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A phase II study of amrubicin as palliative chemotherapy for previously treated malignant pleural mesothelioma

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Abstract

Background Treatment options for malignant pleural mesothelioma (MPM) are limited. Anthracyclines are considered key drugs for treating MPM. However, their use is limited by severe cardiac toxicities. Amrubicin (AMR) is a next-generation anthracycline that is commonly used to treat lung cancer. We conducted a phase II trial of this drug in patients with previously treated MPM.

Methods Eligible patients with MPM having adequate organ function and a performance status of 0–2 were enrolled after disease progression following pemetrexed/platinum therapy. Patients received 35 mg/m^2 AMR on days 1–3 every 3 weeks until tumor progression or the appearance of unacceptable toxicities. The primary endpoint was the objective response rate (ORR). Median progression-free survival (PFS), overall survival (OS), number of treatment cycles, and adverse events (AEs) were evaluated as secondary endpoints.

Results This trial was discontinued because of low accrual. From September 2013 to July 2018, five patients with MPM were enrolled. Stable disease (SD) was observed in three patients (60%), and progressive disease was noted in two patients (40%). The median PFS was 2.4 (range, 1.2–11.2) months, and the median OS was 9.1 (range, 6.2–22.0) months. The median number of treatment cycles was three (range, 2–11). Grade 1/2 toxicities were observed in all patients. Grade 3/4 neutropenia was observed in four patients (80%), but there were no cases of febrile neutropenia.

Conclusion Despite the absence of the responders, the observation of SD in three patients suggests that AMR could have potential for treating MPM.

Trial registration number and date of registration

UMIN000010739, May 16, 2013, retrospectively registered

Background

Asbestos exposure is a well-known high-risk factor for the development of malignant pleural mesothelioma (MPM), and its use is regulated differently by country. Therefore, the mortality rate of MPM is still increasing [1]. In total, MPM is estimated to be responsible for 38,400 deaths globally each year based on extrapolations from asbestos use [2]. The prognosis of MPM is poor, with an estimated median survival time of 4–12 months [3].

MPM is treated using multimodal strategies involving surgery, radiotherapy, and chemotherapy for localized disease [4]. Chemotherapy is used palliatively for extensive disease and postoperative recurrence. Concerning first-line chemotherapy, a phase III study reported the superiority of cisplatin plus pemetrexed over cisplatin alone, including longer survival times and higher response rates [5]. Regarding patients previously treated with platinum-based chemotherapy, a few phase II trials provided a low level of evidence because of their small sample sizes due to the rarity of MPM. To date, single-agent

chemotherapy including nivolumab, vinorelbine, or gemcitabine has been suggested to be effective as a second-line treatment [6, 7]. In addition, anthracyclines, doxorubicin, and pegylated liposomal doxorubicin have been explored in phase II trials of patients with previously treated MPM. However, positive results were not obtained in these trials because of severe cardiac toxicities. Conversely, amrubicin (AMR) is a new-generation anthracycline that is commonly used to treat lung cancer and that is well tolerated.

We conducted a phase II trial to determine whether AMR is effective in patients with previously treated MPM.

Methods

Study oversight

This single-center, open-label, single-arm phase II study was conducted at the Tokyo Metropolitan Cancer and Infectious Disease Center of Komagome Hospital (Tokyo, Japan).

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Research issued by the Japanese Ministry of Health, Labour and Welfare.

All patients provided written informed consent. The protocol was approved by the independent ethics committees of the Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital. The clinical trial registry number is UMIN000010739.

Eligibility criteria

The eligibility criteria were as follows: age of 20–74 years; histological or cytological diagnosis of unresectable advanced MPM; disease progression after one or more regimens including platinum-based chemotherapy; presence of one or more measurable lesions; a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0– 2; and adequate organ function.

Additionally, patients who were previously treated with a critical dose of other cardiotoxic drugs such as other anthracyclines (total dose: daunorubicin, 25 mg/kg; doxorubicin, 550 mg/m^2; epirubicin, 900 mg/m^2; pirarubicin, 950 mg/m^2) were also eligible.

