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CLINICAL TRIAL REPORT

Phase I and pharmacologic study of weekly amrubicin in patients with refractory or relapsed lung cancer: Central Japan Lung Study Group (CJLSG) 0601 trial

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Abstract
Purpose To evaluate the safety and tolerability of amrubicin (AMR), determine its maximum tolerated dose (MTD), its dose-limiting toxicities (DLTs), and its recommended dose (RD), and to conduct a pharmacokinetic study of weekly AMR administrations in patients with chemotherapy-refractory or recurrent small cell or non–small cell lung cancer.
Patients and methods Patients with refractory or relapsed non–small cell and small cell lung cancer after 1 or 2 regimens of chemotherapy were eligible. AMR was initiated at 45 mg/m^2 weekly (repetition of dose on 1st and 8th day with a rest on day 15). The dose level was increased by 5 mg/m^2 by modified Fibonacci dose escalation scheme.
Results Seven patients had small cell lung cancer and 9 had non–small cell lung cancer. Fifty-four courses (median: 3, range: 1–6) were administered at 5 dose levels. At 65 mg/m^2, 3 patients had DLTs as follows: 1 was grade 3 (CTCAE v3.0) in AST/ALT, 1 was grade 3 febrile neutropenia, and 1 was grade 4 neutropenia. Leukocytopenia and neutropenia were correlated with amrubicinol (AMR-OH) C_{max} ($P = 0.042$, $P = 0.047$, respectively). The AUC (area under the curve of plasma concentration versus time extrapolated to concentration zero) of AMR and AMR-OH did not depend on the dose levels.
Conclusion In the present phase I study of AMR administered weekly to previously treated lung cancer patients, the maximum tolerated dose and RD were 65 and 60 mg/m^2,

Translational relevance

Amrubicin (AMR) is classified as an anthracycline agent and a potent topoisomerase II inhibitor. AMR was recently approved for the treatment of NSCLC and SCLC in Japan. AMR 45 mg/m^2 administered by intravenous infusion on days 1–3 of a 21-day course is an approved single-agent treatment schedule. A Japanese phase II study with intravenous infusion of AMR administered according to this schedule in previously untreated extensive-stage SCLC showed a high overall response rate (75.8%) and a long MST (11.7 months). Because of its substantial antitumor activity, the clinical development of AMR has also been focused on the treatment of refractory or recurrent lung cancer. However, severe, occasionally fatal myelotoxicity was found to predominate when AMR was administered to previously treated patients, even at the recommended dose of 45 mg/m^2. Furthermore, previous trials revealed that a weekly schedule of chemotherapy had a higher dose intensity, less severe adverse effects, and antitumor activity as effective as other treatments.

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respectively. The best response rate was 15.4%, and adverse events with this schedule were tolerable.

Keywords Lung cancer · Phase I–III trials · Lung cancer · Pharmacokinetics and pharmacodynamics · Amrubin · Amrubicinol · Weekly chemotherapy

Introduction

Lung cancer is the leading cause of cancer death, and approximately 12–17% of lung cancer patients are classified as having small cell lung cancer (SCLC) [1]. Despite high rates of response to first-line chemotherapy, most SCLC patients experience relapse within 2 years and die from systemic metastases. The 2-year survival rate is 4.6%, and the median survival time (MST) of patients with extensive-stage SCLC is generally less than 10 months [2]. Several studies have suggested the efficacy of combination regimens for relapsed SCLC [3–5]. However, median survival times (MSTs) of these studies are 6.1, 8.0, and 8.1 months, which are unsatisfactory results in terms of the risk–benefit balance.

