Neutron capture therapy of cancer

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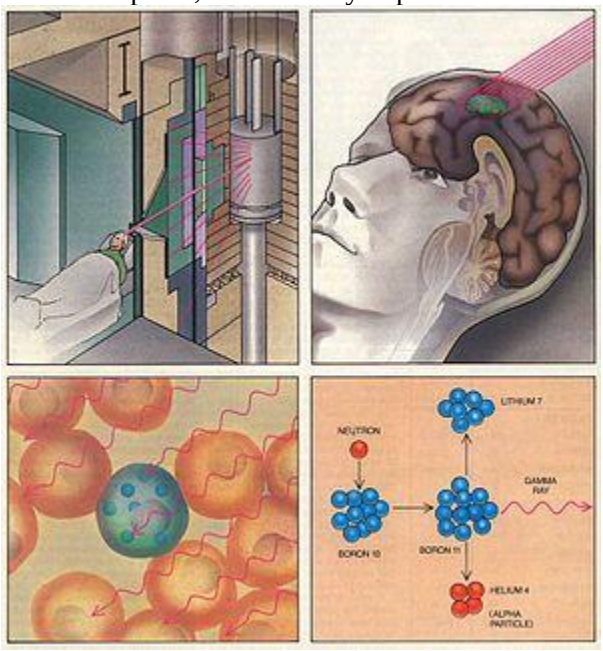


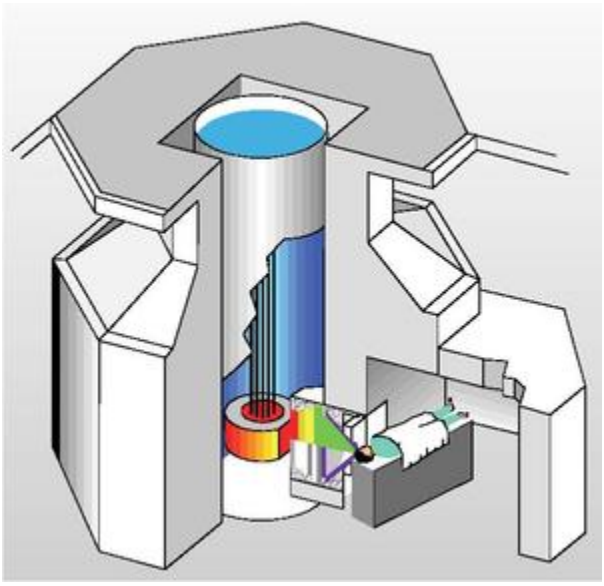
Boron Neutron Capture Therapy (BNCT) can be performed at a facility with a nuclear reactor or at hospitals that have developed alternative neutron sources. A beam of epithermal neutrons penetrates the brain tissue, reaching the malignancy. Once there the epithermal neutrons slow down and these low-energy neutrons combine with boron 10 (delivered beforehand to the cancer cells by drugs or antibodies) to form boron 11, releasing a lethal radiation (alpha particles and lithium ions) that can kill the tumor. Barth. R.F., et al. Boron neutron capture therapy for cancer. Scientific American, 100-107, October 1990.

Neutron Capture Therapy (**NCT**) is a noninvasive therapeutic modality for treating locally invasive malignant tumors such as primary brain tumors and recurrent head and neck cancer. It is a two step procedure: first, the patient is injected with a tumor localizing drug containing a non-radioactive isotope that has a high propensity or cross section (σ) to capture neutrons. This cross section is many times greater than that of the other elements present in tissues such as hydrogen, oxygen and nitrogen. In the second step, the patient is exposed to epithermal neutrons, which after slowing down in the tissue, induce in the NCT agent a localized, biologically destructive nuclear reaction (Fig.1).

Almost all experience to date with NCT is with the neutron-absorbing isotope boron-10. This is known as boron neutron capture therapy, abbreviated BNCT. At this time, the use of other neutron-absorbing nuclides, such as gadolinium, has been limited, and to date, it has yet to be used clinically (i.e., in humans). Gadolinium NCT is usually abbreviated Gd-NCT.

