of 0–2. Additional eligibility criteria were as follows: they had not undergone surgery for LS-SCLC nor had been treated with a radiation field, not including elective nodal irradiation, because the significance of omitting elective nodal irradiation remains unclear (6). Written informed consent was obtained from all patients before treatment. Each patient underwent the following studies: chest radiography and fiberoptic bronchoscopy, complete blood count and biochemical tests, a computed tomography (CT) scan of the thorax and abdomen, a CT scan or magnetic resonance imaging of the brain, and a radionuclide bone scan, or positron emission tomography. Positron emission tomography was used for a few patients (7%) who were treated after 2001 according to the physician's preference. Bone marrow aspiration or biopsy was performed in cases of neutropenia and thrombocytopenia.

Radiation therapy technique

TRT was carried out with linear accelerators, and the energy of 6–10 MV photons was used. The TRT fields were changed from anteroposterior-posteroanterior fields to parallel opposed oblique fields after 30 Gy in the twice-daily regimen and 36–40 Gy in the once-daily regimen. Most patients (83%) that were eligible for this study were treated using conventional fluoroscopic simulation techniques at the start of the TRT, and CT simulation techniques were used only for the planning of the boost fields. The other 17% were treated using CT simulation techniques throughout the entire TRT. The other planning techniques were similar to those in our previous report on non–small-cell lung cancer (7). TRT was administered twice daily (1.5 Gy per fraction, with a 6 h or more interval between fractions) for a total dose of 45 Gy in 3 weeks or once-daily (1.8–2.0 Gy per fraction) for a total dose of 39.6–66 Gy in 4–7 weeks. After the TRT, prophylactic cranial irradiation (PCI) was administered to the patients who had a complete or near-complete response (10). The PCI consisted of 24 Gy in 2 Gy per fractions or 25 Gy in 2.5 Gy per fractions once daily, 5 days per week.

All patients who entered the clinical trial were treated with the AHF regimen. However, there were no adequate rationale for a decision about a patient's TRT dose and fractionation. The TRT dose and fractionation was decided according to the physician's preference.

Chemotherapy

In principle, the patients were treated with four cycles of chemotherapy and received at least one cycle of chemotherapy concurrent with TRT. The chemotherapy was given in a 28-day cycle in the concurrent phase and a 21-day cycle in the sequential phase. The most commonly used regimens were cisplatin/etoposide, carboplatinum/etoposide, and cisplatin/irinotecan. As a general rule, the cisplatin/etoposide regimen consisted of cisplatin (80 mg/m^2 intravenously) on day 1 and etoposide (100 mg/m^2 intravenously) on Days 1, 2, and 3. The carboplatinum/etoposide regimen consisted of carboplatinum (area under the blood concentration-time curve: 5 intravenously) on Day 1 and etoposide (100 mg/m^2 intravenously) on Days 1, 2, and 3. The cisplatin/irinotecan regimen was only performed sequentially with TRT and consisted of cisplatin (80 mg/m^2 intravenously) on Day 1 and irinotecan (60 mg/m^2 intravenously) on Days 1, 8, and 15.

Study design and statistical analysis

All available radiation records and charts were reviewed to assess patient and tumor characteristics and the details of treatment and outcome. Tumor response was classified in accordance with the Response Evaluation Criteria in Solid Tumors criteria (9). Complications were graded in accordance with the National Cancer Institute's Common Toxicity Criteria, version 3.0 (10). The date of the last follow-up was defined as the last recorded information available for the patient. Only 3 patients were lost to follow-up. Survival was measured from the start date of any treatment to the date of the last follow-up or death from any cause. Local failure, defined as locoregional progression on CT (including the primary tumor and the bilateral mediastinal and ipsilateral hilar lymph nodes), was measured from the start date of any treatment to the date of the first evidence of locoregional disease progression. Concurrent local and distant failures were scored as local failures for the first failure sites. Progression-free survival was measured from the start date of any treatment until the date of local or distant failure.

Overall survival (OS), overall local, and overall progression-free survival were calculated using Kaplan-Meier estimates. Subgroup analysis was used to compare the outcomes among the three groups, in which the total radiation doses were 45 Gy with AHF, <54 Gy with SF, and ≥54 Gy with SF, using the log–rank test. Moreover, sex, age at diagnosis, performance status, disease stage (I, II, vs. III), PCI (yes vs. no), total chemotherapy cycles (<3 vs. ≥3), concurrent chemotherapy (yes vs. no), and the duration of TRT (<40 days vs. ≥40 days) were also assessed for their impact on OS using the log–rank test. Fisher's exact test was used for comparisons of categorical data. Cox's proportional hazards model was used for multivariate analysis. $p < 0.05$ was considered significant.

RESULTS

Patient and treatment characteristics

A total of 127 patients were enrolled into the study. The median total dose of TRT with the once-daily regimen was 54 Gy; therefore, we divided the patients that had been treated with the once-daily regimen into two groups using the median total dose of 54 Gy for the subgroup analysis. The characteristics of the 127 eligible patients are shown in Table 1. Fifteen patients (40%) from the AHF group entered a clinical trial, but no patients from the other two groups did. The baseline characteristics were balanced in terms of sex, performance status, stage, and chemotherapy cycles. However, there was a slight imbalance in age; the patients in the AHF group tended to be younger than those in the other two groups, and the rate of patients older than age 75 years was lower than in the other two groups, but these differences were not significant ($p = 0.15$). There were significant differences in the rate of patients that received concurrent chemotherapy and PCI among the three groups ($p = 0.012$, $p < 0.001$, respectively). Fifty-five (43%) patients were alive at the time of this analysis, and the median follow-up time of the surviving patients was 33 months (range, 2–118 months). The median follow-up time of the surviving patients was 34 months (range, 16–96 months) for the AHF group, 67 months (range, 12–91 months) for the SF <54 Gy group, and 22 months (range, 2–118 months) for the SF ≥54 Gy group. There were no significant differences in the median follow-up time of the surviving patients among the three groups ($p = 0.32$).

As a result, 84% received four or more cycles of chemotherapy. Eight percent received three cycles, and 8% received less than two cycles either because the patient refused continuation

Table 1. Patient and tumor pretreatment characteristics

Characteristic	Prescription group: AHF group (n = 37)	SF <54 Gy group (n = 29)	SF ≥54 Gy group (n = 61)	p value*
Age (y)	58 (40–68)	70 (51–82)	66 (29–81)	
≥75 (%)	0 (0%)	3 (10%)	5 (8%)	0.15
Sex (%)				0.59
Male	30 (81%)	25 (86%)	54 (82%)	
Female	7 (19%)	4 (14%)	7 (18%)	
Performance status				0.29
0	13 (35%)	7 (25%)	20 (33%)	
1	24 (65%)	20 (68%)	36 (59%)	
2	0 (0%)	2 (7%)	5 (8%)	
Stage				0.20
I	0 (0%)	1 (3%)	6 (10%)	
II	4 (11%)	0 (0%)	4 (7%)	
IIIA	22 (59%)	11 (38%)	24 (39%)	
IIIB	11 (30%)	17 (59%)	27 (44%)	
CHT cycles	3.9 (2–5)	3.7 (1–6)	3.9 (1–6)	0.72
≥3 cycles	33 (89%)	27 (93%)	56 (92%)	
Concurrent CHT	37 (100%)	23 (79%)	56 (92%)	0.012*
Total dose (Gy)	45 (45)	50 (39.6–52.2)	56 (54–63)	<0.001*
Duration of TRT (days)	21 (19–27)	41 (30–56)	43 (36–59)	<0.001*
PCI	24 (65%)	6 (21%)	18 (30%)	< 0.001*

Abbreviations: AHF = accelerated hyperfractionation; SF = standard fractionation; CHT = chemotherapy; TRT = thoracic radiotherapy; PCI = prophylactic cranial irradiation.

Age and total dose data are presented as the median value. CHT cycles data are presented as the mean value. The numbers in square brackets indicate the range of age and CHT cycles.

* Fisher's exact test.

of the chemotherapy or their leukocyte or platelet counts or renal function did not return to levels at which chemotherapy could be performed. Most patients (91%) received at least one cycle of concurrent chemotherapy with TRT, whereas the remaining 9% only received sequential chemotherapy because the radiation field sizes of these patients were too large as the primary tumor was located in the inferior lobe or the primary tumor was so bulky that concurrent chemoradiotherapy was considered to carry a high risk of severe radiation pneumonitis (11). All patients received at least one cycle of platinum-based agents/etoposide regimen regardless of the TRT regimen. The cisplatin/irinotecan regimen was only performed sequentially with TRT for 24% of patients in the AHF group and 16% of the SF ≥54 Gy group.

