Combination of pimitespib with sunitinib is an effective therapy for imatinib-resistant gastrointestinal stromal tumors

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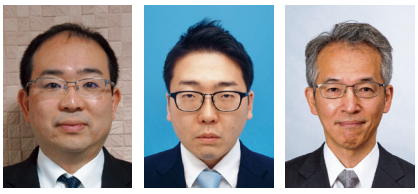

Abstract

This study presents a novel molecularly targeted therapeutic strategy for GIST that have acquired resistance to imatinib. GISTs are driven by gain-of-function mutations in the *KIT* gene, and while imatinib has achieved remarkable clinical success, secondary mutations often lead to therapeutic resistance. We investigated the combined effects of the heat shock protein 90 inhibitor pimitespib and the multi-kinase inhibitor sunitinib using imatinib-resistant GIST cell lines and murine xenograft models. The combination therapy simultaneously suppressed KIT signaling and angiogenic pathways, resulting in synergic inhibition of tumor proliferation. Mechanistically, it reduced autophosphorylated KIT localized on the Golgi apparatus, induced apoptosis, and inhibited angiogenesis through suppression of the PKD2–HIF1α–VEGF pathway. These findings reveal a previously unrecognized molecular mechanism and demonstrate that low-dose combination therapy can achieve potent antitumor effects, providing a promising new direction for GIST treatment.

Background & Results

GIST represents the most common mesenchymal tumor of the gastrointestinal tract. Although imatinib has dramatically improved outcomes, secondary mutations inevitably lead to drug resistance, and the response to second-line sunitinib therapy remains limited. HSP90, a molecular chaperone essential for the stability of oncogenic KIT and its downstream effectors, has recently emerged as a promising therapeutic target. Our previous work identified the efficacy of the selective HSP90 inhibitor pimitespib against GIST, leading to its clinical application. In this study, we comprehensively analyzed the effects of combining pimitespib with sunitinib in imatinib-resistant GIST models. The combination markedly suppressed phosphorylation of KIT and downstream signaling molecules (AKT, ERK, STAT3), resulting in strong growth inhibition and induction of apoptosis. In addition, active KIT localized on the Golgi apparatus was diminished, suggesting a novel degradation mechanism. Furthermore, the combination therapy suppressed VEGF expression through downregulation of PKD2 and HIF1α, reducing tumor micro vessel density and enhancing anti-angiogenic effects. Collectively, these findings demonstrate that dual targeting of KIT signaling and angiogenesis leads to superior antitumor efficacy compared to monotherapy.

Significance of the research and Future perspective

This study provides a molecularly rational strategy to overcome drug resistance, one of the greatest challenges in GIST treatment. The combination of pimitespib and sunitinib simultaneously disrupts KIT-driven oncogenic signaling and tumor angiogenesis, thereby exceeding the therapeutic limits of existing agents. The discovery that HSP90 inhibition promotes degradation of activated KIT within the Golgi apparatus uncovers a unique vulnerability in resistant GIST cells. Clinically, this combination may allow for reduced doses of sunitinib while maintaining antitumor efficacy, minimizing adverse effects and improving patient quality of life. Future clinical trials will clarify its safety and efficacy in patients with advanced GIST, and this dual-targeting approach may further expand to other malignancies driven by kinase signaling and angiogenesis. The university of Osaka –led translational research represents an internationally recognized advancement bridging fundamental discovery and clinical innovation.

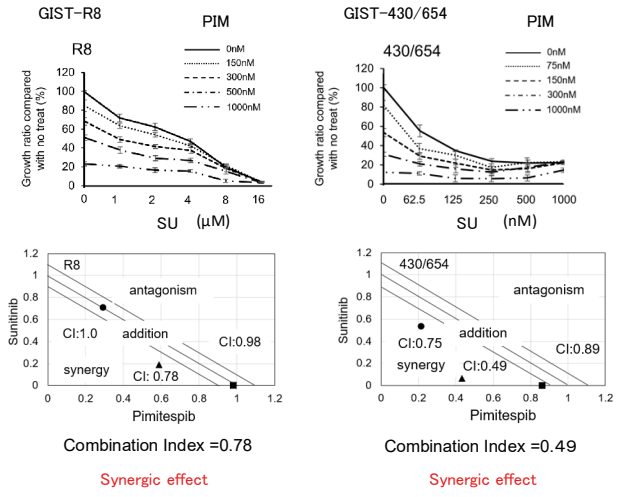

Fig. 1. Effect of pimitespib and sunitinib combination treatment on imatinib-resistant GIST cell lines.

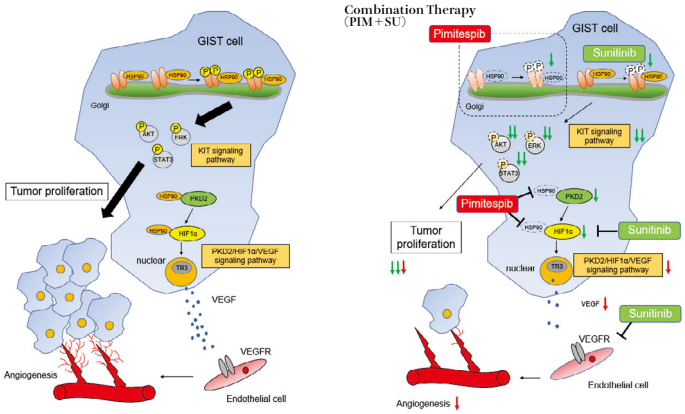

Fig. 2. Models of mutant KIT signaling and PKD2/HIF1α/VEGF signaling on intracellular compartments in GISTs.

(Left) Newly synthesized mutant KIT stabilized by HSP90 activates the Golgi complex. Activation of the mutant KIT signaling pathway by KIT autophosphorylation can activate the PI3K-AKT pathway and ERK. HSP90 binds to and stabilizes PKD2 and HIF1α in GIST cells. Activated PKD2 and HIF1α induces vascular endothelial growth factor (VEGF) expression in tumor cells.
(Right) The combination of pimitespib and sunitinib strongly inhibited the expression of phosphorylated KIT and suppressed downstream signaling. Furthermore, it inhibited the induction of angiogenesis by VEGF suppression.

Patent
Treatise
Teranishi, Ryugo; Takahashi, Tsuyoshi; Obata, Yuuki et al. Combination of pimitespib (TAS-116) with sunitinib is an effective therapy for imatinib-resistant gastrointestinal stromal tumors. Int J Cancer. 2023, 152(12), 2580-2593. doi: 10.1002/ijc.34461
Saito, Yurina; Takahashi, Tsuyoshi; Obata, Yuuki et al. TAS-116 inhibits oncogenic KIT signalling on the Golgi in both imatinib-naïve and imatinib-resistant gastrointestinal stromal tumours. Br J Cancer. 2020, 122(5), 658-667. doi: 10.1038/s41416-019-0688-y
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