Background: Topotecan is a small molecule inhibitor of DNA topoisomerase I, and blocks disassembly of the covalent cleavable complex formed between the enzyme and DNA. Stabilization of cleavable complexes generates DNA single- and double-strand breaks, particularly during S phase, prompting cells to undergo apoptosis. Topotecan has been studied in multiple clinical trials against pediatric solid tumors and leukemias, alone or in combination with established drugs, under various dosing schemes.

Methods: The PPTP includes a molecularly characterized in vivo panel of cell lines (n=27) and in vivo panel of xenografts (n=61) representing most of the common types of childhood solid tumors and childhood acute lymphoblastic leukemia (ALL). Topotecan was tested as a single agent against the PPTP in vivo panel at a dose of 0.6 mg/kg administered intraperitoneally daily x 5 days for 2 weeks, repeated at Day 21. Three measures of antitumor activity were used: 1) an objective response measure modeled after the clinical setting (partial response, PR, complete response, CR, and stable disease, SD) and 2) a time to event (4-fold increase in tumor volume at the end of study).

Results: For each xenograft line, 8 mice were inoculated with 3-5 x 10^6 cells per mouse. For each xenograft line, 10 mice bearing SC tumors initiated treatment when CD45% <1% for 2 consecutive weeks and at end of study CD45% <1%. CD45% never drops below 1%, no events before end of study.

CONCLUSIONS

- Topotecan was administered at a dose and schedule that gives drug systemic exposure similar to that achieved in children when administered on the same schedule. This dosel schedule represents ~30% of the MTD in mice and was well tolerated with 7 out of 431 (1.6%) deaths in the treatment arm versus 1% for the control arm. Forty five xenografts were considered evaluable.

- Topotecan induced significant differences in tumor volume (22 out of 37) and in EFS distributions (32 out of 37) in solid tumor xenografts compared to controls.

- High activity was found in tumors of Wilms, neuroblastoma, glioblastoma and rhabdomyosarcoma histotypes. These results are comparable to those obtained by the PPTP for vincristine (6 objective responses, 3 of them complete) and better than those for cisplatin (7 objective responses, 3 of them complete).

- Topotecan showed a high level of efficacy against the PPTP ALL xenograft panel. It induced significant differences in EFS distributions in all 8 of the ALL xenografts. Objective responses were achieved for seven out of eight xenografts (five being complete responses, and two of those being maintained).

- Topotecan has demonstrated high activity in vivo against tumor xenografts of four different histotypes and against acute lymphoblastic leukemia xenografts, which warrants its inclusion in combination studies with other drugs to be tested by the PPTP.