BNCT has been experimentally tested primarily as an alternative treatment for malignant brain tumors called glioblastoma multiforme as well as recurrent, locally advanced head and neck cancer. Although there are reports of some successful outcomes, this approach has not yet been shown to be superior to other current therapies. Hence, BNCT has not entered routine clinical use. However, a number of authors believe that BNCT holds a great deal of promise for cancer therapy in the future, if present difficulties regarding neutron-sourcing and tumor-specific boron-10 delivery pharmaceuticals, are solved.

Boron neutron capture therapy (BNCT)



Boron Neutron Capture Therapy (BNCT) is performed at a therapy facility in Otaniemi, Finland, with the use of a TRIGA nuclear reactor. The lack of high current neutron sources other than reactors has made this type of therapy difficult to develop. Nuclear reactors themselves are difficult to site and license, as they pose many security problems: a terrorist bomb which destroyed a research reactor of any type would be an extremely dirty bomb.

Boron neutron capture therapy (BNCT) uses a neutron beam that interacts with boron-10 injected into a patient. BNCT depends on the interaction of slow neutrons with boron-10 to produce alpha particles and lithium nuclei, without producing other types of ionizing radiation.

Patients are first given an intravenous injection of a boron-10-containing chemical that preferentially binds to tumor cells. Natural boron many be used, since it contains sufficient boron-10 for the purpose. In clinical trials performed so far, the neutrons are created in a nuclear reactor, but particle accelerators may also be used to produced neutrons through the collision of protons with targets made of lithium or beryllium.

Neutrons produced either by reactor or accelerator must pass through a neutron moderator, which shapes the neutron energy spectrum suitable for BNCT treatment. Before entering the patient, the neutrons flow is shaped into a suitable treatment beam, by a collimator. While passing through the tissue of the patient, the neutrons are slowed by collisions with hydrogen and carbon nuclei, and finally become low-energy thermal neutrons.

The boron-10 (^{10}B) used in BNCT has a neutron capture cross section of 3837 barns (1 b = 10^{-24} cm^2). The thermal neutrons then undergo reaction with the boron-10 nuclei, forming a compound nucleus (excited boron-11) which then promptly disintegrates to lithium-7 and a high energy alpha particle. Thus, Boron Neutron Capture Therapy (BNCT) is based on the nuclear capture and fission reactions that occur when non-radioactive boron-10, which is a constituent of natural elemental boron, is irradiated with neutrons of the appropriate energy to yield high energy alpha particles ("stripped" down ^4He nuclei) and high energy lithium-7 (^7Li) nuclei. The nuclear reaction is:

$$^{10}B + n_{th} \rightarrow [^{11}B] \rightarrow \alpha + {}^{7}Li + 2.31\ MeV.$$

Both the alpha particle and the lithium ion produce closely spaced ionizations in the immediate vicinity of the reaction, with a range of approximately 5-9 micrometres, or roughly the thickness of one cell diameter. Their lethality is primarily limited to boron containing cells. BNCT, therefore, can be regarded as both a biologically and a physically cellular targeted type of radiation therapy. The success of BNCT is dependent upon the selective delivery of sufficient amounts of ^{10}B to cancer cells with only small amounts localized in the surrounding normal tissues.[1] Thus, normal tissues (if they have not taken up boron-10) can be spared from this type of excited boron-11 disintigration radiation. The only remaining radiation damage to normal tissues is from the passage of the neutron beam on its path to the tumor site.

A wide variety of boron delivery agents have been synthesized,[2] but only two of these currently are being used in clinical trials. The first, which has been used primarily in Japan, is a polyhedral borane anion, sodium borocaptate or BSH ($Na_2B_{12}H_{11}SH$), and the second is a dihydroxyboryl derivative of phenylalanine, referred to as boronophenylalanine or BPA. The latter has been used in clinical trials in the United States, Europe, Japan and more recently, Argentina. Following administration of either BPA or BSH by intravenous infusion, the tumor site is irradiated with neutrons, the source of which, to date, has been a nuclear reactor.

