Abstract

Rapamycin: In vitro and in vivo activity.

In vitro and in vivo activity.

Table.

Methods in vitro and in vivo activity.

PPTP In Vitro Testing Methods

In vitro testing was performed using DMSO/1 to assess the sensitivity of a diverse panel of preclinical xenografts to rapamycin. The PPTP in vivo panel includes cell lines representing a wide spectrum of solid tumors, including ovarian cancer (Co11.6, ES-245), breast cancer (BU52), glioblastoma (140455067), and others.

PPTP In Vivo Testing Methods

Solutions: Rapamycin was purchased from LC Laboratories (Woburn, MA). All other reagents were purchased at the highest grade available.

Ethics: The study was conducted in accordance with the recommendations of the Institutional Animal Care and Use Committee (IACUC) of the National Cancer Institute (NCI), and all procedures were approved by the IACUC.

Statistical Analysis: Data were analyzed using GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). The statistical significance of the differences between groups was assessed using Student's t-test or one-way ANOVA, followed by a post-hoc test (Bonferroni). Differences were considered statistically significant at p < 0.05.

CONCLUSIONS

Rapamycin demonstrated significant differences in EFS distributions compared to controls in 27/38 (71%) solid tumor models and 11/20 (55%) ALL models. High EFS was noted in 8/16 (50%) of the solid tumor models, with the most sensitive being a neuroblastoma xenograft. Objective responses were seen in 4 of 26 solid tumor models with a median EFS of 10.8 months, compared to 4.4 months for controls. Objective responses were seen in 2 of 2 ALL models, with one partial response (ALL-4) and one complete response (ALL-16). A 3-month EFS was observed in 8/16 (50%) of the ALL models.

Rapamycin induced significant differences in EFS distribution in 27 of 38 (71%) of solid tumor xenografts and in 5 of 20 (25%) of the ALL xenografts. Using the PPTP in vivo test to measure activity, rapamycin had a high (4) or intermediate (11) level of in vivo activity. Rapamycin variably inhibited growth of the PPTP in vitro panel, with maximal inhibition ranging from 19% to 85% (median 49%). NHL cell panel was 0.7 nM (Molar).

Rapamycin In Vivo Activity

The median IC50 for the in vitro panel was 0.15 nM (range 0.12–1.04 nM). The median IC50 for the in vivo panel was 0.5 nM (range 0.5–4.5 nM).

Graphs: Rapamycin was active against 10 of the 23 cell lines of the PPTP in vitro panel. The median IC50 for the responsive lines was 1.0 nM with RABM0 being the most sensitive with an IC50 of 0.3 nM.

EFS of treated and control lines (intermediate activity required EFS event (4X increase in tumor volume) measure based on the median setting [e.g., partial response (PR), complete response (CR), etc.]; activity were used: 1) response criteria modeled after the clinical setting (e.g., partial response (PR), complete response (CR), etc.)

Response Data for the Entire Panel was 0.7 nM.

In vivo testing was performed using DMSO/1 to assess the sensitivity of a diverse panel of preclinical xenografts to rapamycin. The PPTP in vivo panel includes cell lines representing a wide spectrum of solid tumors, including ovarian cancer (Co11.6, ES-245), breast cancer (BU52), glioblastoma (140455067), and others.

Methods: Methods to evaluate the activity of panel and three of the solid tumor panels. Further work is needed to expand the range of cell lines, with the most sensitive being a neuroblastoma xenograft PRs intermediate activity. Objective responses were observed in a neuroblastoma xenograft.

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