Tumor response

Table 2 shows the tumor response in each group. The overall response rate was 94% (95% confidence interval [CI] 91–98%, 58% complete response rate [CI 50–67%], and 36% partial response rate [CI 28–45%]) for all eligible patients. There was a significantly lower rate of complete response in the SF <54 Gy group than in the AHF and SF ≥54 Gy groups (p = 0.018 and 0.0062, respectively). There was a significantly higher rate of complete response in the AHF group than in the SF ≥54 Gy group (p = 0.042).

Table 2. Tumor response in each group

Response	Prescription group: AHF (n = 37) No.	%	SF <54 Gy (n = 29) No.	%	SF ≥54 Gy (n = 61) No.	%	p value*
Overall response	34	92%	27	93%	59	97%	0.32
CR	27	73%	11	38%	36	59%	0.02*
PR	7	19%	16	55%	23	38%	
SD	0	0%	1	3%	2	3%	
PD	3	8%	1	3%	0	0%	

Abbreviations: AHF = accelerated hyperfractionation; SF = standard fractionation; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

* Fisher's exact test.

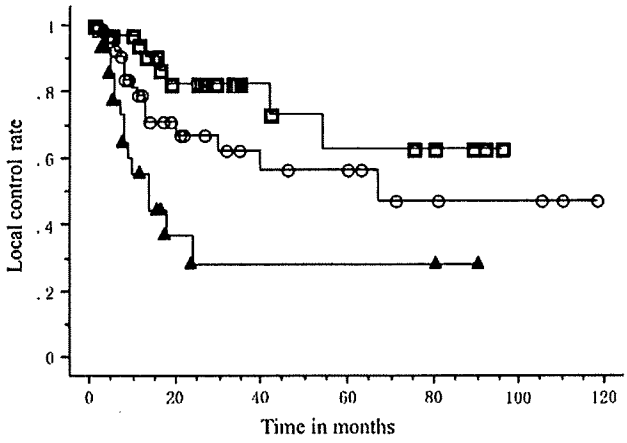

Fig. 1. The local control rates for patients with a total dose of 45 Gy with accelerated hyperfractionation (□), <54 Gy with standard fractionation (▲), and ≥54 Gy with standard fractionation (○).

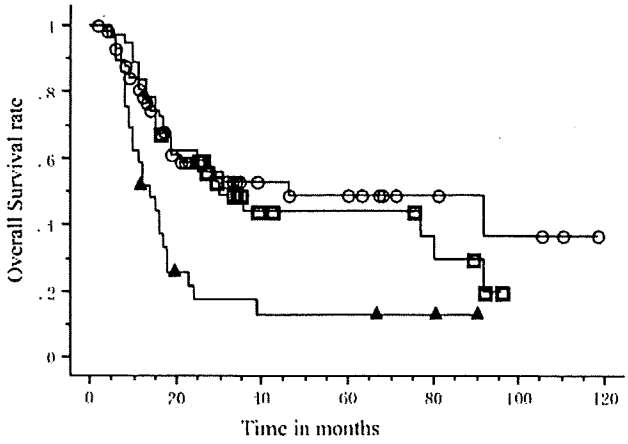

Fig. 2. Overall survival for patients with a total dose of 45 Gy with accelerated hyperfractionation (□), <54 Gy with standard fractionation (▲), and ≥54 Gy with standard fractionation (○).

Local control and progression-free survival

Figure 1 shows the local control rates for each group. The 3-year local control rates were 61.1% (CI 50.3–71.9%) for all eligible patients, 81.3% (CI 67.2–95.5%) for the AHF group, 27.7% (CI 5.0–50.4%) for the SF <54 Gy group, and 61.2% (CI 44.8–77.6%) for the SF ≥54 Gy group. The local control rate was also significantly lower for the SF <54 Gy group than the AHF and SF ≥54 Gy groups (p = 0.0016 and 0.011, respectively). Local control for the AHF group tended to be superior to that for the SF ≥54 Gy group, although no statistically significant difference was found (p = 0.096).

The 3-year progression-free survival rates were 28.1% (CI 19.5–36.7%) for all eligible patients, 37.5% (CI 21.5–53.5%) for the AHF group, 7.5% (CI 0–17.5%) for the SF <54 Gy group, and 33.2% (CI 19.7–46.7%) for the SF ≥54 Gy group. Progression-free survival was also significantly lower for the SF <54 Gy group than for the AHF and SF ≥54 Gy groups (p = 0.015 and 0.013, respectively). Progression-free survival was similar in the AHF group and the SF ≥54 Gy group (p = 0.80).

Overall survival

Figure 2 shows the survival curves for each group. The median survival time of all eligible patients was 24.0 months (CI 18.1–29.9 months). The median survival times were 30.0 months (CI 16.3–43.7 months) for the AHF group, 14.0 months (CI 6.6–21.4 months) for the SF <54 Gy group, and 41.0 months (CI 33.9–48.1 months) for the SF ≥54 Gy group. The 3-year survival rates were 41.2% (CI 31.6–50.8%) for all eligible patients, 44.1% (CI 26.5–61.7%) for the AHF group, 13.8% (CI 0–27.3%) for the SF <54 Gy group and 53.1% (CI 38.6–67.6%) for the SF ≥54 Gy group. There was a significantly lower rate of OS in the SF <54 Gy group than in the AHF and SF ≥54 Gy groups (p = 0.0018 and 0.00036, respectively). OS for the SF ≥54 Gy group seemed to be slightly superior to that for the AHF group, although no statistically significant difference was found (p = 0.64).

Factors associated with overall survival

Table 3 shows the effects of patient characteristics, disease factors, and treatment parameters on OS according to univariate analysis. To evaluate further the independent effects of disease stage, chemotherapy cycles, concurrent chemotherapy, PCI,

Table 3. Factors associated with overall survival according to univariate analysis

Factors	No. of patients	3-year OS (95% CI)	p value
Sex			0.367
Male	109	40.8% (33.1–48.5)	
Female	18	41.8% (36.1–47.5)	
Age (y)			0.652
<75	119	40.6% (33.2–48.0)	
≥75	8	48.6% (43.6–53.6)	
PS			0.546
0, 1	120	42.0% (34.6–49.4)	
2	7	28.6% (23.6–33.6)	
Stage			0.016*
I, II	15	80.0% (78.3–81.7)	
III	112	35.7% (28.3–43.1)	
CHT cycle			0.033*
<3	11	43.4% (35.8–51.0)	
≥3	116	20.0% (14.2–25.8)	
Concurrent CHT			0.026*
Yes	116	43.7% (36.1–51.3)	
No	11	20.0% (17.3–22.7)	
Treatment group			<0.001*
AHF	37	44.1% (26.5–61.7)	
SF ≥54 Gy	29	53.1% (38.6–67.6)	
SF <54 Gy	61	13.8% (0–27.3)	
Duration of RT (days)			0.821
<40	66	41.3% (31.0–51.6)	
≥40	61	40.0% (29.8–50.2)	
PCI			0.089
Yes	48	48.1% (36.6–59.6)	
No	79	35.6% (31.6–39.6)	

Abbreviations: CI = confidence interval; PS = performance status; CHT = chemotherapy; NA = not applicable; AHF = accelerated hyperfractionation; SF = standard fractionation; RT = radiation therapy; PCI = prophylactic cranial irradiation.

* Statistically significant.

Table 4. Factors associated with overall survival according to multivariate analysis

Factors	Hazard ratio of death (95% CI)	*p* value
Stage (I, II vs. III)	0.24 (0.074–0.78)	0.017*
CHT cycle (<3 vs. ≥3)	0.50 (0.24–1.07)	0.073
Concurrent CHT (yes vs. no)	0.61 (0.29–1.31)	0.20
Treatment group (AHF vs. SF ≥54 Gy SF 54 Gy)	NA	0.033*
PCI (yes vs. no)	0.75 (0.43–1.31)	0.31

Abbreviations: CHT = chemotherapy; NA = not applicable; AHF = accelerated hyperfractionation; SF = standard fractionation.
* Statistically significant.

and treatment group on OS, a multivariate Cox proportional hazards regression analysis was performed. This analysis included those factors that had displayed a p value <0.10 in the univariate analysis. As a consequence, disease stage and treatment group remained significant factors in the multivariate analysis (Table 4).

Toxicity

Documentation concerning toxicity data was not available for 6 patients (2 in each group), which left 121 patients assessable for toxicity. Only late toxicity ≥Grade 2 was assessed from the available information of each chart. There were only 2 treatment-related deaths (one in the SF <54 Gy group and the other in the SF ≥54 Gy group). Both patients died of radiation pneumonitis. Five patients developed Grade 2 radiation pneumonitis, 4 in the SF <54 Gy group and 1 in the SF ≥54 Gy group. Apart from the toxicities described, no other information about late toxicity was noted in the charts.