Up to 1994, low-energy (< 0.5 eV) thermal neutron beams were used primarily in Japan,[3] but since they have a limited depth of penetration in tissues, higher energy (>.5eV<10 keV) epithermal neutron beams, which have a greater depth of penetration, have been used in clinical trials in the United States,[4][5] Europe[6][7] and Japan.[8][9]

In summary, BNCT in theory is a highly selective type of radiation therapy that can target the tumor at the cellular level without causing excessive radiation damage to the adjacent normal cells and tissues. Doses up to 60–70 Gy (weighted) can be delivered to ^{10}B

containing tumor cells within approximately one hour instead of 6–7 weeks for conventional external beam photon irradiation. However, the effectiveness of BNCT is dependent upon a relatively homogeneous distribution of ^{10}B within the tumor, and this is still one of the key stumbling blocks that has limited its success.

Gadolinium neutron capture therapy (Gd NCT)

There also has been interest in the possible use of gadolinium-157 (^{157}Gd) as a capture agent for NCT for the following reasons.[10] First, and foremost, has been its very high neutron capture cross section of 254,000 barns. Second, gadolinium compounds, such as Gd-DTPA (gadopentate dimeglumine Magnevist®), have been used routinely as contrast agents for magnetic resonance imaging (MRI) of brain tumors and have shown high uptake by brain tumor cells in tissue culture (in vitro).[11] Second, gamma rays and internal conversion and Auger electrons are products of the ^{157}Gd $(n,\gamma)^{158}Gd$ capture reaction. $^{157}Gd + n_{th}$ (0.025eV) $\rightarrow$ [^{158}Gd] $\rightarrow$ $^{158}Gd + \gamma + 7.94$ MeV. The gamma rays have long pathlengths, which have orders of magnitude greater depths of penetration compared to internal conversion and Auger electrons that have pathlengths of approximately one cell diameter and can directly cause DNA damage. Therefore, it would be highly advantageous for the production of DNA damage if the ^{157}Gd were localized within the cell nucleus. However, the possibility of incorporating gadolinium into biologically active molecules is very limited and only a small number of potential delivery agents for Gd NCT have been studied[12][13] compared to the large number of boron containing compounds (Table 1) have been synthesized and evaluated in vitro and in experimental animals (in vivo). Although in vitro activity has been demonstrated using Magnevist® as the Gd delivery agent,[14] there are very few studies demonstrating the efficacy of Gd NCT in experimental animal tumor models[13][15] and it never has been used clinically.

Radiobiological considerations

The radiation doses delivered to tumor and normal tissues during BNCT are due to energy deposition from three types of directly ionizing radiation that differ in their linear energy transfer (LET), which is the rate of energy loss along the path of an ionizing particle: 1. low LET gamma rays, resulting primarily from the capture of thermal neutrons by normal tissue hydrogen atoms [$^{1}H(n,\gamma)^{2}H$]; 2. high LET protons, produced by the scattering of fast neutrons and from the capture of thermal neutrons by nitrogen atoms [$^{10}N(n,p)^{14}C$]; and 3. high LET, heavier charged alpha particles(stripped down ^{4}He nuclei) and lithium-7 ions, released as products of the thermal neutron capture and fission reactions with ^{10}B [$^{10}B(n,\alpha)^{7}Li$]. Since both tumor and surrounding normal tissues are present in the radiation field, even with an ideal epithermal neutron beam, there will be an unavoidable, nonspecific background dose, consisting of both high and low LET radiation. However, a higher concentration of ^{10}B in the tumor will result in it receiving a higher total dose than that of adjacent normal tissues, which is the basis for the therapeutic gain in BNCT.[16] The total radiation dose delivered to any tissue can be expressed in photon-equivalent units as the sum of each of the high LET dose

components multiplied by weighting factors, which depend on the increased radiobiological effectiveness of each of these components.

