19]. Only one event of increased troponin T was reported as a CTCAE grade ≥3 during AZD7762 monotherapy.

The PK profile reported here is generally consistent with those reported previously in Western patient populations [9, 10]. Systemic exposure to AZD7762 increased in an approximately linear manner with dose over the dose range studied. The PK profile for AZD7762 was similar when administered as monotherapy or in combination with gemcitabine, indicating that gemcitabine has no effect on plasma concentrations and clearance of AZD7762 [10].

No objective tumour responses occurred in this heavily pre-treated population. Similarly, limited efficacy was observed with AZD7762 30 mg in combination with gemcitabine in Western patients [10]. When compared with preclinical studies, the predicted level of Chk1 inhibition associated with AZD7762 in these Phase I studies may have been insufficient to fully inhibit Chk1 kinase activity and achieve significant clinical efficacy. In a separate study in Western patients, a higher MTD of AZD7762 of 96 mg in combination with irinotecan was identified, which led to one complete response and one partial response in a total of 68 patients [9]. Overall, the results obtained in our Japanese patients were similar to those previously reported in a Western population [10]: the DLTs experienced in the monotherapy phases of each study were cardiac in nature, while the DLTs observed in combination with gemcitabine were mainly haematological. The MTD of AZD7762 in combination with gemcitabine 1,000 mg/m^2 was higher in the Western than the Japanese population (30 vs 21 mg) [10], although this is not unexpected. Of note, tumour response rates were highest in patients with lung cancer in both populations, with partial responses observed in the Western population [10] and stable disease achieved in the Japanese patients. The findings suggest that the combination of Chk1/Chk2 inhibitors with DNA-damaging agents, such as gemcitabine, may be of clinical benefit to particular patient populations, such as those with lung cancer.

Conclusion

The MTD of AZD7762 in combination with gemcitabine 1,000 mg/m^2 was 21 mg in Japanese patients. Gemcitabine had little effect on the PK profile of AZD7762. However, due to the incidence of cardiac toxicities reported in the overall Phase I development programme, the balance between benefit and risk has been judged unfavourable and further clinical development of AZD7762 has been discontinued.

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ORIGINAL ARTICLE

Gemcitabine and vinorelbine as second-line or beyond treatment in patients with malignant pleural mesothelioma pretreated with platinum plus pemetrexed chemotherapy

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Abstract
Background Malignant pleural mesothelioma (MPM) is an aggressive neoplasm that responds poorly to chemotherapy. Although treatment with pemetrexed in combination with cisplatin serves as first-line chemotherapy for MPM, the optimal second-line and beyond therapy has not yet been fully examined.
Methods Between March 2008 and October 2011, 17 consecutive Japanese patients pretreated with at least one regimen of platinum plus pemetrexed chemotherapy received gemcitabine and vinorelbine. Responses, survival time, and toxicity were retrospectively evaluated.
Results Response [partial response (PR) + complete response (CR)] and disease control [stable disease (SD) + PR + CR] rates were 18 and 82 %, respectively. The median progression-free survival (PFS) after combination chemotherapy was 6.0 months, whereas the median overall survival (OS) was 11.2 months. Grade 3 or 4 neutropenia and anemia were observed in 41 and 29 % of patients, respectively, and one patient experienced febrile neutropenia. Grade 3 or 4 nonhematologic toxicities included constipation (6 %) and phlebitis (6 %).
Conclusion Combination chemotherapy using gemcitabine with vinorelbine was shown to have moderate activity in Japanese MPM patients pretreated with platinum plus pemetrexed chemotherapy. A further multicenter phase II trial is warranted to confirm the efficacy and safety of this combination treatment.

Keywords Malignant pleural mesothelioma · Gemcitabine · Vinorelbine · Second-line treatment and beyond

Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare tumor arising from mesothelial cells, and prognosis is very poor. Asbestos exposure has been shown to be a main cause of MPM [1], and in Japan, it accounts for approximately 75 % of MPM cases [2]. As another predisposing factor, mutations of BRCA-1-associated protein-1 and neurofibromatosis type 2 can also cause MPM [2, 3]. The natural course of MPM is poor, and median survival ranges from 4 to 12 months without intervention [4]. Although surgical excision can be considered part of multimodal therapy, its impact on patient survival and quality of life is controversial [5, 6]. Therefore, chemotherapy is considered to be the main therapeutic modality.

A phase III study by Vogelzang and colleagues showed the superior activity of treatment with pemetrexed (PEM) plus cisplatin [cis-diamminedichloroplatinum(II) (CDDP)] to CDDP alone for patients with MPM [7]. The median survival time and response rates in the PEM/CDDP arm were 12.1 months and 41.3 % compared with 9.3 months and 16.7 % in the CDDP arm ($P = 0.020$ and $P < 0.0001$, respectively), confirming this combination chemotherapy to be a standard first-line chemotherapy in patients with MPM. However, there have so far been very few reports of a second-line or beyond treatment for patients with MPM

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pretreated with platinum plus PEM chemotherapy as first-line chemotherapy.

The efficacy and safety of vinorelbine (VNR) have been assessed in both second- and first-line settings [8, 9]. In a single-center phase II study, Stebbing et al. reported that VNR monotherapy for relapsed MPM patients produced partial responses (PR) in 16 % of patients and stable disease (SD) in 68 %, with an overall survival (OS) of 9.6 months [9]. In addition, gemcitabine (GEM) proved to be active as both a first- and second-line treatment when used in combination with other drugs, such as CDDP or oxaliplatin [10, 11]. Based on these findings, combination chemotherapy using GEM with VNR, the significance of which was assessed in lung cancer patients [12], was suggested to have potential antitumor activity for patients with MPM as a second-line and beyond therapy. Additionally, the general condition of patients is often good at the time of disease progression following first-line chemotherapy. Therefore, even relapsed patients are considered able to receive this combination therapy. We retrospectively investigated the use of the combination of GEM with VNR for Japanese MPM patients pretreated with platinum plus PEM.

Patients and methods

Patients

We conducted a retrospective search of the medical records at National Kyushu Cancer Center for patients treated from March 2008 through October 2011. Among the 27 patients with MPM during this period, there were 17 consecutive patients with nonresectable or with recurrent disease after surgical resection who had been pretreated with at least one platinum agent plus PEM chemotherapy as a first-line regimen and who received GEM and VNR as a second or beyond treatment. All patients had sufficient data to evaluate their characteristics and clinical outcomes for the analysis. Their age, sex, asbestos exposure, Eastern Cooperative Oncology Group performance status (ECOG-PS), histology, stage, first-line chemotherapy, and responses to the combination chemotherapy were assessed. The clinical or pathological stage of the disease was based on the International Mesothelioma Interest Group (IMIG) staging system [13]. Histological subtypes were determined using the World Health Organization (WHO) classification for cell types. Patients were evaluated for response every two cycles according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria [14]. The National Cancer Institute Common Toxicity Criteria, version 4.0, was applied to evaluate adverse events. Written informed consent was obtained from all patients, and the institutional review board of our institution approved this study.

Treatment schedule and dose adjustment

All patients were treated with GEM 1000 mg/m^2 plus VNR 25 mg/m^2 on days 1 and 8 every 3 weeks, and the treatment was repeated until disease progression or unacceptable toxicity occurred. VNR doses were first reduced by 20 % in patients who experienced grade 4 hematological toxicities or grade 3 or greater nonhematological toxicities or whose scheduled treatment was skipped on day 8 in the previous cycle. Second, GEM doses were reduced by 20 % when these conditions were met again. If further dose reduction was required, the chemotherapy regimen was stopped.

Statistical analysis and survival data

Survival time was calculated from the beginning of GEM plus VNR treatment to disease progression or death from any cause. The survival curve was produced using the Kaplan–Meier method. Univariate and multivariate analyses were performed by the logrank test and a stepwise method.

Results

Patient characteristics

From March 2008 to October 2011, 17 consecutive Japanese patients with MPM who had been pretreated with at least a regimen containing one platinum agent plus PEM as a first-line chemotherapy received GEM and VNR on days 1 and 8. Fourteen of the 17 patients received the combination chemotherapy as a second-line treatment, and three patients received it as a third-line or beyond treatment. Patient characteristics are summarized in Table 1. Median age was 58 (range 41–75) years, and 88 % of patients were men. Although exposure to asbestos was known in 65 % of cases, 6 % of cases showed no findings of asbestos exposure, and it was unclear in 29 %. The majority of patients (71 %) had an ECOG-PS of 1. Histological subtypes were as follows: epithelioid (82 %), biphasic (6 %), and sarcomatoid (12 %). Three patients (18 %) had stage I disease, none (0 %) had stage II, four (24 %) had stage III, and ten (58 %) had stage IV disease. Sixteen of the 17 patients (94 %) had received CDDP plus PEM, and one had received carboplatin (CBDCA) plus PEM as the first-line regimen; ten patients (58 %) achieved PR or SD, and six (35 %) had progressive disease (PD).

