected to increase with the growing geriatric population (1).

Because SCLC is highly sensitive to chemotherapy and radiotherapy, the standard treatment for limited-disease SCLC (LD-SCLC) has been a combination of platinum and etoposide with concurrently administered thoracic radiotherapy, as long as the patients are in good general condition (2, 3). Such elderly patients, however, may show decreased clearance of the anticancer agents commonly used for the treatment of SCLC, including cisplatin and etoposide, because of the decrease of the lean body mass, hepatic blood flow and renal function that are associated with aging. In addition, myelotoxicity is sometimes more severe in this population than in younger populations, because the absolute area of hematopoietic marrow decreases with age (4). Retrospective subset analyses of patients with LD-SCLC treated with concurrent chemotherapy and radiotherapy in phase III trials have shown that the percentage of patients in whom the planned number of chemotherapy cycles can be completed is usually 10% lower in patients

For reprints and all correspondence: Ikuo Sekine, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo, 104-0045, Japan. E-mail: isekine@ncc.go.jp

70 years of age or older as compared with that in younger patients (5). One study reported that myelotoxicity was more severe in elderly patients than in younger patients (5), while another reported no such difference between the patients of the two age groups (6). The delivery of thoracic radiotherapy was not influenced by age in these patients (7). However, 78–85% of patients in these analyses were aged between 70 and 75 years old and a few were over 80 years old. Thus, the most suitable treatment options for elderly patients with LD-SCLC aged 75 years or older still remain unknown.

The objective of this retrospective analysis was to evaluate the patient characteristics and the treatment delivery, toxicity and antitumor efficacy of the administered treatments in LD-SCLC patients 75 years of age or older who were treated with chemotherapy and thoracic radiotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical charts, chest X-rays and computed tomography (CT) scans of LD-SCLC patients aged 75 years or older. To evaluate the thoracic irradiation field, the standard initial field was defined as follows: the field including the primary tumor and involved nodes with a short axis length of 1 cm or more on CT scans with a 1.0–1.5 cm margin, and the subclinical ipsilateral hilum and bilateral mediastinal lymph node regions with a 1.0 cm margin. The supraclavicular lymph node regions were included only if there was tumor involvement of these nodes. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, Japanese edition (8). The objective tumor response was evaluated according to the WHO criteria issued in 1979 (9). The overall survival time was measured from day 1 of chemotherapy to the date of death as a result of any cause or the date of the last follow-up.

RESULTS

Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older (Table 1). During this period, we had three other patients with LD-SCLC who were aged 75 years or older. They were treated with chemotherapy alone because of complications in two patients and refusal of intensive therapy in one patient. There were five males and two females, and four patients were between 75 and 79 years of age and three patients were 80 years old or older. Three patients presented with persistent cough, while the remaining four patients complained of no symptoms and were diagnosed based on the detection of an abnormal shadow on a plain chest X-ray obtained during a mass screening or routine health examination program. All the patients were in good general condition. One patient had a history of inferior wall myocardial infarction suffered 9 years prior to this admission. However, echocardiography at this admission revealed normal heart function with an ejection fraction of 73%. One patient had stage I pulmonary emphysema with % FEV_1 predicted of 58%, but no abnormal findings on blood gas analysis. The % FEV_1 predicted in other four patients was within 98% and 116%, and was not measured in the other two patients. A median (range) PaO_2 level at the room air before treatment in the seven patients was 77.4 (66.9–87.2) Torr. A decreased creatinine clearance, 48.8 ml/min at a urine volume of 600 ml/day, was noted in one patient, while the other patients had a creatinine clearance of 78 ml/min or higher. Four and three patients had a performance status of 0 and 1, respectively, and five patients gave no history of loss of body weight. The diagnosis of small cell carcinoma was confirmed cytologically or histologically in all the patients.

The chemotherapy regimens used were cisplatin at 80 mg/m^2 on day 1 combined with etoposide at 100 mg/m^2 on days 1–3 in four patients aged between 75 and 19 years. For patients aged 80 years of older, carboplatin was dosed to a

Table 1. Patient characteristics

n	Age (yr)/ gender	Smoking history	Symptom	Weight loss (%)	Complications	Performance status	TNM stage
1	81/male	6/day × 62 yr	None	0	Type 2 DM	0	T1N2M0
2	81/female	20/day × 62 yr	None	0	OMI (inferior wall), thoracic aortic aneurysm	0	T1N1M0
3	80/female	20/day × 50 yr	Cough	11	Hypertension	1	T4N3M0
4	78/male	20/day × 46 yr	None	0	None	0	T2N2M0
5	77/male	30/day × 50 yr	Cough	7	COPD, Hypertension	1	T4N3M0
6	75/male	10/day × 55 yr	None	0	None	0	T1N2M0
7	75/male	10/day × 55 yr	Cough, Hoarseness	0	None	1	T4N2M0

