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[1]
- The drug has demonstrated substantial clinical activity in the treatment of lung cancer.[2,3] It is currently approved in Japan for the treatment of both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)
- In Japanese patients with solid tumors, the pharmacokinetics (PK) of AMR is linear over 10 to 130 mg/m^2.[4] Amrubicin was rapidly converted to an active metabolite, amrubicinol (AMROL),[5] which is readily distributed into red blood cells (RBCs) and slowly disappears from circulation. To date, the PK of AMR and AMROL has not been characterized in non-Japanese populations
- Although anthracyclines are known to cause cardiotoxicity, their ability to induce clinically significant delay of cardiac repolarization (measured as QTc prolongation) has not been established as a class effect. Unlike other anthracyclines, classical anthracycline-like cardiotoxicity has not been observed for AMR in both nonclinical and clinical studies.[2,3,6,7] However, the effect of AMR on cardiac repolarization has not been adequately evaluated

OBJECTIVES

Primary objectives

- To characterize the PK of AMR and its active metabolite AMROL
- To evaluate their potential effects on the total cardiac output (QT)/QTc interval
  - Largest mean change in QTc (ΔΔQTc) calculated using Fridericia's equation (ΔΔQTcF) as the primary endpoint
- To determine the safety and tolerability of AMR

Secondary objective

- To explore the relationship between the PK of AMR and AMROL and the potential changes in QT/QTc

METHODS

Study design and study procedures

- Phase 1, open-label, single-arm, multicenter trial
- Off-drug, baseline controlled
- Continuous 12-lead Holter ECG for 11 hrs on off-drug visit, day 1, and day 3; triplicate extraction of ECG at PK sampling time points
- Triplicate 12-lead safety ECG on days 1–9
- Other routine safety monitoring during study and at the end of study

Eligibility

- Histologically or cytologically proven advanced solid tumors
- Men and women aged 18–65 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status score 0 or 1
- Adequate hematologic, hepatic, renal, and cardiac function
- QTcF ≤ 450 ms (men) or ≤ 470 ms (women) within 3 months of screening

Treatment

- AMR hydrochloride: 5-minute intravenous infusions of 40 mg/m^2 on days 1–3 of a single 21-day cycle
- Prophylactic antibiotics: started on day 9 for up to 13 days
- White-blood-cell growth factor (pegfilgrastim): started on day 9 and continued as clinically indicated

Outcome measurements

- PK profile for AMR and AMROL in whole blood, plasma, RBCs, and urine
  - Empirical PK parameters
- Time-matched, baseline-adjusted, and off-drug ΔΔQTc
- Frequency of abnormal QTc intervals
- Relationship between AMR or AMROL concentrations and QTcF changes
- Adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG) assessment

RESULTS

Baseline patient characteristics

- 24 patients with a median age of 58 years were enrolled (Table 1)
  - 71% of patients had an ECOG Performance Status score of 1
  - 33% had been diagnosed with lung cancer
  - All patients received prior radiation therapy and chemotherapy, and 88% had undergone surgery

Table 1. Baseline characteristics (N = 24)

Median age, years (range)	58 (25–65)
Median body surface area, m^2 (range)	1.9 (1.0–3.0)
Median weight, kg (range)	77 (44–145)
Men, n (%)	11 (46)
Race, n (%)	
Caucasian	17 (71)
African American	3 (13)
Asian	3 (13)
Other	1 (4)
ECOG Performance Status score, n (%)	
0	7 (29)
1	17 (71)
Previous cardiac-related complications	0
Lung tumors, n (%)	8 (33)
Previous anticancer therapies, n (%)	
Surgery	21 (88)
Radiation	24 (100)
Chemotherapy	24 (100)

Pharmacokinetics

- AMR
  - Rapid elimination: initial 80% reduction within 10 minutes (Figure 1)
  - Terminal elimination half-life ($t_{1/2}z$), of ~ 4 hours in circulation (Table 2)
  - Almost identical PK profiles between plasma and whole blood
  - Distributed into RBCs 1.4 folds greater than plasma on day 3 (see AUC_{24} in Figure 2)
  - Urinary excretion was < 1.5% of the dose (Figure 3)
- AMROL
  - Formed rapidly in whole blood with a median time to reach the observed maximum concentration (C_{max}) (t_{max}) of 2–4 hours (Table 2)
  - Long half-life ($t_{1/2}z$, = 52.8 hours) with an accumulation ratio of 1.7 for whole blood exposure after 3 doses (Table 2)
  - Whole blood area under the concentration–time curve over 24 hours after dosing (AUC_{24}) equivalent to 67% of AMR after 3 doses (Table 2)
  - Distributed into RBCs 5 folds greater than plasma on day 3 (see AUC_{24} in Figure 2)
  - Daily urinary excretion was < 8% of the AMR dose (Figure 3), but incomplete

