VIII-II-3. Original Research

OR1 Hexamethylenetetramine as a Combined Agent with γ-Ray Irradiation and Cisplatin Treatment *in vivo*, Compared with Tirapazamine

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PURPOSE: To evaluate the potential of hexamethylenetetramine (HMTA) as a combined drug with γ-ray irradiation and cisplatin treatment *in vivo*, compared with tirapazamine (TPZ), referring to the effect on intratumor quiescent (Q) cells.

INTRODUCTION: The development of bioreductive agents that are particularly toxic to hypoxic cells is considered a promising approach to solving the problem of radio-resistant tumor hypoxia in cancer radiotherapy. Tirapazamine (TPZ, 1,2,4-benzotriazine 1,4-di-N-oxide, SR4233), a lead compound in the development of a bioreductive hypoxic cytotoxin, in combination with radiation or standard cytotoxic chemotherapy agents has been shown to be very useful for controlling solid tumors as a whole, especially for controlling hypoxia-rich intratumor Q cell population. Tumor hypoxia results from either limited oxygen diffusion (chronic hypoxia) or limited perfusion (acute hypoxia, transient hypoxia or ischemic hypoxia). Chronically hypoxic tumor cells existing at the rim of the oxygen diffusion distance can be killed by just a single administration of TPZ. Acutely hypoxic tumor cells occurring sporadically throughout solid tumors can be killed by TPZ during long-term continuous administration. In other words, the long-term continuous administration of TPZ can kill both chronically and acutely hypoxic tumor cells. Actually, continuously administered TPZ was reported to be very useful for sensitizing tumor cells *in vivo* [**1**].

Formaldehyde preserves or fixes tissue or cells by irreversibly cross-linking primary amine groups in proteins with other nearby nitrogen atoms in protein or DNA through a -CH2- linkage. An acid-dependent formaldehyde donor, hexamethylenetetramine (HMTA), has been used as an antiseptic for urinary tract infections and it has been supposed to be characterized as a non-carcinogen in animals. In the hypoxic condition in a solid tumor, pyruvate generated by glycolysis induces a low pH environment that produces formaldehyde through dissociation of HMTA. So far, some *in vitro* studies using HMTA were reported, especially referring to its combined effect with adriamycin. However, except for surgical resection, chemotherapy using cis-diamminedichloroplatinum (cisplatin) and radiotherapy are the most frequently employed anticancer therapeutic modalities in real clinics. Accordingly, in this study, the combined effect of HMTA with γ-ray irradiation or cisplatin treatment was examined. With our method for selectively detecting the response of the Q cell populations within solid tumors, we tried to investigate the usefulness of HMTA in combination with γ-ray irradiation or cisplatin treatment to see if it causes selective killing effects on intratumor hypoxia-rich Q cell population, compared with that of TPZ. In addition, the usefulness of continuous administration of HMTA was also evaluated. Further, the current study was the first *in vivo* attempt to assess the usefulness of HMTA as a systemic anti-tumor agent.

MATERIALS AND METHODS: SCC VII tumor-bearing mice were continuously given 5-bromo-2'-deoxyuridine (BrdU) to label all intratumor proliferating (P) cells. Then, they intraperitoneally or continuously received HMTA or TPZ combined with or without γ-ray irradiation or cisplatin treatment. Other tumor-bearing mice intraperitoneally received HMTA or TPZ immediately after γ-ray irradiation. Immediately after γ-ray irradiation or cisplatin treatment following HMTA or TPZ or 24 hours after γ-ray irradiation followed by HMTA or TPZ, the response of Q cells was assessed in terms of the micronucleus frequency using immunofluorescence staining for BrdU. The response of the total (= P + Q) tumor cells was determined from the BrdU non-treated tumors.

RESULTS: HMTA showed a higher toxicity to Q cells than total cells, similarly to TPZ. Radio-sensitizing effect by HMTA was similar to TPZ in both total and Q cells. The recovery inhibiting effect by HMTA was reliable, but not so remarkable as TPZ. Cisplatin-sensitivity enhancing effect by HMTA was similar to or a little larger than TPZ. For HMTA and TPZ, continuous administration produced higher radio- and cisplatin-sensitivity enhancing effects than intraperitoneal single administration.

CONCLUSION: In terms of tumor cell-killing effect as a whole, including Q cells, γ-ray irradiation and cisplatin treatment combined with continuous HMTA administration can be promising, taking it into account that HMTA was used in clinics [**2**].