COPD, Chronic obstructive pulmonary disease; OMI, old myocardial infarction; DM, diabetes mellitus.

target AUC of 5 by Calvert's formula on day 1 combined with etoposide at 80 mg/m^2 on days 1–3 in two patients and cisplatin at 25 mg/m^2 on days 1–3 combined with etoposide at 80 mg/m^2 on days 1–3 in one patient (Table 2). These regimens have been reported to be used in a JCOG phase III trial for elderly patients with extensive SCLC (10). Four cycles of chemotherapy could be completed in four patients, whereas only three cycles could be completed in two patients and only one cycle could be completed in one patient. The reason for discontinuation of the chemotherapy in these patients was prolonged myelosuppression in two patients and patient refusal for continuation of treatment in one patient. The chemotherapy dose was reduced in the subsequent cycles in four patients. The reasons for the dose reduction were grade 4 thrombocytopenia in two patients, grade 4 leukopenia in one patient and both grade 4 thrombocytopenia and leukopenia in one patient. Thoracic radiotherapy was started concurrently with the chemotherapy in five patients (early concurrent chemoradiotherapy). Treatment began with chemotherapy alone in the remaining two patients, because of a mild cytology-negative pleural effusion in one patient and too large an irradiation volume in the other patient. Two cycles of chemotherapy reduced the tumor volume successfully in both the patients and thoracic radiotherapy was then added concurrently with the third and fourth cycles of chemotherapy (late concurrent chemoradiotherapy). Thoracic radiotherapy was delivered using photon beams from a liniac or microtron accelerator with energy between 6 and 20 MV at a single dose of 2 Gy once daily up to a total dose of 50 Gy in four patients aged between 78 years or older and at a single dose of 1.5 Gy twice daily up to a total dose of 45 Gy in three patients aged between 75 and 77 years. This selection of conventional or hyperfractionated radiotherapy was determined arbitrarily. The initial irradiation field was judged as the standard in six patients and reduced in one patient. A multi-leaf collimator and conventional lead blocks were used for shaping of the irradiation field. The median irradiation area was 169 cm^2 (range, 95–278 cm^2). The projected total radiation dose was administered in all the patients, but a treatment delay of 5 days or longer was observed in three patients. The criteria of radiotherapy suspension were white blood cell count $< 1.0 \times 10^9$/L, platelet count $< 20 \times 10^9$/L, esophagitis $\geq$ grade 3, fever $\geq 38^\circ$C and performance status ≥ 3. The reason for the delay in the three patients was esophagitis, decreased platelet count and poor performance status.

The hematological toxicities observed in the patients are summarized in Table 3. Grade 4 leukopenia, neutropenia and thrombocytopenia were noted in four, seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. The non-hematological toxicities included grade 3 or more severe esophagitis, pneumonitis and neutropenic fever in one, two and three patients, respectively. One patient died of radiation pneumonitis that developed 4 months after the end of radiotherapy (Case No. 6).

Of the seven patients, complete response was achieved in six patients and partial response in one patient (Table 3). However, prophylactic cranial irradiation was given in only one patient (Case No. 6). Three patients remained alive for

Table 2. Treatment and its delivery

n	Chemotherapy				Thoracic radiotherapy			
	Regimen (mg/m^2 if not specified)	Number of cycles	Dose reduction	Duration of one cycle (days)*	Timing	Total dose (Gy)/fractions	Field size	Delay (days)
1	C (AUC = 5) d1 + E (80) ds1–3	3	Yes	30	Early Co	50/25	S	4
2	P (25) ds1–3 + E (80) ds1–3	1	NA	NA	Early Co	50/25	S	7
3	C (AUC = 5) d1 + E (80) ds1–3	4	Yes	23	Late Co	50/25	S	14
4	P (80) d1 + E (100) ds1–3	4	Yes	26	Late Co	50/25	R	1
5	P (80) d1 + E (100) ds1–3	4	No	28	Early Co	45/30	S	3
6	P (80) d1 + E (100) ds1–3	4	No	27	Early Co	45/30	S	0
7	P (80) d1 + E (100) ds1–3	3	Yes	35	Early Co	45/30	S	7

*Calculated as follows: Duration of one cycle (days) = (Day 1 of the 1st cycle – Day 1 of the last cycle)/(Number of cycles – 1).
C, carboplatin; E, etoposide; NA, not applicable; P, cisplatin; Co, concurrent; S, standard; R, reduced.

