Biokinetic analysis of tissue boron (¹⁰B) concentrations of glioma patients treated with BNCT in Finland

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HIGHLIGHTS

- Previously no correlation between the radiation dose and survival was found in a clinical BNCT trial on recurrent GBM.
- In this study a kinetic model based on ¹⁸F-BPA-PET study was used to predict the behavior of BPA in the tissues.
- Model predicts +11% and 36% higher average tumor and normal brain doses respectively.

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ABSTRACT

A total of 98 patients with glioma were treated with BPA-F-mediated boron neutron capture therapy (BNCT) in Finland from 1999 to 2011. Thirty-nine (40%) had undergone surgery for newly diagnosed glioblastoma and 59 (60%) had malignant glioma recurrence after surgery. In this study we applied a closed 3-compartment model based on dynamic ¹⁸F-BPA-PET studies to estimate the BPA-F concentrations in the tumor and the normal brain with time. Altogether 22 patients with recurrent glioma, treated within the context of a clinical trial, were evaluated using their individual measured whole blood ¹⁰B concentrations as an input to the model. The delivered radiation doses to tumor and the normal brain were recalculated based on the modeled ¹⁰B concentrations in the tissues during neutron irradiation. The model predicts from −7% to +29% (average, +11%) change in the average tumor doses as compared with the previously estimated doses, and from 17% to 61% (average, 36%) higher average normal brain doses than previously estimated due to the non-constant tumor-to-blood concentration ratios and considerably higher estimated ¹⁰B concentrations in the brain at the time of neutron irradiation.

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1. Introduction

A total of 98 glioma patients have been treated with L-boronophenylalanine-fructose (BPA-F) mediated boron neutron capture therapy (BNCT) in Finland since 1999 (Joensuu et al., 2003; Kankaanranta et al., 2011). Of these, 39 (40%) underwent surgery for newly diagnosed glioblastoma and 59 (60%) had malignant glioma that had recurred after brain surgery. The safety and efficacy of BNCT as treatment of glioma was studied within registered prospective clinical trials (www.clinicaltrials.gov) (Joensuu et al., 2003; Kankaanranta et al., 2011). Radiation doses were estimated according to a conventional BNCT dose calculation protocol, where frequently used radiobiological weighting factors and standard static normal brain-to-blood and tumor-to-blood ¹⁰B concentration ratios of 1 and 3.5, respectively, were used (Coderre and Morris, 1999; Coderre et al., 1998). We found no correlation between the estimated tumor radiation doses and survival in a study population consisting of patients with recurrent malignant glioma treated with BNCT (Kankaanranta et al., 2011), which might suggest for inaccurate estimation of the tumor dose. The temporal changes in the concentrations of ¹⁰B in the normal brain and tumor tissue may differ from those in the blood, and, therefore, the normal brain-to-blood and the tumor-to-blood ratios at the time

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of neutron irradiation might have differed from the values applied in the dose calculations.

In this study the temporal concentrations of BPA-F in the brain and tumor tissues were assessed using a closed 3-compartment pharmacokinetic model (Imahori et al., 1998). The model was applied to patients who were treated in a clinical trial focusing on recurrent gliomas. The delivered radiation doses to tumor and the normal brain were recalculated based on the modeled average ^{10}B concentrations in the tissues during neutron irradiations.

2. Patients and methods

2.1. Patients

The radiation doses received by 22 patients with recurrent glioma and treated within a clinical trial (Kankaanranta et al., 2011) were re-estimated. The patients received 290–450 mg/kg of BPA-F with a 2-h intravenous infusion prior to BNCT. Neutrons obtained from a research nuclear reactor (FiR 1) were delivered through two portals, with irradiation of each portal lasting from 11 to 24 min (mean, 17 min). Neutron irradiation of the first portal was initiated a median of 62 min (range, 46–144 min) after the end of BPA-F infusion. The ^{10}B concentrations of peripheral venous blood samples, collected at 20-min intervals, were analyzed with inductively coupled plasma-atomic emission spectroscopy (ICP-AES) (Laakso et al., 2001; Linko et al., 2008). The first blood sample was taken immediately before the initiation of the BPA F-infusion (the baseline sample), and the last one immediately after the completion of irradiation to the second portal.

2.2. The closed 3-compartment pharmacokinetic model

A closed 3-compartment model, derived from a ^{18}F-BPA-PET study on glioblastoma patients (Imahori et al., 1998), was applied to predict the changes in the total BPA concentration with time in the brain and the tumor tissue during the BNCT treatments. The applied 3-compartment model is shown in Fig. 1. The compartment C_{tot} predicts the total uptake in the two tissue compartments, compartment 1 (C_1) and compartment 2 (C_2), which represent non-specifically bound and specifically bound ^{18}F-BPA in tissue, respectively. The model, and the related rate constants K_1 and k_{2-4} for ^{18}F-BPA kinetics between the plasma and the normal brain or glioma tissue compartments, were determined by Imahori et al. (1998) using a bolus injection of ^{8}F-BPA, and validated by analyzing the ^{10}B concentrations in resected tumor samples consisting of glioblastoma. In addition, the model has been validated using slow (20 and 60 min) intravenous infusions of ^{18}F-BPA (Imahori et al., 1998).