Treatment procedure and dose adjustments

Patients were intravenously treated with AMR at a dose of 35 mg/m^2 body surface area on days 1–3 of each 3-week cycle until tumor progression (as determined according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria [8]) or unacceptable toxicities. After the end of protocol treatment, any treatment was allowed.

Safety and efficacy assessments

Adverse events (AEs) were assessed weekly during the first 3 weeks of the study and every 3 weeks thereafter according to the Common Terminology Criteria for AEs, version 4.0.

Tumor response was assessed every 6–8 weeks until disease progression according to RECIST.

Statistical analysis

The primary endpoint was the overall response rate (ORR) as evaluated by the investigators using RECIST. We assumed a threshold response rate of 10% and an expected response rate of 30% for previously treated MPM. The probabilities of α and β errors were set at 0.1 and 0.2, respectively. According to the Southwest Oncology Group two-stage design, assuming a registration period of 4 years and an observation period of 1 year, the calculated sample size was 24. The planned sample size was 26 considering a disqualification rate of 10%. The secondary endpoints were progression-free survival (PFS), overall survival (OS), safety, and the number of treatment cycles. PFS was defined as the period from the time of registration to that of disease progression or death. OS was defined as the period from the time of registration to that of death. PFS and OS were estimated using the Kaplan–Meier method. Efficacy and safety were assessed in all patients who received at least one dose of the study drug.

All data were analyzed using JMP version 11.2 software (SAS Institute, Inc., Cary, NC, USA, http://www.sas.com).

Results

The current phase II trial was interrupted because of low accrual; therefore, we are publishing this study as a case series.

Patient characteristics and treatment

From September 2013 to July 2018, six patients with MPM were enrolled in this study. After enrollment, one patient did not receive study treatment because of disease exacerbation. This patient was excluded from the study after receiving best supportive care, leaving five patients with MPM in the analysis (Table 1).

Table 1
Patients' characteristics.

	Age	Gender	Asbestos exposure	PS	Smoking status	Pathology	Stage
#1	70	Male	+	0	Ex-smoker	Epithelioid	II
#2	65	Male	+	2	Ex-smoker	Epithelioid	IIIB
#3	49	Male	+	1	Ex-smoker	Epithelioid	IA
#4	57	Male	+	1	Ex-smoker	Epithelioid	IIIB
#5	76	Male	+	1	Current smoker	Unknown	IIIB
PS, performance status							

Table 2
Cases

	Preoperative	1st line	2nd line	3rd line	4th line	5th line	surg	No. of cycles	BR
#1	-	CDDP +PEM	AMR	GEM	–	–	–	2	PD
#2	-	CBDCA +PEM	AMR	GEM	–	–	–	5	SD
#3	CDDP + PEM	PEM	AMR	Clinical trial	ICI	VNR	+	11	SD
#4	-	CDDP +PEM	AMR	GEM	–	–	*	2	PD
#5	-	CDDP +PEM	AMR	ICI	–	–	–	3	SD

CDDP, cisplatin; PEM, pemetrexed; CBDCA, carboplatin; GEM, gemcitabine; ICI, immune checkpoint inhibitor; VNR, vinorelbine; surg, surgery; BR, best response; SD, stable disease; PD, progression disease.

The median patient age was 65 years (range, 49–76), and all patients were men with histories of asbestos exposure and smoking. ECOG-PS was 0 in one patient, 1 in three patients, and 2 in one patient. Four patients had epithelioid type disease, and the remaining patient had an unknown pathology. According to the IMIG classification, one, one, and three patients had Stage IA, Stage II, and Stage IIIB disease, respectively. Only the patient with Stage IA disease had undergone surgery (extrapleural

pneumonectomy) before registration in this study. All patients were treated with platinum plus pemetrexed prior to enrollment, and all patients received the study treatment as a second-line regimen.

The median number of treatment cycles was three (range, 2–11). The reasons for treatment discontinuation were disease progression in four patients and patient preference related to AEs (grade 2 anorexia) in one patient.

Dose reduction was required in one patient because of the occurrence of febrile neutropenia. The reasons for treatment delay were AEs in two patients (febrile neutropenia, neutropenia) and patient's request in one patient.