Table 3. Toxicity, tumor response and survival

n	Hematological toxicity (grade by CTC-AE v3.0)				Blood transfusion	G-CSF support	Non-hematological toxicity ≥ grade 2 (grade by CTC-AE v3.0)	Tumor response	Survival time (mo)/outcome
	WBC	Neu	Hb	Plt					
1	3	4	1	4	Platelet	None	None	CR	80.3/Alive
2	3	4	1	2	None	Used	Pneumoniti (3), esophagitis (2), anorexia (2)	CR	21.3/Dead
3	4	4	3	4	RBC	Used	Neutropenic fever (3), esophagitis (3)	CR	65.6/Alive
4	4	4	2	1	None	Used	None	CR	97.4/Alive
5	3	4	2	3	None	Used	Neutropenic fever (3), esophagitis (2), anorexia (2)	CR	13.1/Dead
6	4	4	2	1	None	None	Pneumoniti (5), neutropenic fever (3)	CR	6.4/Dead
7	4	4	4	4	RBC	Used	None	PR	24.7/Dead

WBC, white blood cell count; Neu, neutrophil count; Hb, hemoglobin; Plt, platelet count; G-CSF, granulocyte- colony stimulating factor; CTC-AE, Common Terminology Criteria for Adverse Events; CR, complete response; RBC, red blood cell; PR, partial response.

more than 5 years without recurrence. The median survival of the seven patients was 24.7 months.

DISCUSSION

The antitumor effects of the treatment regimens were reasonably good, with six complete responses and one partial response and three long-term disease-free survivors in spite of discontinuation/dose reduction of chemotherapy. This is perhaps mainly attributable to the strict selection of patients in good general condition. Thus, we believe that the standard chemoradiotherapy can be applied to LD-SCLC patients aged 75 years or older as long as they are in good general condition.

The general condition of elderly patients, however, varies widely from patient to patient. Thus, in many elderly patients 75 years of age or older, it may be better to reduce the treatment intensity, although it may be difficult to establish the standard schedule applicable to all elderly patients. There are four possible ways to modify the intensity of therapy: (1) administer chemotherapy alone; (2) change the relative timing of chemotherapy and radiotherapy; (3) decrease the drug doses and number of cycles of chemotherapy, and (4) decrease the dose and intensity of thoracic radiotherapy.

Chemotherapy alone versus chemotherapy and thoracic radiotherapy for LD-SCLC were compared in many randomized trials between the 1970s and 1980s. A meta-analysis of these trials demonstrated survival benefit of radiotherapy added to chemotherapy in younger populations of patients less than 65 years of age, but the benefit is still unclear in older patients (11). Although the findings of this meta-analysis indicated that the standard treatment in elderly patients with LD-SCLC might be chemotherapy alone, the result based on the old trials using cyclophosphamide and doxorubicin-based chemotherapy cannot be applied in the current medical setting, because chemotherapy regimens, irradiation delivery equipment and staging procedures have all evolved greatly over time.

The relative timing of chemotherapy and radiotherapy greatly influences the severity of toxicity. In late concurrent chemoradiotherapy that follows induction chemotherapy, the chemotherapy dose can be adjusted to suit each patient by evaluating the toxicity of the previous chemotherapy. In addition, the irradiation volume can be reduced by modifying the radiation treatment planning in accordance with the extent of tumor shrinkage during the induction phase. In the two patients treated by this approach in this study, the dose of the platinum drug during the concurrent chemoradiotherapy phase was reduced to 66–75% of the initial dose and that of etoposide was reduced to 50–75% of the initial dose. Sequential chemoradiotherapy consists of induction chemotherapy and subsequent radiotherapy. Because the two treatment modalities are administered separately, the treatment dose in each can be optimized for the elderly in this approach. A phase III study of concurrent versus sequential chemoradiotherapy in LD-SCLC patients younger than 75 years old revealed a 5-year survival rate of 24% in the concurrent arm and a 5-year survival rate of 18% with a lower incidence of toxicity in the sequential arm (2). The sequential schedule has not yet been evaluated in LD-SCLC patients 75 years of age or older.

A recent phase III trial showed that etoposide at 80 mg/m^2 on days 1–3 combined with either carboplatin at AUC = 5 by Carvert's formula or cisplatin at 25 mg/m^2 on days 1–3 was feasible and effective in elderly patients with extensive-disease SCLC (10). These regimens may, therefore, be applied for the treatment of LD-SCLC as well. The standard number of chemotherapy cycles administered is four. In many elderly patients, however, all four cycles cannot be completed. In two phase II studies of two cycles