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ORIGINAL ARTICLE

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# Phase I and pharmacokinetic study of amrubicin, a synthetic 9-aminoanthracycline, in patients with refractory or relapsed lung cancer

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**Abstract** Amrubicin is a novel synthetic 9-aminoanthracycline derivative and is converted enzymatically to its C-13 hydroxy metabolite, amrubicinol, whose cytotoxic activity is 10–100 times that of amrubicin. We aimed to determine the maximum tolerated dose (MTD) of amrubicin and to characterize the pharmacokinetics of amrubicin and amrubicinol in previously treated patients with refractory or relapsed lung cancer. The 15 patients were treated with amrubicin intravenously at doses of 30, 35, or 40 mg/m$^2$ on three consecutive days every 3 weeks for a total of 43 courses. Neutropenia was the major toxicity (grade 4, 67%). The MTD was 40 mg/m$^2$, with the specific dose-limiting toxicities being grade 4 neutropenia persisting for >4 days, febrile neutropenia, or grade 3 arrhythmia in the three patients treated at this dose. A patient with non-small-cell lung cancer showed a partial response, and ten individuals experienced a stable disease. The area under the plasma concentration versus time curve (AUC) for amrubicin and that for amrubicinol increased with amrubicin dose. The amrubicin AUC was significantly correlated with the amrubicinol AUC. The recommended phase II dose of amrubicin for patients with lung cancer refractory to standard chemotherapy is thus 35 mg/m$^2$ once a day for three consecutive days every 3 weeks.

**Keywords** Amrubicin · Amrubicinol · Lung cancer · Pharmacokinetics · Phase I trial

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## Introduction

Anthracyclines such as doxorubicin have a potent antitumor activity and have been widely used in the treatment of acute leukemia, malignant lymphoma, and solid tumors. Amrubicin (SM-5887) is an entirely synthetic 9-aminoanthracycline anticancer drug and a potent inhibitor of topoisomerase II [1–8]. This novel agent is more potent than doxorubicin with regard to antitumor activity against various mouse experimental tumors and human tumor xenografts [9]. A major pathway of anthracycline metabolism involves reduction of the C-13 carbonyl group to a hydroxyl group by carbonyl reductase. The conversion of anthracycline derivatives to their 13-hydroxy metabolites is primarily regarded as a mechanism for inactivation and elimination of these drugs, with the 13-hydroxy derivatives of doxorubicin, epirubicin, and daunorubicin being less potent than their respective parent compounds [10–12]. Like other anthracycline derivatives, amrubicin is converted to its C-13 hydroxy metabolite, amrubicinol (Fig. 1) [13]. Amrubicin is unique among anthracyclines, however, in that the cytotoxicity of its C-13 hydroxy metabolite in vitro is 10–100 times that of the

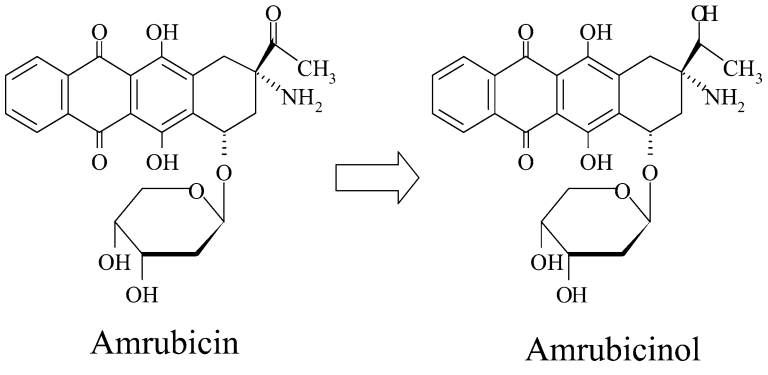


**Fig. 1** Chemical structures of amrubicin and amrubicinol

parent compound [6]. Amrubicinol is also more effective than amrubicin in inducing DNA-protein complex formation and subsequent double-strand DNA breaks [2]. These observations suggest that amrubicin might primarily behave as a prodrug in vivo and that most of its apparent antitumor activity is actually attributable to its more active metabolite, amrubicinol. Investigation of the clinical pharmacokinetic behavior of amrubicin is thus important for our understanding of the clinical effects of this agent. Such information is limited, however.

