COMBINING ATOVAQUONE WITH INTENSIVE CONVENTIONAL CHEMOTHERAPY FOR PEDIATRIC ACUTE MYELOID LEUKEMIA (AML) IS FEASIBLE AND WELL TOLERATED

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Background: Relapse free survival of pediatric AML remains only 60%. Novel therapies with minimal toxicities are needed to improve outcomes. Previously, we found atovaquone (AQ), FDA-approved drug to treat pneumocystis jiroveci pneumonia (PJP), reduces AML burden in xenograft mice. Achievable concentrations of AQ for anti-PJP are 40-80μM, but anti-leukemia effects can be as low as 10μM (Stevens et al, Bld Adv, 2019). This makes AQ an ideal drug to incorporate into AML treatment. However, AQ is a daily administered oral medication, and plasma levels depend on multiple factors that can be compromised by the patient population and adverse events (AE) of chemotherapy. Here we investigated the feasibility of incorporating AQ into standard pediatric AML treatment.

Materials/Methods: Patients with de novo AML were enrolled. Daily administration of AQ was combined with standard chemotherapy for AML. Compliance, AEs, ease of administration, and pharmacokinetics were collected during Induction 1. All gastrointestinal AEs≥ grade 2 and all other AEs ≥ 4 were collected. Patients who took ≥85% of planned doses and missed <2 consecutive doses were included for analyses. Correlative biology studies conducted during the trial assessed AQ induced apoptosis at 30uM, effects on OXPHOS and relevant signaling activities, and patient derived xenograft (PDX) establishment and treatment.

Results: 24 pediatric AML patients were evaluated. 14/24 (58%) patients achieved plasma levels above the target anti-leukemia concentration. 19/24 (75%) patients achieved plasma levels above 10μM, but only 7/24 (29%) patients achieved adequate levels for PJP prophylaxis [FIG A]. For patients ≤ 2.6years, the average score for ease of administration was not significantly different from older patients (ANOVA, $p>0.05$) [FIG B]. These scores also showed no association with plasma levels (Pearson's correlation, $p>0.05$). Finally, correlative biology studies demonstrated robust AQ-induced apoptosis in most patient samples, OXPHOS suppression, and prolonged survival in a PDX model [FIG C].

Conclusions: Our data demonstrate the feasibility of combining AQ with traditional chemotherapy for pediatric AML. Pediatric patients of all ages took AQ without significant difficulty and no AEs were attributable to administration. The target anti-leukemic concentration in the plasma was frequently achieved, but achievement >40uM was rare. Our correlative biology results support suppression of OXPHOS as the primary mechanism by which AQ exerts its anti-leukemia effect.

Images / Graph / Table