Table 1 Patient demographics and baseline characteristics

Characteristics	Number (%)
Median age (range)	58 (41–75)
Sex	
Male	15 (88)
Female	2 (12)
Asbestos exposure	
Yes	11 (65)
No	1 (6)
Unknown	5 (29)
Performance status	
0	5 (29)
1	12 (71)
Histology	
Epithelioid	14 (82)
Biphasic	1 (6)
Sarcomatoid	2 (12)
IMIG stage	
I	3 (18)
II	0 (0)
III	4 (24)
IV	10 (58)
First-line chemotherapy	
Cisplatin + pemetrexed	16 (94)
Carboplatin + pemetrexed	1 (6)
Response to first-line chemotherapy[a]	
CR	0 (0)
SD + PR	9 (53)
PD	6 (35)

IMIG International Mesothelioma Interest Group, *CR* complete response, *SD* stable disease, *PR* partial response, *PD* progressive disease

[a] Responses of two patients were not evaluable

Table 2 Hematological and nonhematological toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	2	4	4	1
Leucopenia	0	5	0	4
Neutropenia	0	0	3	4
Thrombocytopenia	0	2	0	0
Nonhematological				
Nausea	1	0	0	0
Appetite loss	7	0	0	0
General fatigue	8	0	0	0
Constipation	0	0	1	0
Phlebitis	3	2	1	0
Febrile neutropenia	0	0	1	0
AST elevation	2	0	0	0
ALT elevation	1	0	0	0
Creatinine elevation	3	0	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

In total, 106 cycles were delivered to the 17 patients, and 38 cycles (35 % of all cycles: 38 VNR and 24 GEM) were reduced. The median number of cycles of the combination chemotherapy using GEM and VNR was five, with a range from one to 19 cycles, and all but one patient received two or more cycles.

Toxicity

Table 2 demonstrates treatment-related toxicities. Grade 3 or 4 anemia, leucopenia, and neutropenia, respectively, were observed in 29, 24, and 41 % of cases. Although grade 3 or 4 nonhematological toxicities included constipation (6 %) and phlebitis (6 %), these were manageable. One patient experienced febrile neutropenia. There were no treatment-related deaths. Three patients required dose reduction of both GEM and VNR, whereas three and 11 patients required dose reduction of VNR only and no dose reduction, respectively.

Response and survival

All 17 patients were evaluable for response assessment. Three [18 %; 95 % confidential interval (CI) 3.8–43.4 %] achieved PR, 11 (64 %; 95 % CI 38.3–85.8 %) had SD, and PD was observed in three (18 %; 95 % CI 3.8–43.4 %). No complete response (CR) was seen. Response [partial response (PR) + complete response (CR)] and disease control [stable disease (SD) + PR + CR] rates were 18 and 82 %, respectively. The median progression-free survival (PFS) after combination chemotherapy was 6.0 months, and the 1-year PFS rate was 17.6 % (95 % CI 0.0–35.6 %; Fig. 1, solid line). Median OS and the 1-year OS rate after administration of the combination chemotherapy were 11.2 months and 43.9 % (95 % CI 19.6–68.2 %), respectively (Fig. 1, dashed line). As shown in Table 3, the median PFS according to sex (male versus female), IMIG stage (I–III versus IV), and responses (SD + PR versus PD) for platinum plus PEM were 3.0 versus 14.5 months, 8.8 versus 2.4 months, and 6.8 versus 1.6 months, respectively ($P = 0.015$, 0.032 and 0.012, logrank test). No significant impact on PFS was observed for other variables, and none of the variables had any significant impact on OS. On multivariate analysis, relationships between clinical variables and survivals could not be evaluated using a stepwise method for multivariate analysis, because this study did not have a sufficient number of patients.

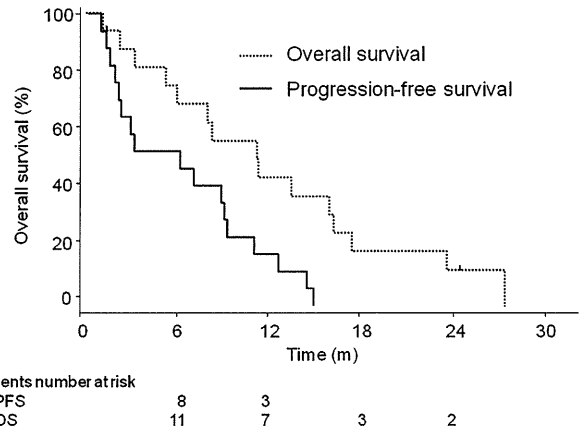

Fig. 1 Progression-free (PFS) (*solid line*) and overall (OS) (*dashed line*) survival after administration of gemcitabine and vinorelbine

Table 3 Progression-free (PFS) and overall (OS) survival according to patient characteristics

Characteristics	Number (%)	PFS (months)		OS (months)	
		Median	*P* value	Median	*P* value
Sex					
Male	15 (88)	3.0		11.1	
Female	2 (12)	14.5	0.0147	25.5	0.0766
Performance status					
0	5 (29)	3.0		11.2	
1	12 (71)	6.4	0.2632	11.1	0.5552
Age					
<65	12 (71)	6.4		9.7	
>65	5 (29)	2.7	0.7521	13.7	0.8299
Curative surgery					
Yes	4 (24)	10.5		16.7	
No	13 (76)	2.7	0.2942	11.1	0.30690
Histology					
Epithelioid	14 (82)	4.5		11.1	
Nonepithelioid	3 (18)	8.6	0.9047	15.9	0.9043
IMIG stage					
I–III	7 (42)	8.8		16.2	
IV	10 (58)	2.4	0.0315	7.9	0.1162
Response to first-line chemotherapy[a]					
SD + PR	9 (53)	6.8		11.2	
PD	6 (35)	1.6	0.0120	5.9	0.2032

IMIG International Mesothelioma Interest Group, *SD* stable disease, *PR* partial response, *PD* progressive disease

[a] Responses of two patients were not evaluable

Discussion

In this study, the efficacy and safety of combination chemotherapy with GEM plus VNR as a second-line and beyond treatment were retrospectively evaluated. Response and disease control rates were 18 and 82 %, respectively, with a median PFS and OS of 6.0 and 11.2 months, respectively. Although this was a retrospective study analyzing a small Japanese population of 17 patients at a single institute, these findings are comparable with or superior to those obtained using other retrospective and prospective second-line cytotoxic agents in pretreated MPM patients (Table 4). With regard to adverse events, grade 3 or 4 anemia, leucopenia, and neutropenia were observed in 29, 24 and 41 % of patients, respectively, and two patients (12 %) experienced grade 3 or 4 nonhematological toxicities, such as constipation and phlebitis. These events were all manageable, and it was also interesting to note that no treatment-related death was observed. These results suggested that combination chemotherapy using GEM with VNR might be a potential therapeutic regimen for MPM patients pretreated with platinum plus PEM chemotherapy. With regard to response evaluations, modified RECIST criteria were applied, as in other studies. However, Tsutani et al. [15] reported on the prognostic significance of metabolic response using positron emission tomography (PET)/computed tomography (CT) after neoadjuvant chemotherapy for resectable MPM, demonstrating that radiological responses did not have prognostic significance in these patients. In our study, metabolic response using PET/CT was not assessed, and a future analysis using PET/CT should therefore be performed to clarify the significance of metabolic response after combination chemotherapy with GEM and VNR.