Amrubicin was recently approved in Japan for the treatment of small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). An initial phase I study was conducted in chemotherapy-naïve patients with advanced NSCLC, and the recommended schedule of administration for amrubicin as a single agent is the daily treatment for three consecutive days every 3 weeks at a dose of 45 mg/m$^2$ [14]. Phase II studies of amrubicin administered according to this schedule have yielded response rates of 76 and 23% in previously untreated SCLC and NSCLC patients, respectively [14, 15]. Given its substantial antitumor activity, the clinical development of amrubicin has also focused on the treatment of refractory or recurrent lung cancer. However, severe myelotoxicity was found to predominate when amrubicin was administered to previously treated patients even at the recommended dose of 45 mg/m$^2$. These observations raise concerns for the dosing of amrubicin in extensively pretreated patients with refractory or recurrent lung cancer.

We now present the clinical and pharmacokinetic results of a phase I trial of amrubicin administered as a bolus intravenous injection on days 1–3, every 3 weeks in previously treated patients with advanced lung cancer. The objectives of the study were (1) to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and a safe dose for phase II testing in this patient population, and (2) to describe the plasma pharmacokinetics of amrubicin and its active metabolite, amrubicinol. For this second goal, we made use of a high-performance liquid chromatography (HPLC)-based method that we established for the simultaneous measurement of amrubicin and amrubicinol.

## Patients and methods

### Patient eligibility

Patients with histological or cytological confirmation of metastatic SCLC or NSCLC who had undergone at least one previous chemotherapy regimen were eligible for the present study. Additional eligibility criteria included: (1) the presence of measurable lesions; (2) an age of ≥20 years; (3) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (4) adequate organ function [white blood cell (WBC) count of ≥4,000/μl, neutrophil count of ≥2,000/μl, platelet count of ≥100,000/μl, hemoglobin content of ≥9.0 g/dl, serum total bilirubin of ≤ 1.5 mg/dl, serum transaminase of ≤ 100 IU/l, serum creatinine of ≤ 1.5 mg/dl, $PaO_2$ of ≥60 mmHg]; and (5) a normal electrocardiogram and a left ventricular ejection fraction of > 60%. Prior therapy also had to have been completed at least 4 weeks previously, and the patients had to have recovered from the toxic effects of such prior therapy. The exclusion criteria included the presence of pulmonary fibrosis or interstitial pneumonitis with symptoms or apparent abnormalities on chest X-rays, massive pleural effusion or ascites, acute inflammation, pregnancy, lactation, symptomatic brain metastases, active concurrent malignancies, severe drug allergies, severe heart disease, cerebrovascular disease, uncontrollable diabetes mellitus or hypertension, severe infection, active peptic ulcer, ileus, intestinal paralysis, diarrhea, and jaundice. The study was approved by the institutional review board of each participating hospital and was conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from all the patients.

### Pretreatment and follow-up studies

Prior to enrollment in the study, a complete history was obtained and a physical examination was performed for each patient. Age, height, weight, performance status, histological diagnosis, tumor stage, details of prior treatment, and the presence of complications were

recorded. Pretreatment laboratory investigations included a complete blood cell count, differential WBC count, platelet count, serum electrolytes, total protein, albumin, total bilirubin, transaminase, alkaline phosphatase, lactate dehydrogenase, blood urea nitrogen, creatinine, creatinine clearance, and urinalysis. After the initiation of therapy, a complete blood cell count and differential WBC count were performed at least once a week. Blood chemistry profiles and chest X-ray films were obtained weekly. Lesion measurements were performed during at least every second course. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2, and tumor responses were assessed with the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [16].

