Abstract

Evaluation of the Safety of Folate Receptor-Targeted Boron Carrier in Boron Neutron Capture Therapy (BNCT) for Malignant Gliomas Using CED Administration †

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1. Introduction

Knowing how to accumulate boron into the tumor cells is a crucial aspect of boron neutron capture therapy (BNCT), which can be targeted at the cellular level, and the development of novel boron agents other than BPA, which is used in clinical practice, is urgently needed. Our previous work demonstrated the efficacy of BNCT in malignant gliomas using PBC-IP, a pteroyl-closo-dodecaborate-conjugated 4-(p-iodophenyl) butyric acid with folate receptor targeting. Administered through convection-enhanced delivery (CED), PBC-IP resulted in long-term survival equivalent to cure, surpassing BPA outcomes. While the local administration method has been employed for the treatment of brain tumors using this drug, its applicability extends to cancers in other organs throughout the body through intravenous administration. Consequently, this report emphasizes the safety of BNCT treatment with this drug, examining both local dosing in the brain and intravenous administration in the experimental investigation. This study focuses on assessing PBC-IP’s safety in CED procedures and implications for clinical application.

2. Methods

PBC-IP was administered intravenously or via CED to normal Fischer rats. At the predetermined time, each organ was collected and boron concentration was measured via Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES). The intravenous administration of PBC-IP aimed to evaluate toxicity in cases where the tip of the CED catheter was implanted in the normal brain or accidentally inserted into a blood vessel. Additionally, CED administration of PBC-IP to normal rats aimed to evaluate the extent
of drug clearance from normal tissues. PBC-IP concentrations were set at a maximum of 5000 µg B/mL for intravenous administration and 1500 µg B/mL for CED.

### 3. Results

Upon PBC-IP administration intravenously, no indications of apparent toxicity were observed in post-administration assessments. Furthermore, the boron concentration in each organ was within acceptable limits. The maximum boron concentration was 10.3 ± 0.8 µg B/g in the liver at a dose of 200 µL of PBC-IP 5000 µg B/mL. The boron concentration in the brain on the same side as PBC-IP CED administration exhibited a gradual decrease, while boron concentrations in other organs were minimal (the boron concentrations in each organ were less than 1 µg B/g).

### 4. Conclusions

Safety assessments revealed no apparent toxicity with intravenous administration, and acceptable boron concentrations in organs. CED administration exhibited gradual brain boron reduction, minimizing concentrations in other organs. Furthermore, the potential of BNCT with intravenous administration of this drug for cancers in organs other than the brain has been explored, and the safety of the drug in such scenarios has been established. PBC-IP emerges as a non-toxic, swiftly cleared boron agent, offering promise for BNCT applications. Future clinical prospects are encouraging, positioning PBC-IP as a potential breakthrough in boron neutron capture therapy.

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