The standard first-line regimen for MPM is CDDP plus PEM, and this regimen gives a median OS of approximately 1 year after administration of the drugs [7]. As shown in Table 4, various types of chemotherapy have been prospectively explored for treating MPM patients as second-line and beyond treatment; however, no standard regimen has been established [16]. Furthermore, very few regimes as second-line chemotherapy after platinum plus PEM chemotherapy as the first-line treatment have so far been assessed. The significance of VNR in the second-line setting has been evaluated by some groups [9, 16]. Stebbing et al. [9] showed the high disease control rate using VNR monotherapy in 84 % of patients with relapsed MPM in a single-center phase II study, with an OS of 9.6 months. With regard to GEM, combination chemotherapy with oxaliplatin was assessed in MPM pretreated with PEM by Xanthopoulos et al. [11], and the median survival time from oxaliplatin/GEM administration and the disease control rate was reported to be 24.3 weeks and 44.8 %, suggesting its efficacy. Additionally, we previously assessed combination chemotherapy using GEM with VNR plus CDDP for MPM patients as first-line therapy and found it highly effective with manageable toxicities [17]. Given these findings and the evidence that combination chemotherapy of CDDP with PEM is a standard first-line therapy,

Table 4 Second-line chemotherapy for patients with malignant pleural mesothelioma

Author	Phase	Chemotherapy	Number	Response rate (%)	Median PFS (months)	Median OS (months)
Xanthopoulos et al.	Retrospective	Oxaliplatin ± GEM	29	7	2.7	5.6
Zucali et al.	II	GEM + VNR	30	10	2.8	10.9
Nowak et al.	II	Sunitinib	53	12	3.5	6.1
Jackman et al.	II	Erlotinib + bevacizumab	24	0	2.2	5.8
Ramalingam et al.	II	Belinostat	13	0	1.0	5.0
Our result	Retrospective	GEM + VNR	17	18	6.0	11.2

GEM gemcitabine, *VNR* vinorelbine, *PFS* progression-free survival, *OS* overall survival

we investigated the efficacy and safety of combination chemotherapy using GEM with VNR for patients with MPM as a second-line and beyond therapy, finding moderate antitumor activity and acceptable toxicities. Zucali and colleagues reported the activity and safety of GEM with VNR for MPM patients pretreated with PEM, and the response rate and PFS were 10 % and 2.8 months, respectively [18]. Our study differs in regard to the fact that all patients were pretreated with platinum plus PEM, whereas four (13 %) were pretreated with PEM monotherapy in the previous report. Furthermore, response rate and PFS were 18 % and 6.0 months, respectively, which were comparable with those reported previously. Based on these findings, our results are considered to support the findings of the phase II trial by Zucali et al., and we considered the combination chemotherapy using GEM with VNR to be one of the effective regimens for relapsed MPM patients after the failure of platinum with PEM.

Molecular-targeted therapy has also been evaluated to treat MPMs. Kindler and colleagues reported in their phase III trial that bevacizumab (BEV), a vascular endothelial growth factor inhibitor, in combination with CDDP plus GEM produced no additional benefit for MPM patients compared with CDDP plus GEM [19]. Median OS time and overall response rate were not significantly different between the two arms of their study (15.6 and 14.7 months, 24.5 and 21.8 %, respectively, $P = 0.91$ and $P = 0.74$). In second-line settings, inhibitors, including sunitinib [20], erlotinib [21], and belinostat [22], specifically targeting some molecules have also been examined, as shown in Table 4. However, these reagents are considered to be less effective than cytotoxic reagents. Therefore, focus should be placed on cytotoxic chemotherapy, such as combination treatment using GEM with VNR, in second-line treatments and beyond for MPM patients.

The optimal regimen to be used as second-line and beyond treatment for patients with MPM remains to be determined. Although this was a retrospective study with only 17 patients, results were comparable with or superior to those obtained using other chemotherapy regimens [18]. A prospective study including multiple centers is needed to clarify the efficacy and safety of this combination therapy.

In conclusion, combination chemotherapy using GEM with VNR showed moderate activity with manageable toxicities in relapsed Japanese patients with MPM after failure of platinum with PEM chemotherapy. A multicenter phase II trial is needed to clarify the efficacy and safety of this combination treatment.

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Amrubicin as Second-line and Beyond Treatment for Platinum-refractory Advanced Thymic Carcinoma

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Objective: Thymic carcinoma is a rare mediastinal neoplasm, and the prognosis of patients with advanced thymic carcinoma is poor. No standard chemotherapeutic regimen has yet been established for the disease. This is the first report to evaluate the role of amrubicin, a novel anthracycline anticancer drug, in second-line and beyond treatment for patients with platinum-refractory advanced thymic carcinoma.

Methods: This study was a review of thymic carcinoma patients who had received amrubicin monotherapy between June 2003 and December 2011 for the progression of disease previously treated with platinum-based chemotherapy. Amrubicin was administered at 35 or 40 mg/m^2 for three consecutive days every 3 weeks, until progression.

Results: Nine patients with recurrent thymic carcinoma were registered. Their median age was 61 years (range 45–72), and the patients included five males and four females. All nine patients had Masaoka's Stage IVb disease. There were three squamous cell carcinomas, one adenocarcinoma, one small-cell carcinoma and two other histological types. The mean number of chemotherapy cycles was five (range 2–13). Grade 3 or higher toxicities included mainly neutropenia (55.5%), anemia (25.0%) and febrile neutropenia (11.1%). No treatment-related deaths were observed. The response rate was 44.4% (95% confidence interval: 19–73). The median progression-free survival after the amrubicin monotherapy was 4.9 months, while the median overall survival was 6.4 months.

Conclusions: Single-agent amrubicin was found to be potentially useful as second-line and beyond chemotherapy for patients with advanced thymic carcinoma. Further multi-institutional prospective studies are warranted.

Key words: thymic cancer – second-line chemotherapy – amrubicin

INTRODUCTION

Thymic carcinoma (TC) is a rare mediastinal neoplasm, and the prognosis of patients with advanced TC is poor. TC is highly progressive, and tends to metastasize and invade surrounding tissues more frequently in comparison to thymoma (1). Kondo and Monden (2) reported that TC had a significantly worse prognosis than thymoma and thymic carcinoid in a clinical study of 1320 patients with thymic epithelial tumors from Japan. TC was, therefore, classified as a distinct entity in the 2004 World Health Organization classification, and 13 histological subtypes have been categorized (3). Whereas the clinicopathological features of TC have often been discussed, studies on the optimal treatment modalities and long-term prognosis have been limited due to the rarity of this disease.

Several reports have indicated the efficacy of cisplatin-based combination chemotherapy, such as ADOC (cisplatin, doxorubicin, vincristine and cyclophosphamide) and CODE (cisplatin, vincristine, doxorubicin and etoposide), against both TC and thymoma (4,5). However, a high incidence of severe toxicities was observed with these treatments. The Eastern Cooperative Oncology Group (ECOG) reported a trial of VIP (etoposide, ifosfamide and cisplatin) treatment for patients with advanced thymoma and TC. The 2-year survival rate of patients with TC was poorer than that of patients with thymoma (50 versus 70%) (6). Moreover, there have been only a few case reports describing chemotherapy for recurrent TC (7). This is the first case series to evaluate the efficacy and feasibility of amrubicin (AMR), a novel anthracycline anticancer drug, as second-line and beyond chemotherapy for recurrent TC.

PATIENTS AND METHODS

Patients

This study analyzed all subjects at the Kyushu Cancer Center between December 2003 and May 2011 who satisfied the following five criteria: (i) histologically confirmed recurrent TC, where the histological diagnosis was based on a needle biopsy performed under computed tomographic (CT) guidance or on examination of surgical specimens, (ii) the existence of measurable target lesions, (iii) age <80 years, (iv) an Eastern Cooperative Oncology Group Performance Scale status (ECOG PS) of ≤ 2 and (v) adequate bone marrow, hepatic and renal function and no other serious diseases. The disease stage was evaluated by Masaoka's staging (8). In the same period of this study, a total of 27 patients with advanced TC received chemotherapy, and one patient did not receive chemotherapy due to poor PS. Of 27 patients, 15 patients received AMR-based chemotherapy (AMR monotherapy in nine patients and cisplatin/AMR in six patients). TC is a very rare disease, so it is difficult to conduct a prospective study. The use of AMR for TC was approved by the Review Committee of chemotherapy regimens in the Kyushu Cancer Center. All patients signed a written informed consent before the study entry.

Treatment Methods

The patients received an infusion of 35–40 mg/m^2 AMR over 5 min on Days 1–3, and the treatment course was repeated every 3 weeks until disease progression. The administration of a granulocyte colony-stimulating factor (G-CSF) was permitted as a therapeutic intervention for the development of neutropenia as a Grade 4 hematological toxicity and Grade 3 febrile neutropenia, but it was not mandatory as a prophylactic measure. Subsequent doses were modified on the basis of the hematological and non-hematological toxicities.

