Study on Microdosimetry for Boron Neutron Capture Therapy

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A brain tumor, a malignant melanoma and recently a head-neck cancer have been treated by Boron Neutron Capture Therapy (BNCT). Neutrons from a research reactor have been used for BNCT. The therapeutic gain of BNCT depends on intercellular distributions of ¹⁰B and behavior of particles generated in the tumor cell. Two typical boron compounds of BSH (sodium borocaptate) and BPA (p-boronophenylalanine) have been used for BNCT. The BSH is especially accumulated around the cell membrane and the BPA around the cell nucleus. We have studied microdosimetry concerning on behavior of α and ⁷Li particles by simulating a single and a multi-cell models, where the ¹⁰B distributions of BSH and BPA were assumed above accumulation conditions. The PHITS code developed in Japan Atomic Energy Agency was used for calculation of α and ⁷Li particles with nuclear data library of ENDF/B-VI. The SPAR code including in the PHITS was also used for calculation of stopping power of these particles. We also evaluated LET values of α and ⁷Li particles and dose distributions for BPA and BSH compounds by considering the influence from neighbor cells in a multi-cell model.

KEYWORDS: PHITS, microdosimetry, Boron neutron capture therapy, LET, dose distributions

I. Introduction

A brain tumor, a malignant melanoma and recently a head-neck cancer have been treated by Boron Neutron Capture Therapy (BNCT). Neutrons from a research reactor have been used for BNCT. This therapy takes ¹⁰B to cancer cells which are destroyed by α and ⁷Li particles from ¹⁰B(n,α)⁷Li reactions. The flight-paths (ranges) of these charged particles in tissue are around ten micrometers that are the same order of cell diameter. Therefore, cytotoxic effect would be very high. If a ¹⁰B compound could be highly accumulated into the cancer cell, only the cancer cells would be broken as shown in Fig. 1.

Two typical boron compounds shown in Fig. 2, BSH (sodium borocaptate) and BPA (p-boronophenylalanine) are currently tested in clinical trial. One of the boron compounds, BSH will not take up into normal brain cells because of the BBB (Blood Brain Barrier) effect. Although BBB of tumor cell are damaged so that BSH is able to accumulate in tumor cells, especially around the cell membrane. The other boron compounds, BPA has inherent accumulation in malignant melanoma because its chemical structure resembles tyrosine and DOPA (dihydroxy-phenylalanine) which is the precursor of the melanin metabolism. In addition, BPA is an amino acid analogue thus it is taken up by the cells that amino acid metabolism is active and pass through the BBB barrier. Also BPA especially accumulates around the cell nucleus.¹¹

From the above features of two boron compounds, distribution of boron in the cells would be different. The cytotoxic effect could be specialized by the distributions of α and ⁷Li particles in the cells.

In this paper, we evaluated the values of dose and LET respectively in the cells, by clarifying the behavior of α and ⁷Li particles produced from the ¹⁰B(n,α)⁷Li reactions.

II. Calculation Method

1. Calculation Code

The PHITS (Particle and Heavy Ions Transport code system)²³ developed in Japan Atomic Energy Agency was used for the calculation of α and ⁷Li particles with nuclear
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Table 1  Thickness of area in cell

<table>
<thead>
<tr>
<th>Area</th>
<th>nucleus</th>
<th>cytoplasm(A)</th>
<th>cytoplasm(B)</th>
<th>cell membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>thickness(um)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

data library of ENDF/B-VI. The SPAR code including in the PHITS was also used for the calculation of stopping power of these particles.

2. Single Cell Model

A single cell model was used to simplify the calculation of the behavior of particles. The area (thickness) in the cell was set as shown in Table 1 corresponding to the region in Fig. 3. To clarify distributions of $\alpha$ and $^7$Li particles a single-cell model is first examined. The compositions of a cell referred ICRU reports. It was assumed that $^{10}$B was accumulated in the cell membrane for BSH and in the cytoplasm(A) for BPA. The $^{10}$B concentration in a cell is 24 ppm for both compounds. The thermal neutron fluence of $5 \times 10^{12}$ n/cm$^2$ was distributed entirely in the cell. The number of particles generated, ranges, Lineal Energy Transfer (LET) and dose-distributions were calculated.

3. Multi-Cell Model

The multi-cell model consisted of 7 cells was applied to evaluate the influence from the neighbor cells as shown in Fig. 4.  

The dose distributions and LET values at center of cell for the multi-cell model have been calculated. The $^{10}$B concentration of each cell in the multi-cell model was the same accumulation as that of a single-cell model.