DISCUSSION

In our study, the comparison of overall, progression-free, and local control survival rates and the rate of complete response suggested that TRT administered with a total dose of <54 Gy by once-daily regimen was more disadvantageous than TRT treated with a total dose of ≥54 Gy in a once-daily regimen or a total dose of 45 Gy administered using the AHF regimen, and the difference was statistically significant for all outcomes. These results clearly demonstrate that radiation intensification improves the complete response rate and local control and that improved local control translates into improved OS. Furthermore, these results also suggest the importance of a high dose of radiation when using a once-daily regimen.

Because SCLC has high radiation sensitivity (12), recent pattern of care studies have shown that the traditional modest doses of TRT that are used in once-daily 1.8- to 2-Gy fractions are also widely used for LS-SCLC in Japan and Turkey (4, 5). However, although response rates are high, local control rates have been poor in this TRT setting. Intensifying the radiotherapy effect by accelerating its delivery was one of the initial strategies explored in prospective trials. Turrisi *et al.* (2) randomly assigned 471 LS-SCLC patients to either 45 Gy in 5 weeks (1.8 Gy once-daily for 25 fractions) or 45 Gy in 3 weeks (1.5 Gy twice-daily for 30 fractions) beginning with the first of four cycles of PE. The 5-year survival rate was 26% with accelerated TRT compared with 16% for the conventional TRT ($p = 0.04$), and the accelerated TRT arm was also superior to conventional TRT in local tumor control ($p = 0.06$). These data strongly suggest that attempts designed at improving local tumor control can favorably impact on the long-term outcome of patients with LS-SCLC. However, despite the significant improvement in long-term survival, only 10% of patients with LS-SCLC received a twice-daily regimen (3). Moreover, a second trial performed by the North Central Cancer Treatment Group reported negative results with a twice-daily regimen, although overall treatment times and total radiation doses were identical in each arm of the North Central Cancer Treatment Group trial (13). Therefore, different strategies were considered that might increase the local control rate with chemoradiotherapy. Accelerated fractionation via the concomitant boost technique uses once-daily irradiation early in the course of treatment and then twice-daily irradiation toward the end. Komaki *et al.* (14) reported a Phase I study (Radiation Therapy Oncology Group 97-12) using this regimen to improve local control by increasing the dose of TRT given with concurrent cisplatin/etoposide without causing acute severe esophagitis. They found that 61.2 Gy was the maximum tolerated dose, and there was a suggestion of improvement in the estimated short-term survival rate (18 months) by dose escalation from 50.4 Gy to 61.2 Gy (25% and 82%, respectively). Roof *et al.* (15) also showed a clear dose–response curve between 54 and 63 Gy with a once-daily regimen, although they did not find a significant difference in outcome because of their small sample size of 54 patients.

Obviously, there are problems that limit the interpretation of a single institutional retrospective review. We recognize the imbalance among our three groups. The rates of patients receiving PCI and concurrent chemotherapy were significantly different among the three groups (Table 1), although the multivariate analysis proved that these factors were not associated with OS. Another difficulty associated with retrospective reviews is the accurate assessment of toxicity. The rate of Grade 2-4 toxicities in our study was lower than those reported elsewhere. Although the patient charts were thoroughly scrutinized, the documentation concerning complications may not have been as thorough as it would have been in a prospective trial.

Whether twice-daily TRT to 45 Gy in 3 weeks is superior to a higher total dose than traditional modest doses delivered with a once-daily regimen is still unclear. Our results did not find a significant difference in outcome between the AHF group with a total dose of 45 Gy and the SF group with a total dose of ≥54 Gy. However, there was a significantly higher

rate of complete response in the AHF group compared with the SF ≥54 Gy group ($p = 0.042$), and the local control for the AHF group tended to be superior to that for the SF ≥54 Gy group. These results indicate that in the once-daily regimen much more than 54 Gy is necessary to achieve local control at the same level as 45 Gy with the AHF regimen. Despite the significantly higher rate of complete response and local control in the AHF group compared with the SF ≥ 54 Gy group, progression-free survival and OS were similar between the AHF group and the SF ≥54 Gy group ($p = 0.80$ and 0.64, respectively). We think that the reason was our small sample size. On the other hand, these data indicated that patients in the AHF group died from systemic disease as did those in the SF ≥54 Gy group, despite the better local control in the AHF group compared with the SF ≥54 Gy group. Therefore, another chemotherapy strategy such as integrating newer chemotherapy agents (16) or dose-intense regimens using either growth factors or stem-cell support (17) may be necessary for the platform of the curative approach to LS-SCLC.

Further intensification of TRT regimens such as a Phase III trial is under development by the Cancer and Leukemia Group B and the Radiation Therapy Oncology Group (18). This randomized trial is designed to compare three TRT approaches with four cycles of PE, with the three regimens being 45 Gy in 3 weeks (1.5 Gy twice-daily for 30 fractions), 70 Gy in 7 weeks (2.0 Gy once-daily for 35 fractions), and 61.2 Gy in 5 weeks (1.8 Gy accelerated fractionation via concomitant boost). We think that this trial will demonstrate the optimal method of radiation dose intensification. However, at this time, 45 Gy twice-daily TRT should be considered as the standard treatment for LS-SCLC because there are no Phase III once-daily trials that have shown better outcomes than the twice-daily regimen.

In conclusion, this analysis suggests that disease stage and treatment groups that are stratified according to 45 Gy with AHF, <54 Gy with SF, and ≥54 Gy with SF are independent factors associated with improved OS in patients with LS-SCLC and the potential importance of a high dose of radiation when using a once-daily regimen. However, there are problems that limit the interpretation of our single institutional retrospective review. There were some prognostic differences in the three groups compared, especially in the rates of patients receiving PCI and concurrent chemotherapy. A future prospective study of TRT regimens in the setting of chemoradiotherapy for LS-SCLC is needed to establish optimal radiation doses and fractionation, and such a study is under development by the Cancer and Leukemia Group B and Radiation Therapy Oncology Group.

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ORIGINAL PAPER

Clinical outcomes of advanced non-small cell lung cancer patients screened for epidermal growth factor receptor gene mutations

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Abstract
Purpose To evaluate the relationship between the epidermal growth factor receptor (EGFR) mutation status and the effectiveness of gefitinib monotherapy or chemotherapy in patients with advanced non-small cell lung cancer (NSCLC).
Methods We retrospectively analyzed a cohort of 100 patients with stage IIIB/IV NSCLC screened for two major EGFR mutations (exon 19 deletions and L858R mutation).
Results Forty-six out of 48 EGFR mutation-positive patients (96%) received gefitinib, whereas only 3 out of 52 EGFR mutation-negative patients (6%) received gefitinib. Favorable objective response rates to gefitinib as first- and second-line treatment (87 and 80%, respectively) were observed in EGFR mutation-positive patients. Overall response rate to chemotherapy as first-line treatment did not differ significantly between patients with EGFR mutations and those without mutation (32 vs. 28%, respectively; $P = 0.7198$). As to first-line treatment, EGFR mutation-positive patients treated with gefitinib experienced significantly longer progression-free survival (PFS) than did patients who received chemotherapy (median survival, 7.8 months vs. 5.1 months, respectively; $P = 0.0323$). Similarly, as to second-line treatment, EGFR mutation-positive patients treated with gefitinib had significantly longer PFS than did patients who received chemotherapy (median survival, 6.5 months vs. 4.0 months, respectively; $P = 0.0048$). Patients with EGFR mutations survived longer than those without EGFR mutations after first-line treatment (median, 24.3 vs. 12.6 months, respectively; $P = 0.0029$).
Conclusion EGFR mutation-positive patients benefit from either first- or second-line gefitinib monotherapy. Further large-scale prospective studies to confirm this finding are needed.

Keywords Epidermal growth factor receptor · Mutation screening · Gefitinib · Non-small cell lung cancer · Cytotoxic chemotherapy · Clinical outcomes

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Introduction

Gefitinib, an orally bioavailable, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), was the first targeted drug for non-small cell lung cancer (NSCLC). Phase II trials of gefitinib monotherapy in unselected NSCLC patients showed antitumor activity, but demonstrated objective response rates of only 8–18% (Fukuoka et al. 2003; Kris et al. 2003). However, subset analyses of these trials and a retrospective study showed that favorable response to gefitinib was observed in certain

patient subgroups, such as females, patients with adenocarcinoma, Asian patients, and nonsmokers (Fukuoka et al. 2003; Kris et al. 2003; Miller et al. 2004). These results suggest that identifying predictive molecular or genetic biomarkers for gefitinib sensitivity may help to select patients who are most likely to benefit from treatment.