Clinical dosimetry

Biological weighting factors have been used in all of the recent clinical trials in patients with high grade gliomas, using boronophenylalanine (BPA) in combination with an epithermal neutron beam. The $^{10}B(n,\alpha)^{7}Li$ component of the radiation dose to the scalp has been based on the measured boron concentration in the blood at the time of BNCT, assuming a blood: scalp boron concentration ratio of 1.5:1 and a compound biological effectiveness (CBE) factor for BPA in skin of 2.5. A relative biological effectiveness (RBE) factor of 3.2 has been used in all tissues for the high LET components of the beam, such as alpha particles. The RBE factor is used to compare the biologic effectiveness of different types of ionizing radiation. The high LET components include protons resulting from the capture reaction with nitrogen, and recoil protons resulting from the collision of fast neutrons with hydrogen.[16] It must be emphasized that the tissue distribution of the boron delivery agent in humans should be similar to that in the experimental animal model in order to use the experimentally derived values for estimation of the radiation "Gray" (Gy) doses for clinical radiations.[16] For more detailed information relating to computational dosimetry and treatment planning, interested readers are referred to a comprehensive review on this subject.[17]

Boron delivery agents

The development of boron delivery agents for BNCT began approximately 50 years ago and is an ongoing and difficult task of the highest priority. A number of boronated pharmaceuticals using boron-10, have been prepared for potential use in BNCT.[18] The most important requirements for a successful boron delivery agent are: 1. low systemic toxicity and normal tissue uptake with high tumor uptake and concomitantly high tumor: to brain (T:Br) and tumor: to blood (T:Bl) concentration ratios (> 3-4:1); 2. tumor concentrations in the range of ~20 μg ^{10}B/g tumor; 3. rapid clearance from blood and normal tissues and persistence in tumor during BNCT. However, it should be noted that at this time no single boron delivery agent fulfills all of these criteria. With the development of new chemical synthetic techniques and increased knowledge of the biological and biochemical requirements needed for an effective agent and their modes of delivery, a number of promising new boron agents has emerged (see examples in Table 1).

Table 1. Examples of new low- and high-molecular-weight boron delivery agents that currently are being evaluated[34]

Dodecaborate cluster lipids and cholesterol derivatives	Carboranyl nucleosides
Carboranyl thymidine analogues	Carboranyl porphyrins
Cholesteryl ester mimics	Boronated EGF and anti-EGFR

	mAbs
Boronated DNA metallo-intercalators	Boron-containing nanoparticles
Transferrin–polyethylene glycol (TF–PEG) liposomes	Carboranyl porphrazines
Unnatural amino acids	Boronated cyclic peptides
Dodecahyrdo-closo-dodecaborate clusters	Boron carbide particles

The major challenge in their development has been the requirement for selective tumor targeting in order to achieve boron concentrations sufficient to deliver therapeutic doses of radiation to the tumor with minimal normal tissue toxicity. The selective destruction of brain tumor (glioma) cells in the presence of normal cells represents an even greater challenge compared to malignancies at other sites in the body, since malignant gliomas are highly infiltrative of normal brain, histologically complex and heterogeneous in their cellular composition. In principle, NCT is a radiation therapy that could selectively deliver lethal doses of radiation to tumor cells while sparing adjacent normal cells.

