Phase 1 Study to Assess Pharmacokinetics (PK), QT/QTc Effect, and Safety of Amrubicin in Patients With Advanced Solid Tumors

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BACKGROUND

Amrubicin (AMR) is a third-generation synthetic anthracycline analogue and a potent topoisomerase II inhibitor. The drug has demonstrated substantial clinical activity in the treatment of lung cancer. A phase I trial in 10 patients with stage IV non-small cell lung cancer (NSCLC) showed an encouraging activity profile. The drug is on pace to be in the clinic within the next 5 years. In the current phase I study, we aimed to evaluate the pharmacokinetics (PK), QTc effect, and safety of AMR in patients with advanced solid tumors.

OBJECTIVES

1. To explore the relationship between the PK of AMR and AMROL and the potential changes in the QT interval.
2. To determine the safety and tolerability of AMR.
3. To establish the appropriate doses for the subsequent phase II study.

METHODS

Study design and study procedures
- Phase I, open-label, single-arm, multicenter trial
- B-60 study design
- Dose escalation
- 10 patients for each of 4 dose levels: 30, 40, 50, and 60 mg/m²/day

Eligibility
- Patients with histologically confirmed advanced solid tumors
- ECOG performance status ≤ 2
- Adequate hematologic, hepatic, renal, and cardiac function

Outcome measurements
- Pharmacokinetic analysis of AMR and AMROL
- QTc interval
- Clinical laboratory tests, vital signs, and 12-lead electrocardiogram
- Relationship between AMR or AMROL concentrations and QTc changes
- Frequency of abnormal QTc intervals

RESULTS

Phase 1: Pharmacokinetics
- AMR hydrochloride: 5-minute intravenous infusions of 40 mg/m² on days 1–3 of a single 21-day cycle

Safety
- 24 patients with a median age of 58 years were enrolled (Table 1)
- 33% had been diagnosed with lung cancer
- Whole blood exposure to AMROL averaged 67% of AMR, based on the AUC 24 after 3 doses (Table 2)

Pharmacokinetic–pharmacodynamic relationship

CONCLUSIONS

AMR did not cause a clinically significant prolongation of the QTc interval in patients with advanced solid tumors.