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Pharmacokinetics of amrubicin in lung cancer patients with impaired hepatic function ☆

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ABSTRACT

Objective: The pharmacokinetics of amrubicin in patients with impaired hepatic function have not been reported. The aim of this study was to compare the pharmacokinetics of amrubicin and its major metabolite, amrubicinol, and to assess the safety of amrubicin in lung cancer patients with impaired hepatic function and those with normal hepatic function.

Materials and methods: Five patients with impaired hepatic function (arm I) and 10 patients with normal hepatic function (arm N) with small or non-small cell lung carcinoma were enrolled. Liquid chromatography with tandem mass spectrometry was used to determine the amrubicin and amrubicinol concentrations. Pharmacokinetic parameters were estimated by non-compartmental analysis.

Results: The terminal half-lives of amrubicin and amrubicinol in whole blood and plasma were slightly longer in arm I than in arm N. The area under the concentration–time curve ($AUC_{0–24h}$) values of amrubicin in plasma and $AUC_{0–120h}$ of amrubicinol in whole blood in arm I were not larger than those in arm N because of dose adjustments based on prior treatment history and baseline values of total bilirubin, aspartate aminotransferase and alanine aminotransferase. The dose-normalized AUCs (dose 40 mg/m^2) of amrubicin and amrubicinol in arm I were slightly larger than those in arm N. There were two deaths in arm I, one related to disease progression and one from an unknown cause.

Conclusion: If an adjusted dose of amrubicin is used in patients with impaired hepatic function, the exposure of amrubicin and amrubicinol would be within the range of variation observed in patients with normal hepatic function.

1. Introduction

Amrubicin, a totally synthetic 9-amino-anthracycline and potent inhibitor of DNA topoisomerase II, is converted to its active 13-hydroxy metabolite, amrubicinol, through the reduction of its C-13 ketone group to a hydroxy group by the action of cytoplasmic carbonyl reductase in liver, kidney, and tumor tissues [1]. In preclinical studies, amrubicin has been found to exert more potent

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration–time curve; ECOG, Eastern Cooperative Oncology Group; PS, performance status; T-bil, total bilirubin

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antitumor activity than doxorubicin, an anthracycline, in several human tumor xenografts implanted in nude mice [2]. Amrubicin does not cause typical anthracycline cardiotoxicity [3].

The dose of doxorubicin, an anthracycline drug, in patients with impaired hepatic function is usually decreased based on serum bilirubin or aspartate aminotransferase (AST) concentrations because plasma doxorubicin concentrations are reportedly increased in these patients [4–6]. Anthracyclines should therefore be carefully administered to patients with liver dysfunction for safety reasons. The pharmacokinetics of amrubicin and amrubicinol have been reported for patients with normal hepatic function but not for patients with impaired hepatic function [7]. Therefore, we evaluated the pharmacokinetics of amrubicin and amrubicinol, and the safety of amrubicin in lung cancer patients with or without impaired hepatic function. We also assessed the validity of amrubicin dose adjustment based on hepatic function.

2. Materials and methods

2.1. Patient selection

Eligibility criteria included the presence of histologically or cytologically proven SCLC or NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, 20–70 years of age, life expectancy of at least 1 month, and no evidence of hepatitis B virus infection. Patients were required to have adequate organ function, a white blood cell count between 4000/μL and 12,000/μL, neutrophil count $\geq$2000/μL, platelet count $\geq 10.0 \times 10^4$/μL, hemoglobin level $\geq$8.0 g/dL, serum creatinine concentration $\leq$1.5 mg/dL, partial pressure of arterial oxygen $\geq$70 mmHg, and no abnormal electrocardiogram requiring treatment.

Exclusion criteria included symptomatic brain metastases, uncontrolled diabetes (hemoglobin A_{1c} $\geq$8.0%), massive pericardial or pleural effusion requiring drainage, superior vena cava syndrome, gastric or duodenal ulcer, severe heart disease, interstitial pneumonia or pulmonary fibrosis as shown by chest radiography. Pregnant or nursing women were also excluded.

