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Efficacy of a phosphoinositol 3 kinase (PI3K) inhibitor in gastrointestinal stromal tumor (GIST) models.

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Research Funding:

Background:

PI3K signaling is crucial for GIST proliferation and survival. We assessed the efficacy of the PI3K inhibitor NVP-BEZ235 (BEZ), alone or in combination with imatinib (IM), in GIST xenografts.

Methods:

Nude mice were grafted bilaterally with human GIST, carrying either *KIT* exon 9 (GIST-BOE, dose-dependent IM resistant) or exon 11 (GIST-DFR, IM sensitive) mutations. Animals, randomized into four groups (n=8/group) were dosed orally for 2 weeks with either vehicle, IM (50mg/kg/bid), BEZ (10mg/kg/qd), or IM+BEZ. Treatment efficacy was assessed by tumor volume, histopathology and Western immunoblotting. Moreover tumor regrowth was evaluated for 3 weeks after treatment cessation.

Results:

As a single agent IM and BEZ stabilized tumor growth of both GIST-BOE and DFR. Moderate to significant tumor regression was observed in GIST-BOE under BEZ (by 27%), and IM+BEZ (66%), and also in GIST-DFR under IM (75%) and IM+BEZ (75%). In GIST-BOE significant reduction in mitotic index was observed under BEZ (8.5 fold) and IM+BEZ (8.5 fold) as compared to control. In GIST-DFR mitotic activity was virtually absent under all regimens. Apoptotic activity increased significantly after treatment with IM (5.5 fold) and IM+BEZ (14.0 fold) in GIST-DFR, whereas it was almost unaffected by BEZ as single agent, as well as in all treatment groups in GIST-BOE. By Western, PI3K signaling was incompletely inhibited in all groups in GIST-DFR, and after BEZ in GIST-BOE. Complete inhibition of PI3K signaling was observed only after combination treatment. After treatment cessation long-lasting growth-inhibition was observed in IM+BEZ treated GIST-DFR. Moreover, mitotic index after BEZ and BEZ+IM in GIST-DFR was lower than in control even after treatment withdrawal.

Conclusions:

BEZ shows significant efficacy in GIST xenografts. Furthermore, combination with IM shows synergistic and long-lasting effects even after treatment withdrawal, which is not the case with drugs routinely used for GIST treatment.

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