Amrubicin (AMR) is classified as an anthracycline agent and a potent topoisomerase II inhibitor and is a promising agent for treating both small cell and non–small cell lung cancer. A completely synthetic 9-aminoanthracycline, AMR, is converted to the active metabolite amrubicinol (AMR-OH), which has a higher antitumor activity than its parent molecule. AMR was recently approved for the treatment of NSCLC and SCLC in Japan. AMR 45 mg/m^2 administered by intravenous infusion on days 1–3 of a 21-day course is an approved single-agent treatment schedule. A Japanese phase II study with intravenous infusion of AMR administered according to this schedule in previously untreated extensive-stage SCLC showed a high overall response rate (75.8%) and a long MST (11.7 months) [6]. This result is as effective as combination therapy. Because of its substantial antitumor activity, the clinical development of AMR has also been focused on the treatment of refractory or recurrent lung cancer. However, severe, occasionally fatal myelotoxicity was found to predominate when AMR was administered to previously treated patients, even at the recommended dose of 45 mg/m^2 [6, 7]. A phase I study was conducted for patients with refractory or relapsed lung cancer, and the recommended schedule of administration for AMR as a single agent is a daily treatment for 3 consecutive days every 3 weeks at a dose of 35 mg/m^2 [8]. Furthermore, previous trials showed that a weekly schedule of chemotherapy had higher dose intensity, less severe adverse effects, and an equivalent antitumor activity [9].

The purpose of this study was to evaluate the safety and tolerability of AMR and determine the maximum tolerated dose (MTD) and its dose-limiting toxicities (DLTs). The authors sought to determine the recommended dose (RD) of AMR for a weekly schedule, and to conduct a pharmacokinetic study of patients with chemotherapy-refractory or recurrent lung cancer.

Patients and methods

Patients who met the following criteria were enrolled in this study: histologically or cytologically confirmed refractory or relapsed SCLC or NSCLC patients who had undergone 1 or 2 previous chemotherapy regimens; received no therapy within 4 weeks before entry; were aged between 20 and 80 years; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and had adequate bone marrow function, normal hepatic function (total bilirubin <1.5 mg/dL, AST/ALT <2 times upper limit of normal [ULN]), and normal renal function (serum creatinine <ULN) , SpO_2 >90%, and left ventricular ejection fraction of >60%. Prior radiation therapy or major surgery was to be completed at least 3 weeks before enrollment, and patients were required to have completely recovered from all adverse effects.

Patients were ineligible for participation in the study if they had contraindication to AMR, uncontrolled effusion (pleural, pericardiac, or other effusion which requires drainage), serious systemic disease, clinically significant cardiovascular disease, uncontrolled diabetes mellitus and hypertension, active malignancy, or active serious infection.

This study was approved by the institutional review boards of the participating hospitals and conducted in accordance with Japanese Clinical Practice guidelines. Written informed consent was obtained from all patients.

Study design and treatment plan

This was an open-label, multi-center, non-randomized, dose-escalating phase I study. AMR was dissolved in 12 mL of normal saline and administered intravenously as a 5-min infusion on day 1 and day 8 every 3 weeks. The starting dose of AMR on this weekly schedule was 45 mg/m^2. Treatment was administered every 3 weeks until disease progression or unacceptable toxicity was apparent, or until refusal by the patient. Dose escalation was based on a modified Fibonacci schedule. If there was no dose-limiting toxicity (DLT) in any 3-person cohort, the AMR dosage was incrementally increased by 5 mg/m^2/day (45–65 mg/m^2/day) to determine the MTD. DLTs were assessed in the 1st course. Intrapatient dose escalation was not allowed.

Before the start of treatment, patients had to have adequate hematologic (leukocyte count >3,000/mm^3, ANC > 1,500/mm^3, and platelet count >100,000/mm^3), hepatic (total bilirubin <1.5 times ULN, AST/ALT <2 times ULN), and renal (serum creatinine <1.5 times ULN) function. When the leukocyte count decreased to <1,000/mm^3 after administration of AMR and the decrease persisted for 4 days or longer, or when the lowest platelet count was <50,000/mm^3, the dosage was reduced for the following course by 5 mg/m^2/day. Dose reduction was allowed up to two times. Patients who needed a third dose reduction were withdrawn from the study. Patients could receive full supportive care but were not prohibited from receiving immunotherapy or other cytotoxic agents.