Neutron sources

Nuclear reactors

Neutron sources for NCT have been limited to nuclear reactors and in the present section we only will summarize information that is described in more detail in a recently published review.[19] Reactor derived neutrons are classified according to their energies as thermal (E_n <0.5 eV), epithermal (0.5 eV <E_n <10 keV) or fast (E_n >10 keV). Thermal neutrons are the most important for BNCT since they usually initiate the $^{10}B(n,\alpha)7Li$ capture reaction. However, because they have a limited depth of penetration, epithermal neutrons, which lose energy and fall into the thermal range as they penetrate tissues, are now preferred for clinical therapy. A number of reactors with very good neutron beam quality have been developed and used clinically. These include: 1. Kyoto University Research Reactor (KURR) in Kumatori, Japan; 2. JRR4 at the Japan Atomic Energy Research Institute (JAERI); 3. the FRi1 clinical reactor in Helsinki, Finland; 4. the RA-6 CNEA reactor in Bariloche, Argentina, the High Flux Reactor (HFR) at Petten in the Netherlands, the Brookhaven Medical Research Reactor (BMRR) at Brookhaven National Laboratory and the Massachusetts Institute of Technology Research Reactor (MITR). The neutron irradiation facility at the MITR currently represent the state of the art in epithermal beams for NCT, with the capability of completing a radiation field in 10–15 minutes with close to the theoretically maximum ratio of tumor to normal tissue dose. Unfortunately, however, no clinical studies currently are being carried out at the HFR, MITR and the BMRR. Finally, an “in-hospital” compact nuclear reactor has been designed and built in Beijing, China, which will be used exclusively for NCT.[20] It currently is undergoing performance evaluation, and this will be followed by radiation dosimetric evaluation prior to it being used for clinical and experimental BNCT studies.

Accelerators

Accelerators also can be used to produce epithermal neutrons and accelerator-based neutron sources(ABNS) are being developed in a number of countries. Interested readers are referred to the recently published Proceedings of the 14th International Congress on Neutron Capture Therapy for information on this subject. For ABNSs, one of the more promising nuclear reactions involves bombarding a ^{7}Li target with high energy protons. Recently, a prototypic Cyclotron-Based Neutron Source (C-BENS) has been developed by Sumitomo Heavy Industries in Japan.[21] It has been installed at KURRI and should be ready for clinical use in the near future. However, it remains to be seen how well these first generation ABNSs are able to perform relative to the reactor based irradiation facilities.

History

After the initial discovery of the neutron in 1932 by Sir James Chadwick, a study by H. J. Taylor in 1935 showed the ability of the boron-10 nuclei to capture thermal neutrons. The neutron capture initiated the fission of the boron-10 nuclei into helium-4 alpha particles as well as lithium-7 particles. In 1936, Locher realised the potential of this discovery in the field of medicine and subsequently suggested that neutron capture could be used to treat tumours. A binary system uses two separate components for the therapy of cancer. Each component in itself is relatively harmless to the cells, but when combined together for treatment they produce a highly cytocidal effect which is lethal. As development on neutron capture therapy continued, other radioactive isotopes such as uranium-235 were researched. However, studies in the late 1950s by Lussenhop et al. showed that the amounts of uranium needed for successful neutron capture therapy was too toxic for human use.[22]

Clinical Studies of BNCT for Brain Tumors

Early Studies in the U.S.A. and Japan

It was not until the 1950s that the first clinical trials were initiated by Farr at the Brookhaven National Laboratory (BNL) in New York[23] and by Sweet and Brownell at the Massachusetts General Hospital (MGH) using the Massachusetts Institute of Technology (MIT) nuclear reactor (MITR)[24] and boric acid as the boron containing drug. However, the results of these studies were disappointing, and no further clinical trials were carried out in the United States until the 1990s. Following a two year fellowship in Sweet's laboratory, clinical studies were started by Hiroshi Hatanaka in Japan in 1967. He used a low energy thermal neutron beam, which has low tissue penetrating properties and sodium borocaptate (BSH). This had been developed as a boron delivery agent by Albert Soloway at the MGH. In Hatanaka's procedure,[25] as much of the tumor was surgically removed as possible ("debulking"), and at some time thereafter, sodium borocaptate (BSH) was administered by a slow infusion, usually intra-arterially, but later intravenously. Twelve to 14 hours later, BNCT was carried out at one

or another of several different nuclear reactors using low energy thermal neutron beams. The less tissue-penetrating properties of the thermal neutron beams necessitated reflecting the skin and raising a bone flap in order to directly irradiate the exposed brain, a procedure first used by Sweet and his collaborators. Approximately 200+ patients were treated by Hatanaka, and subsequently by his associate, Nakagawa.[26] Due to the heterogeneity of the patient population, in terms of the microscopic diagnosis of the tumor ("grade"), and its size, and the age and the ability of the patient to carry out normal daily activities ("performance status"), it was not really possible to come up with definitive conclusions about therapeutic efficacy, as measured by a prolongation in the mean survival time (MST). However, the survival data were no worse than those obtained by standard therapy at the time, and there were several patients who were long-term survivors, and most probably they were cured of their brain tumors.[26]