Evaluation of the Response and Toxicity

The tumor response was classified in accordance with the Response Evaluation Criteria for Solid Tumors (RECIST version 1.0). The disease stage was evaluated by a complete medical history and physical examination, chest X-rays, CT of the chest and abdomen and other staging procedures, such as magnetic resonance imaging of the head, combined positron emission tomography/CT and bone scintigraphy at the time when the disease progression or relapse were identified. The adverse events were recorded and graded using the Common Toxicity Criteria for Adverse Events (CTCAE, version 4.0)

Statistical Analysis

The overall survival (OS) was measured from the first day of treatment with AMR to the day of death from any cause or the last follow-up. The progression-free survival (PFS) was defined as the time elapsed between the initiation of AMR treatment and tumor progression or death from any cause, with censoring of patients who were lost to follow-up. The survival curve was estimated using the Kaplan–Meier method.

RESULTS

Patient Characteristics

The clinical profiles of the nine patients are shown in Table 1. The median age of the patients was 61 years (range, 45–72), and the patients included five males and four females. All the patients had Masaoka Stage IVb disease. The histological classifications were squamous cell carcinoma in three patients, undifferentiated carcinoma in two, adenocarcinoma in one, poorly differentiated neuroendocrine carcinoma in one, small-cell carcinoma in one and basaloid carcinoma in one patient. The majority of patients (77.7%) enrolled in this study had received one previous line of chemotherapy (two patients had received second-line or more chemotherapy).

Toxicity

The treatment cycles and dose delivery of all nine patients are shown in Table 2. In total, 44 cycles of AMR were given. The median number of cycles of AMR administered per patient was four (range, 2–13). The starting doses of AMR were 35 mg/m^2 in three patients and 40 mg/m^2 in six patients. The two of the nine patients required a dose reduction (one time in one patient and two times in one patient). Three patients needed to use a G-CSF due to neutropenia, at Cycles 1 and 2. The modified relative dose intensity (modified relative dose intensity = actual dose/starting dose $\times$ cycles) was 0.97%. The toxicities in the nine patients are summarized in Table 3. The most common major toxicity (Grade 3/4) was bone marrow suppression with a decreased neutrophil count (55.5%). Two patients (25.0%) had Grade 3 anemia and one patient (11.1%) had Grade 3 febrile neutropenia. None of the patients had a decreased platelet count. No Grade 3 or higher non-hematological toxicities were observed, including the patients who had received second-line or more chemotherapy. In addition, there were no treatment-related deaths in this study.

Table 1. Patient characteristics

No. of patients	Age, gender	ECOG PS	Masaoka's stage	Histological subtype	Previous regimens (response)	No. of treatment cycles	Response to AMR
1	70, F	1	IVb	Undifferentiated carcinoma	1. CbP (SD)	2	PD
2	45, F	1	IVb	Squamous cell carcinoma	1. CbP (PR)	9	PR
3	63, F	1	IVb	Small-cell carcinoma	1. PI (PR)	6	PR
4	50, M	1	IVb	Adenocarcinoma	1. CbP (SD)	2	PD
5	61, M	1	IVb	Poorly differentiated neuroendocrine carcinoma	1. CbP (PD)	2	PD
6	65, F	1	IVb	Undifferentiated carcinoma	1. CbP (SD)	13	PR
7	72, M	0	IVb	Squamous cell carcinoma	1. CbP (PR)	6	SD
8	45, M	1	IVb	Basaloid carcinoma	1. CS-1 (PR), 2. CbP (PR), 3. GV (PD)	2	PD
9	50, M	1	IVb	Squamous cell carcinoma	1. CbP (SD), 2. CGV (SD), 3. PD (SD), 4. PI (SD), 5. UFT/GEM (SD)	4	PR

ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CbP, carbolpatin/paclitaxel; PI, cisplatin/irinotecan; CS-1, cisplatin/TS-1; CGV, cisplatin/gemcitabine/vinorelbine; PD, cisplatin/docetaxel; AMR, amrubicin.

Table 2. Treatment and dose delivery

No. of patients	Starting dose of AMR (mg/m^2)	No. of cycles	No. of dose reduction	Planned dose[a] of AMR (mg/m^2)	Actual dose of AMR (mg/m^2)	Modified relative dose intensity[b]	Use of G-CSF	Reason of treatment-off	PFS (months)	OS (months)
1	35	2	0	70	70	1	None	Disease progression	1.41	11.5
2	35	9	0	315	315	1	None	Disease progression	14.5	20.0
3	40	6	0	240	240	1	None	Disease progression	4.9	5.4
4	40	2	0	80	80	1	None	Disease progression	0.7	5.9
5	40	2	1	75	80	0.94	Cycle 1	Disease progression	1.8	4.8
6	40	13	2	405	520	0.78	Cycles 1 and 2	Ongoing	13.0	13.0
7	40	6	0	240	240	1	None	Ongoing	5.4	5.4
8	35	2	0	70	70	1	None	Disease progression	1.3	5.7
9	40	4	0	160	160	1	Cycle 1	Disease progression	5.7	6.4

G-CSF, granulocyte-colony stimulating factor; PFS, progression-free survival; OS, overall survival.
[a]Planned dose = starting dose × cycles.
[b]Modified relative dose intensity = actual dose/planned dose.

Efficacy

A partial response was confirmed in four patients, stable disease in one patient and progressive disease in four patients, giving a response rate (RR) of 44.4% [exact 95% confidence interval (CI): 13.7–78.8%, Table 3]. The median OS and the median PFS were 6.4 and 4.9 months, respectively (Fig. 1).

DISCUSSION

AMR hydrochloride, a completely synthetic 9-aminoanthracycline, is converted to the active metabolite, amrubicinol, via the reduction of its C-13 ketone group to a hydroxyl group by carbonyl reductase (9). AMR and amrubicinol are inhibitors of DNA topoisomerase II, which exerts a cytotoxic effect by

Table 3. Hematological and non-hematological toxicities

	No. of patients ($n = 9$)				
	G1	G2	G3	G4	G3/4 (%)
Hematological					
Neutropenia	0	0	1	4	5 (55.5)
Anemia	0	2	2	0	2 (25.0)
Thrombocytopenia	1	0	0	0	0
Non-hematological					
Febrile neutropenia	0	0	1	0	1 (11.1)
Fatigue	4	0	0	0	0
Anorexia	4	0	0	0	0
Diarrhea	0	0	0	0	0
Constipation	0	0	0	0	0
Pneumonitis	0	0	0	0	0
Creatinine increase	0	0	0	0	0
AST increase	2	0	0	0	0
ALT increase	4	0	0	0	0
Phlebitis	0	1	0	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

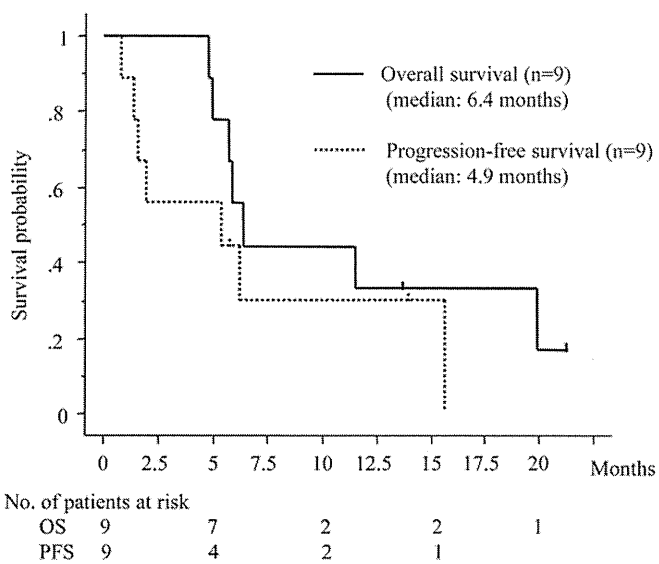

Figure 1. The survival curve of the patients with thymic carcinoma (TC) treated with amrubicin (AMR). Kaplan–Meier curves show the progression-free survival (PFS) and overall survival (OS) for relapsed TC patients who received AMR monotherapy ($n = 9$).

stabilizing a topoisomerase II-mediated cleavable complex, although they may also exert a minority of their effects as a result of DNA intercalation. Amrubicinol is 5–100 times more active than AMR (10,11).