### Drug administration and dose levels

Amrubicin was supplied by Sumitomo Pharmaceuticals (Osaka, Japan) as a freeze-dried powder in vials containing 20 mg of the drug, which was reconstituted in 20 ml of normal saline. The starting dose of amrubicin was 30 mg/m$^2$ administered as an intravenous infusion over 5 min on days 1–3. All patients were allowed to receive antiemetics with dexamethasone and granisetron. Treatment was administered every 3 weeks, until disease progression or unacceptable toxicity was apparent or until refusal by the patient. In the event of DLT, treatment was continued, after recovery, at an immediately lower dose level or the dose was reduced by 25%. The dose was increased in increments of 5 mg/m$^2$ in subsequent groups of patients to determine the MTD. Intrapatient dose escalation was not allowed. Three patients were initially treated at each dose level, and then three additional patients entered at the same dose, if DLT was observed in one of the first three patients. The MTD was defined as the dose level at which more than two out of three patients, or more than three out of six patients, experienced DLT. The definition of DLT included (1) grade 4 leukopenia, (2) grade 4 neutropenia for $>4$ days, (3) thrombocytopenia of $\leq 20{,}000/\mu l$, (4) grade 3 febrile neutropenia, or (5) grade 3 nonhematologic toxicity with the exception of nausea-vomiting.

### Pharmacokinetics

Blood samples were collected (in tubes containing EDTA as an anticoagulant) during the first course of treatment both before drug infusion and then 0, 0.5, 1, 2, 3, 4, 6, 8, and 24 h after the end of the infusion. The plasma concentrations of amrubicin and amrubicinol were determined by HPLC as described previously [5] but with some modifications. Plasma (200 µl) was diluted with 200 µl of a solution containing 16 mM citric acid, 16 mM $Na_2HPO_4$, and 0.9% NaCl and with 600 µl 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. The cartridge was activated with 1 ml of methanol and 1 ml of water before use, and was washed with 1 mL of 5% methanol after sample loading. It was then subjected to elution with 300 µl of methanol. The eluate was combined with 100 µl of a mixture (27:73, v/v) of $CH_3CN$ and of 50 mM sodium phosphate (pH 3.0) containing 2% $(CH_3)_4NCl$. A portion (200 µl) of the resulting solution was injected into the HPLC system, which included a $C_{18}$ reversed-phase column (Sumipax ODS A-212, 150 by 6 mm, with a particle size of 4 µm; Sumika Chemical Analysis Service, Osaka, Japan). The mobile phase consisted of a mixture of tetrahydrofuran, acetonitrile, and 10 mM sodium phosphate buffer (pH 2.6) (1:30:80, v/v/v), and the flow rate was 1.0 ml/min at a column temperature of 40°C. The fluorescence detector was set at excitation and emission wavelengths of 465 and 560 nm, respectively. The assay was carefully validated according to currently recommended guidelines. The lower limit of quantification was 3.0 ng/ml for both amrubicin and amrubicinol. Standard curves for amrubicin and amrubicinol in plasma at concentrations ranging from 3 ng/ml to 5,000 ng/ml were linear with an $r$ value of $>0.999$.

Pharmacokinetic parameters for amrubicin and amrubicinol were derived by noncompartmental methods with the use of WinNonlin version 3.1 software (Pharsight, Cary, NC, USA). The area under the curve of plasma concentration versus time (AUC) was calculated by the linear trapezoidal rule from time 0 h to 24 h ($AUC_{0-24}$). The extent of metabolism of amrubicin to amrubicinol was expressed as a metabolic ratio value, defined as the ratio of the amrubicinol AUC to that of the amrubicin AUC.

## Results

### Demographic characteristics of the study patients

Fifteen patients, whose characteristics are listed in Table 1, were enrolled in the study between September 2003 and September 2004. All patients were eligible and assessable for toxicity and response. Patients had been treated with a median of three prior chemotherapy regimens (range, 1–4), including at least one platinum-based regimen. The total number of assessable courses of amrubicin treatment was 43. The median number of courses per patient was two (range, 1–10).

### Dose levels and DLT

The dose escalation scheme and toxicities observed during the first course of amrubicin treatment are shown in Table. 2–4. The dose levels studied were 30 (level 1),

**Table 1** Characteristics of the study patients

| | |
|---|---|
| No. of patients | 15 |
| Median age (range) in years | 65 (54–75) |
| Sex (male/female) | 11/4 |
| Performance status (0/1/2) | 4/10/1 |
| Histology (NSCLC/SCLC) | 8/7 |
| Previous treatment | |
| Surgery | 1 |
| Radiation | 4 |
| Chemotherapy | 15 |

