Table 3 Baseline patient characteristics *(Continued)*

Before bevacizumab therapy	25 (51)	9 (43)	7 (58)	
Yes (%)	24 (49)	12 (57)	5 (42)	P = 0.236[†]
No (%)	12	5	25	
Response rate for prior irinotecan-containing therapies (%)				
Pathological classification				
G1, G2 (%)	42 (86)	20 (95)	11 (92)	P = 0.481[†]
G3, G4 (%)	7 (14)	1 (5)	1 (8)	

ECOG PS Eastern Cooperative Oncology Group performance status.
[†]: Fisher's exact test.
[‡]: Kruskal–Wallis test.

Survival

The median PFS among patients with all wild-type tumors ($N = 49$), *KRAS* codon 12 or 13 mutations ($N = 21$), and *KRAS* codon 61, *KRAS* codon 146, *BRAF*, *NRAS*, or *PIK3CA* mutations ($N = 12$) was 6.1 months (95% confidence interval (CI) 3.1–9.2), 2.7 months (1.2–4.2), and 1.6 months (1.5–1.7), respectively (Table 4, Figure 2A). Median OS was 13.8 months (9.2–18.4), 8.2 months (5.7–10.7), and 6.3 months (1.3–11.3), respectively (Table 4, Figure 2B).

We observed statistically significant differences in both PFS and OS between patients with all wild-type tumors and those with *KRAS* codon 61, *KRAS* codon 146, *BRAF*, *NRAS*, or *PIK3CA* mutations [PFS: hazard ratio (HR), 0.22; 95% CI, 0.11–0.44; $P < 0.0001$] (OS: HR, 0.30; 95% CI, 0.15–0.61; $P < 0.0001$) (Figure 2A and 2B). Differences in PFS and OS between patients with wild-type mutations and the 8 patients with *KRAS* codon 61, *KRAS* codon 146, *NRAS*, or *PIK3CA* mutations were statistically significant (PFS: P = 0.001, OS: P = 0.001), but this was not the case for the 4 patients with *BRAF* mutations. The median PFS and OS for these 4 patients were 0.9 months and 11.4 months, respectively.

On the other hand, there were no statistically significant differences between patients with *KRAS* codon 12 or 13 mutations and those with *KRAS* codon 61, *KRAS*

Table 4 Efficacy in the test population determined on the basis of gene status

	All wild-type ($N = 49$)	*KRAS* codon 12, 13 mutations ($N = 21$)	*KRAS* codon 61, codon 146, *BRAF*, *NRAS* or *PIK3CA* mutations (any other mutations) ($N = 12$)	
Complete response	1	0	0	
Partial response	18	1	0	
Stable disease	19	11	4	
Progressive disease	11	9	8	
Total	49	21	12	
Response rate (%)	38.8	4.8	0	P = 0.006[*] (All wild-type vs. Any other mutations)
Disease control rate (%)	77.6	57.1	33.3	P = 0.006[*] (All wild-type vs. Any other mutations)
Progression-free survival [Median (95% CI) (months)]	6.1 (3.1, 9.2)	2.7 (1.2, 4.2)	1.6 (1.5, 1.7)	P < 0.0001[**] (All wild-type vs. Any other mutations)
Overall survival [Median (95% CI) (months)]	13.8 (9.2, 18.4)	8.2 (5.7, 10.7)	6.3 (1.3, 11.3)	P < 0.0001[**] (All wild-type vs. Any other mutations)
Relative dose intensity				
Irinotecan [Median (range) (%)]	72.8 (13.0–100)	81.0 (38.4–100)	98.0 (49.3–100)	P = 0.108[***]
Cetuximab [Median (range) (%)]	86.0 (35.7–100)	86.3 (11.1–100)	100 (80.0–100)	P = 0.042[***]
Number of treatment cycles [Median (range)]	12 (1–86)	5 (1–23)	3 (1–12)	P < 0.0001[***]

[*]: Fisher's exact test.
[**]: log rank test.
[***]: Kruskal–Wallis test.

