GSH-conjugation improves efficacy of Doxil against intracranial xenografts

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BACKGROUND

High-grade glioma is a uniformly fatal disease with an unmet need for better therapy. A major reason for this poor outcome is the invasive nature of gliomas. Novel therapies that target invasive brain tumor cells should be invented, but a major impediment to the delivery of adequate amounts of therapeutics is the blood-brain barrier (BBB), which is largely intact in regions where invasive cells reside. Glutathione (GSH)-conjugated PEGylated liposomes (G-Technology<sup>®</sup>) may be suitable vehicles for targeted delivery of small molecule cytotoxic drugs across the BBB. GSH is a natural anti-oxidant that is found at high levels in the brain and its active transporter is abundantly expressed at the BBB. Previous studies using microdialysis with an increasing % of GSH conjugated to liposomes carrying ribavirin have shown a %GSH-dependent increase of drug levels in brain interstitial fluid (up to 5-fold higher), and GSH-liposomes carrying endomorphin-1 were more effective in hot-plate tests when compared to unconjugated liposomes.

OBJECTIVES

To establish whether glutathione-conjugated liposomes carrying doxorubicin (Brain-Doxil, or 2B3-101) are efficacious in the treatment of an intracranial tumor model.

RESULTS

• In the first series, the animals received repeated administrations of unconjugated liposomes (Caelyx/Doxil) or Doxil conjugated with 3%GSH or 5%GSH, all at a dose of 5 mg/kg (n=10 per group).
• Based on the bioluminescence signal between day 0 (start of treatment) and day 10, Doxil and 3%GSH-Doxil were minimally effective at this dose, whereas the 5%GSH-Doxil demonstrated a better response.
• After day 10, some animals were lost due to tumor progression, which makes the course of the tumor growth curves beyond day 10 less accurate.
• In line with the bioluminescence results, the 5%GSH-Doxil treatment group also displayed a longer median survival (18.5 days), than 3%GSH (15.5 days), Doxil (15 days) or controls (13 days).
• In the second series, the animals received only the 5%GSH-Doxil, but at a more intense dose regimen, namely 10 mg/kg/q4d x4 or 18 mg/kg/q8d x2.
• Although some animals were lost due to effects of the treatment (n=4 for 10 mg/kg and n=2 for 18 mg/kg), most animals tolerated the treatment well.
• The median survival was significantly better in both treatment arms compared to the control group (15 days), whereas there was a trend towards a better survival for the 18 mg/kg/q8d x2 group (24 days) relative to 10 mg/kg/q4d x4 (23.5 days).
• This latter schedule will be employed to confirm these results using a second independent intracranial tumor model.

CONCLUSION

GSH conjugation of Caelyx/Doxil results in a more efficacious treatment of intracranial U87 tumor model than unconjugated liposomes. We will perform additional experiments in order to confirm these results in other intracranial tumor models.