Several reports have demonstrated a high RR to first-line combination chemotherapies involving ADOC and CODE in Japanese patients with advanced TC (4,5). Doxorubicin is considered to be a highly reliable agent against TC. However, anthracycline-based regimens are associated with cardiomyopathy and heart failure. Therefore, it is necessary to establish a more effective and less toxic regimen for TC.

Very low levels of AMR accumulate in the soluble and membrane fractions of human myocardial strips, in comparison to doxorubicin or epirubicin. Therefore, AMR accumulates at lower levels in the heart than doxorubicin or epirubicin (12). As a result, AMR, an anthracycline, could potentially be an effective second-line and beyond chemotherapy for TC, with lower toxicity compared with the existing regimens.

There have been a few case reports of alternative chemotherapy for TC. For example, Igawa et al. reported a marked response to AMR monotherapy (7). In addition, there have been some case reports that have shown a response to cytotoxic monotherapy, such as AMR (7) or S-1 (13) as second-line chemotherapy. However, to the best of our knowledge, this is the first report to evaluate the feasibility and efficacy of AMR, a novel anthracycline anticancer drug, as a second-line and beyond chemotherapy for recurrent TC. This retrospective study was, therefore, conducted to analyze the efficacy and safety of AMR in previously treated patients with recurrent TC.

AMR was administered as second-line and beyond chemotherapy for patients with recurrent TC. The RR was 44.4%. Although the present study was a retrospective analysis, and the number of patients was very small, AMR treatment might be active for relapsed TC. Grade 3 or higher toxicities were neutropenia (55.5%), anemia (25.0%) and febrile neutropenia (11.1%), including heavily treated patients. Moreover, cardiomyopathy and heart failure were not observed in any of the patients. The AMR treatment was, therefore, less toxic and more tolerable than other anthracycline agents, which could make it suitable for the second-line and beyond treatment of TC.

In summary, AMR as a single agent was found to be potentially useful as second-line and beyond chemotherapy for patients with recurrent advanced TC. Further multi-institutional prospective phase II studies are warranted.

Conflict of interest statement

Takashi Seto received grants from Dainippon Sumitomo Pharma Co., Ltd. Payment for lectures including service on speakers bureaus received from Nippon Kayaku Co., Ltd. Yukito Ichinose received payment for lectures including service on speakers bureaus from Nippon Kayaku Co., Ltd.

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A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (*EGFR*) mutation-positive advanced non-small-cell lung cancer (NSCLC)☆

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ABSTRACT

Introduction: The epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib is associated with survival benefits in patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). This phase II, single-arm study examined the efficacy and safety of first-line erlotinib in Japanese patients with *EGFR* mutation-positive NSCLC.
Methods: Eligible patients received erlotinib 150 mg/day until disease progression or unacceptable toxicity. The primary endpoints were progression-free survival (PFS) and safety.
Results: A high degree of concordance was observed between different mutation testing methodologies, suggesting feasibility of early, rapid detection of *EGFR* mutations. Median PFS was 11.8 months (95% confidence interval [CI]: 9.7–15.3) at data cut-off (1 June 2012) ($n = 102$). Exon 19 deletions seemed to be associated with longer PFS compared with L858R mutations; T790M mutations were tentatively linked with shorter PFS. The safety profile was as expected: rash (any grade; 83%) and diarrhea (any grade; 81%) were most common. Six interstitial lung disease (ILD)-like cases were reported, and 5 were confirmed as ILD-like events by the extramural committee. Two patients died of treatment-related pneumonitis (JAPIC Clinical Trials Information number: Japic CTI-101085).
Conclusion: Erlotinib should be considered for first-line treatment in this subset of Japanese patients, with close monitoring for ILD-like events.

1. Introduction

Non-small-cell lung cancer (NSCLC) remains a significant global health burden, with high mortality and poor prognosis for patients diagnosed at an advanced stage. Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI), which has been approved for the treatment of advanced NSCLC. Originally approved as second- or third-line treatment in patients refractory to chemotherapy, erlotinib showed overall survival (OS) and progression-free survival (PFS) improvements compared with

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placebo in a large phase III trial (OS: 6.7 vs. 4.7 months, respectively, hazard ratio [HR] = 0.7, 95% confidence interval [CI]: 0.58–0.85, $p < 0.001$; PFS: 2.2 vs. 1.8 months, respectively, HR = 0.61, 95% CI: 0.51–0.74, $p < 0.001$) [1]. Further trials have expanded its use to maintenance therapy (SATURN) [2] and to first-line treatment of *EGFR* mutation-positive disease (OPTIMAL and EURTAC) [3,4]. The latter 2 studies reported significant PFS benefits with erlotinib as first-line treatment for *EGFR* mutation-positive NSCLC compared with chemotherapy in Chinese and European populations (OPTIMAL: 13.1 vs. 4.6 months, respectively, HR = 0.16, 95% CI: 0.10–0.26, $p < 0.0001$; EURTAC: 9.7 vs. 5.2 months, respectively, HR = 0.37, 95% CI: 0.25–0.54, $p < 0.0001$).

Until now, erlotinib has not been prospectively evaluated in Japanese patients with *EGFR* mutation-positive NSCLC. This prospective, phase II, open-label study (JO22903) was initiated to obtain confirmatory efficacy and safety data in the first-line setting for Japanese patients with *EGFR* mutation-positive NSCLC, in order to corroborate data from Chinese and Caucasian populations.

2. Materials and methods

2.1. Study design and patients

JO22903 was a phase II, multicenter, open-label, non-randomized study conducted at 25 centers in Japan. Eligible patients were aged ≥20 years with advanced, untreated, metastatic (stage IIIB/IV), or relapsed NSCLC, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and tumors harboring confirmed activating mutations of *EGFR* (exon 19 deletion or L858R point mutation in exon 21), with at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Staging was assessed by TNM classification (7th edition). The study was carried out in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice guidelines. The protocol was approved by ethics committees and all patients gave informed consent for study participation.

2.2. Procedures

Eligible patients received oral erlotinib 150 mg/day until disease progression (PD) or unacceptable toxicity (Fig. 1). Dose reductions (in 50-mg decrements) and/or interruptions (of up to 2 weeks) were permitted to manage adverse events (AEs) related to erlotinib treatment. Treatment was interrupted if interstitial lung disease (ILD) was suspected; for patients with confirmed ILD diagnosis, erlotinib was discontinued immediately. In cases of gastrointestinal perforation or any grade 4 AE, erlotinib was discontinued.

Patients were screened for *EGFR* mutations in a local or central laboratory. In the central laboratory, *EGFR* mutation status was determined using Scorpion ARMS [5]. For exploratory analyses, tumor samples were obtained from hospital archives for patients who were screened in their local laboratory to confirm the concordance between several local methods and Scorpion ARMS. In addition, serum samples were collected at screening from all patients who provided informed consent to participate in the exploratory research ($n = 95$). DNA was isolated from serum with the QIAmp MinElute Virus Spin kit (Qiagen, Hilden, Germany). Scorpion ARMS was used for *EGFR* mutation testing for circulating DNA in the serum.

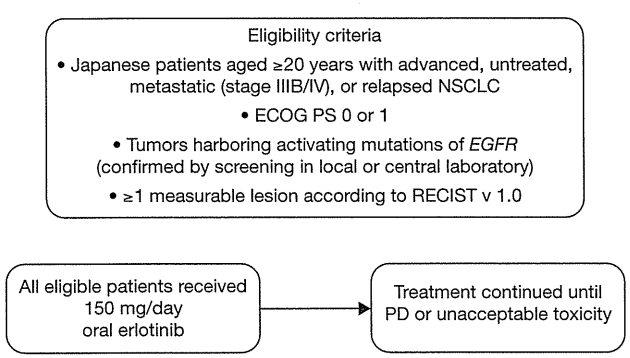

Fig. 1. Study design and eligibility criteria.

Tumor response was assessed by an independent review committee (IRC) using RECIST version 1.0. Tumor response evaluation was scheduled every 6 weeks. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AE) version 4.0.

At baseline mandatory lung and abdominal scans (CT/MRI), brain scans (CT/MRI) and bone scans (bone scintigraphy, PET, CT and MRI) were performed. During treatment until disease progression, lung and abdominal scans were mandatory. Brain scans were required for those patients who revealed brain metastases at baseline. When confirming complete or partial tumor response, bone scans were required for patients with bone metastases at baseline.