Assessment efficacy and safety

Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.0. Baseline evaluation was performed within 4 weeks before the first course of treatment. The same measurements were taken again every 4 weeks from the first set of treatments. The judgment of response was confirmed at least 4 or 6 weeks after it was first documented. Complete response (CR) was defined as the disappearance of all lesions, and partial response (PR) as reduction by 30% or more in the size of total of measurable lesions, and no new lesions. Stable disease (SD) was confirmed with repeat assessments no less than 6 weeks after the initial claim of response. Progressive disease (PD) was defined as an increase of 20% or more in the total size of measurable lesions. Laboratory evaluation was performed weekly during the first course.

Adverse events were recorded and graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system, ver. 3.0. After the start of administration, echocardiogram was not mandatory. But when some cardiac symptom had occurred, it was required.

Dose-limiting toxicities were defined as a continuance of grade 4 leukocytopenia and neutropenia for more than 4 days, grade 3 febrile neutropenia, grade 4 thrombocytopenia, or grade 3 non-hematologic toxicity (with the exceptions of alopecia and anorexia).

Pharmacokinetics

Heparinized 2-mL blood samples were collected before the end of AMR infusion and 0.05, 0.5, 1, 3, 8, and 24 h after the end of infusion on day 1, and also before the end of AMR infusion and 0.05, 0.5, and 8 h after the end of infusion on day 8, during the first course of treatment. The blood was centrifuged immediately (3,000 rpm, 15 min, 4°C), and the plasma obtained was stored at −30°C. The plasma concentrations of AMR and AMR-OH were determined by HPLC. Plasma (0.2 mL) was diluted with 0.2 mL of a solution containing 16 mM citric acid, 16 mM of Na_2HPO_4, 0.9% of NaCl, and with 0.6 mL of 0.5 mM H_3PO_4. The resulting sample was then applied to a solid-phase extraction cartridge (Oasis HLB; Waters, Milford, MA, USA) before HPLC analysis.

Pharmacokinetic parameters for AMR and AMR-OH were derived by non-compartmental methods with the use of WinNonlin version 6.1 software (Pharsight, Cary, NC, USA). The area under the curve of plasma concentration versus time (AUC) was calculated by the linear trapezoidal rule from 0 to 24 h (AUC_{0-24}) for AMR, and from 0 to 8 h (AUC_{0-8}) for AMR-OH.

Results

Patient characteristics

Sixteen patients with histological or cytological confirmation of metastatic SCLC or NSCLC were enrolled between July 2006 and March 2008. Seven patients had small cell lung cancer and 9 patients had non–small cell lung cancer. A profile of the patient population is shown in Table 1. Six patients were women, 10 were men, and their median age was 68.5 years (range, 38–76). They had been treated with at least 1 platinum-based regimen. Seven patients were given one platinum-based regimen, four patients were given 2 platinum-based regimens, and 5 patients were given 1 platinum-based regimen and other non-platinum regimens. As for the response to prior chemotherapy, in one regimen population, three cases were PR, three were SD, and one was PD. In the population that received two regimens before the registration, at the first-line treatment, two were PR, 4 were PR, 1 was SD, and 2 had a response that could not be evaluated. At the second-line treatment, 2 were PR, 4 were SD, 1 was PD, and 2 had an invaluable response. The durations from the end date of just before chemotherapy were 461 days (range: 92–1,034) in non–small cell cancer patients who received 1 regimen of chemotherapy, 563 days (range: 46–773) in small cell cancer patients who received 1 regimen of chemotherapy, 101 days (range: 45–576) in non–small cell cancer patients who received 2 regimens of chemotherapy, and 89 days (range: 34–180) in small cell cancer patients who received 2 regimens of chemotherapy.

