

Intratumoral Injection of BCNU in Ethanol (DTI-015) and BCNU in Ethanol/PEG400 Cure Subcutaneous C26 Tumors

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MOTIVATION

- Solvent facilitated perfusion (SFP) after intratumoral (IT) injection is a promising anti-cancer therapy.
- Optimization of solvent type may enhance efficacy by enhancing facilitated perfusion into the tumor tissue, while minimizing systemic toxicity.

AIMS

- To compare efficacy of the IT injection of two BCNU based SFP treatments with systemic BCNU treatment in subcutaneous c26 tumors.
- To compare toxicity of the IT injection of two BCNU based SFP treatments with systemic BCNU treatment in subcutaneous c26 tumors.

BACKGROUND

SFP TREATMENT

- Solvent facilitated perfusion (SFP) is a promising new approach to local chemotherapeutic delivery by direct injection. It utilizes the high translational mobility of certain organic solvents in the aqueous phase, and their ability to cross cell membranes.
- In an orthotopic model of glioma, direct injection of BCNU dissolved in EtOH (DTI-015), has demonstrated 100 times greater BCNU concentration in tumor than normal tissue, and increased efficacy and survival compared with systemic injection [1-4].

SUBCUTANEOUS C26 MODEL

- C26 tumor fragments were implanted subcutaneously in Balb/c mice by trocar.
- When tumors reached a mean size of 100mg, mice were randomly distributed into treatment groups (see Table).
- Direct injection into the tumor center (50 μ l/min) was accomplished using a hand held micro-injector.

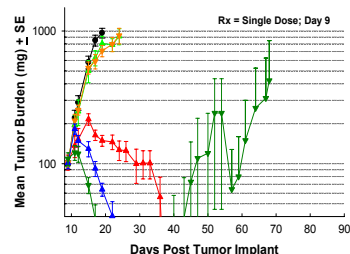
ENDPOINTS

- Caliper based measurement of tumor growth.
- Tumors that underwent regression by 50% of the initial tumor weight were designated as partial regressions.
- Tumors that regressed to unpalpable size were designated as complete regressions.
- Tumor free survivors were defined as complete regressions that persisted to the study end (86 days).

REFERENCES

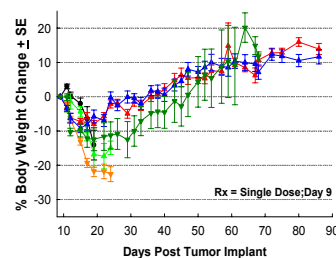
- Hamstra, D.A., et al. J Neurooncol 2005;73:225-38.
- Hall, D.E., et al. Clin Cancer Res 2004;10:7852-9.
- Hassenbusch, S.J., et al. Neoplasia 2003;5:9-16.
- Pietronigro, D., et al. Neoplasia 2003;5:17-22.

Tumor Growth



- Untreated Control (Grp. 1)
- EtOH Vehicle (Grp. 2); 50 μ L/mouse, IT
- BCNU/EtOH (Grp. 3); 0.5mg/mouse, IT
- EtOH/PEG400 Vehicle (Grp. 5); 50 μ L/mouse, IT
- BCNU/EtOH/PEG400 (Grp. 6); 0.5mg/mouse, IT
- BCNU/EtOH:Saline (Grp. 8); 0.5mg/mouse, IP

Body Weights



RESULTS AND CONCLUSIONS

- ⇒ Both SFP therapies showed 100% cure rate at the 0.5mg BCNU dose.
- ⇒ Systemic BCNU at 0.5mg dose resulted in only 40% cure rate.

Group #	N	Treatment	Max. Mean BW Loss (%)	Treatment Related Deaths	Median Survival (Days)	Cures
1	5	Untreated Control	14	0/5	21	0/5
2	5	EtOH vehicle (IT)	16	0/5	25	0/5
3	8	0.5mg BCNU in 50 μ l EtOH (IT)	8	0/8	>86	8/8
4	8	1mg BCNU in 50 μ l EtOH (IT)	28	2/8	>86	6/8
5	5	EtOH/PEG400 vehicle (IT)	22	0/5	25	0/5
6	8	0.5mg BCNU in 50 μ l EtOH/PEG400 (IT)	9	0/8	>86	8/8
7	8	1mg BCNU in 50 μ l EtOH/PEG400 (IT)	25	3/8	>86	5/8
8	5	0.5mg BCNU in 50 μ l EtOH/Water (IP)	12.5	0/5	60	2/5
9	5	1mg BCNU in 50 μ l EtOH/Water (IP)	19	5/5	14	0/5

- ⇒ The control group showed 14% maximum mean body weight (BW) loss.
- ⇒ The SFP therapies produced less than 10% mean body weight (BW) loss at the 0.5mg BCNU dose.
- ⇒ Systemic BCNU at the 0.5mg dose resulted in 12.5% mean BW loss.

Conclusions

- ⇒ Both IT injection of BCNU in EtOH and EtOH/PEG400 solvents showed significantly greater activity against C26, than the equivalent systemic dose of BCNU.
- ⇒ There was a trend toward less toxicity of the SFP therapies than equivalent systemic doses of BCNU.
- ⇒ The EtOH and EtOH/PEG400 solvents could not be distinguished in terms of efficacy or toxicity.