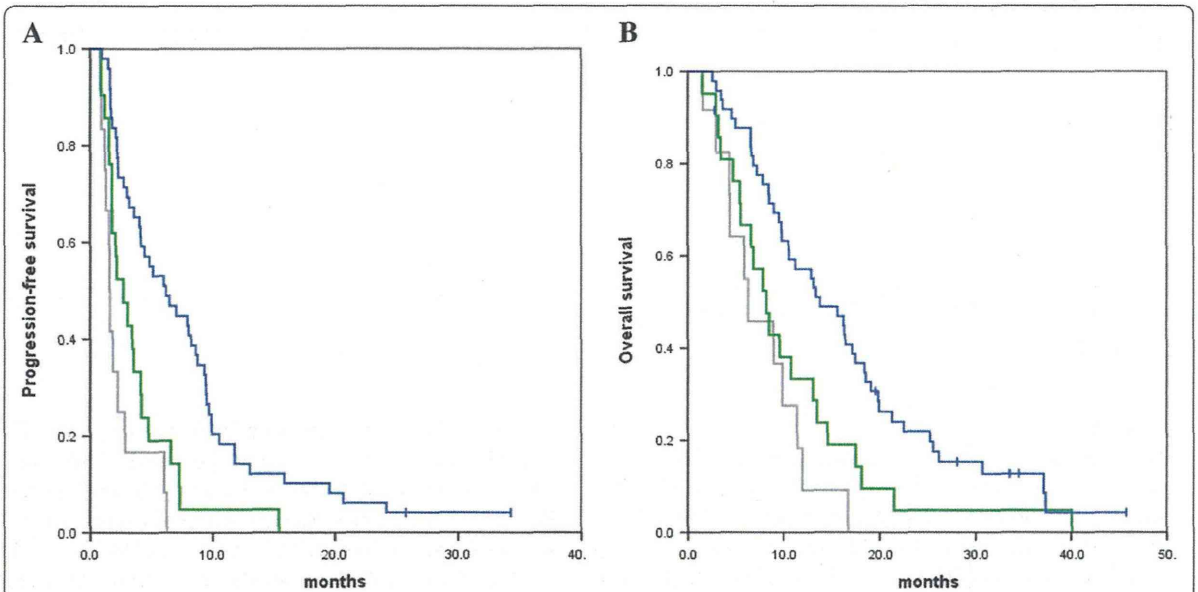

Figure 2 Kaplan–Meier plots of progression-free survival (PFS) and overall survival (OS) according to *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* gene status. Figure 2A. PFS: Median PFS values were 6.1 months [95% confidence interval (CI): 3.1–9.2], 2.7 months (1.2–4.2), and 1.6 months (1.5–1.7) among patients with all wild-type tumors (N = 49, blue line), *KRAS* codon 12 or 13 mutant tumors (N = 21, green line), and *KRAS* codon 61, *KRAS* codon 146, *BRAF*, *NRAS*, or *PIK3CA* mutant tumors (N = 12, gray-line), respectively. Differences in PFS values between patients with all wild-type tumors and those with *KRAS* codon 61, *KRAS* codon 146, *BRAF*, *NRAS*, or *PIK3CA* mutant tumors were statistically significant (hazard ratio, 0.22; 95% CI, 0.11–0.44; $P < 0.0001$). **Figure 2B. OS:** Median OS values were 13.8 months [95% confidence interval (CI): 9.2–18.4], 8.2 months (5.7–10.7), and 6.3 months (1.3–11.3) among patients with all wild-type tumors (N = 49, blue line), with *KRAS* codon 12 or 13 mutant tumors (N = 21, green line), and with *KRAS* codon 61, *KRAS* codon 146, *BRAF*, *NRAS*, or *PIK3CA* mutations (N = 12, gray-line), respectively. Differences in OS values between patients with all wild-type tumors and those with *KRAS* codon 61, *KRAS* codon 146, *BRAF*, *NRAS*, or *PIK3CA* mutant tumors were statistically significant (hazard ratio, 0.30; 95% CI, 0.15–0.61; $P < 0.0001$).

codon 146, *BRAF*, *NRAS*, or *PIK3CA* mutations (PFS: $P = 0.091$, OS: $P = 0.236$) (Figure 2A and 2B).

We also analyzed the differences in PFS and OS between patients with *KRAS* codon 12 mutations and those with *KRAS* codon 13 mutations. Similar to our previous study in a different population [17], there were no statistically significant differences between these groups (median PFS: *KRAS* codon 12, 2.1 months vs. *KRAS* codon 13, 3.4 months, P = 0.682; median OS: *KRAS* codon 12, 6.8 months vs. *KRAS* codon 13, 9.6 months, P = 0.147).

Discussion

This study is the first to verify the relevance of the mutation status of *KRAS* codons 61 and 146, *BRAF*, *NRAS*, and *PIK3CA*to the clinical efficacy of anti-EGFR antibody therapy among Asian patients. As reported in a pooled analysis from a European population, patients with the aforementioned less-frequent mutations exhibited statistically significant worse outcomes equivalent to those of *KRAS* codon 12 and 13 mutants [8]. Though systemically analyzed studies have not been reported since the first European analysis, our results strongly support the usefulness of the expanded pretreatment test for anti-EGFR therapies.

Because our aim was to compare the outcomes of *KRAS* codon 12 and 13 mutant cases with those characterized by other mutations, clinical data and FFPE specimens of the patients treated with cetuximab-containing regimens at seven Japanese cancer centers from July 2008 to April 2010 were collected. At that time, the Japanese authorities did not require pretreatment *KRAS* tests, and patients with *KRAS* codon 12 and 13 mutations were eventually treated with cetuximab. However, the proportion of patients with *KRAS* codon 12 or 13 mutant tumors in this study (25.6%) was slightly lower than that in previous reports of Western and Asian study populations [18], supposedly because several participating institutions had established lab-based tests and used the data for selecting nonbeneficiary populations. Among *KRAS* codon 12 and 13 wild-type cases, the proportion with mutations of overall tested genes (12/61, 19.7%) was similar to that of previous reports, suggesting that such expanded testing would be equally useful in Western and Asian countries.

