Abstract

Ciplorix (CPX) is contained in a number of FDA-approved antifungal oral drug products as the free base and saline salt. CPX possesses antitumor activity in a number of in vitro and in vivo preclinical models. Its clinical utility is limited as an oral anticancer agent, however. The oral bioavailability of CPX is quite low due to extensive first-pass effect. The poor water solubility of CPX and its saline salt prevent formulation as an injectable drug product. Thirdly, dose-limiting gastrointestinal toxicities were observed following four-times daily oral dosing of CPX in patients with advanced hematologic malignancies. Ciplorix Prodrug (CPX-POM), in contrast, has demonstrated excellent bioavailability via injectable routes of administration. Here, we describe the preclinical characterization of CPX-POM, a novel anticancer agent being developed as a treatment of non-muscle invasive (NMIBC) and muscle-invasive (MIBC) bladder cancer. Following IV, SQ and IP administration to mice, CPX-POM is rapidly and completely metabolized to CPX in blood via circulating phosphatases. CPX and its major, inactive metabolite glucuronide metabolites are extensively eliminated in urine. At well-tolerated doses, steady-state urine concentrations of CPX exceed in vivo IC50 values in mice by 15-30 fold. CPX inhibited cell proliferation, colony formation, and bladdersphere formation in vitro in T24 (NMIBC) and 5637B (MIBC) human cell lines in both concentration- and time-dependent manners with IC50 values of 2.4 μM. CPX exposure increased the percentage of NMIBC and MBC cells arrested at the G0 and G1 phases, and induced cell death. CPX exposure significantly reduced expression of genes at the mRNA level involved in cancer stem cell signaling pathways including Notch, Wnt, and Hedgehog. CPX was shown to inhibit bladder cancer cell growth in vitro by inhibiting the Notch 1 signaling pathway. The validated N-butyl-4-(4-hydroxybutyl) nitroxime (BBN) bladder carcinogenic mouse model of bladder cancer was employed to establish in vivo preclinical proof of principle for CPX-POM. Over the once-daily IP dose range of 25-200 mg/kg, CPX-POM treatment resulted in significant decreases in bladder weight, a clear migration to lower stage tumors, dose-dependent reductions in K57 and PCNA staining, as well as a reduction in PCNA-expressing cells. All CPX-POM doses were well tolerated with no evidence of toxicity to the urinary tract based on blinded pathological evaluation. There were also dose-dependent decreases in Notch 1, Presenilin 1, and Hey 1 in bladder cancer tissues obtained from CPX-POM-treated animals. Tumor response was similar, in vivo, following once-daily and three-times-weekly CPX-POM administration. CPX-POM has received FDA clearance to proceed to Phase I, and is currently being evaluated in a first-in-human trial in patients with advanced solid tumors.

Background & Significance

Bladder cancer is a devastating disease that currently ranks as the fourth most common cancer among men and the sixth most common among men and women combined. The American Cancer Society estimates that in 2018 alone, 81,130 new cases will be diagnosed in the U.S. and 17,450 will die of the disease. Bladder cancer is two defined as two diseases, each with different treatment approaches and outcomes. Eighty percent of newly diagnosed patients have non-muscle invasive bladder cancer (NMIBC) (Heney 1992). Despite endoscopic resection followed by topical administration (via bladder instillation) of either immunotherapy (i.e., the Bacillus Calmette-Guerin vaccine) or chemotherapy (e.g., mitomycin C, cisplatin), 60-70% of NMIBC will recur (Zotte 2000; Ablbildarn 2010). Twenty to thirty percent of NMIBC cases progress to MIBC (Zotte 2000; Ablbildarn 2010) for which the gold standard treatment is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (Millan-Rodriguez 2000; National Comprehensive Cancer Network 2013). Patients who progress from NMIBC to MIBC have a lower survival rate than for those who present with de novo MIBC (Forsman 2003).

Urothelial cell carcinomas most commonly occur in the bladder, but can involve the upper urinary tract as well. The incidence of upper urinary tract disease ranges from 5-10% (Slovis 2005) and increases with multiple and high risk tumors (Bouquet 2013). Delivery of immunotherapy and chemotherapy by bladder instillation fails to reach cancer located in the upper urinary tract. Novel treatment strategies that prevent recurrence and progression of high grade urothelial cell carcinomas are needed (Shahigh 2009).

Funding

Research presented was supported by The Institute for Advancing Medical Innovation at the University of Kansas Medical Center and CicloMed LLC, Kansas City, MO through a unique public-private partnership.

Ongoing and Future Studies

IND 133145 received FDA clearance to proceed with a first-in-human Phase 1 trial on September 2017. The safety, dose tolerance, pharmacokinetics and pharmacodynamics of CPX-POM are currently being evaluated in patients with advanced solid tumors at four US sites (NCT03134815) sponsored by CicloMed LLC. Development of a subcutaneous injectable formulation of CPX- POM, would provide a more convenient dosage form for self administration by bladder cancer patients.

Acknowledgements

Research reported in this presentation was supported by the National Cancer Institute Cancer Center Support Grant P30 CA168524 and used the CSSG Lead Development and Optimization Shared Resource. Several studies described herein were funded by a public-private partnership between The Institute for Advancing Medical Innovation at the University of Kansas Medical Center and CicloMed LLC, Kansas City, MO.

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