Dose levels and DLT

The dose escalation scheme and toxicities observed during the first course of AMR treatment are shown in Table 2. At the dose of 65 mg/m^2, a DLT was apparent in 3 of 4

Table 1 Patient characteristics

Characteristics	No. of patients	%
Patients enrolled	37	
Sex		
Male	10	62
Female	6	38
Age (years)		
Median	68.5	
Range	38–76	
PS (ECOG)		
0	8	50
1	7	44
2	1	6
Histology		
Adenocarcinoma	6	38
Large cell carcinoma	1	6
Small cell carcinoma	7	44
Non–small cell carcinoma	2	12
Prior therapy		
Chemotherapy		
1 platinum doublet	7	44
2 platinum doublets	4	25
1 platinum doublet and others	5	31
Radiotherapy	3	19
Operation	2	13

ECOG Eastern Cooperative Oncology Group

patients. All of these 3 patients had grade 4 neutropenia that persisted for 4 days or longer. Because all 3 patients in the 65 mg/m^2 dose cohort experienced DLT, this dose level was determined to be the MTD. The recommended dose level for phase II studies in previously treated patients was therefore determined to be 60 mg/m^2.

Treatment delivery

Sixteen patients received AMR at dose levels 1–5, and a total of 54 courses of treatment were performed. A median of 3 courses of treatment was performed at all dose levels. The dose was reduced in the second and subsequent courses at all levels. Two of 4 patients in 65 mg/m^2 cohorts were given a reduced dose. One patient received 4 courses after dose reduction. Another patient was administered 2 courses after dose reduction. The median quantity administered per course ranged from 27 mg/m^2/week with dose level 1 to 33.6 mg/m^2/week with dose level 5 and was not related to the quantity per dose (Table 2).

Toxicities

During the first courses, grade 4 neutropenia was observed at level 5, and grade 3 neutropenia was observed in one patient each in levels 2, 3, 4, and 5. Non-hematologic toxicities were transaminase (AST and ALT) elevation, nausea, vomiting, and hyperbilirubinemia, but these were generally mild and clinically reversible. One patient who experienced hyperbilirubinemia had a lymph node enlargement in the hepatic portal region.

In other treatment courses, grade 3 leukocytopenia was observed in levels 3, 4, and 5, and grade 3 neutropenia was observed in levels 3 and 5. One patient experienced grade 1 palpitation. Non-hematologic toxicities were grade 3 ALT and AST abnormalities, which were noted only in 1 patient. No treatment-related death occurred during this trial.

Responses

Of the 16 extensively pretreated patients with advanced lung cancer enrolled in the present study, 2 patients exhibited a partial response. One was a non–small cell cancer patient at level 1 (treated with 6 courses), and the other was a small cell cancer patient at level 3 (5 courses). Seven patients showed stable disease. Four were non–small cell cancer patients; one was at level 1 (2 courses), two at level 2 (6 courses and 4 courses), and one at level 5 (3 courses). The remaining three were small cell cancer patients; one was at level 4 (3 courses) and the others at level 5 (5 courses and 3 courses).

Table 2 Dose-limiting toxicity (DLT) and treatment delivery

Level	AMR dose (mg/m^2)	No. of patients	No. of patients with DLT	Course		Total exposure dose (mg/m^2/week)	
				Median	Range	Median	Range
1	45	3	0	3	2–6	27.0	27.0–31.7
2	50	3	0	3	4–6	33.3	28.9–33.0
3	55	3	0	3	1–5	31.0	28.9–33.0
4	60	3	0	3	1–4	30.0	30.0
5	65	4	3	3	1–5	33.6	28.1–36.5

Pharmacokinetics

Pharmacokinetic data were obtained in the first course of treatment for all patients enrolled in the study. The plasma concentration–time profiles of AMR and AMR-OH for the recommended dose (60 mg/m^2) on day 1 and day 8 are shown in Fig. 1. Plasma concentrations of both AMR and AMR-OH peaked at the end of AMR infusion and decreased rapidly thereafter. The concentrations of AMR and AMR-OH on day 1 and day 8 were approximately the same level.