In 2004, three independent groups of investigators reported that somatic EGFR mutations correlate with sensitivity of NSCLC to the EGFR TKIs, gefitinib or erlotinib (Lynch et al. 2004; Paez et al. 2004; Pao et al. 2004). Subsequently, multiple groups of researchers confirmed and extended this striking correlation between EGFR mutations and gefitinib sensitivity, reporting response rates ranging from approximately 60 to 94% in retrospective analyses (Cortes-Funes et al. 2005; Han et al. 2005; Huang et al. 2004; Kim et al. 2005; Mitsudomi et al. 2005; Takano et al. 2005; Taron et al. 2005; Tokumo et al. 2005). Recently, several prospective phase II studies also confirmed the correlation (Asahina et al. 2006; Inoue et al. 2006; Sequist et al. 2008; Sugio et al. 2009; Sunaga et al. 2007; Sutani et al. 2006; Tamura et al. 2008; Yang et al. 2008; Yoshida et al. 2007), and a combined analysis from seven phase II trials in Japan (I-CAMP; Iressa Combined Analysis of Mutation Positives) demonstrated a total response rate of 76.4% (Morita et al. 2009).

To date, many types of mutations in NSCLC patients have been reported, but only four types of TKI-sensitive mutations, including exon 18 and 21 point mutation (G719A/C, L858R and L861Q) and exon 19 in-frame deletion, have been elucidated (Greulich et al. 2005). Of these mutations, the two most common, representing approximately 90% of all EGFR mutations, are the exon 19 deletions and L858R point mutation (Uramoto and Mitsudomi 2007). In a previous study on prospective validation for prediction of gefitinib sensitivity by these two common hot spots for EGFR mutations, we reported a promising overall response rate of 90.5% (Yoshida et al. 2007). Therefore, in order to select patients who might benefit from gefitinib treatment, we continued to screen patients for the two hot spot mutations.

To clarify the relationship between EGFR mutation status and the effectiveness of gefitinib monotherapy or cytotoxic chemotherapy in patients with NSCLC, we performed a retrospective analysis of clinical outcomes of consecutive patients who were screened for two major EGFR mutations.

Patients and methods

Patients

A cohort of 100 patients with inoperable stage IIIB/IV NSCLC were screened for EGFR mutations prior to selection for gefitinib treatment or cytotoxic chemotherapy at Aichi Cancer Center Hospital in Nagoya, Japan, between November 2004 and December 2006. Eligibility criteria were adults (defined as $\geq$20 years of age) with cytological or histological confirmation of locally advanced (stage IIIB for which thoracic irradiation was not indicated) or metastatic (stage IV) NSCLC who underwent prospective screening of EGFR mutations; $\geq$1 measurable or assessable lesion, according to the Response Evaluation Criteria in Solid Tumors (Therasse et al. 2000); and written informed consent, in accordance with institutional regulations. Eligible patients were admitted to the study regardless of prior chemotherapy, performance status (PS), or functions of main organs. Exclusion criteria were pulmonary fibrosis, interstitial pneumonia, or prior treatment with an EGFR TKI or antibody. This study was approved by the institutional review board of Aichi Cancer Center Hospital.

EGFR mutation analysis

Mutational analysis of the exon 19 deletion and the L858R mutation in the EGFR gene was performed as described previously (Yatabe et al. 2006). Briefly genomic DNA was extracted from tumors embedded in paraffin blocks or from aspirated tumors obtained from pleural effusions, superficial lymph nodes, or subcutaneous metastases. One reference pathologist (Y.Y.) reviewed all specimens and marked grossly near the tumor-rich lesion on an unstained slide in order to enrich the tumor cell population as much as possible. The exon 19 deletion mutation was determined by common fragment analysis using polymerase chain reaction (PCR) with an FAM-labeled primer set; the PCR products were subjected to electrophoresis on an ABI PRISM 310 instrument (Applied Biosystems, Foster City, CA, USA). The shorter segment of DNA amplified by PCR showed a deletion mutation in a new peak in the electropherogram. The L858R mutation was detected by the Cycleave real-time quantitative PCR technique, using the Cycleave PCR core kit (Takara Co. Ltd., Ohtsu, Japan) with an L858R-specific cycling probe and a probe specific for the wild-type gene. Fluorescence intensity was measured with a Smart Cycler system (SC-100, Cepheid, Sunnyvale, CA, USA).

Statistical analysis

Data were analysed using the chi-square test; $P < 0.05$ was regarded as statistically significant. Confidence intervals (CIs) were calculated using binomial values. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method; survival differences were analysed by log-rank test. All analyses were performed with Stat View version 5 software (SAS institute Inc, Cary, NC, USA) on a Macintosh computer.

Results

Patients characteristics

From November 2004 through December 2006, 100 consecutive patients with NSCLC at Aichi Cancer Center hospital were examined to detect EGFR mutations. Patient characteristics are shown in Table 1. All patients were Japanese. EGFR mutations were detected in 48% (48/100) of the patients. Of the patients with EGFR mutations, 23 had the exon 19 deletions, and 25 had the L858R mutation. EGFR mutations were detected more frequently in women and patients who never smoked, whereas fewer EGFR mutations were detected in stage IIIB patients.

Figure 1 depicts the treatment of EGFR mutation-positive patients. Of the 48 EGFR mutation-positive patients, 96% (46/48) received gefitinib monotherapy; 47.9% (23/48), 31.3% (15/48), and 25% (12/48) of the EGFR mutation-positive patients received gefitinib as first-, second- and third-line treatment, respectively. Of the 12 patients with EGFR mutation who were treated with gefitinib as third-line treatment, two patients received gefitinib monotherapy as first-line, two patients received gefitinib monotherapy as second-line, and eight patients received cytotoxic chemotherapy as both first- and second-line.

Only 6% (3/52) of the 52 patients without EGFR mutations received gefitinib monotherapy as first- (two patients) or second-line (one patient) treatment, whereas 96.2% (50/52) of the patients without EGFR mutations received cytotoxic chemotherapy as first-line treatment.

In this study, all patients received first-line treatment, 65% (65/100) of the patients received second-line treatment and median follow-up time for the survivors was 20.2 months (ranging from 9.5 months to 74.6 months).

Table 1 Patient characteristics according to EGFR mutation status

	EGFR mutation status		*P*
	Mutation	Wild-type	
All cases	48	52	
Sex			<0.0001
Male	15	38	
Female	33	14	
Age, years			0.4942
≤60	18	23	
>60	30	29	
Histology			0.1985
Adenocarcinoma	47	48	
Non-adenocarcinoma	1	4	
Smoking status			<0.0001
Never smoker	32	11	
Smoker	16	41	
Stage at initial diagnosis			0.0341
IIIB	7	17	
IV	41	35	
ECOG PS at initial diagnosis			0.169
0/1	42	40	*P* (0/1 vs. ≥2)
2	2	7	
3	3	3	
4	1	2	
Timing of mutation screening			0.4803
Pre-treatment	31	30	
After first-line treatment	11	16	
After second-line treatment	6	5	
After third-line treatment	0	1	
Mutation genotype			
Exon 19 deletion	23	–	
L858R	25	–	

EGFR epidermal growth factor receptor, *PS* performance status

EGFR mutations and response to gefitinib

Objective response rate (complete response rate + partial response rate) to first-line gefitinib therapy was 87% in patients with EGFR mutations. Disease control rate (complete response rate + partial response rate + stable disease rate) in response to first-line gefitinib therapy was 87% in patients with EGFR mutations. Objective response rate for second-line gefitinib therapy was 80% in patients with EGFR mutations. Disease control rate in response to second-line gefitinib therapy was 86.7% in patients with EGFR mutations (Table 2). No objective responses were observed in patients with wild-type EGFR treated with first- or second-line gefitinib.

No statistically significant differences in rates of objective response and disease control between first- and second-line gefitinib treatments were observed. Furthermore, response rate to gefitinib monotherapy in patients with exon 19 deletions, compared with that in patients with the L858R mutation, did not differ significantly in either first- or second-line treatment (data not shown).

EGFR mutations and response to cytotoxic chemotherapy

Objective response to first- and second-line cytotoxic chemotherapy was not influenced by EGFR mutation status (Table 3). Objective response rate to first-line cytotoxic chemotherapy was 32% in patients with EGFR mutations and 28% in patients with wild-type EGFR ($P = 0.7198$).