2.3. Study endpoints

Primary endpoints were PFS, as assessed by an IRC, and safety profile. Secondary endpoints included overall response rate (ORR), disease control rate (DCR), and OS. Exploratory analyses examined concordance between different *EGFR* mutation testing methodologies, and concordance between serum and tumor tissue at screening. *EGFR* mutation status alterations in serum before and after treatment were observed.

2.4. Statistical analyses

The statistical plan assumed a median PFS of 7 months in the historical control group and 11 months in the erlotinib treatment group. The primary analysis was planned for 11 months after the last patient was enrolled to confirm superiority of erlotinib over the historical control.

Given an expected median PFS of 11 months, 93 patients were necessary to provide statistical power of 80% to confirm the superiority of the lower confidence boundary of the observed median PFS compared with the threshold median PFS of 7 months. The target sample size was 100 patients, taking into consideration patients who would prove to be ineligible for the study. For PFS (the primary efficacy endpoint), OS, and duration of response, median and 95% CIs were estimated using Kaplan–Meier survival methodology. CI limits were calculated according to the Greenwood method. Response rate and DCR were summarized by presenting the rate and 95% CIs according to Pearson–Clopper.

The analysis of safety parameters (co-primary endpoint) was descriptive: all AEs were converted to MedDRA preferred terms and summary tables were produced. For laboratory parameters, descriptive summary tables or graphs of change over time were produced.

According to the statistical analysis plan, all patients who received at least 1 dose of study treatment would be included in the safety population. The modified intention-to-treat (ITT) population for the efficacy analysis excluded all patients with major protocol violations.

3. Results

3.1. Patient population

Between 8 April 2010 and 6 October 2010, 103 patients with confirmed *EGFR* mutations were enrolled and received erlotinib,

Table 1
Baseline characteristics for the safety population ($n = 103$).

Characteristics	n (%)
Median age, years (range)	65.0 (36–86)
Gender	
Female	70(68)
Male	33(32)
ECOG PS	
0	49(48)
1	54(52)
Smoking status	
Current smoker	7(7)
Former smoker	37(36)
Never smoker	59(57)
Median Brinkman index (range) ($n = 44$)	580.0 (3–1720)
Type of *EGFR* mutation	
Exon 19 deletion	50(49)
L858R mutation	51(50)
L858R mutation + T790M	2(2)
EGFR mutation in serum ($n = 95$)	
EGFR mutation detected	25(26)
EGFR mutation not detected	70(74)
Histology	
Adenocarcinoma	102(99)
Other	1(1)
Stage	
IIIB	4(4)
IV	74(72)
Post-operative recurrence	25(24)
Previous treatment	
Surgery	
Yes	25(24)
No	78(76)
Induction or adjuvant chemotherapy[a]	
Yes	12(12)
No	91(88)
Radiation	
Yes	17(17)
No	86(84)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor.

[a] Patients may have had prior therapy providing the following conditions were met: platinum-based chemotherapy: wash-out period of 6 months; non-platinum-based chemotherapy: wash-out period of 4 weeks.

comprising the safety population. The majority of patients (95/103; 92%) had their samples screened in local practice, while the remaining 8 (8%) had their samples screened at a central laboratory. One patient was excluded from the modified ITT population as they had a major protocol violation after enrollment. The baseline characteristics for the safety population are shown in Table 1. At the time of data cut-off for the primary analysis (1 September 2011), 44 patients remained in the study, either on treatment or in follow-up.

3.2. Efficacy analyses

At the primary analysis (data cut-off 1 September 2011), median PFS with first-line erlotinib was 11.8 months (95% CI: 9.7 to not reached). The 1-year event-free survival rate was 49% (95% CI: 39–59). Eighty patients had a complete or partial response with erlotinib, giving an ORR of 78% (complete response: 4 patients; partial response: 76 patients); a further 17 patients had stable disease, giving a DCR of 95%.

In the follow-up analysis (data cut-off 1 June 2012), the median PFS was 11.8 months (95% CI: 9.7–15.3) (Fig. 2) and had not changed after a longer follow-up. The 1-year event-free survival rate was 50% (95% CI: 40–60). The median duration of response was 11.1 months (95% CI: 9.7–13.9). Full response data also did not change with a follow-up analysis by IRC.

Subgroup analyses of baseline characteristics and PFS are summarized in Fig. 3. All patient subgroups showed favorable PFS regardless of gender, age, smoking status, disease stage, or type of *EGFR* mutation.

Examining the PFS results by *EGFR* mutation type, i.e., exon 19 deletions vs. L858R point mutations, demonstrated that exon 19 deletions seemed to be associated with longer PFS (Fig. 4a). Median PFS with exon 19 deletions ($n = 50$) was 12.5 months (95% CI: 10.3–16.6), while with L858R mutations ($n = 50$) it was 11.0 months (95% CI: 6.9–15.2). Two patients whose tumors harbored the T790M mutation with L858R had poor outcomes, with PFS of 2.9 and 4.6 months, respectively. It should be noted that it is impossible to distinguish between prognostic or predictive effects of different mutations without a control arm. In this study, however, the 4 patients with complete response to erlotinib all had tumors with exon 19 deletions (Fig. 4b). Response rate with exon 19 deletions ($n = 50$) was 84%, while with L858R mutations ($n = 50$) it was 76%.

Examining PFS by grade of skin rash determined that higher grades (grade ≥ 2) of rash were associated with longer PFS with erlotinib (Supplementary data, Fig. S1).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.07.003.

By the second cut-off date, 28 of 102 patients had died. The median survival time could not be calculated.

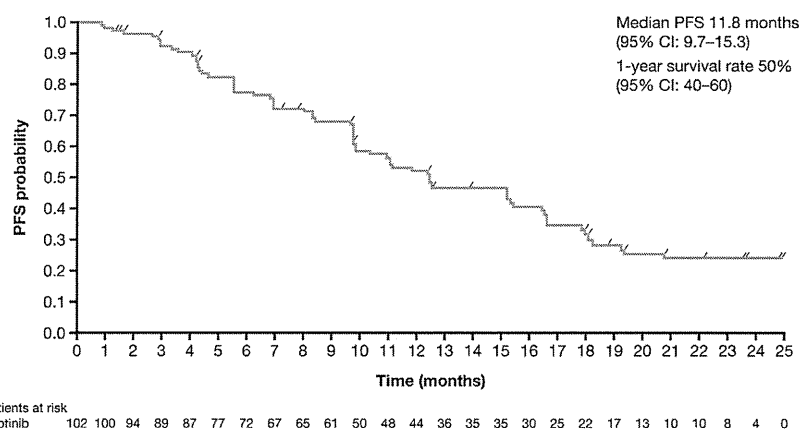

Fig. 2. PFS in the modified ITT population by the follow-up analysis (1 June 2012 data cut-off). PFS = progression-free survival; ITT = intention-to-treat; CI = confidence interval.

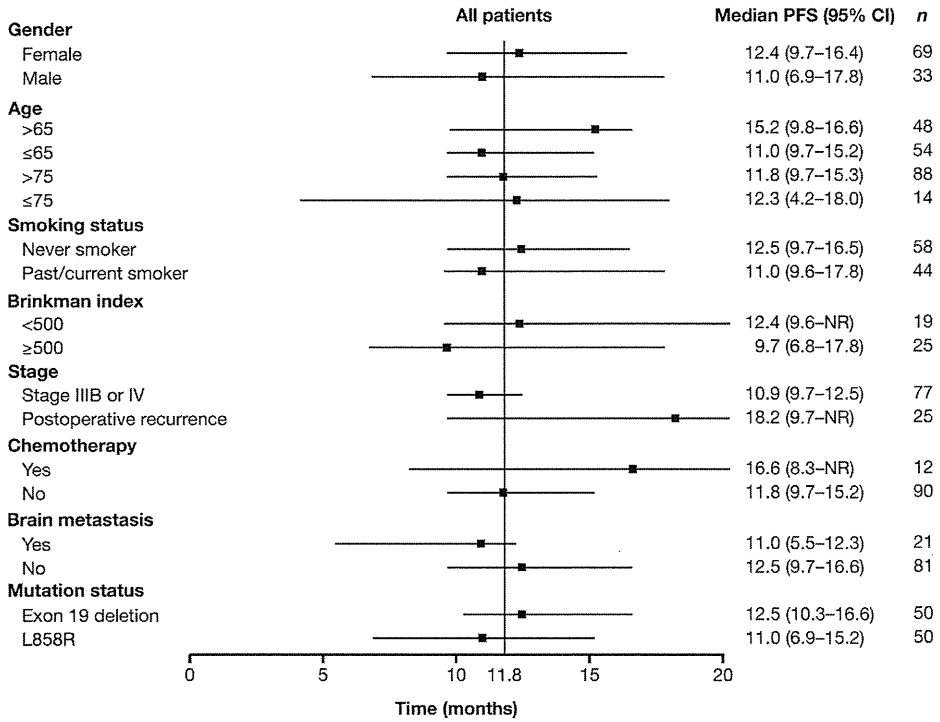

Fig. 3. Forest plot of subgroup analyses for PFS (1 June 2012 data cut-off). PFS = progression-free survival; CI = confidence interval.

