



Safety and tolerance of multiple weekly intracavitary injections of ¹³¹I-chlorotoxin (TM-601): Preliminary results of a prospective clinical trial in patients with recurrent glioblastoma multiforme

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Background

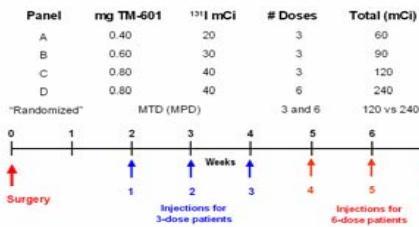
¹³¹I-chlorotoxin is a peptide originally derived from scorpion venom that will specifically bind to tumor cells targeting lamellipodia and produces a variety of secondary messenger effects through phosphatidylinositol signaling. Preclinical studies suggest it is both a radiation and chemotherapy sensitizer. A previous phase I/II clinical trial defined the distribution and dosimetry of single injection intracavitary ¹³¹I-chlorotoxin and suggested clinical activity in patients with recurrent glioblastoma multiforme.

Methods

15 patients with recurrent GBM after prior treatment (radiation therapy), were enrolled in this sequential, multiple-dose escalation study with re-resection and implantation of a ventricular access device (VAD) into the resection cavity. Dose limiting toxicity was defined as any grade 3 or greater toxicity judged probably related to study drug and occurring within 7-11 days of the last dose. Dosing cohorts of 3-5 patients were entered at each of the listed dose levels designed to maintain a constant drug specific activity. The median clinical follow-up was 213 days (range 61-384 days).

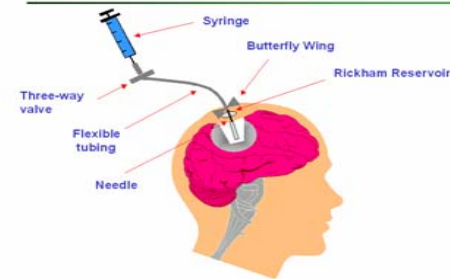
Study Schema

¹³¹I-TM-601 Phase I/II Clinical Trial Design



Schema for current clinical trial. Four panels of dose escalation are followed by a randomized phase II trial comparing three vs. six intracavitary injections. Since dose limiting toxicity did not occur at dose panel D, the randomized portion of the current trial is comparing 40 mCi x 3 (120 mCi) vs 40 mCi x 6 (240 mCi).

Placement of Delivery Apparatus for Intracavitary ¹³¹I-chlorotoxin



Results

One subject did not complete treatment due to thrombocytopenia possibly related to a VAD infection necessitating removal of the VAD following the initial dose of study drug. To date, 13 serious adverse events (SAEs) were observed in 15 patients after study drug administration. These included seizure, cerebral edema, and gait disturbances. None were judged to be both unexpected and related to study drug. Five SAEs were judged by the investigator to be at least possibly related to ¹³¹I-chlorotoxin. These events are described in detail in table 1. No dose limiting toxicity was observed. Two subjects experienced Grade 1/2 CTC 3.0 neutropenia.

Serious Adverse Events*

| # of patients | SAE | Timing |
|---------------|--------------------------------|--|
| 3 | Seizure | Range: Day of dose – 20 days post; 1 pt. with sub-therapeutic AED levels |
| 1 | Cerebral edema | 63 days post last dose in setting of reduced steroids |
| 1 | Thrombocytopenia (CTC grade 3) | 7 days post first dose |

•One day prior to last dose of ¹³¹I-chlorotoxin patient 203 had an episode of nausea and vomiting. This event was later interpreted as seizure and was associated with a low Dilantin level.

•On the day of the last treatment with ¹³¹I-chlorotoxin patient 401 experienced left paraplegia thought to be associated with seizure activity. The patient had a previous seizure prior to any ¹³¹I-chlorotoxin. This event was associated with nausea and vomiting which complicated administration of oral anti-seizure medications. This patient had another seizure 20 days after the last dose of ¹³¹I-chlorotoxin.

•63 days after the last dose of ¹³¹I-chlorotoxin patient 301 experienced left upper extremity weakness and generalized weakness. This event was associated with discontinuing oral steroids. The patient was admitted and symptoms resolved after one day of IV Decadron.

•Seven days after the first and only dose of ¹³¹I-chlorotoxin patient 404 experienced thrombocytopenia with a platelet count of 47K down from 103K the week prior. 15 days after dosing the patient experienced a VAD infection requiring IV antibiotics and surgical removal of the device.

Conclusions

The safety profile of weekly intracavitary injections of ¹³¹I-chlorotoxin was acceptable. Dose limiting toxicity was not reached at the final planned dose level D (6 x 40 mCi/0.8 mg peptide, total 240 mCi), which is the maximum practical dose. Accrual to the randomized phase II portion of this trial comparing three vs. six weekly injections began 12/2005.

*As determined by investigator to be at least possibly related to ¹³¹I-chlorotoxin