More recent clinical studies in the U.S.A. and Japan

BNCT of patients with brain tumors and a few with cutaneous melanoma was resumed in the United States in the mid-1990s at the Brookhaven National Laboratory Medical Research Reactor (BMRR) and at Harvard/Massachusetts Institute of Technology (MIT) using the MIT Research Reactor (MITR). For the first time, BPA was used as the boron delivery agent, and patients were irradiated with a collimated beam of higher energy epithermal neutrons, which had greater tissue-penetrating properties than thermal neutrons. This was well tolerated, but there were no significant differences in the MSTs compared to patients that had received conventional therapy.[4][5]
Miyatake and Kawabata[8][9] in Japan have initiated several protocols employing the combination of BPA (500 mg/kg) and BSH (100 mg/kg), infused i.v. over 2 hrs, followed by neutron irradiation at Kyoto University Research Reactor Institute(KURRI). The MST of 10 patients was 15.6 months, with one long-term survivor (>5 years).[9] Based on experimental animal data,[27] which showed that BNCT in combination with X-irradiation produced enhanced survival compared to BNCT alone, Miyatake and Kawabata combined BNCT, as described above, with an X-ray boost.[8] A total dose of 20 to 30 Gy was administered, divided into 2 Gy daily fractions. The MST of this group of patients was 23.5 months and no significant toxicity was observed, other than hair loss (alopecia). These results suggest that the combination of BNCT with X-irradiation deserves further evaluation in a larger group of patients. In another Japanese trial, carried out by Yamamoto et al., BPA and BSH were infused over 1 hr, followed by BNCT at the Japan Research Reactor (JRR)-4 reactor.[28] Patients subsequently received an X-ray boost after completion of BNCT. The overall median survival time (MeST) was 27.1 months, and the 1 year and 2 year survival rates were 87.5 and 62.5%, respectively. Based on the reports of Miyatake, Kawabata, and Yamamoto, it appears that combining BNCT with an X-ray boost can produce a significant therapeutic gain. Further studies are needed to optimize this combined therapy, and to evaluate it using a larger patient population.

Clinical studies in Finland

The team of clinicians and physicist at the Helsinki University Central Hospital and VTT Technical Research Center of Finland have reported on 22 patients with malignant

gliomas (glioblastomas) who had undergone standard therapy, recurred, and subsequently received BNCT at the time of their recurrence using BPA as the boron delivery agent.[6] The median time to progression was 3 months, and the overall MeST was 7 months. It is difficult to compare these results with other reported results in patients with recurrent malignant gliomas, but they are a starting point for future studies using BNCT as salvage therapy in patients with recurrent tumors.

Over 100 patients with recurrent head and neck cancers and brain tumors have been treated in Finland with BNCT using the Otaniemi nuclear reactor.[29]

Clinical studies in Sweden

Finally, to conclude this section, the following is a brief summary of a clinical trial that was carried out in Sweden using BPA and an epithermal neutron beam, which had greater tissue penetration properties than the thermal beams originally used in Japan. This study differed significantly from all previous clinical trials in that the total amount of BPA administered was increased (900 mg/kg), and it was infused i.v. over 6 hours.[30][31] The longer infusion time of the drug was well tolerated by the 30 patients who were enrolled in this study. All were treated with 2 fields, and the average whole brain dose was 3.2-6.1 Gy (weighted), and the minimum dose to the tumor ranged from 15.4 to 54.3 Gy (w). There has been some disagreement among the Swedish investigators who carried out this study in terms of evaluation of the results. One group reported that the MeST was 14.2 months and the time to tumor progression was 5.8 months, and that there was decreased quality of life following BNCT.[30] Another group[31] subjected the survival data to more rigorous analysis and concluded that the MeST was 17.7 months compared to 15.5 months that has been reported for patients who received standard therapy of surgery, followed by radiotherapy (RT) and the drug temozolomide (TMZ).[32] Furthermore, the frequency of adverse events were lower after BNCT (14%) than after RT alone (21%) and both of these were lower than those seen following RT in combination with TMZ. If this improved survival data, obtained using the higher dose of BPA and a 6-hour infusion time, can be confirmed by others, preferably in a randomized clinical trial, it could represent a significant step forward in BNCT of brain tumors, especially if combined with a photon boost.