**Table 2** Dose escalation scheme and dose-limiting toxicity (DLT)

| Dose level | Amrubicin dose (mg/m$^2$) | No. of patients | No. of patients with DLT | DLT |
|---|---|---|---|---|
| 1 | 30 | 6 | 1 | G3 thrombocytopenia |
| 2 | 35 | 6 | 2 | Febrile neutropenia<br>G3 thrombocytopenia |
| 3 | 40 | 3 | 3 | Febrile neutropenia<br>G3 arrhythmia<br>G4 neutropenia |

35 (level 2), and 40 (level 3) mg/m$^2$, with the drug administered intravenously on days 1–3 and courses repeated once every 21 days. Six patients were entered at each of the levels 1 and 2, and three patients at level 3. At the dose of 30 mg/m$^2$, one patient required a platelet infusion because of thrombocytopenia of $<20{,}000/\mu l$, considered to be a DLT. At the dose of 35 mg/m$^2$, a DLT was encountered in two of the six patients, out of which one received a platelet infusion because of thrombocytopenia of $<20{,}000/\mu l$ and the other experienced febrile neutropenia. At the dose of 40 mg/m$^2$, a DLT was apparent in three consecutive patients: one patient developed febrile neutropenia, another experienced grade 4 neutropenia persisting for $>4$ days, and the third presented with symptomatic atrial fibrillation during amrubicin administration on day 2. The grade 3 atrial fibrillation in the latter individual was resolved after antiarryhythmia therapy with disopyramide. The event was thus considered to be related to the study drug. Because all three patients in the 40-mg/m$^2$ dose cohort experienced DLT, this dose level was determined to be the MTD. The recommended dose level for phase II studies with previously treated patients was thus determined to be 35 mg/m$^2$ (dose level 2 in the present study).

## Toxicities

The major toxicities recorded after all courses of amrubicin treatment are listed in Table 5. The most acute severe toxicities were hematologic. Grade 3 or 4 leukopenia and grade 3 or 4 neutropenia were noted in 17 (40%) and 26 (60%) out of 43 courses, respectively. Grade 3 thrombocytopenia occurred in 7 (16%) out of 43 courses, with two patients receiving platelet transfusions (one patient each at dose levels 1 and 2). However, no patient had hemorrhagic complications. The most frequent nonhematologic toxicities were appetite loss, nausea, and elevation of serum transaminase activity, but these effects were generally mild and clinically reversible. One patient at dose level 2 (35 mg/m$^2$) experienced grade 3 pneumonitis after the second course of treatment. The patient had undergone thoracic radiation (2 Gy/day; total 60 Gy) before use of amrubicin (28 months previously). The radiation ports were localized to the primary tumor in the right upper lobe with right hilar lymph node metastasis. Chest X-ray or computed tomography showed no preexisting interstitial pneumonitis until amrubicin was administered. On day 14 of the second cycle of amrubicin treatment, the patient developed dyspnea with hypoxemia. A chest computed tomography scan revealed new ground-glass opacities distributed diffusely in both lungs. The patient's history and clinical examination did not provide any evidence of toxic origin, collagen vascular disorders, or other usual causes. The exclusion of these (other) causes indicated that the pulmonary impairment was most likely attributable to amrubicin. The patient responded well to steroid therapy and improved. There were no treatment-related deaths.

## Responses

Of the 15 extensively pretreated patients with advanced lung cancer enrolled in the present study, ten individuals (five with NSCLC and five with SCLC) exhibited stable disease for 2–6 months and four subjects manifested disease progression. A partial response was apparent in one patient with NSCLC (adenocarcinoma) who was treated at a dose of 30 mg/m$^2$.

## Pharmacokinetics

Pharmacokinetic data were obtained in the first course of treatment for all patients enrolled in the study. Repre-

**Table 3** Hematologic toxicity grades after the first cycle of amrubicin treatment

| Dose (mg/m$^2$) | No. of patients | Leukopenia | | | | Neutropenia | | | | Thrombocytopenia | | | | Anemia | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| 30 | 6 | 0 | 1 | 3 | 1 | 0 | 1 | 1 | 3 | 0 | 1 | 2 | 0 | 0 | 0 | 1 | 1 |
| 35 | 6 | 0 | 2 | 2 | 2 | 0 | 0 | 1 | 5 | 0 | 2 | 1 | 0 | 0 | 1 | 1 | 1 |
| 40 | 3 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 |

