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

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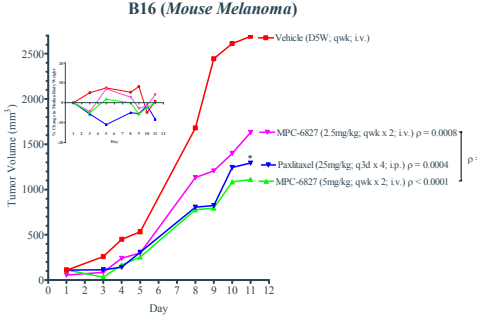
ABSTRACT

MPC-6827 is a lead molecule derived from a medicinal chemistry effort, which was based on a hit from a proprietary caspase-based high-throughput screening 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 or until the study was halted. Statistically significant ($\rho > 0.05$) inhibition of tumor growth was observed in all five tumor lines. In the B16, OVCAR-3, MCF-7 and MiaPACA xenografts, the activity of MPC-6827 was greater than or equal to that observed with paclitaxel, carboplatin, doxorubicin and gemcitibine, respectively. Attempts were made to dose paclitaxel, doxorubicin, carboplatin, irinotecan and gemcitibine at the maximum tolerated dose (MTD). In the case of paclitaxel, doxorubicin, and irenotecan, the MTD was exceeded ($>LD_{10}$). These results suggest that MPC-6827 may be an effective therapy against multiple tumor types in humans.

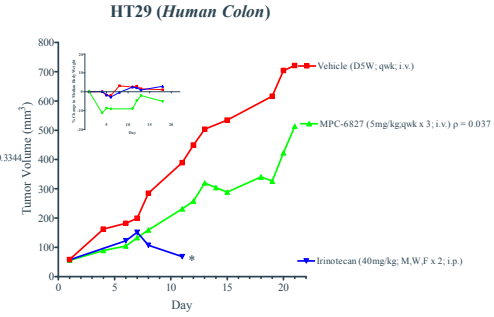
METHODOLOGY

Tumor lines were isolated and suspended in Hanks Buffered Salt Solution (HBSS) for subcutaneous injection into the right flank of Crl:Nu/Nu mice (Charles River Labs). Tumors were grown to an average size of 100mm^3 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 at or near the maximum tolerated dose. Tumors were measured at least twice a week (depending on tumor growth rate) with hand held calipers. Body weight was determined when tumors were measured. Toxicity and morbidity were assessed and documented on a daily basis. Any mice that lost > 20% of their original body weight or had individual tumor masses > 1500mm^3 were euthanized using CO2 asphyxiation.

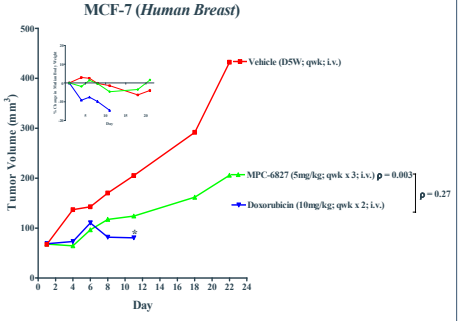
Means and standard deviations were obtained using Microsoft Excel 2000 (Microsoft; Redmond, WA). Values were then transferred to Prism software for graphing (GraphPad; San Diego, CA). Analysis of variants with unadjusted pair wise comparison was performed using SAS software (SAS; Cary, NC).



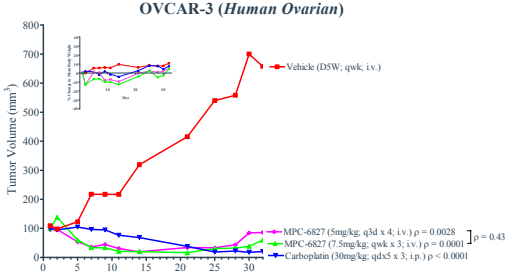
*LD_{20} - Paclitaxel dose related death