At each dose level studied, the corresponding mean AUCs of AMR and AMR-OH were ranged from 4,274 to 6,487 /ng h/mL and from 690 to 1,032 /ng h/mL, respectively, and did not depend on the AMR dose on day 1 and day 8 (Table 3). No significant differences in pharmacokinetics parameters were observed between the MTD (65 mg/m^2)-treated group and the other dose-treated group. There are negative correlations between AMR dose levels and leukocyte (A), neutrophil (B), and platelet (C) nadirs (Fig. 2).

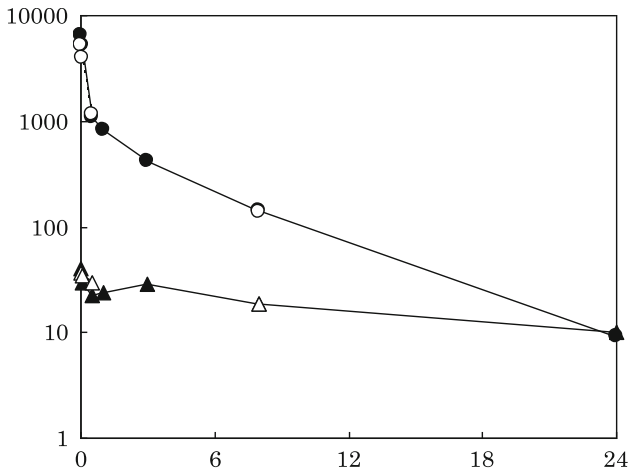

Fig. 1 Plasma concentration versus time profiles for amrubicin (*closed circles*: day 1, *open circles*: day 8) and amrubicinol (*closed triangles*: day 1, *open triangles*: day 8) in three patients treated with amrubicin at a dose of 60 mg/m^2

Discussion

In a prior phase I study of AMR as monotherapy in previously treated refractory or relapsed patients, the DLT was neutropenia and the MTD was 40 mg/m^2. The recommended dose of AMR was 35 mg/m^2 when administered intravenously on 3 consecutive days every 3 weeks. Although AMR on this schedule was generally well tolerated, patients heavily pretreated with platinum-based regimens may sometimes be susceptible to severe hematologic toxicities. In the phase II study of AMR at a dose of 35 mg/m^2, grade 3 or 4 neutropenia and febrile neutropenia were observed in 41.4% and 3.4% of all patients, respectively [10]. Furthermore, 3 daily infusions in an office or treatment center may be inconvenient for the patients. As for cardiac function, we performed heart echocardiography before beginning chemotherapy. The ejection fraction at baseline was distributed between 60 and 75%. Patients did not indicate a problem with this test. Four people underwent heart sonography after the treatment. One who was examined after 8 months and another who was inspected after 18 months did not show any change in ejection fraction. One examination was conducted 8 months later, and the ejection fraction decreased to 50% from 60% at the start of therapy. This patient was treated with irinotecan and ifosfamide after treatment in AMR. One felt palpitations during exercise for 2 months after starting treatment and received echocardiography and Holter monitoring. The ejection fraction decreased slightly from 60% before the start of chemotherapy to 55–60%. With Holter monitoring, the heart rate was 135 times/min from 73 times/min. The heart rate was 85 times/min by electrocardiogram before the start of therapy. However, no necessity for treatment was found.