The model requires the ^{10}B concentration in the plasma (C_p) as an input. For most patients in our series, only the whole blood ^{10}B concentrations were available. Therefore, as suggested by Imahori et al. (1998), we applied a constant multiplicative factor of 1.3 to

convert the ^{10}B concentrations measured in the whole blood to approximate plasma ^{10}B concentrations. Both plasma and whole blood ^{10}B concentrations were available for one patient, and in this case both plasma and blood ^{10}B concentration-based BPA-F kinetics were calculated in the brain and the tumor tissue.

To estimate the total ^{10}B uptake in the brain and glioma tissues (C_{tot}), we used the 3-compartment model simulating program p2t_3c available at the Turku PET center (http://www.turkupetcentre.fi, Turku PET Centre, Finland). The p2t_3c program is based on numerical integration, and uses the approach of Kuwabara et al. (1993) for partial solutions of the differential equations. The average rate constants from Imahori et al. (1998) for the normal brain (K_1=0.011 ml/gmin, k_2=0.025 min^{-1}, k_3=0.033 min^{-1} and k_4=0.009 min^{-1}) and glioma (K_1=0.040 ml/gmin, k_2=0.034 min^{-1}, k_3=0.018 min^{-1} and k_4=0.011 min^{-1}) were applied to the model. The plasma ^{10}B concentration input for the model was estimated using the measured blood ^{10}B concentrations, and was obtained by multiplying the blood concentrations with a constant factor of 1.3.

2.3. Dose calculation

As reported in a detail in Kankaanranta et al. (2011), the dose calculation was performed with the SERA treatment planning system (Nigg et al., 1999). The radiation doses in the brain and the tumor due to the nitrogen neutron capture reaction and proton recoils from hydrogen nuclei were calculated assuming hydrogen and nitrogen composition of the brain tissue according to Brooks et al. (1980) (10.6 mass% of hydrogen and 1.84 mass% of nitrogen), as was done in the Brookhaven clinical trials (Chanana et al., 1999). The weighting factor of 3.2 was applied to define recoil proton ('fast neutron') and nitrogen capture doses in weighted Gray (Gy (W)) units. A weighting factor of 1 was applied to the photon dose, and weights of 1.3 and 3.8 for the ^{10}B dose in the brain and the tumor, respectively. The ^{10}B concentration in the brain was assumed to be the same as in the blood, and 3.8 times higher than this in the tumor during irradiation. In this study, we recalculated the ^{10}B doses based on the modeled average total ^{10}B concentrations in the brain and glioma tissue (compartment C_{tot}, Fig. 1) during neutron irradiation.

3. Results and discussion

Three examples of the estimated total ^{10}B concentrations in the tumor and the brain tissue based on the closed 3-compartment model are provided in Figs. 2, 3 and 4. Each of the three patients was infused with a different BPA-F dose, either 290 mg/kg, 400 mg/kg or 450 mg/kg, over 2 h. The 3-compartment model predicts different pharmacokinetics for BPA in the tumor tissue, the brain tissue, the plasma and the blood, which results in distinct and non-constant tumor-to-blood, tumor-to-normal brain and plasma-to-blood concentration ratios. The highest tumor-to-
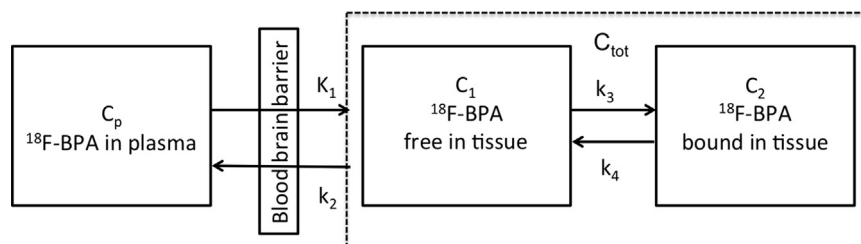
Fig. 1. A 3-compartment model for ^{18}F-BPA uptake. The rate constants K_1, k_2, k_3, and k_4 define the transport between the central compartment C_p (plasma), the tissue compartment C_1 represents non-specifically bound ^{18}F-BPA, and the deeper tissue compartment C_2 represents ^{18}F-BPA bound in the tissue (cell). K_1 and k_2 are the rate constants for forward and reverse transport of ^{10}B-BPA across the blood brain barrier, respectively. k_3 and k_4 are the anabolic and the reverse process rate constants.