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γ線照射やシスプラチンを用いた抗癌治療における併用薬剤としての Hexamethylenetetramine の有用性について-Tirapazamine との比較- 独自研究

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OR2 A Feasibility Study on Multi Prompt-Gamma-Ray Telescope System for BNCT

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INTRODUCTION: We are improving the dose simulation system for boron neutron capture therapy (BNCT) and constructing the on-line dose-estimation technique using the prompt gamma-ray telescope system [1]. Our telescope system counts the prompt gamma rays from hydrogen which uniformly distributes in human body, and from boron-10 which locally distributes in target volume. However, this system cannot get the detail information for several changes of counting rates according to the motions and shape-changes of target volume only using the mono-energetic gamma rays. Then, we are studying the "multi prompt-gamma-ray telescope system" utilizing gadolinium-157 (^{157}Gd).

GAMMA-RAY ENERGY SPECTRUM: The natural abundance of ^{157}Gd is 15.7%, and it reacts with neutron as follows; ^{157}Gd+n→^{158}Gd+ γ +7.94 MeV. The capture crosssection for thermal neutron is 255,000 barn, almost 66 times larger than 3,840 barn for the ^{10}B(n, α)^{7}Li reaction. The released energy per one reaction (Q-value) is almost 2.5 times larger than 2.79 MeV for the ^{10}B(n,α)^{7}Li reaction. Approximately 99.2% of the Q-value is released as gamma rays. The energy spectra for the prompt gamma-ray from ^{157}Gd(n,γ)^{158}Gd are shown in Fig. 1 [2,3]. The data in these figures are calculated to the number of the gamma rays integrated for 10-keV energy-bin. The following peaks can be easily distinguishable; the peaks at 79.5keV, 182keV, etc. for the lower energy, and the peak at 6.75 MeV for the higher energy.

GAMMA-RAY ATTENUATION: The energy dependency of gamma-ray attenuation coefficient for tissue is shown in Fig. 2 [4]. The tissue composition is H:11.1%, C:12.7%, N:2% and O:74.2% in weight percent. The coefficients for the 79.5-keV and 182-keV gamma rays are almost 6.9 and 5.3 times larger than that for the 6.75-MeV gamma ray, respectively. The penetration rate for the 1-cm-thick tissue is almost 90% for the lower energy, and 97% for the higher energy. The difference between the lower and higher energies is about 10%. For the 5-cm-thick tissue, the penetration rate is almost 50% for the lower energy, and 90% for the higher energy. The former value is almost two times larger.

GAMMA-RAY TELESCOPE: The "dual gamma-ray telescope system" is one component of the "dose estimation joint-system under NCT clinical irradiation" that is installed in the KUR-HWNIF [1]. These units are placed on the upper-side of the irradiation room ceiling of the facility, symmetrically against the central axis of the facility. Each unit consists of (i) an HPGe semiconductor detector, (ii) a collimator system including the sight-regulating equipment, and (iii) position-fixing and sight-checking equipments. The length and width of the detect-ing-sight can be regulated from 0 to 20 cm corresponding to the conditions.

FEASIBILITY STUDY: A feasibility study was performed on the assumption of the irradiation to a human body using the epi-thermal neutron beam, which was applied to the actual BNCT. For the ^{157}Gd-concentration, the lower detection-limit was estimated to almost 1,000 ppm at the small volume of 1 cm^3. This is due to the detection-limit for 6.75-MeV gamma ray, because its detection efficiency is smaller. From this study, the feasibility and the limit of this system could be confirmed.

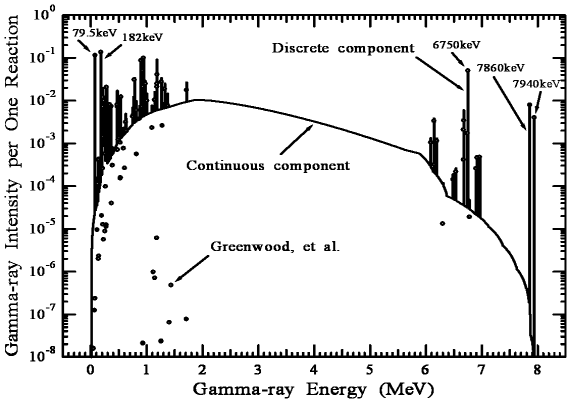

Fig. 1. Energy spectrum of the prompt gamma rays from ^{157}Gd(n,γ)^{158}Gd.

