https://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.7084

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

LEUKEMIA, MYELODYSPLASIA, AND TRANSPLANTATION (ADULT)

An oral dosage formulation of azacitidine: A pilot pharmacokinetic study

M. R. Ward , M. L. Stoltz , J. B. Etter , L. M. Patton , G. Garcia Manero , S. Sharma

Show More

Abstract

7084

Background: Azacitidine, a cytidine analog, induces DNA demethylation that leads to tumor suppressor gene expression. Cellular effects of azacitidine treatment include differentiation, cell cycle arrest and/or apoptosis. There is a complex, non-linear relationship between plasma exposure and pharmacodynamic effect of azacitidine that can be fully explored with an oral formulation of azacitidine, enabling alternate dosing strategies ranging from intermittent high dose to continuous, low-dose approaches to DNA demethylation. **Methods and Results:** A pharmacokinetic study in dogs given oral azacitidine demonstrated rapid absorption with absolute bioavailability of 67% (compared to 71% following SC dosing). When comparing a single parenteral dose of 75 mg/m² (~2 mg/kg) given SC to humans vs. a single oral dose of 16 mg/m² (0.8 mg/kg) given to dogs, plasma concentrations of azacitidine were similar despite the 4- to 5-fold difference in dose as calculated by body surface area (BSA). A 14-day toxicology study in dogs evaluated the oral doses of 0.2, 0.4, and 0.8 mg/kg/day. The high dose is the previously identified MTD of 0.55 mg/kg/day based on an oral bioavailability of 67% (approximately equal to 16 mg/m²/day). Hematologic toxicity, a known and expected effect of azacitidine administered in a repeat-dose regimen was observed at the two highest doses. The oral MTD was determined to be 0.2 mg/kg/day for 14 consecutive days followed by a 21-day recovery period. This provides a cumulative MTD of 2.8 mg/kg for the14 day dosing regimen, which is similar to that seen with IV dosing (2.75 mg/kg over 5 days). Based on the preclinical studies, a multicenter, single-treatment study of oral azacitidine is underway in subjects with MDS, AML, or solid tumors. The trial assesses the safety, tolerability and pharmacokinetics of escalating single doses of orally administered azacitidine. Clinical data from this study will be presented.

Author Disclosure

Employment or Leadership	Consultant or Advisory	Stock Ownership	Honoraria	Research	Expert Testimony	O Remu
	Pharmion		Pharmion	Pharmion		

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

DOI: 10.1200/jco.2007.25.18_suppl.7084
Journal of Clinical Oncology 25, no. 18_suppl (June 20 2007) 7084-7084.

Published online December 12, 2016.

WE RECOMMEND

Phase I Study of Oral Azacitidine in Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Acute Myeloid Leukemia
Guillermo Garcia-Manero et al., J Clin Oncol, 2011

Phase I clinical and pharmacologic study of eniluracil plus fluorouracil in patients with advanced cancer.
R L Schilsky, J Clin Oncol, 2016

Pharmacokinetic, bioavailability, and feasibility study of oral vinorelbine in patients with solid tumors.
E K Rowinsky, J Clin Oncol, 2016

Phase I and pharmacologic study of oral topotecan administered twice daily for 21 days to adult patients with solid tumors.
C J Gerritz et al., J Clin Oncol, 2016

Etoposide bioavailability after oral administration of the prodrug etoposide phosphate in cancer patients during a phase I study.
J P Armand et al., J Clin Oncol, 2016

Volasertib Plus Nintedanib for Advanced Solid

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.