**Table 4** Nonhematologic toxicity grades after the first cycle of amrubicin treatment

| Dose ($mg/m^2$) | No. of patients | Nausea | | | | Vomiting | | | | Appetite loss | | | | Arrhythmia | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| 30 | 6 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| 35 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 40 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

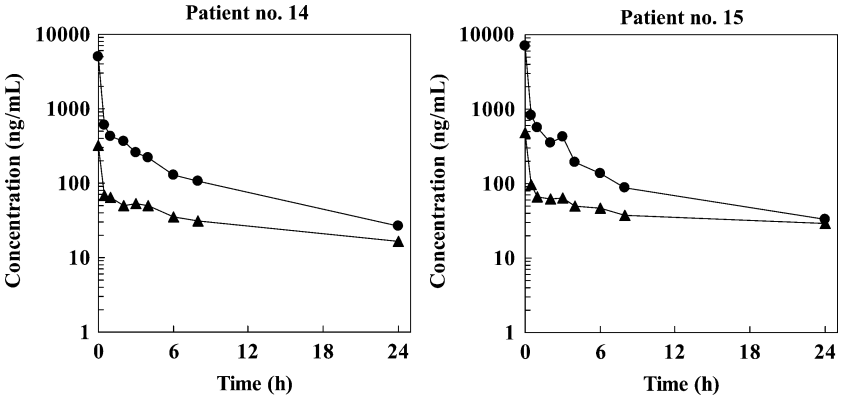


**Fig. 2** Plasma concentration versus time profiles for amrubicin (*circles*) and amrubicinol (*triangles*) in two representative patients treated with amrubicin at a dose of 40 $mg/m^2$. The end of amrubicin infusion is time zero

sentative plasma concentration-time profiles of amrubicin and amrubicinol are shown in Fig. 2. Plasma concentrations of both amrubicin and amrubicinol peaked at the end of amrubicin infusion and decreased rapidly thereafter. Mean pharmacokinetic parameters for amrubicin and amrubicinol, determined by noncompartmental analysis, are summarized in Table 6. The mean terminal half-life of amrubicin was $6.2 \pm 2.0$ h, whereas that of amrubicinol was $16.2 \pm 4.6$ h. The mean maximal plasma concentration ($C_{max}$) for amrubicin or amrubicinol ranged from 1,693 ng/ml to 4,869 ng/ml and from 77 ng/ml to 333 ng/ml, respectively, and the corresponding mean AUCs ranged from 8,601 ng/ml to 16,706 ng h/ml and from 1,361 ng h/ml to 4,097 ng h/ml. Although marked interpatient variability in the AUC and $C_{max}$ for both compounds was apparent at each dose level, the mean values of these parameters increased with increasing dose of amrubicin (Fig. 3). The amrubicinol/amrubicin AUC ratio remained relatively constant over the entire dose range (mean ± SD, $13.6 \pm 3.3\%$), with a coefficient of variation of 24%. At each dose level studied, a linear relation was apparent between the amrubicin AUC and the amrubicinol AUC ($r = 0.85$, $P < 0.0001$) (Fig. 4). The interpatient variability in metabolism of amrubicin to amrubicinol was thus small. Intrapatient variability was also assessed in four patients by comparing the $AUC_{0-24}$ values during the first course with the corresponding values during the second course. In general, systemic exposure during the first course did not differ markedly from that during the second course, with $AUC_{0-24}$ ratios (first course/second course) ranging from 0.81 to 1.43 for amrubicin and from 0.99 to 1.54 for amrubicinol.

**Table 5** Toxicities after all 43 cycles of amrubicin treatment

| | Grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Leukopenia | 1 | 14 | 13 | 4 |
| Neutropenia | 1 | 7 | 13 | 13 |
| Thrombocytopenia | 1 | 8 | 7 | 0 |
| Anemia | 0 | 11 | 5 | 1 |
| Nausea | 3 | 1 | 0 | 0 |
| Vomiting | 1 | 1 | 0 | 0 |
| Appetite loss | 9 | 3 | 1 | 0 |
| Fatigue | 2 | 0 | 0 | 0 |
| Transaminase | 1 | 2 | 2 | 0 |
| Arrhythmia | 0 | 0 | 1 | 0 |
| Pneumonitis | 0 | 0 | 1 | 0 |

## Discussion

In a prior phase I study of amrubicin as monotherapy in previously untreated NSCLC patients, the DLT was myelosuppression and the MTD was 50 $mg/m^2$, with a recommended dosage of 45 $mg/m^2$ administered intravenously on three consecutive days every 3 weeks [14]. However, the optimal dosage of amrubicin administration for previously treated patients has been unclear because of the severe myelotoxicity. The present phase I study of amrubicin in previously treated lung cancer patients has determined the MTD and dose suitable for future trials in a similar patient population.