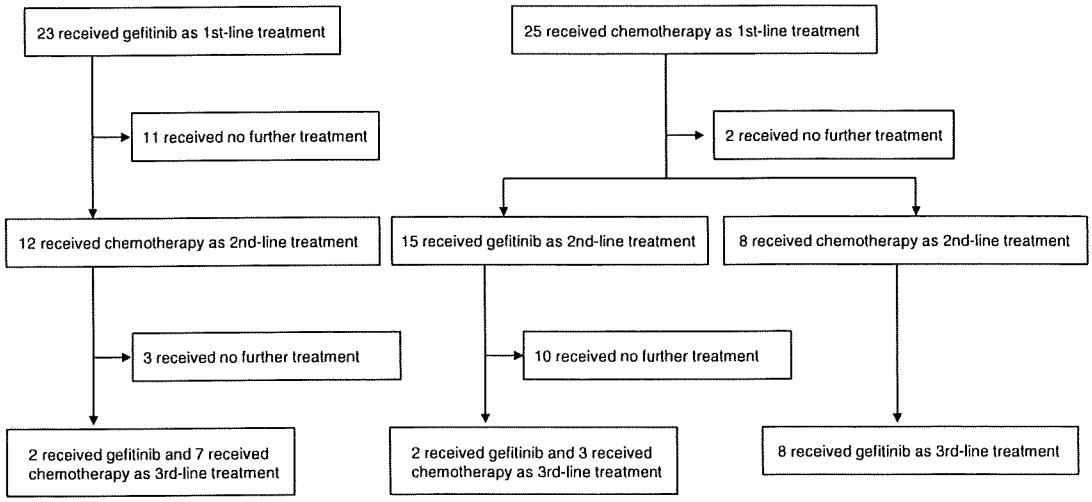

Fig. 1 Treatment flow chart for 48 EGFR mutation-positive patients

Table 2 Response to gefitinib monotherapy in EGFR mutation-positive patients (%)

	First-line ($n = 23$)	Second-line ($n = 15$)
CR	1 (4.3)	1 (6.7)
PR	19 (82.6)	11 (73.3)
SD	0 (0)	1 (6.7)
PD	3 (13.0)	2 (13.3)
OR	20 (87.0)	12 (80.0)
DC	20 (87.0)	13 (86.7)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *OR* objective response (CR + PR), *DC* disease control (CR + PR + SD)

Objective response rate to second-line cytotoxic chemotherapy was 20% in patients with EGFR mutations and 6.9% in patients with EGFR wild-type ($P = 0.1690$).

EGFR mutation status significantly affected the disease control rate to first-line cytotoxic chemotherapy, but not to second-line cytotoxic chemotherapy. The disease control rate to first-line cytotoxic chemotherapy was 88% in patients with EGFR mutations and 60% in patients with wild-type EGFR ($P = 0.0132$). The disease control rate to second-line cytotoxic chemotherapy was 60% in patients with EGFR mutations and 48.3% in patients with EGFR wild-type ($P = 0.4190$).

PFS in EGFR mutation-positive patients

As illustrated by the Kaplan–Meier curves in Fig. 2a and b, EGFR mutation-positive patients treated with gefitinib monotherapy as first-line treatment experienced significantly longer PFS than did patients who received first-line cytotoxic chemotherapy (median survival, 7.8 months vs. 5.1 months, respectively; $P = 0.0323$). Similarly, EGFR mutation-positive patients treated with gefitinib monotherapy as second-line treatment had significantly longer PFS than did patients who received cytotoxic chemotherapy as second-line treatment (median survival, 6.5 months vs. 4.0 months, respectively; $P = 0.0048$). All 15 patients who received gefitinib monotherapy as second-line treatment had previously received cytotoxic chemotherapy as first-line treatment.

Of the 20 patients who received cytotoxic chemotherapy as second-line treatment, 12 of the patients had received gefitinib as first-line treatment and 8 of the patients had received cytotoxic chemotherapy as first-line treatment previously; no statistically significant difference in PFS was observed between these two groups that had been treated with gefitinib monotherapy as first-line vs. cytotoxic chemotherapy as first-line (data not shown).

In patients treated with gefitinib as first- or second-line treatment, no statistically significant difference in PFS was observed in patients with exon 19 deletions, as compared with patients with the L858R mutation (data not shown).

PFS after cytotoxic chemotherapy, according to EGFR mutation status

In patients treated with cytotoxic chemotherapy as first-line treatment, no significant difference in PFS was observed in patients with EGFR mutations vs. patients who were EGFR wild-type (median survival, 5.1 months vs. 4.4 months, respectively; $P = 0.7184$) (Fig. 3a). Similarly, in patients treated with cytotoxic chemotherapy as second-line treatment, no significant difference in PFS was observed in

Table 3 Response to chemotherapy according to EGFR mutation status (%)

	Chemotherapy as first-line treatment			Chemotherapy as second-line treatment		
	Mutation (n = 25)	Wild-type (n = 50)	P	Mutation (n = 20)	Wild-type (n = 29)	P
Type of chemotherapy regimen						
Platinum plus newer agents[a]	22 (88.0)	41 (82.0)		17 (85.0)	18 (62.1)	
Single newer agent	3 (12.0)	9 (8.0)		3 (15.0)	11 (37.9)	
Response						
CR	0 (0)	0 (0)		0 (0)	0 (0)	
PR	8 (32.0)	14 (28.0)		4 (20.0)	2 (6.9)	
SD	14 (56.0)	16 (32.0)		8 (40.0)	12 (41.4)	
PD	3 (12.0)	17 (34.0)		6 (30.0)	14 (48.3)	
NE	0 (0)	3 (6)		2 (10.0)	1 (3.4)	
OR	8 (32.0)	14 (28.0)	0.7198	4 (20.0)	2 (6.9)	0.1690
DC	22 (88.0)	30 (60.0)	0.0132	12 (60.0)	14 (48.3)	0.4190

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *OR* objective response (CR + PR), *DC* disease control (CR + PR + SD

[a] Newer agents were consisted of paclitaxel, docetaxel, vinorelbine, gemcitabine, irrinotecan, amurubicin, and TS-1

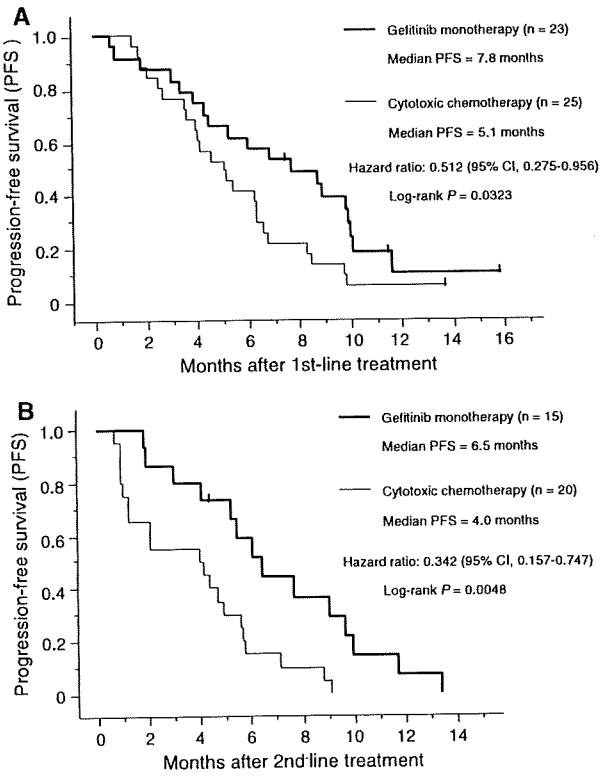

Fig. 2 **a** Kaplan–Meier estimates of progression-free survival of patients with EGFR mutations treated with first-line gefitinib or cytotoxic chemotherapy. **b** Kaplan–Meier estimates of progression-free survival of patients with EGFR mutations treated with second-line gefitinib or cytotoxic chemotherapy

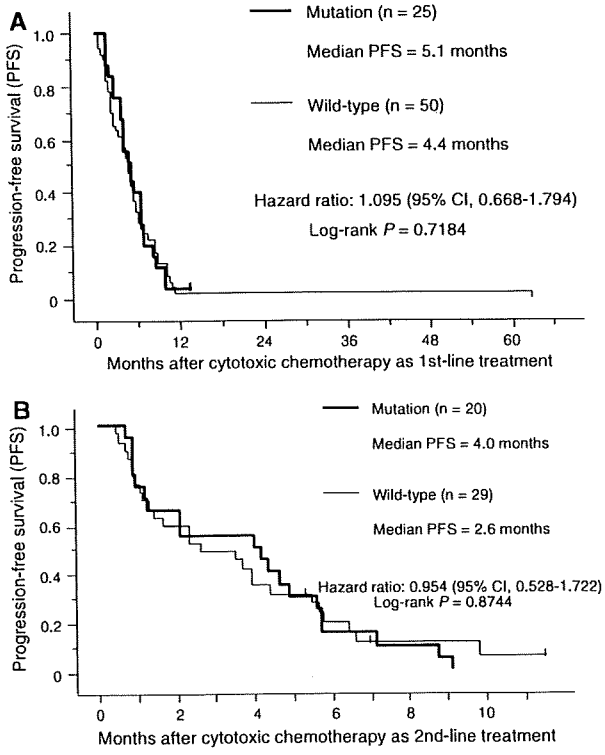

Fig. 3 Kaplan–Meier estimates of progression-free survival of patients grouped by EGFR mutation status who were treated with either first-line (**a**) or second-line (**b**) cytotoxic chemotherapy

patients with EGFR mutations vs. patients with EGFR wild-type (median survival, 4.0 months vs. 2.6 months, respectively; $P = 0.8744$) (Fig. 3b).