Because the potential usefulness of multiplex mutation analyses is demonstrated, the development of robust *in vitro* diagnostic systems is needed for clinical application. The application of multiplex mutation detection systems in colorectal cancer specimens has been reported.

Lurkin I. et al. reported the validity of multiplex assays using a SNaPshot® Multiplex kit (Life Technologies), which detects 22 mutations in *KRAS, BRAF, NRAS,* and *PIK3CA* [19]. Here we evaluated a quality-controlled kit detecting 36 mutations of *KRAS* codons 61 and 146, *BRAF, NRAS,* and *PIK3CA* using Luminex (xMAP) technology. Data obtained by this kit were fully concordant with those by conventional direct sequencing, regardless of any variation in fixation methods between participating institutes (unpublished data).

This kit has several advantages with regard to its development for routine clinical use. It is manufactured under the same quality as the hitherto approved *in vitro* diagnostic kit detecting mutations in *KRAS* codons 12 and 13. Design of the hands-on operations is simple and easy; detection of the 36 mutations is performed in a single reaction of multiplex PCR followed by Luminex bead assay, with an overall hands-on time of 4.5 h. In addition, the requirement for template DNA is as low as 50 ng. We collected a median of 370 ng (range: 154–889) DNA per 10-μm biopsy slice in this study, which is sufficiently large to perform the test and to reserve backup DNA. Meanwhile, the ARMS–Scorpion assay, another approved *in vitro* diagnostic kit, requires larger amounts of template DNA. The currently approved *KRAS* codons 12 and 13 kit consists of 8 (1 control and 7 mutations) PCR reactions. A total of 80–160 ng of template DNA (10–20 ng for each PCR reaction) are needed to examine a sample [20], and it would be difficult to expand the PCR reactions because of the limitation of template DNA.

It has been estimated that approximately 10%–20% of all patients with colorectal cancer have either *KRAS* codon 61, *KRAS* codon 146, *BRAF, NRAS,* or *PIK3CA* gene mutations, suggesting that approximately 60,000–120,000 patients (10%–20% of the 600,000 who die annually from colorectal cancer) worldwide could be screened by this expanded mutation test. Furthermore, because the usefulness of regular administration of aspirin for patients with mutated *PIK3CA* colorectal cancer and the possibility of combining EGFR and BRAF inhibitors for patients with mutated *BRAF* colorectal cancer have been reported, detection of those mutations could become of greater importance in many ways [21,22]. Once further studies with larger sample sizes and a range of clinical samples provide evidence of its clinical utility, this technique might advance the precision of colorectal cancer treatment.

Conclusions

Our newly developed multiplex kit is practical and feasible for investigating various types of FFPE samples. Moreover, mutations in *KRAS* codon 61, *KRAS* codon 146, *BRAF, NRAS,* or *PIK3CA* detected in Asian patients were not predictive of clinical benefits from cetuximab treatment, similar to the result obtained in European studies.

Abbreviations

EGFR: Anti-epidermal growth factor receptor; PFS: Progression-free survival; OS: Overall survival; CI: Confidence interval; FFPE: Formalin-fixed, paraffin-embedded; CT: Computed tomography; H-E: Hematoxylin–eosin; PCR: Polymerase chain reaction; RR: Response rate; DCR: Disease control rate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TY and KT conceived the study design. HB carried out the majority of molecular genetic studies and analyses of the clinical data. ES, TN, KY, KY, SY, and SK provided clinical data and helped collect tumor tissues. SF carried out the pathological diagnoses. TY statistically analyzed the clinical data. AO coordinated the study and helped to draft the manuscript. All authors have read and approved the final manuscript.

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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.

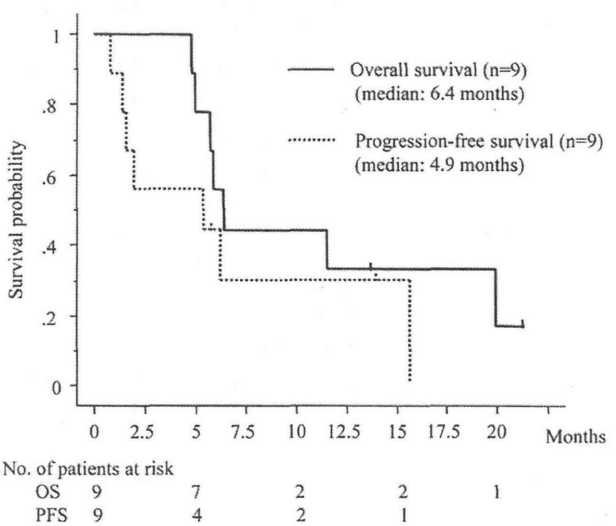

Figure 1. The survival curve of the patients with thymic carcinoma (TC) treated with amrubicin (AMR). Kaplan–Meier curves show the progression-free survival (PFS) and overall survival (OS) for relapsed TC patients who received AMR monotherapy ($n = 9$).

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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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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