Consistent with the results of the previous phase I and II studies of amrubicin, the predominant dose-limiting toxicity in the present study was myelosuppression, especially neutropenia and thrombocytopenia, with most patients (10 of 15, or 67%) developing grade 4 neutropenia. The MTD for amrubicin in our study was 40 $mg/m^2$, given that all three patients at this dose level

**Table 6** Pharmacokinetic parameters of amrubicin and amrubicinol

| Dose ($mg/m^2$) | No. of patients | $C_{max}$(ng/mL) | | Total AUC (ng h/ml) | | Terminal half-time (h) | | Amrubicin |
|---|---|---|---|---|---|---|---|---|
| | | Amrubicin | Amrubicinol | Amrubicin | Amrubicinol | Amrubicin | Amrubicinol | Clearance (L/h) |
| 30 | 6 | 1,693 ± 1,271 | 77 ± 50 | 8,601 ± 3,099 | 1,361 ± 318 | 4.7 ± 1.2 | 13.8 ± 6.8 | 16.3 ± 7.5 |
| 35 | 6 | 3,414 ± 1,744 | 170 ± 119 | 13,071 ± 2,931 | 2,476 ± 439 | 7.1 ± 1.3 | 18.0 ± 3.0 | 10.1 ± 2.7 |
| 40 | 3 | 4,869 ± 2,244 | 333 ± 139 | 16,706* | 4,097* | 7.4 ± 2.9 | 17.9 ± 1.6 | 8.8 ± 2.6 |
| Mean ± SD | | | | | | 6.2 ± 2.0 | 16.2 ± 4.6 | 12.3 ± 5.9 |

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 (administration on day 3 was discontinued in one patient as a result of toxicity)

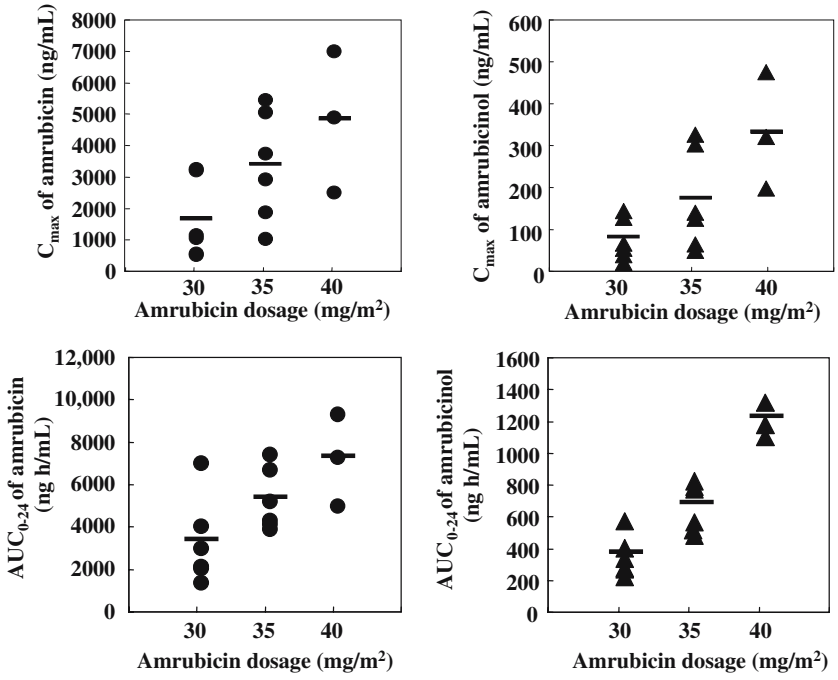


**Fig. 3** Relation between amrubicin dose level and the $C_{max}$ (*upper panels*) and $AUC_{0-24}$ (*lower panels*) values for amrubicin (*circles*) and amrubicinol (*triangles*)

