Absorbable Gel-forming Controlled Release Paclitaxel Formulation for Retarding Tumor Cell Growth

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Statement of Purpose: The objective of the study is to investigate a new paclitaxel controlled release system using a vehicle for subcutaneous administration. Paclitaxel has been successfully used in treatment of solid tumors. The vehicle for administration of the drug is Cremophor EL® which causes hypersensitivity reactions requiring that patients receive prophylactic steroids prior to treatment. Efforts have been made with limited success to develop new delivery systems which incorporate paclitaxel into absorbable microspheres[1], liposomes[2] and polymeric pastes[3] and do not require Cremophor EL® as the vehicle. The obvious need for non-allergenic, easy-to-administer, absorbable vehicle and the availability of a family of gel-forming absorbable liquid polymer [4] with demonstrated effectiveness in a controlled release system prompted the pursuit of the present study.

Methods: Pairs of primary liquid gel-forming copolyesters were mixed separately to produce binary systems. Two formulations, M3 and M6, were chosen based on release profiles and ease of injectability. Paclitaxel was dissolved in acetonitrile and then added to gels which were further diluted 50:50 with poly(ethylene glycol) (PEG400). Paclitaxel release profiles from the gels and PEG were analyzed by HPLC following an incubation period of either 4 or 6 hr at 37ºC. The animal model was 6-8 wk old female C57BL/6 mice. A murine carcinoma cell line, Lewis Lung Carcinoma (LLC) (ATCC, Manassas, VA), was used to generate tumors by injecting 200µ1of $1x10^6$ cells/ml subcutaneously into the right flank of the mice. Once tumors were palpable the mice were injected with the gel forming copolyesters (M3 or M6) diluted with PEG and containing paclitaxel at 300 mg/kg mouse weight. Two dosing regimes were followed: (1) a single dose (2) multiple doses of one injection every 72 hr x5. Mice that did not receive any drug were the controls. The mice were weighed and tumor sizes measured every day. The mice were euthanized prior to tumors reaching 15 mm or one week post the last injection of the multiple dosing schemes. Tumors were excised and (1) sectioned for immunohistochemical staining according to the Hypoxyprobe™ - 1 Plus Kit instructions to detect hypoxia (2) disaggregated in 1% (w/v) paraformaldehyde prior to staining for flow cytometry analysis using the APO-DIRECT™ Kit (CHEMICON, Temecula, CA). Pharmacokinetic profiles of paclitaxel in the gel-forming copolyesters are being assessed 6 hrs post-injection. Plasma samples are obtained from mice by cardiac puncture prior to euthanasia and assayed for paclitaxel using HPLC.

Results / Discussion: Paclitaxel release from M3, M6 and PEG were measured by HPLC. Relevant results are depicted in Fig. 1 and led to the selection of two gel forming copolyester formulations suitable for in vivo application.

Subcutaneous injection of paclitaxel at a concentration of 300 mg/kg in both gel systems resulted in retardation of tumor growth as compared to the control animals (Fig.2). Single doses of M3/PEG were slightly more effective in retarding growth than M6/PEG. The slow release of paclitaxel from M3/PEG provided enough drug initially to be effective but the effect was not sustainable.

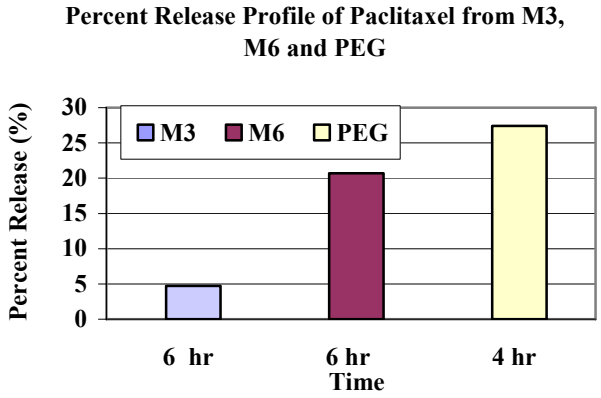

Fig. 1 Comparison of paclitaxel percent release from M3, M6 and PEG as measured by HPLC.

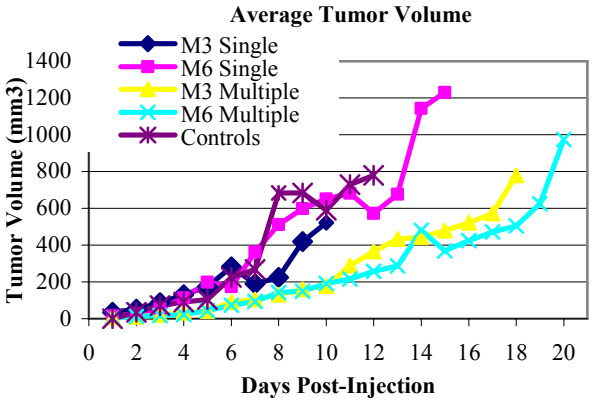

Fig. 2 Effect of the release of paclitaxel on tumor.

The multiple dosing schemes produced a significant retardation of tumor growth when both gels were injected as compared to the controls. M6/PEG was slightly more effective than M3/PEG. A continuous injection of the moderately releasing M6/PEG gel provided available drug to the actively growing tumor enough to retard growth for at least 2 weeks.

Conclusions: Binary gel systems have been selected and effectively used as carriers of paclitaxel for attaining slow and moderate release profiles

References:

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