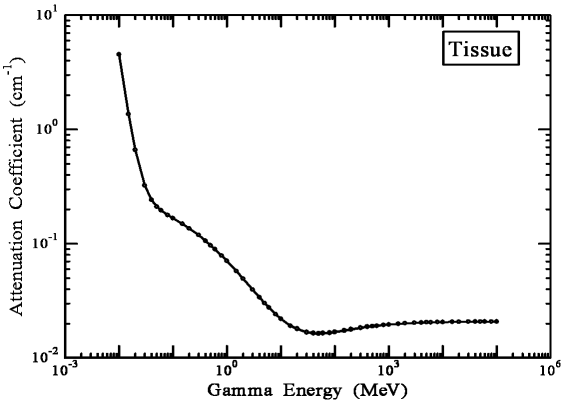

Fig. 2. Gamma-ray attenuation coefficient for tissue

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ＢＮＣＴのための多重即発γ線テレスコープシステムの可能性検討　　独自研究

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OR3 Assessment of Environmental and Social Impacts Originating from the Use of Nuclear Energy

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INTRODUCTION: The government of Japan has a policy to promote utilization of nuclear energy and continues to invest a large amount of budget every year to establish its nuclear fuel cycle. According to a public opinion poll by the government in 2006, however, 66 % of respondents were worrying about safety aspect of nuclear energy. The decision whether or not our society relies on nuclear energy should be made by the public taking into account its merits and demerits. For the purpose to provide reasonable information for the public decision, our group has been investigating environmental and social impacts originating from the use of nuclear energy. Main themes are: a) analysis of radiological consequences of hypothetical accidents at nuclear facilities, b) analysis of the consequences of actual nuclear accidents such as Chernobyl-4 (1986), JCO criticality accident (1999), Mihama-3 (2004) *etc.*, c) monitoring of radioactivity pollution around nuclear facilities such as Ikata NPP, Rokkasho reprocessing plant, Semipalatinsk nuclear test site in Kazakhstan *etc.*, d) radioactivity measurements in food and other materials, e) analysis of social issues related with nuclear energy and f) hosting of open-seminars on various aspects of nuclear safety issues.

RECENT TOPICS

The Rokkasho Reprocessing Plant began its active test using real spent nuclear fuels in March 2006. Although this test was scheduled to finish before the end of 2007, currently no perspective is given for its completion because of a series of serious troubles that occurred at the glass-solidification facility for high level liquid waste. No perspective also can be seen for commercial use of fast breeder reactor that was considered to be the main part of the future nuclear fuel cycle in Japan. Under such circumstances, MOX fuels are planned to be used in thermal reactors to avoid accumulation of excess plutonium in Japan. Koide analyzed various problems related with the plutonium nuclear fuel cycle policy in Japan. He pointed out that the reprocessing is economically nonsense and inevitably cause serious environmental pollution by releasing a large amount of radioactive effluents [1,2].

A new international collaboration project, "Historical review of nuclear disasters during the process of nuclear development program by the former USSR" was launched in 2008 for three years under a support of KAKENHI. Based on the long period experience for Chernobyl research, the project leader, Imanaka intends to investigate consequences of a series of radiological incidents that occurred in the former USSR: Techa river contamination in 1948-1951, the explosion of radioactive waste storage at the Mayak complex in 1957, various accidents at USSR nuclear submarines as well as the Chernobyl accident in 1986[3]. Four foreign researchers (two in Russia, one in Ukraine and one in Belarus) participate in the collaboration.

External radiation exposure due to neutron-induced radionuclides by the Hiroshima-Nagasaki atomic bombings was evaluated based on neutron fluence of DS02 (Dosimetry System 2002) [4]. Cumulative exposure from the time of explosion to infinite was 1.2 and 0.6 Gy at the Hiroshima and the Nagasaki hypocenter, respectively. Radiation intensity rapidly decreased with the time after detonation as well as the distance from the hypocenter. Significant exposure was considered feasible to the people who entered into the area less than 1,000 m from the hypocenter within one week after the bombing.

An Excel Basic program, FPCOMP.xls was developed to calculate fission product composition at any time after fission reaction[5]. It was applied to estimate radiation exposure from local fallout deposition in villages around the Semipalatinsk Nuclear Test Site, Kazakhstan as well as from "black rain" areas in Hiroshima and Nagasaki.

The following two open-seminars were held in 2008-09:

- 105th: July 22, 2008, "Kashiwazaki-Kariwa NPP and the Damages by the Chuetsu-oki Earthquake" by H. Koide and "Fraud in Guidance for Earthquake-resistance Design Disclosed by the Chuetsu-oki Earthquake" by K. Shouwaki.

- 106th: March 3, 2009, "Recent Reports about Low Level Radiation Effects" by T. Imanaka and "Risk from Medical Radiation" by H. Sakiyama. Summaries of these seminars as well as the title list of all previous lectures are on http://www.rri.kyoto-u.ac.jp/NSRG/.

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原子力利用にともなう環境影響ならびに社会的影響に関する研究　　独自研究

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