

Clinical Potential of Combretastatin A1 Diphosphate for the Treatment of Relapsed Pediatric Acute Myeloid Leukemia

Fatih M. Uckun, Vuong N. Trieu

Immuno-Oncology Program, Mateon Therapeutics, Agoura Hills, CA 91301, United States

Acute leukemia is the most common cancer in children accounting for one-third of all childhood cancers. Acute lymphoblastic leukemia (ALL) accounts for 80% and acute myeloid leukemia (AML) accounts for 15% of all acute leukemia cases in children.^[1-3] Children with AML have a worse prognosis with a 5-year survival rate of 64% than children with ALL who have a 5-year survival rate of ~90% on contemporary risk-adjusted treatment programs. Children with AML who have unfavorable risk factors, such as adverse cytogenetics, have a particularly poor survival outcome even after intensive multimodality therapy and hematopoietic stem cell transplantation.^[1-3] Approximately one-third of children with AML relapse after induction chemotherapy and only one-third of these patients become long-term survivors. Relapsed disease is the greatest challenge to a better survival outcome in AML.^[1-7] Although new drugs have recently been developed against several molecular targets in AML blast cells, the vast majority of relapsed pediatric AML patients still die of leukemia.^[1-3] Therefore, novel therapies are urgently needed for pediatric AML.

Combretastatins are phenolic-stilbene natural products that bind to the colchicine binding site of tubulin and exhibit antimitotic as well as antiangiogenic/vascular disrupting activity and cytotoxicity. The vascular disrupting agent OXi4503 is a synthetic, diphosphorylated prodrug of *cis*-combretastatin A1 (OXi4500), a naturally occurring derivative of the South African bush willow tree, *Combretum caffrum*, that reversibly binds tubulin at the colchicine binding site to inhibit microtubule assembly. OXi4503 is a compound with a dual mechanism of action involving both anti-vascular effects and direct cytotoxicity toward tumor cells [Figure 1].^[8-10] OXi4503 has potent nanomolar cytotoxicity/antiproliferative activity against

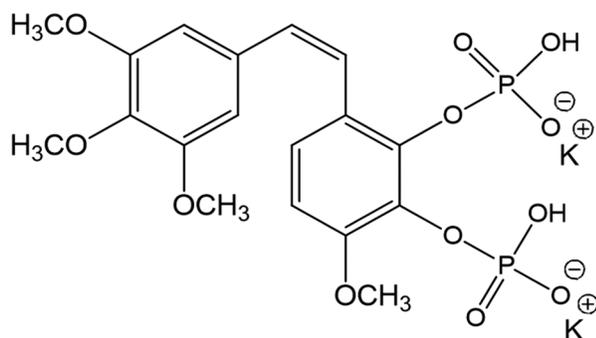
leukemia cells and it has been shown to disrupt the bone marrow endothelial cell support for AML clones.^[11,12] The phosphate prodrug, OXi4503, is activated to OXi4500 by endogenous phosphatases and OXi4500 has direct vascular disrupting activity. Evidence suggests that OXi4500 is also metabolized to a reactive orthoquinone species that is also directly cytotoxic to tumor cells. Non-clinical studies have also shown that OXi4503 enhances the efficacy of conventional cytotoxic agents, as well as radiotherapy and anti-angiogenic therapy including monoclonal antibodies and tyrosine kinase inhibitors.^[8-13]

OXi4503 exhibited single-agent anti-leukemia activity in animal models of AML and in a Phase 1A clinical study for relapsed/refractory (R/R) AML. Notably, the combination of OXi4503 with cytarabine (ARA-C) in xenografted human AML models was more effective than either drug alone. The clinical safety profile of OXi4503 as a single agent has previously been evaluated in Phase 1A clinical trials. In the NCT00977210 Phase 1 dose-finding study in 43 advanced solid tumor patients, OXi4503 doses were escalated from 0.06 to 15.4 mg/m², and 8.5 mg/m² was defined as the maximum tolerated dose (MTD). In the NCT01085656 Phase 1A trial designed to evaluate the safety profile, MTD, and recommended Phase 2 dose of OXi4503 in patients with R/RAML and MDS, a total of 18 patients were treated with single-agent OXi4503 and showed a manageable safety profile at single-agent dose levels up to of 7.81 mg/m² and there was early evidence of possible single-agent anti-AML activity.^[14,15] More recently, a Phase 1B study was performed to evaluate the safety, tolerability, and clinical activity of a combination of OXi4503 and the standard anti-AML drug ARA-C.^[16,17] The combination therapy exhibited a manageable toxicity and a promising benefit to risk profile in adults with

Address for correspondence:

Fatih M. Uckun, Immuno-Oncology Program, Mateon Therapeutics, Suite 107, Agoura Hills, CA 91301, United States.
E-mail: fatih.uckun@att.net

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OXi4503
C₁₈H₂₀O₁₂P₂-K₂
FW 568.49

Figure 1: Molecular structure of OXi4503

relapsed AML.^[16,17] An MTD level of OXi4503 was identified as the recommended dose for further clinical development of this novel two-drug combination. In 26 evaluable AML patients, there were four complete remissions (CR/CRi) and one partial remission. The median overall survival time for the four patients who achieved a CR/CRi was 528 days (95% confidence interval [CI]: 434 – NA), which was significantly longer than the median overall survival time of 113 days (95% CI: 77–172) for the remaining 22 patients who did not achieve a CR (Log rank Chi-square = 11.8, *P*-value = 0.0006). The safety, feasibility, and clinical activity of OXi4503 + ARA-C combination regimen in R/R AML deserve further clinical validation in a randomized registration study.^[16,17]

Taken together, the preclinical and clinical studies to date demonstrate the potential of OXi4503 as a promising new drug in the treatment of pediatric AML in relapse, an orphan disease with a low survival rate and no established or effective standard of care. OXi4503 has received orphan drug designation for AML in both the US and the European Union. Further, the US FDA has granted fast track designation to OXi4503 for the treatment of R/R AML. OXi4503 may offer renewed hope for salvage therapy of pediatric AML patients in relapse who have this rare and fatal disease.

CONFLICTS OF INTEREST

F.M.U. and V.N.T. are employees and shareholders of Mateon Therapeutics, the sponsor for clinical development of OXi4503.

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