Antitumor efficacy

The outcome of treatment with stable disease (SD) in three patients and progressive disease (PD) in two patients. Thus, the ORR was 0%, and the disease control rate (DCR) was 60% (90 confidence interval = 27.2–85.7).

The median PFS was 2.4 (range, 1.2–11.2) months, and the median OS was 9.1 (range, 6.2–22.0) months.

Safety.

There were no treatment-related deaths in this study (Table 3). Grade 1/2 toxicities were observed in all patients. Nine grade 3 or higher AEs were observed in four patients, including eight hematologic toxicities and one nonhematologic toxicity. Neutropenia was the most common grade 3 or higher hematologic toxicity, occurring in four patients, and leukopenia, anemia, thrombocytopenia, and febrile neutropenia occurred in one patient each.

Table 3
Adverse events in all patients

	Any grade (%)	Grade ≤ 2 (%)	Grade ≥ 3 (%)
Any event	5 (100)	5 (100)	4 (80)
Event leading to discontinuation of amrubicin	1 (20)	0 (0)	1 (20)
Event leading to death	0 (0)	0 (0)	0 (0)
Hematological event			
Decreased white blood cell count	4 (80)	3 (60)	1 (20)
Neutropenia	4 (80)	0 (0)	4 (80)
Anemia	5 (100)	4 (80)	1 (20)
Platelet count decreased	1 (20)	0 (0)	1 (20)
Non-hematological event			
Decreased appetite	4 (80)	4 (80)	0 (0)
Constipation	4 (80)	4 (80)	0 (0)
Nausea	3 (60)	3 (60)	0 (0)
Fatigue	3 (60)	3 (60)	0 (0)
Hypoalbuminemia	3 (60)	3 (60)	0 (0)
Hyponatremia	3 (60)	3 (60)	0 (0)
Alopecia	2 (40)	2 (40)	0 (0)
Extravasation/angialgia	2 (40)	2 (40)	0 (0)
Diarrhea	1 (20)	1 (20)	0 (0)
Stomatitis	1 (20)	1 (20)	0 (0)
aspartate aminotransferase level increased	1 (20)	1 (20)	0 (0)
alanine aminotransferase level increased	1 (20)	1 (20)	0 (0)
Dizziness	1 (20)	0 (0)	1 (20)
Hypertension	1 (20)	1 (20)	0 (0)

The nonPhematologic AE was dizziness. One patient requested treatment discontinuation because of grade 2 anorexia.

Discussion

This phase II study of AMR in patients with previously treated MPM was interrupted because of low accrual. Additionally, no responder was identified in the trial. However, the DCR was acceptable, and some patients continued treatment for a long time without serious side effects.

For patients with previously treated MPM, vinorelbine and gemcitabine are considered key chemotherapeutic drugs (ORR = 7–24%, OS = 8–10.6 months) based on the results of phase II trials [6, 7]. In recent studies, nivolumab was associated with an ORR of 26%, PFS of 6.1 months, and OS of 17.3 for patients with MPM who were previously treated with chemotherapy [7].

Meanwhile, doxorubicin was associated with response rates of 25–46% and median survival time of 8.8–10 months [9–12]. However, efficacy was limited by grade 3/4 myelosuppression, mucositis, nausea, vomiting, hair loss, and cardiotoxicity. Liposomal doxorubicin in combination with cisplatin was linked to a median time to progression of 4.6 months and a median OS of 19.6 months [13]. No complete or partial responses were observed in the current study, and the results of this study were inferior to those of nivolumab. However, the response rate of AMR was inferior to those of vinorelbine and gemcitabine, but the OS was similar. Therefore, AMR might be a potential treatment option. The clinical behavior of MPM is characterized by local spread, large pleural effusions, and metastasis to regional lymph nodes. The sarcomatous subtype of MPM is more frequently associated with distant metastases but little or no effusion, whereas mixed mesotheliomas have intermediate features. Most patients in the current study had epithelioid subtypes. The most effective drugs may differ by subtype, as pemetrexed is preferable for epithelioid MPM [14] and bevacizumab is effective against sarcomatoid MPM [15].

