The heterogeneity of pediatric oncological patients treated with selumetinib

Köllő Z[1†], Kovács J[2†], Vásárhelyi B[1], Brückner E[2], Garami M[2], Karvaly GB[1]

[1]Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary
[2]Department of Pediatrics, Semmelweis University, Budapest, Hungary

[†]Z. Köllő and J. Kovács contributed equally to this work.

Background

Selumetinib (SLT) is an orally administered selective mitogen-activated protein kinase (MEK1/2) inhibitor currently used for treating pediatric patients diagnosed with neurofibromatosis type I (NF-1) and symptomatic, inoperable plexiform neurofibromas, while being under clinical investigation concerning other malignancies. Our aim was to explore the clinical pharmacokinetics of SLT in pediatric oncology patients treated with NF-1 by performing nonparametric population pharmacokinetic modeling.

Methods

This study was approved by the National Institute of Pharmacy and Nutrition of Hungary. In the first stage of this researcher-initiated, unicentric, prospective, non-randomized, observational cohort study, sixteen patients (8 males and 8 females, median age: 11.5 years) receiving SLT in fixed or alternating doses of 10-35 mg b.i.d. were involved. On a single occasion, following the insertion of an intravenous cannula, blood samples were drawn from each patient 30 minutes before, as well as at 5-7 time points between 15 and 360 minutes after drug intake. SLT concentrations were evaluated in plasma using liquid chromatography-tandem mass spectrometry and a validated laboratory-developed method. Individual data series underwent exploratory noncompartmental analysis. Population pharmacokinetic modeling was conducted using the nonparametric adaptive grid approach.

Results

An assay error equation $y=0.8790+0.0743\times$concentration was established. SLT displayed one-, as well as two-compartment pharmacokinetics in different individuals. A two-compartment model including bioavailability as a random-effect variable and a multiplicative error constant could be fit to the data of thirteen patients, yielding 9 support points. The regression line fitted to the observed versus predicted concentrations had a slope of 0.990 [95% confidence interval (CI): 0.859-1.120], an intercept of 128 (CI: 27.5-229), and a correlation coefficient (r) of 0.846. The shrinkage of the random-effect variables was 0.204-23.6%. The mean weighted prediction error was 0.053, the bias-adjusted mean weighted squared prediction error was 3.344. The value of the Akaike information criterion was 1224 after convergence.

Conclusions

The results of this preliminary pharmacokinetic analysis suggest that pediatric NF-1 patients receiving SLT comprise a very heterogeneous population. Targeting individual SLT exposure based on pharmacokinetic modeling is important for optimizing treatment, especially when alternating doses are taken.

Key Words

therapeutic drug monitoring; oncology; pediatrics; selumetinib; nonparametric pharmacokinetic modeling