experienced DLT, consisting of febrile neutropenia, prolonged grade 4 neutropenia, or grade 3 atrial fibrillation. The patient who developed atrial fibrillation during amrubicin administration had no prior history of atrial arrhythmia including atrial fibrillation. He was closely monitored in our hospital for the subsequent 3 months and did not manifest episodic atrial fibrillation. We therefore could not rule out an etiologic connection between drug administration and the atrial fibrillation. Our results indicate that administration of amrubicin at a dose of 35 $mg/m^2$ on three consecutive days every 3 weeks is appropriate for subsequent phase II studies with previously treated patients. This recommended dose is lower than that for chemotherapy-naïve patients, suggesting the possibility that amrubicin monotherapy at 35 $mg/m^2$ might be insufficient to treat refractory or relapsed lung cancer. Although evaluation of antitumor activity was not the primary objective of the present study, the disease stabilization observed in 8 of 12 (67%) patients at dose levels 1 (30 $mg/m^2$) and 2 (35 $mg/m^2$) and the presence of an objective response in a heavily pretreated NSCLC patient who received amrubicin at 30 $mg/m^2$ are indicative of potential activity of amrubicin in this patient population. The efficacy of amrubicin in refractory or relapsed lung cancer patients remains to be demonstrated, however.

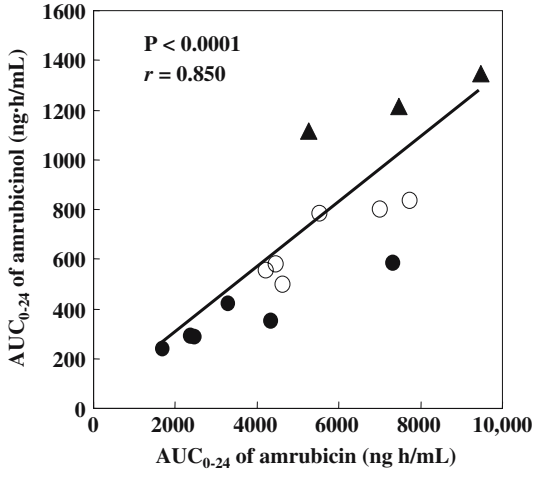


**Fig. 4** Relation between the $AUC_{0-24}$ of amrubicin and that of amrubicinol in patients treated with amrubicin at doses of 30 (*closed circles*), 35 (*open circles*), or 40 (*triangles*) $mg/m^2$

Amrubicin is converted enzymatically to the C-13 hydroxy metabolite amrubicinol, whose cytotoxicity is about 10- to 100-fold greater than that of the parent drug [6]. By measuring the plasma concentrations of both amrubicin and amrubicinol, we were able to gain insight into the pharmacological nature of the two drug forms in patients treated with amrubicin. We demonstrated a dose dependency of the plasma pharmacokinetics of amrubicin and amrubicinol. Furthermore, we found that the amrubicinol/amrubicin AUC ratio was similar among patients treated with the different doses of amrubicin, suggesting that there were no substantial interindividual differences in the activity of carbonyl reductase or other, as yet unknown, enzymes that are responsible for the metabolism of amrubicin. The mean terminal half-life of amrubicinol ($16.2 \pm 4.6$ h) in plasma was longer than that of amrubicin ($6.2 \pm 2.0$ h), which, given the higher cytotoxic activity of amrubicinol, may prove advantageous for antitumor activity.

In conclusion, the MTD of amrubicin was 40 mg/m$^2$ when administered on days 1–3, every 3 weeks in previously treated patients with refractory or relapsed lung cancer. The DLT was a combination of neutropenia, febrile neutropenia, thrombocytopenia, and arrhythmia. On the basis of our results, the recommended dose for phase II studies of amrubicin in such patients is 35 mg/m$^2$, which is substantially lower than that recommended for chemotherapy-naïve patients. Given that myelosuppression is the major DLT of this agent, the administration of recombinant human granulocyte colony-stimulating factor might allow treatment with higher doses of amrubicin even in previously treated patients. The clinical efficacy of amrubicin for 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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