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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Population Pharmacokinetic-Pharmacodynamic Modeling of Neutrophil and Platelet Count for Lower-Intensity Therapy of CPX-351 Combined with Venetoclax in Acute Myeloid Leukemia

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Background:
Improved survival outcomes and a comparable safety profile with CPX-351 (a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio) vs conventional 7+3 chemotherapy in a pivotal phase 3 trial led to the approval of CPX-351 for newly diagnosed therapy-related acute myeloid leukemia (tAML) or AML with myelodysplasia-related changes (AML MRC) in adults and pediatric (aged ≥1 year) patients in the United States and in adults in Europe. The approved induction dose is 1-2 cycles of CPX-351 100 units/m ^{2} (daunorubicin 44 mg/m ^{2} and cytarabine 100 mg/m ^{2}) as a 90-minute intravenous infusion on days 1, 3, and 5 (days 1 and 3 for second induction). In this study, we developed a population pharmacokinetic-pharmacodynamic (PK-PD) model of absolute neutrophil count (ANC) and platelet count to determine the optimal dose for a lower-intensity therapy (LiT) of CPX-351 combined with venetoclax.
Methods:
The CPX-351 population PK-PD analysis was based on data collected from 3 clinical studies (phase 1 study [NCT00389428; *J Clin Oncol* 2011; 29(8):979-85];phase 2 study [NCT02238925; *Cancer Chemother Pharmacol* 2019; 84(1):163-73];phase 3 study [NCT01696084; *J Clin Oncol* 2018; 36(26):2684-92]) in patients with newly diagnosed high-risk/secondary AML. Venetoclax population PK-PD analysis was based on data from a comprehensive safety analysis of venetoclax monotherapy (*Clin Cancer Res* 2018; 24(18):4371-9). ANC and platelet data used in the analysis were from 94 patients for CPX-351 and 272 patients for venetoclax.
Generalized semi-mechanistic population PK-PD analyses were performed using non-linear mixed-effects modeling to characterize the time-course of ANC and platelet count following administration of CPX-351 and venetoclax monotherapy. The majority of system parameters were shared across the 2 therapies and a limited number of treatment-specific parameters were estimated by fitting CPX-351 and venetoclax PK time-courses simultaneously. An R Shiny app was developed for the simulation of different dosing regimens with favorable safety profiles to guide optimal dose selection for LiT of CPX-351 combined with venetoclax, assuming the 2 drug effects on ANC and platelet count were additive.
Results:
The generalized PK-PD model included multi-compartment transit models for ANC and platelet count with separate semi-mechanistic compartments to represent proliferating, maturing, and circulating cells. The model fitted CPX-351 and venetoclax PK-PD data with shared system parameters except for the drug-specific parameter IC_{50} (concentration producing 50% of maximal inhibition of cell proliferation). For ANC, the estimated IC_{50} values for CPX-351 and venetoclax were 295 μM (relative standard error [RSE]: 8.96%) and 120 μM (RSE: 18.0%), respectively; the shared mean transit time (MTT) estimate for ANC maturation was 66.6 h (RSE: 4.95%), and shared maximal inhibition of cell proliferation (I_{max}) was fixed to 1. For platelet count, the estimated IC_{50} values for CPX-351 and venetoclax were 0.0109 μM (RSE: 50.2%) and 16.5 μM (RSE: 8.73%); the shared MTT estimate for platelet maturation was 87.2 h (RSE: 9.01%) and shared I_{max} estimate was 0.313 (RSE: 11.2%).
Simulations with different doses of CPX-351 in combination with 400 mg venetoclax were performed. The simulated mean nadir ANC were 2.1, 1.5, 1.1, and 0.6 × 10 ^{9}/L for CPX-351 doses of 20, 40, 60, and 100 units/m ^{2}, respectively, when administered on days 1 and 3 and combined with venetoclax 400 mg daily for 28 days. The simulated mean nadir platelet counts were 31.0, 30.3, 30.0, and 29.7 × 10 ^{9}/L for CPX-351 doses of 20, 40, 60, and 100 units/m ^{2}, respectively, when administered on

days 1 and 3 and combined with venetoclax 400 mg daily for 28 days. Model-based simulated outcomes of ANC and platelet count were consistent with the observed trial data.

C onclusions:

A generalized semi-mechanistic population PK-PD model was developed to adequately describe the time-courses of ANC and platelet counts in patients with AML following the administration of CPX-351 and venetoclax monotherapy and was used to infer the impact on ANC and platelet count when given in combination. Model-based simulations supported initial dose selection in the phase 1b study of combined CPX-351 LiT plus venetoclax as first-line treatment for patients with AML who are unfit for intensive chemotherapy (NCT04038437).

Disclosures Liang: *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Cook:** *Jazz Pharmaceuticals:* Consultancy; *Enhanced Pharmacodynamics:* Current Employment. **Cheung:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Zhou:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Coppola:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Wang:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Mager:** *Enhanced Pharmacodynamics:* Current Employment. **Van Wart:** *Enhanced Pharmacodynamics:* Current Employment; *Jazz Pharmaceuticals:* Consultancy.

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