

Effects of ABCB1 polymorphisms on the transport of ponatinib into the cerebrospinal fluid in Japanese Philadelphia chromosome-positive acute lymphoblastic leukaemia patients

Yayoi Fukushi¹, Yumiko Akamine², Maiko Abumiya¹, Nagi Tozawa³, Takaya Yamashita³, Miho Nara³, Yoshihiro Kameoka³, Naoto Takahashi³, and Masatomo Miura⁴

¹Akita University

²Affiliation not available

³Akita University Graduate School of Medicine School of Medicine

⁴Akita University Hospital

October 28, 2022

Abstract

The effects of polymorphisms of ABCB1 and ABCG2 on the dose-adjusted plasma trough concentrations and cerebrospinal fluid (CSF)-to-plasma ratios of ponatinib were evaluated. Blood (C4) and CSF (CSF4) concentrations at 4 h after administration were determined. The median (95% confidence interval (CI)) CSF4-to-C4 ratio of ponatinib in subjects homozygous for ABCB1 variants 1236T/T, 2677T/T+T/A, or 3435T/T were significantly higher than that in a group of subjects with other genotypes ($P = 0.026$, 0.012 , and 0.015 , respectively). The median (95% CI) CSF4-to-C4 ratio of ponatinib in four patients with the combination of ABCB1 variants 1236T/T-2677T/T+T/A-3435T/T was 2.62 ($1.42 - 3.42$); this ratio was significantly higher than that in subjects with other genotypes [1.08 ($0.89 - 1.47$); $P = 0.006$]. The brain distribution of ponatinib was affected by ABCB1 polymorphisms and therefore seems to be modulated by P-glycoprotein at the blood-brain and blood-CSF barriers.

Hosted file

MiuraM-ponatinib manuscript for BJCP-editedJ.doc available at <https://authorea.com/users/518273/articles/592489-effects-of-abcb1-polymorphisms-on-the-transport-of-ponatinib-into-the-cerebrospinal-fluid-in-japanese-philadelphia-chromosome-positive-acute-lymphoblastic-leukaemia-patients>

Hosted file

MiuraM-Figure 1-95-CI.pptx available at <https://authorea.com/users/518273/articles/592489-effects-of-abcb1-polymorphisms-on-the-transport-of-ponatinib-into-the-cerebrospinal-fluid-in-japanese-philadelphia-chromosome-positive-acute-lymphoblastic-leukaemia-patients>

Hosted file

MiuraM-Table 1-95-CI.xls available at <https://authorea.com/users/518273/articles/592489-effects-of-abcb1-polymorphisms-on-the-transport-of-ponatinib-into-the-cerebrospinal-fluid-in-japanese-philadelphia-chromosome-positive-acute-lymphoblastic-leukaemia-patients>