3.3. Safety analyses

AEs reported in more than 20% of patients in the safety population are presented in Table 2. Two patients died of treatment-related pneumonitis; in both cases, simultaneous PD was reported by the investigators. A total of 43 patients required dose modification due to AEs of grade ≥2, the majority of which were skin toxicities (n = 22). Ten patients (10%) discontinued erlotinib due to AEs: ILD or ILD-like events (n = 6), abnormal liver function or liver enzyme levels (n = 3), and skin rash (n = 1).

Six ILD-like cases were reported, and 5 cases were confirmed as ILD-like events according to the extramural committee. Three cases were grade 1/2, 2 were grade 5, and the 1 unconfirmed ILD case was grade 1. One fatal ILD case that occurred 9 months after treatment initiation showed co-existence of aspiration pneumonia. The extramural committee suggested the possibility that ILD developed as a secondary complication following the aspiration pneumonia. By the second cut-off date (1 June 2012), no further ILD or ILD-like events had been observed.

Table 2
AEs occurring in >20% of the safety population (n = 103).

	Any grade		Grade 1		Grade 2		Grade ≥3	
	n	%	*n*	%	*n*	%	*n*	%
Rash	85	83	27	26	44	43	14	14
Diarrhea	83	81	58	56	24	23	1	1
Dry skin	79	77	45	44	29	28	5	5
Paronychia	68	66	17	17	50	49	1	1
Pruritus	66	64	36	35	27	26	3	3
Stomatitis	65	63	45	44	19	18	1	1
Decreased appetite	36	35	20	19	13	13	3	3
Nasopharyngitis	34	33	25	24	9	9	–	–
ALT increased	34	33	21	20	5	5	8	8
Alopecia	28	27	27	26	1	1	–	–
AST increased	27	26	19	18	5	5	3	3
T-Bil increased	26	25	11	11	15	15	–	–

Abbreviations: AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T-Bil = total bilirubin. No patient counted here had a grade 4/5 adverse event.

3.4. Exploratory analyses

This study offered an opportunity to assess concordance across different methodologies. Forty archive samples from local testing were assessed at a central laboratory; for 38 of the samples (95%), the central laboratory testing produced identical results to the original local laboratory testing. Baseline serum samples were available from 95 patients, and *EGFR* mutations were detected in 25 patients (centrally by Scorpion ARMS), which showed the same mutation type as the tumor (Supplementary data, Tables S1–S3 and Fig. S1). No patients showed T790 M mutation in serum at baseline. In the serum samples obtained from the 2 patients whose tumors showed T790 M at baseline, no mutation at baseline was observed in the serum sample.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.07.003.

4. Discussion

JO22903 is the first prospective study to investigate erlotinib for the first-line treatment of *EGFR* mutation-positive NSCLC in Japanese patients. In this study, the lower boundary of the 95% CI was 9.7 months, which was longer than the 7 months threshold value, and the median PFS reached 11.8 months in this patient population.

The median PFS of 11.8 months is similar to that reported for Chinese patients with *EGFR* mutation-positive disease in the phase III OPTIMAL study, which was 13.1 months [3]. The PFS of both the present study and OPTIMAL were slightly higher than the PFS in European patients with *EGFR* mutation-positive NSCLC (9.7 months) [4]. Gefitinib has also been evaluated as a first-line treatment for NSCLC in Asian patients. According to a retrospective

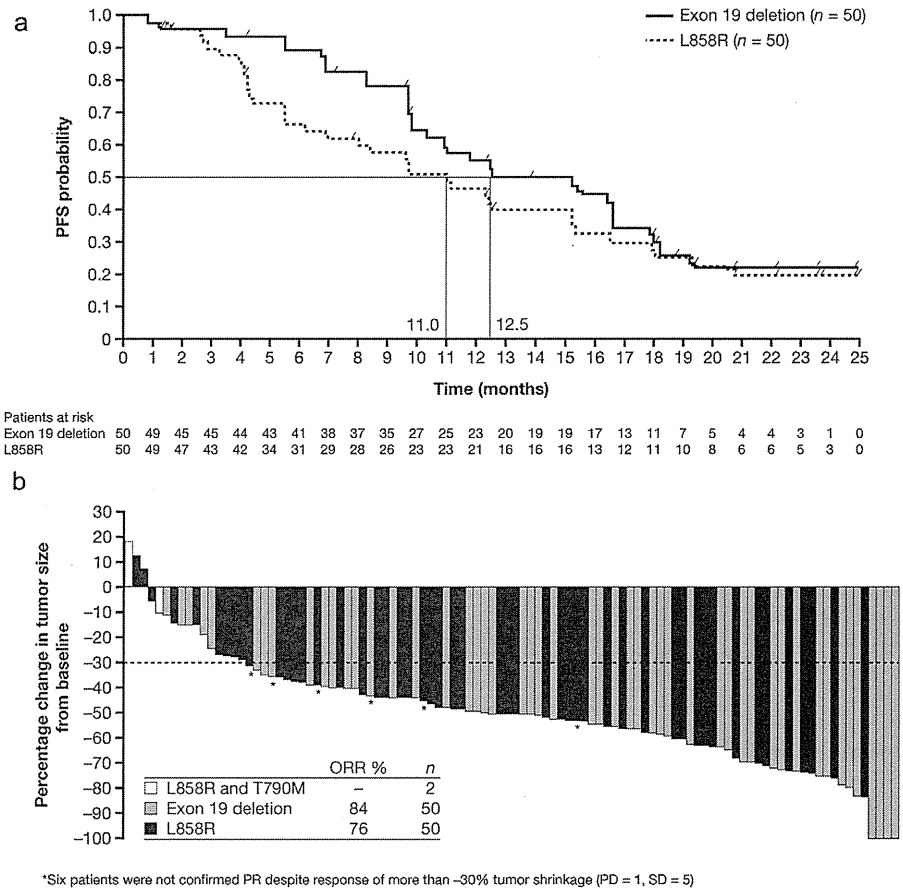

Fig. 4. (a) PFS according to type of *EGFR* mutation (1 June 2012 data cut-off). PFS = progression-free survival; EGFR = epidermal growth factor receptor. (b) Waterfall plot of tumor response by type of *EGFR* mutation. Negative values represent a decrease in tumor size from baseline and positive values represent an increase in tumor size from baseline. The dashed line represents partial response indicated by 30% tumor shrinkage. EGFR = epidermal growth factor receptor; ORR = overall response rate; PR = partial response; PD = progressive disease; SD = stable disease.

analysis of the IPASS study by *EGFR* mutation status, the subgroup of patients with *EGFR* mutation-positive NSCLC had a median PFS of 9.5 months [6]. In addition, 2 Japanese studies in patients with *EGFR* mutation-positive NSCLC showed median PFS of 9.2 and 10.8 months (WJTOG3405 and NEJ002, respectively) [7,8]. Again, these medians are similar to that achieved in the present study (Supplementary data, Table S4).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.07.003.

According to an analysis of data from an online tumor registry examining first-line EGFR TKI treatment, all efficacy outcomes (ORR, time to progression, OS) were better in patients with exon 19 deletions compared with L858R mutations [9]. In the EURTAC study, a similar trend was observed. However, this association has not been observed in gefitinib studies (IPASS, NEJ002 and WJTOG3405) [6–8]. The present study also showed longer PFS in patients with exon 19 deletions rather than L858R mutations (median PFS of 12.5 and 11.0 months, respectively). This study suggests that the difference seen in efficacy outcomes between patients with exon 19 deletions mutations and those with L858R is specific to erlotinib, as also demonstrated in the EURTAC study [4].