Most toxicities recorded in the study were controllable. Meanwhile, cardiac toxicities, which often occur in patients treated with anthracyclines, were not observed. These toxicities were similar to those observed in patients who received AMR for lung cancer [16]. Thus, AMR may have an acceptable adverse event profile in patients with previously treated MPM.

Several limitations in this study must be acknowledged. First, the sample size was too small to illustrate efficacy, and no responders were identified. Second, most patients in this study had epithelioid MPM, and sarcomatoid and biphasic subtypes were not registered. Third, this was a single-institutional clinical trial. Given that MPM is a rare cancer, further prospective, multi-institutional studies cannot realistically be conducted because of the regulations of the Clinical Trial Act. In addition, anthracycline-based chemotherapy may not be a sufficient treatment option in the immuno-oncology era for MPM. However, anthracyclines could be a key drug for treating MPM until novel treatments are identified.

Although the study result was not statistically significant, the findings have clinically significant implications considering that treatment options for MPM are limited. AMR monotherapy is a promising treatment approach for patients with previously treated MPM.

Conclusion

Three patients exhibited SD following treatment with AMR monotherapy. Our data suggested that AMR is a potential treatment option for MPM in later lines of chemotherapy.

Abbreviations

AMR, amrubicin; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; MPM, malignant pleural mesothelioma; ORR, overall response rate; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; PS, performance status; PFS, progression-free survival; PD, progressive disease

Declarations

Ethics approval and consent to participate

The protocol was approved by the independent ethics committees of the Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital. Written informed consent from each patient was required to participate. The clinical trial registry number is UMIN000010739.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

None declared.

Funding

Not applicable

Authors' contributions

MN and YO planed the current study and wrote the protocol. SK, KW, YO, MN, and YH collected and analyzed data. KW and YO wrote the manuscript. KW, YO, SK, MN, and YH approved the article.

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Figures

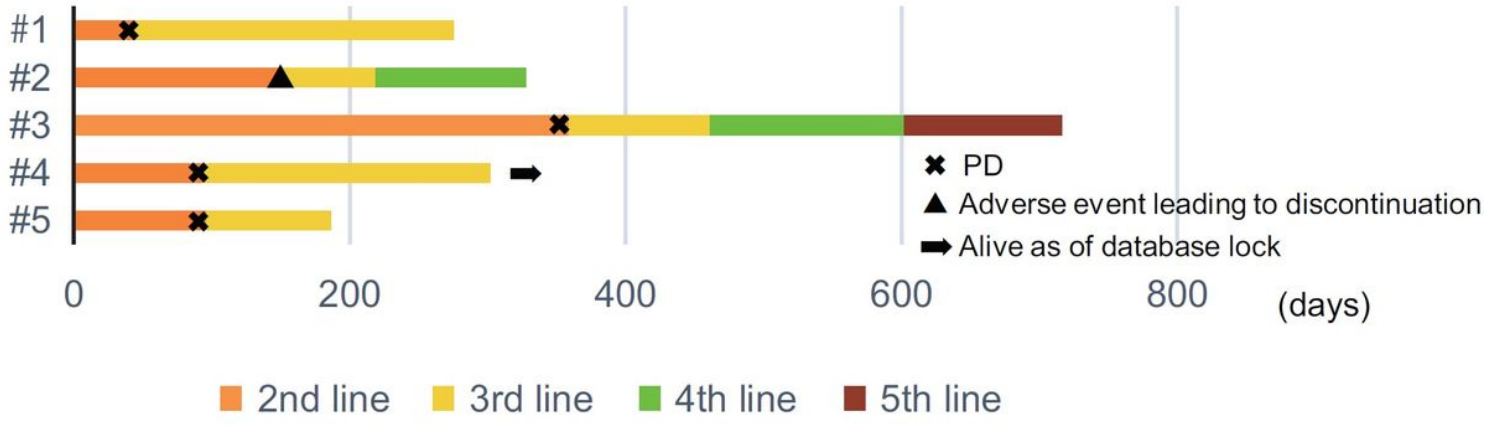


Figure 1

Swimmer's plot.

Supplementary Files

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