III. Results and Discussion

1. Single Cell Model

(1) Number of Particles Generated

Equation (1) shows a typical $^{10}$B(n,$\alpha$)$^7$Li reactions used for BNCT. The numbers of particles calculated by the PHITS code are shown in Table 2 when thermal neutron fluence of $5 \times 10^{12}$ n/cm$^2$ was irradiated at a cell. The total number of $\alpha$ and $^7$Li particles was 14.7 for both BSH and BSH compounds which was equal to the value deduced from Eq. (2).

$$^{10}\text{B} + n \rightarrow ^7\text{Li} + \alpha + 2.79\text{MeV} \ (6.3\%)$$

$$\rightarrow ^7\text{Li}^+ + \alpha + 2.31\text{MeV} \ (93.7\%)$$

$$\text{LET} \rightarrow ^7\text{Li} + \gamma + 0.478\text{MeV}$$

(1)

$$N_B \times \sigma_{\text{cap}} \times \Phi_{th} = R,$$

(2)

where $N_B$: atomic number density of $^{10}$B,

$\sigma_{\text{cap}}$: cross section of $^{10}$B(n,$\alpha$)$^7$Li reaction,

$\Phi_{th}$: thermal neutron fluence,

$R$: number of reaction.

Figure 5 shows calculated spectrum of $\alpha$ and Li particles from the $^{10}$B(n,$\alpha$)$^7$Li reactions. The energies of $\alpha$ and $^7$Li particles can be recognized according to the reaction ratio as shown in Table 2. The gamma-rays of 0.48 MeV and 2.2 MeV are also found, which are from $^7$Li$^+$ particle and $^1$H(n,$\gamma$)$^2$D reactions, respectively. The proton of 0.63 MeV from $^{14}$N(n,p)$^{14}$C reactions are slightly recognized.

(2) Energy Deposit and LET Values

Figure 6 shows energy deposit distributions obtained for $\alpha$ and $^7$Li particles. The $^{10}$B compounds have been accumulated in 0-1 $\mu$m area. The $\alpha$ and $^7$Li particles lost their energies at 9 $\mu$m and 4 $\mu$m, respectively.
Figure 7 shows relations between energy deposit and LET values at the distance from 1 µm to 2 µm. The α and 7Li particles were originally emitted from the 10B accumulation area, such as cytoplasm(A) for BPA and cell membrane for BSH. The LET values of α and 7Li particles were 200 and 400 keV/µm, in 1-2 µm range respectively.

The dose-LET distributions from 7Li cannot be observed at the distance greater than 3 µm, because of the shorter range of the particle.

(3) Dose Distribution

Figures 8-11 illustrate α and 7Li particles produced in a single-cell model, for BPA and BSH compounds respectively. It is clear that a range of α particles is larger than that of 7Li particles in both compounds. We can see large number of these particles outside cell for a BSH model. The hit numbers in nucleus for BSH model are very small.
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Table 3 shows the dose distributions at each area in a cell obtained for BPA and BSH compounds. The doses in the cell nucleus are 24.1 Gy for BPA and 0.9 Gy for BSH. The average dose is about two times smaller than BPA dose because $\alpha$ particles in a BSH model run away to outside.

### Table 3: Dose by $\alpha$ and $^7$Li particles in a single-cell model [Gy]

<table>
<thead>
<tr>
<th>area</th>
<th>nucleus</th>
<th>cytoplasm(A)</th>
<th>cytoplasm(B)</th>
<th>cell membrane</th>
<th>cell average</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPA (total)</td>
<td>24.1 ±0.9</td>
<td>27.3 ±0.4</td>
<td>4.3 ±0.1</td>
<td>1.2 ±0.0</td>
<td>4.2 ±0.0</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>8.9 ±0.3</td>
<td>10.1 ±0.1</td>
<td>2.5 ±0.1</td>
<td>0.1 ±0.0</td>
<td>2.3 ±0.0</td>
</tr>
<tr>
<td>$^7$Li</td>
<td>15.2 ±0.6</td>
<td>17.2 ±0.3</td>
<td>1.8 ±0.0</td>
<td>0.1 ±0.0</td>
<td>1.9 ±0.0</td>
</tr>
<tr>
<td>BSH (total)</td>
<td>0.9 ±0.1</td>
<td>1.1 ±0.1</td>
<td>2.1 ±0.0</td>
<td>3.7 ±0.0</td>
<td>2.8 ±0.0</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.9 ±0.1</td>
<td>1.0 ±0.1</td>
<td>1.3 ±0.0</td>
<td>1.7 ±0.0</td>
<td>1.4 ±0.0</td>
</tr>
<tr>
<td>$^7$Li</td>
<td>0.0 ±0.0</td>
<td>0.8 ±0.0</td>
<td>2.0 ±0.0</td>
<td>1.3 ±0.0</td>
<td>0.0 ±0.0</td>
</tr>
</tbody>
</table>

