Ponatinib

货号：P2687

储存条件：粉末-20°C 可保存 3 年；液体-80°C 可保存 12 月。

产品描述

The oncogenic tyrosine kinase Bcr-Abl plays a central role in the pathogenesis of chronic myelogenous leukemia, thus makes it as the therapy drug target. However, it is demonstrated that the mutations of Bcr-Abl kinase, especially the mutation of T315 residue in the gatekeeper region of the ATP-binding site, have been the most common mechanism of drug resistance, such as imatinib, nilotinib and dasatinib. Ponatinib is a multi-target inhibitor with IC50 values of 0.37nM, 1.1nM, 1.5nM, 2.2nM, 5.4nM and 12.5nM for Abl, PDGFRα, VEGFR2, FGFR1, c-Src and c-Kit, respectively. Distinguished with other Bcr-Abl inhibitors like imatinib, nilotinib and dasatinib, Ponatinib was effective against the ABLT315I mutant with significant inhibition on autophosphorylation of Abl and Abl^{T315I} mutant at concentration≥100nM, whereas the other compound did not. Consistent with the in vitro study, Ponatinib inhibited the cellular proliferation of Ba/F3 expressing various Bcr-Abl mutations with IC50 ranging in 0.5-36nM, as well as CML leukemia cells K562, KY01 and LAMA cell line with IC50 ranging in 0.3-3.9nM, but anti-proliferative on parental Ba/F3 cells and non CML leukemia cells at micromolar concentration. Treatment with Ponatinib at concentration>100nM for 4h can potently suppress the tyrosine phosphorylation status of BCR-ABL and the direct BCR-ABL substrate CrkL in both Ba/F3 cells expressing native BCR-ABL and $Bcr\text{-}Abl^{T315I}$ mutant, further confirming the inhibition of Bcr-Abl-mediated signaling in cells expressing $Bcr\text{-}Abl^{T315I}$ mutant. Oral administration of Ponatinib at dose of 5, 15 and 25mg/kg for 19 days prolonged median survival to 19.5, 26, and 30 days, respectively compared to 16 days for control group in a survival model in which mice were injected with Ba/F3 $Bcr\text{-}Abl^{T315I}$ cells. Daily oral administration of 50mg/kg Ponatinib caused significant tumor regression with a 96% reduction in mean tumor volume in mice injected subcutaneously with Ba/F3 cells expressing $Bcr\text{-}Abl^{T315I}$ mutant.

作用机制

Ponatinib can occupy the adenine pocket of Abl, especially making favorable van der Waals interactions with the I315 mutated residue.

产品信息

CAS 号	943319-70-8	
分子式	C29H27F3N6O	
分子量	532.56	
别名	AP-24534	
溶解度	DMSO	25.0 mg/mL (46.9 mM)
	Water	insoluble