Overall survival and multivariate analysis

Patients with EGFR mutations survived for a significantly longer time, as calculated from the initial day of first-line treatment, than did patients who were EGFR wild-type

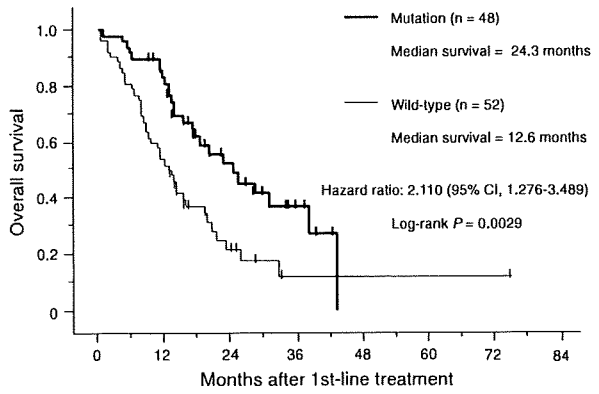

Fig. 4 Kaplan–Meier estimates of overall survival for patients, according to EGFR mutation status

Table 4 Multivariate analysis for overall survival after first-line treatment

Variables	Hazard ratio	95% CI	*P*
EGFR mutation (yes/no)	1.928	1.048–3.545	0.0347
Stage (IIIB/IV)	0.663	0.337–1.306	0.2348
Age (>60/≤60)	1.250	0.741–2.107	0.4028
Gender (male/female)	1.093	0.482–2.481	0.8312
Smoking history (yes/no)	1.268	0.551–2.916	0.5769
Performance status (0–1/2–4)	0.148	0.078–0.282	<0.0001

(median survival, 24.3 months vs. 12.6 months, respectively; $P = 0.0029$; Fig. 4).

Multivariate analysis revealed that EGFR mutations and PS significantly and independently affected overall survival (Table 4).

Discussion

Various cytotoxic chemotherapy agents are utilized in the treatment of advanced or metastatic NSCLC. In the first-line setting, combination chemotherapy such as platinum-based regimens are given empirically to most stage IIIB or IV NSCLC patients, resulting in objective response rates of 30–40%, median survival times of 8–10 months, and 1-year survival rates of 30–40% (Kelly et al. 2001; Schiller et al. 2002). Recently, novel, small molecule therapeutic agents that specifically target certain molecular pathways, including the EGFR TKIs, gefitinib and erlotinib, have been developed. A new approach for selecting patients by the presence of molecular or genetic biomarkers, such as EGFR mutations and gene copy number, is evolving (Cappuzzo et al. 2005, 2007; Han et al. 2006).

Cappuzzo et al. demonstrated that, in NSCLC patients treated with gefitinib, a high gene copy number, rather than EGFR mutations, was a better predictor of survival (Cappuzzo et al. 2005). Furthermore, molecular analyses from large placebo-controlled phase III trials of TKIs also showed that EGFR gene copy number was superior to mutations as a predictor of clinical benefit (Hirsch et al. 2006; Tsao et al. 2005). These studies included mostly Caucasian patients with NSCLC. On the other hand, studies in Japan and Korea demonstrated that EGFR mutation was the most important biomarker to identify NSCLC patients for treatment with gefitinib (Han et al. 2006; Ichihara et al. 2007; Sone et al. 2007; Takano et al. 2005).

In the INTACT and TRIBUTE studies, which were conducted to compare TKIs (gefitinib in the INTACT trial, and erlotinib in the TRIBUTE trial) with placebo in combination with cytotoxic chemotherapy, patients with EGFR mutations exhibited better PFS after cytotoxic chemotherapy than did patients without mutations (Bell et al. 2005; Eberhard et al. 2005). Similarly, Hotta et al. reported that EGFR mutation-positive patients treated with first-line cytotoxic chemotherapy yielded better PFS than did EGFR mutation-negative patients, and furthermore, no significant difference in PFS in patients (with and without mutations) who were treated with cytotoxic chemotherapy following gefitinib monotherapy. Therefore, they suggested that early use of cytotoxic chemotherapy prior to gefitinib treatment was advantageous for EGFR mutation-positive patients (Hotta et al. 2007).

This study assessed whether EGFR mutation-positive status of NSCLC patients influenced clinical outcome of first- and second-line treatment with cytotoxic chemotherapy or gefitinib monotherapy. In contrast to the findings of Hotta et al. (2007), we observed that PFS following first- and second-line cytotoxic chemotherapy was not associated with EGFR mutation status (Fig. 3a, b). Moreover, in our study, EGFR mutation-positive patients treated with first- or second-line gefitinib exhibited better PFS than did patients treated with first- or second-line cytotoxic chemotherapy (Fig. 2a, b). Thus, our findings suggest that patients with EGFR mutations might benefit from either first- or second-line gefitinib monotherapy. The reason for different clinical outcomes in our study and previous studies by other investigators (Bell et al. 2005; Eberhard et al. 2005; Hotta et al. 2007) is unclear. However, possible explanations include differences in ethnicity of study participants and eligibility criteria (e.g., stage of disease and prior treatment) in the various studies. Most of the study participants in the INTACT and TRIBUTE trials were non-Asian patients. In our study, which was conducted in Japan, the EGFR mutation-positive patients had stage IIIB and IV disease. In the study conducted by Hotta et al. (2007), 82% of the EGFR mutation-positive patients had recurrent disease after surgery. Previous research by other investigators has not elucidated how EGFR mutations affect clinical outcomes in

Asian vs. non-Asian NSCLC patients, or in early-stage operable NSCLC patients vs. NSCLC patients with advanced/metastatic disease (Jackman et al. 2006). Recent reports from Asia demonstrated that there was no significant difference in OS between gefitinib-first group and chemotherapy-first group (Morita et al. 2009; Wu et al. 2008).

Because our study population consisted of NSCLC patients screened for EGFR mutation in order to select patients for gefitinib treatment, only three patients who were EGFR wild-type received gefitinib treatment. Therefore, it is difficult to assess whether gefitinib treatment affects clinical outcomes according to EGFR mutation status of NSCLC patients. Nevertheless, we observed similar PFS in patients treated with first- or second-line cytotoxic chemotherapy, regardless of the EGFR mutation status of the patients (Fig. 3a, b). Thus, the longer PFS seen in EGFR mutation-positive patients treated with gefitinib than in patients treated with cytotoxic chemotherapy (Fig. 2a, b) might be attributable to a superior OS than that exhibited by patients who were EGFR wild-type. Our finding is consistent with a subset analysis of a recently completed phase III study (Iressa Pan-Asia Study) showing that gefitinib monotherapy significantly improved the PFS of EGFR mutation-positive patients compared with carboplatin and paclitaxel in the first-line setting (Mok et al. 2009).

Our multivariate analysis indicated that PS and EGFR mutations were significant prognostic factors (Table 4 and Fig. 4), which is consistent with the first report of prospective EGFR mutation screening for NSCLC patients by Sutani et al. (2006). Many investigators believe that patients with EGFR mutations who are treated with EGFR TKIs have significantly longer survival than do patients with EGFR wild-type who are treated with EGFR TKIs (Han et al. 2005; Mitsudomi et al. 2005; Takano et al. 2005). However, this point is still controversial, because some researchers demonstrated that chemotherapy patients with EGFR mutations survived for a longer period than did chemotherapy patients who were EGFR wild-type (Bell et al. 2005; Eberhard et al. 2005). Takano et al. (2008) reported that EGFR mutations are both prognostic and predictive factors. Furthermore, after approval of gefitinib in Japan, median survival of EGFR mutation-positive patients with advanced lung adenocarcinoma was 27.2 months. The median survival time, which was similar to that observed in our study, was never observed in advanced/metastatic NSCLC patients treated with conventional chemotherapy. According to Takano et al. (2008), the favorable median survival time was caused mainly by gefitinib treatment.

Several recent studies have reported that patients with exon 19 deletions had superior response rates, PFS, and OS, as compared with patients with the L858R mutations (Jackman et al. 2006; Mitsudomi et al. 2005; Riely et al. 2006). In this study, clinical outcomes in patients with exon 19 deletions, compared with outcomes in patients with the L858R mutation, did not differ significantly (data not shown). This finding is consistent with previous reports from East Asia showing almost the same survival benefit of gefitinib in patients with either type of mutation (Morita et al. 2009; Takano et al. 2008; Wu et al. 2008).

