Antitumor Activity of MPC-6827 in Human Breast, Colon, Pancreatic, Ovarian and Mouse Melanoma Tumor Xenografts in Athymic Nude Mice

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MPC-6827 is a lead molecule derived from a medicinal chemistry effort, which was based on a hit from a proprietary compound-based high-throughput screen system. This molecule displays pro-apoptotic activity, with potency at low nanomolar concentrations in multiple cancer types including pancreatic, prostate, breast, colorectal, non-small cell lung, small cell lung, melanoma, ovarian and leukemia. These studies were designed to assess the ability of MPC-6827 to inhibit the growth of MCF-7, HT-29, MiaPACA, OVCAR-3 and B16 tumor lines subcutaneously implanted into athymic nude mice. In most of the xenografts, MPC-6827 was dosed at 5mg/kg intravenously on a once a week schedule for three weeks at which time the study was halted. Statistically significant (p < 0.05) inhibition of tumor growth was observed in all five tumor lines. In the B16, HT-29, A549 and MCF-7 xenografts, the activity of MPC-6827 was dose dependent in most of the xenografts that were treated with paclitaxel, carboplatin, Gemcitabine and Gemcitabine, respectively. Animals were dosed to at least the maximum tolerated dose (MTD). In the case of pantratuzumab, doxorubicin and irinotecan, the MTD was exceeded in all cases. These results suggest that MPC-6827 may be an effective therapy against multiple tumor types in humans.

RESULTS AND CONCLUSIONS

MVC-6827 is equally effective as carboplatin (30mg/kg; qwk; i.v.) and Gemcitabine (1000mg/kg; qwk x 2; i.v.) dosing regimes in B16-F1 xenografts in Nu/Nu mice. A safety analysis of the MVC-6827 (5mg/kg;qwk x 3; i.v.) and MCF-6827 (5mg/kg; q3d x 4; i.p.) treatment groups was significantly reduced when compared to vehicle treatment alone. Neither of the compound treated animal groups was significantly

SAFETY OF MPC 6827

The growth of B16-F1 xenografts observed in animals treated with irinotecan (40mg/kg; M,W,F x 2; i.p.) and MPC-6827 (5mg/kg; qwk x 3; i.v.) was significantly reduced when compared to vehicle treatment alone. A p value for irinotecan (5mg/kg; qwk x 3; i.v.) was not determined as this study group was dosed above the LD50. These results demonstrate that MPC-6827 is equally effective as paclitaxel (25mg/kg; qwk x 2; i.p.) at both 2.5mg/kg qwk x 2; i.v. and 5mg/kg qwk x 3; i.v. dosing regimes in B16-F1 xenografts in Nu/Nu mice.

METHODOLOGY

Tumor lines were isolated and transferred to Flask and Stabilized Salt Solution (HS5) for subcutaneous injection into the right flank of 9-10 weeks old female Sprague-Dawley. The xenografts were grown to a volume of 800mm3 and then randomized into dose groups. Animals were dosed with MPC-6827 or a clinically relevant standard of care therapeutic, with appropriate vehicle controls. All drugs were administered as a single daily intravenous injection. Tumors were measured at least twice a week (depending on tumor growth rate) with calipers. Tumor volumes (Tumor Volume = l x w x h) were measured twice a week with an electronic caliper. The tumor size for the study day was calculated as

% Change in Mean Body Weight

% Change in Median Body Weight

The growth of HT-29 xenografts observed in animals treated with irinotecan (40mg/kg; M,W,F x 2; i.p.) and MPC-6827 (5mg/kg; qwk x 3; i.v.) was significantly reduced when compared to vehicle treatment alone. A p value for irinotecan was not determined as this study group was dosed above the LD50. These results demonstrate that MPC-6827 is equally effective as paclitaxel (25mg/kg; qwk x 2; i.p.) at both 2.5mg/kg; qwk x 2; i.v. and 5mg/kg; qwk x 3; i.v. dosing regimes in B16-F1 xenografts in Nu/Nu mice.

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SAFETY OF MPC 6827

When dosed up to 7.5mg/kg, MPC-6827 was observed to be well tolerated in Nu/Nu mice. Histologic findings from organs were reviewed and were consistent with the 20% guideline recommended by the National Cancer Institute.

REFERENCES

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