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The present status of boron–neutron capture therapy for tumors

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Abstract. The present status of boron-neutron capture therapy (BNCT) for brain tumors and examples of survivors of grade III-IV astocytomas which include glioblastomas are described. Application of BNCT to the biggest killer cancers such as gliomas, melanomas and hepatomas is discussed.

It is a shame that Hatanaka is the only practitioner of Boron-neutron capture therapy (BNCT) for brain tumors. The reasons are various. Reactors are not so available - politically, economically technically, or geographically. In the meantime, reactors are even being decommissioned in the midst of a hostile public debate.

Even though there are already a number of malignant brain tumor patients who have been definitely cured, they are outnumbered by sceptical physicians. Even if interested, some established physicians lose their enthusiasm for dealing with malignant tumors which are difficult to treat and less rewarding than benign disease.

As of February 10, 1990, 104 patients with brain tumors and one patient with a neck tumor were treated by HH. Among the many survivors, six patients have already lived more than 10 years. (As the types of tumor and methods of treatment vary considerably, analysis of survival for all the patients will remain a topic for the future. At this point, I refer only to the most typical tumor treated by BNCT alone.) The following are examples of survivors of grade III-IV astrocytomas which include glioblastomas:

An ex-glioblastomas patient, now 68 years old, has lived 18 years as of June, 1990, and is in good shape except for a lumbar disc problem of several years duration and a cataract. A 73-year-old woman has served as a part-time employee in my laboratory for 13 years after BNCT for grade III astrocytoma. A man operated on for a grade III astrocytoma was given a course of accelerator radiation, then underwent Boron-neutron capture therapy, and went back to his post-office job for 5 years and then quit the job when he had a localized cerebral necrosis (probably caused by the previous radiotherapy which impaired the blood-brain barrier of the brain matter around the tumor, leading to increased uptake of boron by the normal brain matter). In spite of the complications which are undoubtedly related to previous conventional radiotherapy, he has survived 12 years and his mind is clear. A young woman recently got a job as an architectural assistant after graduating from a technical college without being suspected even slightly by her employer of her brain tumor history, 9 year after her operation for a grade III astrocytoma which was a huge tumor of 9 cm in diameter in the right frontal lobe. In fact she has no trace of surgery or radiation damage in her appearance or performance.

The 5-year survival rate of grade III-IV malignant glioma patients who had been treated with BNCT alone, as calculated in 1986, was 58% for with tumors within 6 cm from the brain surface (6 cm ≅ maximum therapeutical depth for a less penetrating thermal neutron facility). The 3-year survival rate being obtained after April 1986 is slightly lower than expect-

ed: 55% for the same grade gliomas which were treated by BNCT alone. Among the 5 patients who died in the past 3 years in this group, three died of new tumors in the contralateral hemisphere which had not been radiated with neutron; in addition, these three had been initially operated on more than a month before BNCT. (Another possible reason for the result is the delay in BNCT - lengthened time between the first craniotomy and BNCT, during which the rapidly-growing tumor may spread throughout the central nervous system; this delay is due to the patient's late transfer from other countries). One patient, who was carelessly and mistakenly told by a local radiologist that he had a recurrence, committed suicide. One patient died of status epilepticus while the tumor was still undergoing the degenerative process of a huge glioblastoma. It seems that pre-BNCT and post-BNCT care is crucially important to ensure what BNCT can achieve.

Before BNCT, a radical tumor excision is essential to reduce the complications which arise from the tumor swelling in the course of its slow degeneration - a process which may take even more than a year. Post-operatively, precise interpretation of computed images (like CT or MRI) is crucial. These two factor seem to be as important as the BNCT technique itself.

Technically, introduction of D_2O to replace brain water content facilitates better penetration of thermal neutrons. It also seems - judging from our limited experience - to help the tumor retain a higher concentration of boron-10 isotope and protects the patient's body from whole-body exposure to scattered rays.

A fractionated schedule, as is sometimes advocated by conventional radiologists, is not acceptable because exposure of the cerebral blood vessels to radiations before a BNCT impairs the blood-brain barrier which should bar the penetration of boron-10 into the normal brain. This fact is being demonstrated by boron-10 uptake studies in animals.

As far as BNCT for brain tumors is concerned, the presently-used technique is the state of the art and requires little change; and mercaptoundecahydrododecaborate, a least toxic substance, is the compound of choice.

Besides brain-tumor treatments, 8 cases of human melanoma were treated in the past 3 years with boronophenylalanine by Mishima, a long-time member of my cooperative team, and demonstrated a local cure using BNCT. Hepatoma treatment with monoclonal antibody conjugated with boron-10 was a subject advocated by me initially and has been enthusiastically studied in animal models by surgeons, Sekiguchi, Fujii, Yanagiye, and Takahashi, who form a subgroup of my cooperative team. In fact, a human hepatoma was about to be treated by us in 1988 when one of the collaborating pathologists himself died of this disease. The late Prof. Urano of the University of Tokyo had studied 18 autopsied BNCT-treated brain tumor series and was interested in BNCT treatment for his own hepatoma. (Prof. Urano was the pathologist of the medical corps attending the late Emperor of Japan). A boronated porphyrine derivative (by Kahl) is attracting attention because of promising uptake such as glioma and osteosarcoma (studied by Takeuchi et al.). From our own studies of the pharmacology of these derivatives, however, we must say that the toxicity and complications - particularly hyper-photo-sensitization effect - require more thorough study before any human treatment can be contemplated with porphyrine derivatives.

Although BNCT has not been as widely used as it should be, its application to the biggest killer cancers such as gliomas, melanomas, and hepatomas is slowly gaining support from knowledgeable and dedicated physicians throughout the world, and the need for better-equipped nuclear reactors and for a more versatile boron carrier will soon be a matter of more serious interest.

Current BNCT technique with thermal neutrons and mercaptoundecahydrododecaborate should be applied to save the lives of cerebral glioma patients who are dying every day by the thousands throughout the world. Meanwhile, further studies of compounds and beams can be carried out with increased funds.