Recently, a Japanese phase II trial of first-line gefitinib for patients with advanced NSCLC harboring EGFR mutations without indication for chemotherapy demonstrated the benefit of first-line gefitinib for EGFR mutation-positive patients with extremely poor PS and/or with high age, yielding a favorable response rate of 66%, median survival time of 17.8 months and 1-year survival rate of 63% (Inoue et al. 2009). However, we cannot make a conclusion with respect to the timing of gefitinib therapy in the gefitinib-first group and chemotherapy-first group for EGFR mutation-positive patients with good PS and an age <75 years. Our results suggest that EGFR mutation-positive patients benefit from either first- or second-line gefitinib monotherapy. Currently in Japan, two ongoing, prospective, randomized trials are exploring treatment with gefitinib or standard chemotherapy (cisplatin + docetaxel in the trial conducted by the West Japan Oncology Group; carboplatin + paclitaxel in the trial conducted by the North-East Japan Gefitinib Study Group), with the primary endpoint of PFS in patients with EGFR mutations. Results from these trials will provide conclusive results with respect to gefitinib timing for NSCLC patients with EGFR mutations in terms of both PFS and OS.

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Conflict of interest statement All authors have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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JOURNAL OF MEDICAL CASE REPORTS

Case report

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Malignant pleural mesothelioma with long-term tumor disappearance of a local relapse after surgery: a case report

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Abstract

Introduction: There have been few reports of spontaneous regression of malignant pleural mesothelioma, but the mechanism for this is unknown. We present a case report on a patient with malignant pleural mesothelioma showing apparent tumor disappearance in a local relapse after surgery.

Case presentation: A 73-year-old man presented with malignant pleural mesothelioma in the right thoracic cavity. A pleurectomy was performed, and as expected, the tumor locally relapsed with increasing chest pain. However, the symptoms suddenly improved while the tumor was apparently reduced, and spontaneous tumor regression was initially considered. The patient confessed that he had self-administered a mushroom extract with alternative parasympathetic nerve stimulation therapy thereafter. The complete disappearance of the tumor was clinically achieved during a 29-month follow-up with continuing self-treatment.

Conclusion: This is the first report describing a malignant pleural mesothelioma patient in Japan showing long-term complete disappearance of a local relapse after surgery. This event was a tumor regression possibly due to an immunological effect of combined complementary and alternative therapy.

Introduction

Although the standard therapy for malignant pleural mesothelioma (MPM) is still undetermined, the major therapeutic modality for this disease is surgery, radiation and chemotherapy. The majority of cases are at an advanced stage, thus several novel modalities to improve the overall survival time have been preliminarily explored. Immunotherapy, molecular-targeted therapy, and gene therapy are candidate therapies, but cases of long-term survival are exceptional.

In spite of the advanced-stage disease, complete or marked regression of MPM has been described [1–4]. These surprising events are mostly due to chemotherapy achieving complete remission [1], and only three reports have described spontaneous regression of this disease [2–4]. Recently, a patient with MPM experienced a complete tumor regression of a local relapse after cytoreduction surgery. It is possible that this unique favorable event was due to the effect of combined complementary and alternative self-therapy.

Case presentation

A 73-year-old man with a 75-pack-year history of cigarette smoking and asbestos exposure between the ages of 30 and 40 years had been admitted to undergo an extrapleural pneumonectomy due to MPM in the right pleural cavity. However, only a cytoreduction pleurectomy was performed on 30 September 2003 (Figure 1A), because of the aggressiveness of the local tumor. The lesion remained mainly in the mediastino-hilar region adjacent to the carina, esophagus, and the right main bronchus. Histologically, the tumor was epithelioid type (Figure 1B) with T4N0, stage IV (IMIG staging). Then, postoperative intrathoracic chemothermotherapy using carboplatin (CBDCA, 450mg intrapleurally, one course) was administered, followed by systemic chemotherapy using gemcitabine (GEM, 0.8mg/m^2, biweekly, 6 courses). Chest computed tomography (CT) in December 2003 showed that the effect of these postoperative therapies on the residual tumor was stable disease (SD).

In May 2004, the patient felt increasing chest pain with poor general condition. Chest CT showed local relapse broadly in the right pleural cavity causing airway narrowing (Figure 2A). However, he refused further chemoradiation therapy, and in June 2004, without consulting

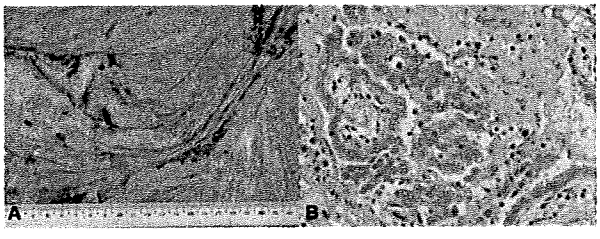

Figure 1.
Macroscopic (A) and microscopic (B) findings of the surgically resected malignant pleural mesothelioma. Multiple nodules of malignant pleural mesothelioma were macroscopically scattered throughout the resected parietal pleura **(A)**. Hematoxylin-eosin-stained light micrograph of the resected pleural tumor. The lesion was histologically diagnosed as epithelioid-type malignant pleural mesothelioma **(B)**.

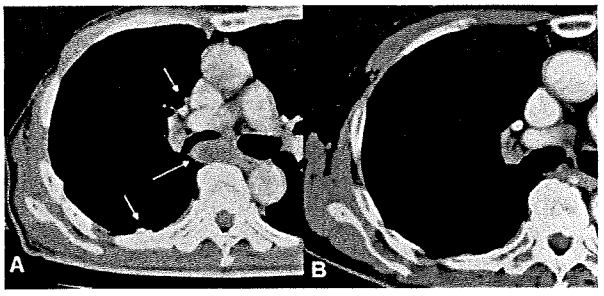

Figure 2.
Local relapse before treatment (A) and tumor disappearance after treatment (B) on chest computed tomography. Chest computed tomography scan **(A)** before the combined therapy showing local relapse of malignant pleural mesothelioma in the right pleural cavity, especially with tumor mass formation in the mediastino-hilar region causing airway narrowing. White arrows show relapsed lesions in the right pleural cavity. After the combined therapy, chest computed tomography scan **(B)** shows complete tumor disappearance in the right pleural cavity.

with the physicians, he orally self-administered a mushroom extract containing Agaricus blazei Murill Kyowa (ABMK) [5], in addition to alternative parasympathetic nerve stimulation therapy in another hospital. This is a modified acupuncture modality providing possible immune-modulation [6]. After experiencing high fever for about 2 weeks, his general condition distinctly improved. Four months after these therapies, the relapsed bulky tumor in the pleural cavity had significantly decreased, and finally completely disappeared on chest CT (Figure 2B). Then, the patient continued this self-treatment with neither symptoms nor radiological evidence of tumor relapse in May 2007. Tumor disappearance was completely achieved during a 29-month follow-up.

Unfortunately, local relapse was detected on chest CT in August 2007. In November 2008, although the relapsed tumor was again growing slowly, the patient was alive while continuing this self-treatment.

Discussion

The median survival times for patients with an unresectable or postsurgical recurrent MPM are usually reported to be in the 6- to 12-month range with the best supportive care, and even now, most chemotherapeutic regimens have shown no or only a minor benefit to the survival rate. In this patient, although an extrapleural pneumonectomy was initially selected as the first step, only a cytoreduction pleurectomy was performed. Therefore, postoperative treatment including intrathoracic chemothermotherapy and systemic chemotherapy was positively administered yielding SD, but

unfortunately, a local re-growth of the tumor occurred later. Surprisingly, considering the usually poor prognosis of this disease, the present clinical course after a local relapse seems unique. It is extremely interesting to elucidate the mechanism of regression of the tumor.

Initially, the disappearance of the tumor was viewed as a result of the delayed effect of postoperative chemotherapy; however, by reviewing the clinical course and condition of the patient, this judgment was found to be negative. In addition, since the patient had taken non-steroidal anti-inflammatory drugs (NSAIDs) continuously after undergoing a pleurectomy, it also seemed that this medication had had little effect on the observed tumor regression. Next, a so-called "spontaneous regression" of the tumor was considered, because the patient did not reveal that he had received the "complementary or alternative combined therapy". Spontaneous regression of MPM has been described in only three reports [2–4]. A clinical summary of these reported cases is shown in Table 1. According to these reports, spontaneous regression of MPM may be strongly associated with lymphocyte-mediated immunity. Robinson *et al.* [2] emphasized an association between MPM regression and some immunological mechanism based on the histological observation of massive lymphoid infiltration within the tumor tissue. Pilling *et al.* [3] also reported similar histological findings. In our patient, however, such histological evidence was not seen in the surgically resected tissue.

Thirdly, after having revealed this "hidden combined therapy", tumor disappearance could be rather considered as a "therapeutic effect" of achieving complete remission. ABMK, a mushroom extract, is considered a health food in many countries after it was reported to be a potential source of anti-tumor, anti-metastatic, cytotoxic and immunoactive compounds [5, 7]. Experimentally, Kimura *et al.* [7] showed that some substances isolated from ABMK inhibited tumor growth through the mechanism of both anti-angiogenic and immune-modulatory activity. Ahn *et al.* [5] reported that natural killer cell activity was clinically elevated by ABMK-treated gynecological cancer patients. Another therapy, parasympathetic nerve stimulation therapy with a minor modification using a laser machine, is widely performed as alternative therapy for patients suffering from cancer as well as various other types of disease in Japan [6]. In particular, for cancer-bearing patients, it was said that acupuncture therapy could provide a beneficial effect in anti-cancer treatment by enhancing the cellular immune function [8]; however, so far, there has been no report describing the clinically complete remission of malignancy by these therapies.