This study was approved by the institutional review board of each site and was conducted in accordance with the Declaration of Helsinki and guidelines on good clinical practice. All patients gave written informed consent prior to entering this study. This study was registered with the Japan Pharmaceutical Information Center, number JapicCTI-122036.

2.2. Dosage and drug administration

The dose of amrubicin was adjusted from 25 to 45 mg/m^2/day (iv, days 1–3, q3w) based on prior treatment history and baseline values of total bilirubin (T-bil), AST and alanine aminotransferase (ALT) (Table 1). The number of treatment cycles was at least one cycle (21 days) and a maximum of four cycles.

2.3. Pharmacokinetic evaluation

Concentrations of amrubicin and amrubicinol in plasma and whole blood were determined and their pharmacokinetic parameters were evaluated on cycle 1, as described in the Supplementary information.

Liquid chromatography with tandem mass spectrometry was used to determine the amrubicin and amrubicinol concentrations in human whole blood, plasma and samples for protein binding. All analytical methods were validated, and all samples were analyzed at JCL Bioassay Corporation (Hyogo, Japan).

Non-compartmental analysis was used to determine the following pharmacokinetic parameters for amrubicin and amrubicinol: area under the concentration–time curve from 0 to 24 h ($AUC_{0–24h}$), terminal half-life ($t_{1/2}$) and total clearance of amrubicin on day 1, area under the concentration–time curve from 0 to 120 h ($AUC_{0–120h}$) and $t_{1/2}$ of amrubicinol on day 3.

Table 1
Criteria for hepatic function and selecting the amrubicin dose.

Amrubicin dose (mg/m^2/day) 1st-line/ 2nd-line or more		AST or ALT (baseline)		
		WNL	> ULN to ≤ 2.5 × ULN	> 2.5 × ULN
T-bil (baseline)	WNL	45/40 [a]		40/35 [b]
	> ULN to ≤ 1.5 × ULN			35/30 [b]
	> 1.5 × ULN to ≤ 3.0 × ULN	–	35/30 [b]	30/25 [b]

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-bil, total bilirubin; WNL, within normal limits; ULN, upper limit of normal.
[a] Normal hepatic function (arm N).
[b] Impaired hepatic function (arm I).

The dose-normalized AUCs ($AUC_{0–24h}$ of amrubicin and $AUC_{0–120h}$ of amrubicinol) in patients with impaired hepatic function (arm I) were estimated to compare amrubicin and amrubicinol exposure in whole blood or plasma between patients in arm I and patients with normal hepatic function (arm N). The dose-normalized AUCs were estimated by the following equation:

Dose-normalized AUC = $AUC_{0–24h}$ of amrubicin and $AUC_{0–120h}$ of amrubicinol × 40/dose of each patient in arm I.

In the phase 1 clinical study, amrubicin and amrubicinol concentrations in blood cells or plasma were evaluated at doses from 10 to 130 mg. In this dose range, amrubicin and amrubicinol concentrations (AUCs) in blood cells or plasma were well correlated with dose, and the AUC levels in the phase 1 study covered the AUC range in this study [7]. Therefore, the AUCs of amrubicin and amrubicinol were normalized by the dose ratio.

2.4. Safety evaluation

Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 3.0.

3. Results

3.1. Patients

Five patients in arm I and ten patients in arm N were enrolled between January 2010 and December 2012 at nine participating sites. The demographic and baseline patient characteristics are shown in Table 2. The doses of amrubicin in arm I and arm N were 25–35 mg/m^2/day and 40 mg/m^2/day, respectively.

3.2. Pharmacokinetic analysis

All 15 patients received amrubicin on days 1–3. Full whole blood and plasma samples were collected for pharmacokinetic analysis. Whole blood and plasma concentration–time curves of amrubicin and amrubicinol are shown in Fig. 1, and the pharmacokinetic parameters of each patient in arm I and in arm N are shown in Table 3. A comparison of exposure (AUC) of amrubicin and amrubicinol between arm N and arm I is shown in Fig. 2. Amrubicin concentrations in whole blood and plasma were similar, and amrubicinol concentrations in whole blood were higher than those in plasma. Whole blood and plasma concentration profiles of amrubicin and amrubicinol were similar between the