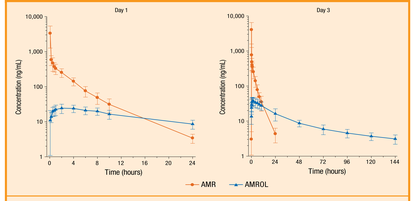
Table 2. PK parameters of AMR and AMROL in whole blood

	AMR (N = 24)		AMROL* (N = 24)	
	Day 1	Day 3	Day 1	Day 3
Mean t_{max}, h (range)	0.067 (0.067–0.25)	0.067 (0.014–0.433)	4.00 (0.067–6.083)	2.00 (0.5–6.017)
Mean C_{max}, ng/mL (CV%)	3,254 (56.9)	3,608 (53.1)	57 (25.0)	102.9 (37.4)
Mean AUC_{24}, h•ng/mL (CV%)	2,253 (25.3)	2,348 (21.5)	905 (25.2)	1,525 (26.5)
Mean $t_{1/2}z$, h (CV%)	3.76 (18.7)	4.48 (23.5)	17.6 (31.0)	52.8 (28.6)
Mean CL, mL/min (CV%)	573 (37.1)	534 (33.2)	NA	NA
Mean V_{ss}, L (CV%)	125 (36.7)	125 (27.6)	NA	NA
Mean $Rac(C_{max})$ (CV%)	NA	1.41 (76.4)	NA	1.79 (21.4)
Mean $Rac(AUC_{24})$ (CV%)	NA	1.06 (15.6)	NA	1.70 (14.7)
Mean MR-AUC_{24} (CV%)	NA	NA	0.42 (33.9)	0.67 (30.7)

*For some outcome parameters less than 24 patients were evaluable.

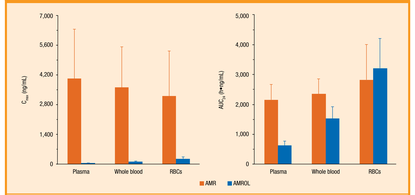
CL, total clearance; CV%, coefficient of variation in percentage; h, hours; MR-AUC_{24}, molar ratio of AMROL to AMR based on AUC_{24}; NA, not applicable; $Rac(C_{max})$, accumulation ratio based on C_{max}; $Rac(AUC_{24})$, accumulation ratio based on AUC_{24}; V_{ss}, volume of distribution at steady state.

Figure 1. Concentrations of AMR and AMROL in whole blood over time



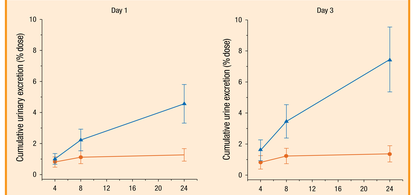
Bars indicate standard deviation (SD).

Figure 2. Exposure to AMR and AMROL in whole blood, plasma, and RBCs on day 3



Bars indicate standard deviation (SD).

Figure 3. Urinary excretion of AMR and AMROL



Bars indicate standard deviation (SD).

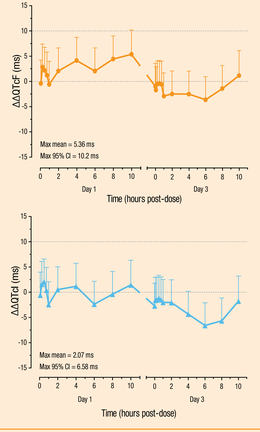
	AMR (N = 24)		AMROL (N = 24)	
	Day 1	Day 3	Day 1	Day 3
Mean Ae_{24}, µg (CV%)	909 (30.3)	971 (32.6)	3,274 (29.9)	5,351 (30.8)
Mean $\%fe_{24}$, % dose (CV%)	1.27 (31.7)	1.37 (38.2)	4.56 (27.3)	7.45 (28.1)
Mean CL_u, min/mL (CV%)	8.38 (44.2)	8.18 (44.9)	154 (42.0)	154 (46.0)

Ae_{24}, total amount excreted in urine over 24 hours; $\%fe_{24}$, percentage of administered dose excreted in urine over 24 hours; CL_u, renal clearance.

Pharmacodynamics

- The upper one-sided 95% confidence interval (CI) for ΔΔQTcF was below 10 ms at 20 of 21 time points, and was marginally above 10 ms at a single time point (day 1, 10 hours) (Figure 4)
- The upper one-sided 95% CI for QT corrected by individual equation (ΔΔQTcI) was below 10 ms at all time points (Figure 4)
- Holter ECG (days 1 and 3): None of the patients exceeded the clinically relevant thresholds of 480 ms for absolute QTcF and 60 ms for QTcF increase from baseline (Table 3)
  - Absolute QTcF 451–480 ms or QTcF increase of 31–60 ms was only observed in 2–3 patients
  - Frequency of abnormal intervals was comparable between off-drug and treatment days
- 12-lead safety ECG (days 1 to 9): No patient had an absolute QTcF value ≥ 450 ms; only 1 patient had a QTcF increase of > 30 ms

Figure 4. Baseline-adjusted QTc changes* from off-drug over time (Holter ECG)



*Least square means and the upper one-sided 95% CI estimated by repeated-measure analysis of variance.