Alternative, but more scientific, immunotherapy has been clinically explored to treat MPM [9]. One is specific immunotherapy which targets particular antigens in MPM tissue, and the other is a non-specific, but anti-tumor immunotherapy using such cytokines as interleukin 2 (IL-2), tumor necrosis factor (TNF), and interferon (INF) [9]. In fact, complete remission of MPM was experienced by INF administration through intra-pleural administration [10].

In our patient, considering that the timing of the improvements in his general condition after a high fever and tumor disappearance accorded with the influence of this "complementary or alternative treatment", it is likely that this successful clinical outcome resulted in complete remission. However, it is unknown whether the AGMK or parasympathetic nerve stimulation or both combined brought about the most favorable effect, and importantly, there are no scientific grounds to confirm the direct effect of this treatment. Several immunological blood parameters such as serum IL-2, INF-alpha, INF-gamma, and CD4/CD8 ratio were examined after the tumor disappearance, but all were within the normal range (data not shown).

Table 1. Reported cases of spontaneous regression of malignant pleural mesothelioma

Reporter Country	Year	Gender	Age	Histology	Previous therapy	Patient Time to regression Period of regression	Outcome	Mechanism
Robinson et al. [2] Australia*	2001	Female	54	Mixed (with lymphoid infiltration)	No	3 months Unknown	Died	Immunological reaction?
Pilling et al. [3] UK**	2007	Male	58	Epithelioid (with inflammatory response)	Surgery	Unknown 7 years	Survival without relapse	Host response
Allen RKA [4] Australia**	2007	Female	61	Epithelioid (poorly differentiated)	No	6 months 5 years	Survival without relapse	Immunological reaction?
The present case Japan**	2009	Male	73	Epithelioid	Surgery Chemotherapy	4 months 29 months	Survival with re-relapse	Complementary and alternative therapy?

*Case of spontaneous marked regression
**Cases of spontaneous complete regression

In summary, this report presents a patient with MPM with a clinical tumor disappearance after a local relapse during a 29-month follow-up period. The mechanism of this tumor disappearance could not be sufficiently explained. Importantly, the mechanism of spontaneous regression of this disease in previous reports [2–4] is considered to be strongly associated with some immunological reaction, and the good effect of such complementary or alternative treatment modalities [5–8] is also caused by a similar immune response. Considering these data together, some immunological reactions of the host to the tumor are thus suggested to be responsible in this patient.

Conclusion

This is the first report describing a MPM patient in Japan showing long-term complete disappearance of a local relapse after surgery. The mechanism of this surprising tumor disappearance cannot be categorically explained. However, the clinical course suggests that some immunological reactions of the host to the tumor may be responsible.

Abbreviations

ABMK, Agaricus blazei Murill Kyowa; CBDCA, carboplatin; CT, computed tomography; GEM, gemcitabine; MPM, malignant pleural mesothelioma; IL-2, interleukin-2; IMIG, International Mesothelioma Interest Group; INF-alpha, interferon-alpha; INF-gamma, interferon-gamma; SD, stable disease; TNF, tumor necrosis factor.

Consent

Written consent was obtained from the patient for publication of the case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of the journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MH conceived the study concept and design, was involved with patient care and drafted the manuscript and literature review. KO, JO, JM: conceived the study concept and design, were involved with patient care and drafting the manuscript. KK: was involved with formation of the study concept and design and drafting the manuscript, FI: was involved with formation of the study concept and design, patient care and drafting of the manuscript and literature review. All authors have read and approved the final version of the manuscript.

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LETTER TO THE EDITOR

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Effect of low-dose aspirin for skin rash associated with erlotinib therapy in patients with lung cancer

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To the Editor

These days the application range of antiplatelet therapy is expanding, because activated platelets are implicated in various clinical conditions. We recently reported that the serum levels of soluble P-selectin and thromboxane (TX) B_2 were elevated in lung cancer patients treated with gefitinib and that low-dose aspirin improved the associated skin eruption, a common adverse effect of gefitinib [1]. Although we were unable to fully clarify the mechanisms involved, we suggested that epithelial growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) may activate platelets and contribute to several related adverse effects. On the other hand, erlotinib is the new approved EGFR-TKI and is administered as an oral medicine. 'Erlotinib has been reported to improve the survival rate of patients with non-small cell lung cancer (NSCLC) after first- or second-line chemotherapy [2] and to significantly improve the patients' quality of life [3]. However, skin rash and diarrhea are common adverse effects of EGFR-TKIs including erlotinib [3]. Here, we describe two NSCLC patients who received erlotinib therapy and developed a skin rash, and were measured for their serum levels of TXB_2. We finally used low-dose aspirin to treat the skin rash in both patinets. To the best of our knowledge, this is the first report that aspirin is effective for skin rash after erlotinib therapy.

Case 1 was a 69-year-old Japanese female who was diagnosed with adenocarcinoma (stage VI). Although conventional chemotherapy (carboplatin and paclitaxel) was performed, tumor markers increased again. Therefore, erlotinib (150 mg/day) was started. At first, skin lesions below grade 1 with acne developed. However, the skin lesions progressed to grade 2 (Figure 1A) with severe itching. Low-dose aspirin (100 mg/day) was started with the patient's consent without dose reduction of erlotinib. The skin lesions were ameliorated (Figure 1B) with improved itching. Case 2 was a 77-year-old Japanese male and was diagnosed with squamous cell carcinoma (stage IIIb) without metastasis. He also did not respond to conventional chemotherapy (docetaxel hydrate). After 1 week of treatment with erlotinib, a grade 2 skin rash developed (Figure 1C) with severe itching. This case also observed the improvement of skin rash after low-dose aspirin treatment (Figure 1D). In both cases, TXB_2 was elevated after erlotinib treatment, and low-dose aspirin finally exhibited the decrease of TXB_2. Our results suggest that the mechanism of the skin rash development after erlotinib treatment involves platelet activation.

Cyclooxygenase (COX) must play an important role in platelet activation by erlotinib because TXA_2

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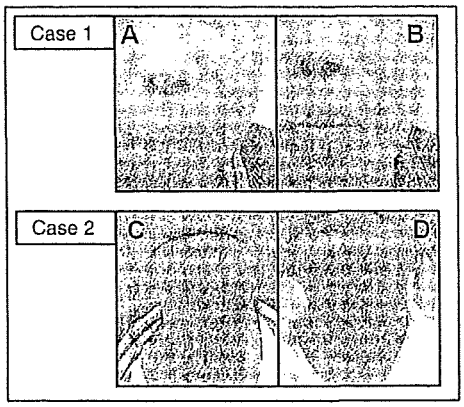

Figure 1. Case 1, (A) the skin lesions progressed to grade 2 with severe itching. (B) The skin lesions were ameliorated with improved itching after low-dose aspirin was started without dose reduction of erlotinib. Case 2, (C) After 1 week of treatment with erlotinib, a grade 2 skin rash developed with severe itching. (D) The skin lesions were ameliorate with improved itching after low-dose aspirin was started without dose reduction of erlotinib.

is synthesized by platelets through COX. Low-dose aspirin mainly inhibits COX-1, and has a weak inhibitor effect on COX-2. Therefore, we propose that inhibition of COX-1 is very important as a preventative measure against skin rash development after erlotinib administration. Our only concern is that low-dose aspirin may have a negative association with the therapeutic effect of erlotinib for lung cancer. If platelet activation is related to the anti-cancer effect the use of aspirin would decrease the effect of the EGFR-TKI. However, our previous study with gefitinib suggested that the effects of aspirin through inhibition of platelet COX-1 reduced the adverse effects of gefitinib but not its anti-cancer effects [4–6].

The anti-cancer effects of EGFR-TKIs differ among races [7]. In addition, their effects on platelet functions may differ among races. The anti-cancer effects of gefitinib at less than its maximum tolerated dose also differ among races. One of the awkward diverse effects of EGFR-TKIs in Japanese patients is interstitial pneumonitis [8]. Recently Nomura et al. [9] reported that platelets were activated in scleroderma patients with interstitial pneumonitis. This observation suggests that platelet activity is one of the factors for the interstitial pneumonitis associated with EGFR-TKI therapy. We hope that low-dose aspirin prevents the adverse effects of erlotinib and that we will be able to use EGFR-TKIs more safely in cancer patients. Additional randomized studies are required to determine the usefulness of our new therapy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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