Table 3 Pharmacokinetic parameters of amrubicin and amrubicinol

Dose (mg/m^2)	No. of patients	C_{max} (ng/mL)		AUC_{0-24h} (ng h/mL)		$t_{1/2}z$ (h)		CL (L/h/m^2)	Vss (L/m^2)
		Amrubicin	Amrubicinol	Amrubicin	Amrubicinol	Amrubicin	Amrubicinol	Amrubicin	Amrubicin
45	3	5,649 ± 3,276	235.4 ± 208.0	3,850 ± 1,026	554 ± 95	4.95 ± 2.91	28.68 ± 13.16	11.45 ± 3.15	52.26 ± 19.27
50	3	12,071 ± 6,234	437.7 ± 229.2	5,982 ± 2,789	586 ± 139	3.87 ± 1.26	12.18 ± 0.53	9.47 ± 4.68	32.61 ± 3.71
55	3	8,427*	212.3*	6,018 ± 2,312	490 ± 142	5.42 ± 0.62	14.66 ± 2.27	9.70 ± 3.35	44.38 ± 13.77
60	3	7,919*	44.8*	5,737 ± 364	378 ± 182	3.63 ± 0.67	13.39 ± 1.99	10.09 ± 0.99	33.02 ± 7.46
65	4	7,290 ± 3,681	64.9 ± 9.6	5,279 ± 1,814	265 ± 227	4.66 ± 0.54	13.13 ± 4.05	13.07 ± 3.81	46.66 ± 10.51

Data at each dose level are means ± SD with the exception of those indicated by an asterisk, which are means obtained from only two patients (blood samples were not collected before the end of AMR infusion)

C_{max} maximal plasma concentration, *AUC* area under the concentration–time curve, $t_{1/2}z$ half-life time at terminal phase, *CL* total body clearance, *Vss* volume of distribution at steady state