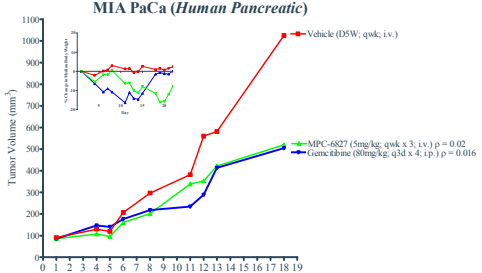


*LD_{40} - Irinotecan dose related death



*LD_{40} - Doxorubicin dose related death





RESULTS AND CONCLUSIONS

(B16)

Significant inhibition of the growth of B16-F1 xenografts was observed in animals treated with paclitaxel (25mg/kg; q3d x 4; i.p.), MPC-6827 (5mg/kg;qwk x 2; i.v.) and MPC-6827 (2.5mg/kg;qwk x 2; i.v.) when compared to vehicle treatment alone. On day eleven, the ρ values for paclitaxel, 5mg/kg MPC-6827, and 2.5 mg/kg MPC-6827 were $\rho = 0.0004$, $\rho < 0.0001$, and $\rho = 0.0008$, respectively. None of the compound treated animal groups was significantly better than the others.

MPC-6827 is equally effective as paclitaxel (25mg/kg; q3d x 4; i.p.) at both 5mg/kg;qwk x 2; i.v. and 2.5mg/kg;qwk x 2; i.v. dosing regimes in B16-F1 xenografts in Nu/Nu mice.

(HT-29)

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 inhibited when compared to vehicle treatment alone. On day twenty-two, the ρ values for 5mg/kg MPC-6827 was $\rho = 0.037$. A ρ value for irinotecan was not determined as this study group was dosed above the LD_{10} and thus overdosed. The tumor volumes for irinotecan are carried out until the LD_{10} date occurred (Day 12).

These results demonstrate that MPC-6827 (5mg/kg; qwk x 3; i.v.) is effective at inhibiting the growth of HT-29 xenografts in Nu/Nu mice.

(MCF-7)

Significant inhibition of the growth of MCF-7 xenografts was observed in animals treated with doxorubicin (10mg/kg; qwk x 3; i.v.) and MPC-6827 (5mg/kg; qwk x 3; i.v.) when compared to vehicle treatment alone. On day eleven, the ρ values for 5mg/kg MPC-6827 was $\rho = 0.003$. A ρ value for doxorubicin was not determined as this study group was ended on day eleven due to compound toxicity.

MPC-6827 is effective at 5mg/kg; qwk x 3; i.v. on MCF-7 xenografts in Nu/Nu mice.

(OVCAR-3)

The growth of OVCAR-3 xenografts was observed in animals treated with carboplatin (30mg/kg; qdx5 x 3; i.p.), MPC-6827 (7.5mg/kg;qwk; i.v.) and MPC-6827 (5mg/kg;q3d x 4; i.v.) was significantly reduced when compared to vehicle treatment alone. Neither of the compound treated animal groups was significantly better than the others.

MPC-6827 is equally effective as carboplatin (30mg/kg; qdx5 x 3; i.p.) at both the 5mg/kg;q3d x 4; i.v. and 7.5mg/kg;qwk; i.v. dosing regimes on OVCAR-3 xenografts in Nu/Nu mice.

(MIA PaCa)

Significant inhibition of the growth of MIA PaCa xenografts was observed in animals treated with MPC-6827 (5mg/kg; qwk x 3; i.v.) when compared to vehicle treatment alone. On day 18, the ρ values for 5mg/kg MPC-6827 was $\rho = 0.02$. A ρ value for the gemcitibine treatment group was $\rho = 0.016$.

MPC-6827 (5mg/kg; qwk x 3; i.v.) is equally effective as gemcitibine (80mg/kg; q3d x 4; i.p.) on MIA PaCa xenografts in Nu/Nu mice.

SAFETY OF MPC 6827

When dosed up to 7.5mg/kg , MPC-6827 was observed to be well tolerated in Nu/Nu mice. Individual animal body weight loss never exceeded the 20% guideline recommended by the National Cancer Institute