Bars indicate upper 95% CI.

Table 3. Number of patients with abnormal QTcF intervals (Holter ECG; days 1 and 3, hours 0–10)

QTcF, n (%)	Off-drug	Day 1	Day 3	Day 1 + 3
Maximum interval				
≤ 450 ms	22 (91.7)	21 (87.5)	22 (91.7)	21 (87.5)
> 450 to ≤ 480 ms	2 (8.3)	3 (12.5)	2 (8.3)	3 (12.5)
> 480 to ≤ 500 ms	0	0	0	0
> 500 ms	0	0	0	0
Maximum increase from baseline				
≤ 30 ms	21 (91.3)	21 (91.3)	23 (100)	22 (91.3)
> 30 to ≤ 60 ms	2 (8.7)	2 (8.7)	0	2 (8.7)
> 60 ms	0	0	0	0

Figure 5. QTcF changes from baseline over time in patients with an absolute QTcF value < 450 on days 1–9 (12-lead safety ECG)

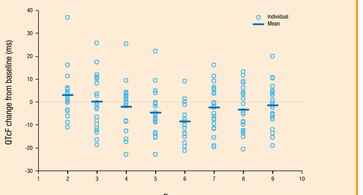
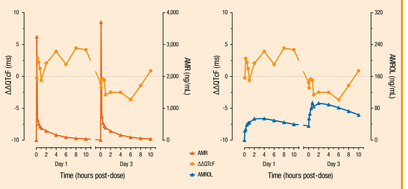


Figure 6. Mean concentrations and mean baseline-adjusted QTcF change from off-drug



Pharmacokinetic–pharmacodynamic relationship

- No apparent relationship was observed between whole blood concentrations of AMR or AMROL and QTcF changes (Figure 7 and Figure 8)
- There was no clear pattern indicating a delayed QTc effect relative to the change in AMR or AMROL concentrations (Figure 6)

Safety

- The most common grade 3 or 4 AEs were neutropenia, leukopenia, and thrombocytopenia (Table 4)
- Febrile neutropenia occurred in 4 patients

Figure 7. Whole blood AMR and AMROL concentrations versus time-matched baseline-adjusted QTcF change from off-drug (Holter ECG)

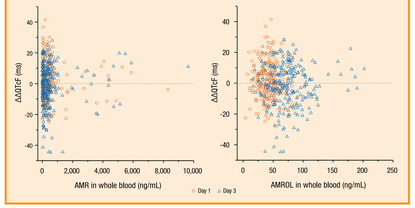


Figure 8. Whole blood AMROL concentrations versus time-matched QTcF change from baseline (12-lead safety ECG)

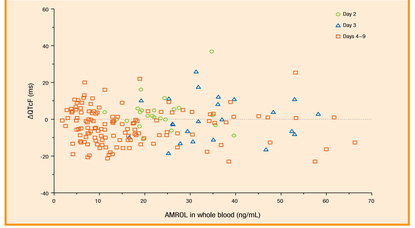


Table 4. Treatment-emergent grade 3 or 4 AEs* (N = 24)

Grade 3 or 4 AE	n (%)
Neutropenia	11 (46.0)
Leukopenia	9 (38.0)
Thrombocytopenia	9 (38.0)
Anemia	6 (25.0)
Fatigue	5 (21.0)
Lymphopenia	4 (17.0)
Febrile neutropenia	4 (17.0)
Hypokalemia	2 (8.0)
Dyspnea	2 (8.0)
Dehydration	1 (4.0)
Hypophosphatemia	1 (4.0)
Hyponatremia	1 (4.0)
Cough	1 (4.0)
Hypoxia	1 (4.0)
Hemoptysis	1 (4.0)

*AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs Version 3.0.

CONCLUSIONS

- Full PK profiles of AMR and its active metabolite AMROL were defined for non-Japanese patients with advanced solid tumors
- Whole-blood exposure to AMROL averaged 67% of AMR, based on the AUC_{24} after 3 consecutive doses
- Amrubicin given as a 5-minute intravenous infusion at 40 mg/m^2 for 3 consecutive days did not cause a clinically significant prolongation of the QTc interval in patients with advanced solid tumors
- The safety profile of AMR is consistent with findings from phase 2 and 3 studies of AMR in patients with SCLC

References

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