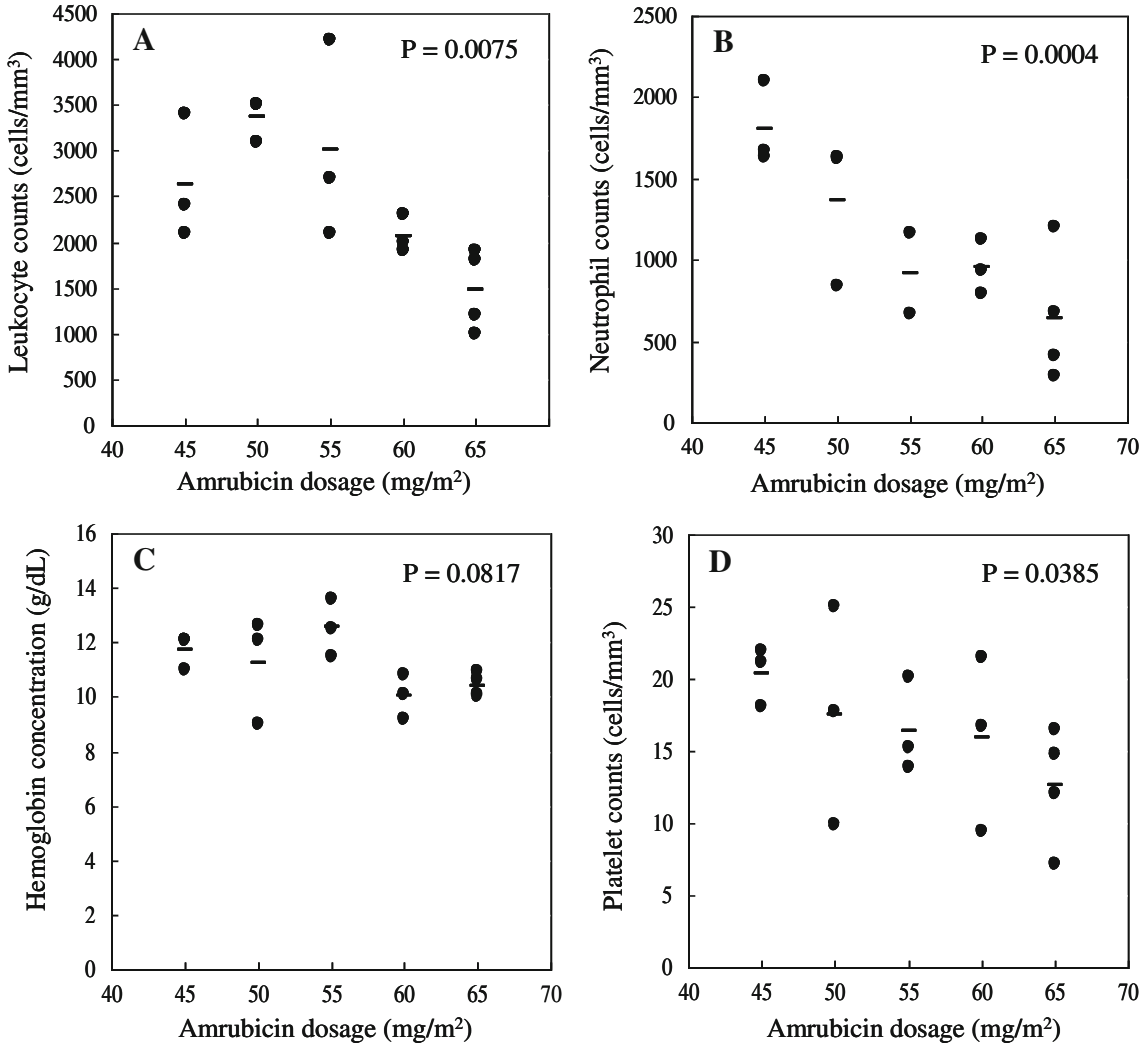

Fig. 2 Relationship between amrubicin dose level and leukocyte counts (**a**), neutrophil counts (**b**), hemoglobin concentration, (**c**) and platelet counts (**d**)

Weekly administration is a candidate dosing regimen alternative for reducing toxicity without compromising efficacy. Preclinical studies involving nude mice demonstrated that administration of AMR for 3 consecutive weeks is more tolerable than administration for 3 consecutive days. In light of these observations, we conducted this phase I study of AMR for the treatment of patients with advanced lung cancer.

In the present phase I study of AMR administered weekly in previously treated lung cancer patients, the MTD for AMR was 65 mg/m^2, given that 3 out of 4 patients at this dose level experienced DLT consisting of grade 4 neutropenia. The results indicated that administration of AMR at a dose of 60 mg/m^2 on day 1 and day 8 every 3 weeks is appropriate for subsequent phase II studies in previously treated patients, given that no patient experiences DLT with this regimen.

Although evaluation of antitumor activity was not the primary objective of the present study, partial response was observed in 2 of 16 (12.5%) patients at dose levels 1 (45 mg/m^2) and 3 (55 mg/m^2). The efficacy of AMR in refractory or relapsed lung cancer patients remains to be demonstrated in further phase II trials.

AMR is converted enzymatically to the C-13 hydroxy metabolite AMR-OH, of which cytotoxicity is about 10- to 100-fold greater than that of the parent drug. In both AMR and AMR-OH at the recommended dose (60 mg/m^2), there was no difference in the measured plasma concentration between day 1 and day 8. Plasma concentrations of AMR and AMR-OH at dose levels 1–5 were further measured to calculate the pharmacokinetic parameters of these two compounds. The AUCs of AMR and AMR-OH were virtually constant regardless of the dose, and no difference was noted between the dose of 65 mg/m^2, at which DLTs occurred, or at other doses. Similar trends were seen in $t_{1/2}$ and Vss (volume of distribution at steady state). As the $t_{1/2}$ of AMR-OH is longer than that of AMR, its antitumor

activity may be sustained along with persistent adverse reactions due to the long-term presence of highly cytotoxic AMR-OH in the body.

Conclusion

The maximum tolerated dose was 65 mg/m^2 when administered on days 1 and 8 every 3 weeks to previously treated patients with refractory or relapsed lung cancer. The DLTs were neutropenia and transaminase elevation. On the basis of this trial's findings, the recommended dose for phase II studies of AMR in previously treated patients is 60 mg/m^2 on days 1 and 8. Adverse events with this schedule are tolerated. The clinical efficacy of AMR for the treatment of refractory or relapsed SCLC or NSCLC is currently under investigation in phase II trials at multiple sites in Japan.

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