The safety profile of erlotinib in this study was as expected, with rash and diarrhea being the most common AEs. Although patients in this study received treatment with erlotinib for a longer duration than patients treated in the second- and third-line Japanese studies, due to the longer PFS, the common AEs were similar to previous studies [10,11]. No long-term toxicity was observed.

Six out of the total 108 patients included in the erlotinib second-/third-line Japanese studies were confirmed to have *EGFR* mutations [10,11]. Common AEs were similar between patients with *EGFR* mutation-positive NSCLC receiving first-line or second-/third-line erlotinib.

Six occurrences (6%) of treatment-related ILD or ILD-like events were reported by investigators, among which 5 (5%) were confirmed as ILD cases but 1 case was denied by an extramural committee. Two (2%) of these 5 were classified as severe and resulted in death. The WJTOG3405 and NEJ002 studies reported an ILD incidence of 2% (2/87, with 1 fatal case) and 5.3% (6/114 patients, with 1 fatal case), respectively [7,8]. According to a recent large-scale surveillance study of erlotinib in the second-/third-line treatment of Japanese NSCLC patients, the incidence of ILD was 4.5% and the mortality rate was 1.6% [12]. Thus, the incidence of ILD/ILD-like events in the JO22903 study was generally as expected. Close monitoring of Japanese patients for symptoms of ILD and immediate cessation of erlotinib therapy on diagnosis is recommended.

In this study, the incidence of grade 3 rash was 14%, compared with 2% in the WJTOG3405 study of gefitinib [7] and 5% in the NEJ002 study of gefitinib [8]. A higher incidence of grade 3 rash was observed in this study; however, with the exception of 1 patient, it was possible for patients to continue receiving erlotinib with dose modification and/or AE treatment.

The incidence of grade ≥3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation was 8% and 3%, respectively. In addition, the incidence of grade ≥3 abnormal hepatic function or liver disorder was 4% in this study. Three patients were withdrawn from erlotinib treatment due to abnormal liver function or liver enzyme levels. Despite these 3 patients showing normal enzyme levels for AST and ALT at screening, they showed severe changes approximately 1 month after treatment initiation.

A total of 43 patients required dose modification due to AEs, and 10 patients (10%) discontinued erlotinib in this study. In the WJTOG3405 study, 14 of 87 patients (16%) discontinued gefitinib due to AEs. Although the safety profile of these 2 EGFR TKIs seem to be slightly different, this study suggests that erlotinib has similar tolerability to gefitinib in the first-line treatment of Japanese patients with *EGFR* mutation-positive NSCLC.

A final exploratory aspect of this study concerned the *EGFR* mutation assessment for circulating DNA in serum. Twenty five (26%) of 95 patients showed *EGFR* mutation-positive disease assessed by Scorpion ARMS. This 26% detection rate was lower than in the EURTAC study (58 [53%] of 109 serum samples) [4], and seemed to be insufficient for the screening test. However, although low detection rates were seen in serum samples, both studies showed high concordance (~100%) between serum and tumor samples at baseline. Thus, we cannot make definitive conclusions regarding the utility of serum samples as *EGFR* mutation assessment specimens.

5. Conclusions

This study indicates that early, local testing of *EGFR* mutation status is feasible and can reliably identify patients with *EGFR* mutation-positive NSCLC. The reported PFS in this study of Japanese NSCLC patients was 11.8 months with first-line erlotinib treatment, which is comparable to PFS outcomes seen with this agent in other *EGFR* mutation-positive populations, confirming that erlotinib can provide a good PFS benefit in this subgroup. Erlotinib was generally well tolerated, although 6 (of 103) patients reported ILD/ILD-like events and 5 were confirmed by an extramural committee, confirming that ILD remains a risk with EGFR TKI treatment in Japanese patients. Continued monitoring for symptoms of ILD and prompt action on diagnosis is recommended. Despite this, the efficacy and manageable safety profile demonstrated by erlotinib in this study confirms that erlotinib should be recommended for the first-line treatment of Japanese NSCLC patients with *EGFR* mutation-positive disease.

Role of the funding source

This trial was designed, funded by and monitored by Chugai Pharmaceuticals Ltd. Data were collected, analyzed and interpreted by Chugai with input from the authors and investigators. The initial draft of the manuscript was reviewed and commented on by all authors and by employees of Chugai. The corresponding author was provided data from Chugai and took full responsibility for the final decision to submit the paper.

Conflict of interest statement

K. Goto, M. Nishio, M. Maemondo, T. Seto, and T. Tamura have received lecture fees from Chugai Pharmaceutical Co. Ltd. N. Katakami has previously received payment from Chugai Pharmaceutical Co. Ltd. for writing or reviewing manuscripts. T. Fukuyama is an employee of Chugai Pharmaceutical Co. Ltd. All remaining authors have declared no conflicts of interest.

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Preoperative Concurrent Chemoradiotherapy of S-1/Cisplatin for Stage III Non-Small Cell Lung Cancer

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Background. Concurrent chemoradiotherapy using S-1 containing tegafur, an oral 5-FU prodrug, plus cisplatin has been reported to show promising efficacy against locally advanced non-small cell lung cancer with acceptable toxicity. The purpose of this study is to assess the impact of this induction treatment followed by surgery on survival for those patients.

Methods. Potentially resectable locally advanced non-small cell lung cancer patients were eligible. The concurrent phase consisted of S-1 (orally at 40 mg/m^2 twice a day on days 1 to 14 and 22 to 36) and cisplatin (60 mg/m^2 on days 1 and 22) with radiation of 40 Gy/20 fractions beginning on day 1 followed by surgical resection.

Results. Forty-two consecutive patients, between June 2005 and February 2011, were retrospectively analyzed. The median age was 59 (42 to 77) years, there were 34 males and 8 females, 26 cStage IIIA and 16 IIIB, each 21 adenocarcinomas and others. There were 26 partial responses and 16 stable disease cases after current induction treatment without uncontrollable toxicity. Of the 42 patients, 39 underwent surgical resection; 27 underwent a lobectomy and 12 pneumonectomies. One patient died due to thoracic empyema 65 days after surgery. The median follow-up time was 32.0 months. Three- and 5-year disease-free survival rates in all 39 resected patients were 52.0% and 44.0%, respectively, and 3- and 5-year overall survival rates were 77.4% and 61.7%, respectively.

Conclusions. Concurrent chemoradiotherapy using S-1 plus cisplatin followed by surgery may provide a better prognosis for locally advanced non-small cell lung cancer patients. Further prospective clinical investigation should be required.

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Stage III locally advanced non-small cell lung cancer (LA-NSCLC) comprises more than 30% of cases at the time of diagnosis [1]. Recent randomized phase III trials of concurrent chemoradiotherapy have shown better locoregional control, which leads to higher survival rates and is considered to be the current standard treatment for LA-NSCLC [2].

We previously reported concurrent chemoradiotherapy using uracil-tegafur (a 5-FU prodrug, UFT; Taiho Pharmaceutical Co, Ltd, Tokyo, Japan) plus cisplatin with concurrent thoracic radiotherapy of 60 Gy (UP-RT). The response rate and median survival time for unresectable LA-NSCLC patients treated with UP-RT were 80% and 16.5 months, respectively, with a lower incidence of adverse events than those of other trials [3]. The S-1 (TS-1; Taiho Pharmaceutical Co) is a second generation oral anticancer agent based on uracil-tegafur, which has a dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine. The S-1 is composed of tegafur, 5-chloro-2,4-dihydroxypyridine (an inhibitor of DPD) and potassium oxonate (an inhibitor of phosphoribosyl transferase), in a molar ratio of 1:0.4:1, and combination treatment with S-1 and cisplatin (SP) for advanced NSCLC has shown a better response rate of 33% to 47% and a median survival time of 11 to 16 months [4, 5] compared with the usual response rate of 29.1% and median survival time of 40 weeks for combination chemotherapeutic regimens using UFT plus cisplatin [6]. Of interest, the incidence of grade 3/4 hematologic and non-hematologic adverse events was lower in our study than that of other platinum-based combination regimens [7, 8]. According to the recent results of 2 randomized phase III trials of S-1 and carboplatin or cisplatin for advanced NSCLC, this regimen is now a standard regimen for chemotherapy in Japan [9, 10]. In addition, the West Japan Thoracic Oncology Group has reported a better prognosis; a median progression-free survival of

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