Figures 12-15 illustrate $\alpha$ and $^7$Li particles produced in a multi-cell model, for BPA and BSH compounds, respectively. It is found that the dose distributions in a multi-cell model are similar to these of a single-cell model for BPA and BSH, even though the influence from neighbor cells is added. Table 4 shows the dose distributions at each area in a center of cell for the BPA and PSH compounds. The average doses in a center cell were 4.6 Gy for BPA and 3.5 Gy for BSH. The average dose in a multi-cell model was higher than a single-cell model for both compounds because $\alpha$ and $^7$Li particles from neighbor cells influenced to other cells especially for BSH. The doses in the nucleus were 25.6 Gy for BPA and 1.0 Gy for BSH. The $\alpha$ particles gave 20% and 24% dose enhancement to cytoplasm and cell membranes doses, respectively, because of relatively longer flight-path than $^7$Li particles.

### Table 4: Dose by $\alpha$ and $^7$Li particles in a multi-cell model [Gy]

<table>
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<tr>
<td>BPA (total)</td>
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<td>4.6 ±0.1</td>
<td>1.6 ±0.1</td>
<td>4.6 ±0.1</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>10.0 ±0.5</td>
<td>10.7 ±0.2</td>
<td>2.7 ±0.1</td>
<td>1.5 ±0.1</td>
<td>2.6 ±0.1</td>
</tr>
<tr>
<td>$^7$Li</td>
<td>15.6 ±0.8</td>
<td>17.2 ±0.3</td>
<td>1.9 ±0.0</td>
<td>0.1 ±0.0</td>
<td>2.0 ±0.0</td>
</tr>
<tr>
<td>BSH (total)</td>
<td>1.0 ±0.1</td>
<td>1.5 ±0.2</td>
<td>2.6 ±0.1</td>
<td>4.6 ±0.1</td>
<td>3.5 ±0.2</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>1.0 ±0.1</td>
<td>1.4 ±0.1</td>
<td>1.8 ±0.1</td>
<td>2.3 ±0.1</td>
<td>2.0 ±0.1</td>
</tr>
<tr>
<td>$^7$Li</td>
<td>0.0 ±0.0</td>
<td>0.1 ±0.1</td>
<td>0.9 ±0.1</td>
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2. Multi Cell Model

Figures 12-15 illustrate $\alpha$ and $^7$Li particles produced in a multi-cell model, for BPA and BSH compounds, respectively. It is found that the dose distributions in a multi-cell model are similar to these of a single-cell model for BPA and BSH, even though the influence from neighbor cells is added. Table 4 shows the dose distributions at each area in a center of cell for the BPA and PSH compounds. The average doses in a center cell were 4.6 Gy for BPA and 3.5 Gy for BSH. The average dose in a multi-cell model was higher than a single-cell model for both compounds because $\alpha$ and $^7$Li particles from neighbor cells influenced to other cells especially for BSH. The doses in the nucleus were 25.6 Gy for BPA and 1.0 Gy for BSH. The $\alpha$ particles gave 20% and 24% dose enhancement to cytoplasm and cell membranes doses, respectively, because of relatively longer flight-path than $^7$Li particles.

IV. Conclusion

We have studied microdosimetry for boron neutron capture therapy. The boron concentrations in tumor were assumed depending on the boron distribution of BPA and BSH compounds. This study clearly shows as followings.

We calculated the number of $\alpha$ and $^7$Li particles, ranges,
LET values and dose distributions by using PHITS code. The number of $\alpha$ and $^7$Li particles produced in a tumor cell containing 24 ppm of $^{10}$B were 14.7 respectively, when irradiating thermal neutron fluence of $5 \times 10^{12}$ n/cm$^2$. The flight-paths of $\alpha$ and $^7$Li particles were 9 $\mu$m and 4 $\mu$m respectively. The LET values of $\alpha$ and $^7$Li particles were 200 keV/$\mu$m and 400 keV/$\mu$m, respectively. The average doses were 4.2 Gy for BPA and 2.8 Gy for BSH in a single-cell model. Those doses increased to 4.6 Gy for BPA and 3.5 Gy in a multi-cell model by influence from the neighbor cells. From these results we understood the behavior of $\alpha$ and $^7$Li particles in a cell, and found that the average dose in a cell could increase when $^{10}$B accumulated near the cell nucleus like a BPA compound. To clarify the BNCT mechanism in details by microdosimetry, it is necessary to calculate the dose by using a three dimensional multi-cell model under the accurate intracellular $^{10}$B distributions. The experiments of cell survival should be also examined.

References