Clinical studies in Italy

On 19 December 2001, BNCT was successfully used for the first time in Pavia (Italy) on a 42-year-old man to treat liver cancer. His liver was explanted, was subjected to the treatment, and was reimplanted.[33]

Clinical study in Argentina

The first clinical trial of BNCT in Argentina was performed on 9 October 2003.[34] BNCT has been used in Japan for head and neck cancers in 2009.[35] Taiwan BNCT group also

started treating head and neck cancers at the Tsing Hua Open-pool Reactor (THOR) of National Tsing Hua University on 11 August 2010.[36]

Table of clinical trials of BNCT for glioma (brain tumor)

Table 2. BNCT clinical trials using an epithermal neutron beams for BNCT of patients with gliomas

Facility*	No. of patients & duration of trial	Delivery agent	Median survival time (months)	Reference no.
BMRR, U.S.A	53 (1994–1999)	BPA 250–330 mg/kg	13-14	4[4]
MITR, MIT, U.S.A.	20 (1996–1999)	BPA 250 or 350 mg/kg	13	5[5]
KURRI, Japan	>50 (2002-)	BPA 500 mg/kg	20.7	8,9[8][9]
JRR4, Japan	15	BPA 250 mg/kg + BSH 5 g	not indicated	26[28]
R2-0, Studsvik Medical AB, Sweden	30 (2001–2007)	BPA 900 mg/kg	17.7	27,28[30][31]
FiR1, Finland	22 (1999-)	BPA 290–400 mg/kg	7 (Recurrent Patients)	6[6]
HFR, Netherlands	26 (1997–2002)	BSH 100 mg/kg	13.2-15.0	30[37]

Clinical Studies of BNCT for extracranial tumors

Head and neck cancers

The single most important clinical advance over the past 5 years has been the application of BNCT to treat patients with recurrent tumors of the head and neck region who had failed all other therapy. These studies were first initiated by Kato et al.[38] and subsequently followed by several other groups in Japan and by Kankaanranta and her co-workers in Finland.[7] All of these studies employed BPA as the boron delivery agent, either alone or in combination with BSH. A very heterogeneous group of patients with a variety of histopathologic types of tumors have been treated, the largest number of which had recurrent squamous cell carcinomas. Kato et al. have reported on a series of 26 patients with far-advanced cancer for whom there were no further treatment options.[38] Either BPA + BSH or BPA alone were administered by a 1 or 2 hr intravenous (i.v.) infusion, and this was followed by BNCT using an epithermal beam. There were

complete regressions in 12 cases, 10 partial regressions, and progression in 3 cases. The MST was 13.6 months, and the 6-year survival was 24%. Significant treatment related complications ("adverse" events) included brain necrosis, osteomyelitis, transient mucositis, and alopecia. Kankaanranta et al. have reported their results in a prospective Phase I/II study of 30 patients with inoperable, locally recurrent squamous cell carcinomas of the head and neck region.[7] Patients received either two or, in a few cases, one BNCT treatment using BPA (400 mg/kg), administered i.v. over 2 hours, followed by neutron irradiation. Of 29 evaluated patients, there were 13 complete and 9 partial remissions, with an overall response rate of 76%. The most common adverse event was oral mucositis, oral pain, and fatigue. They concluded that BNCT was effective for the treat¬ment of localized, recurrent, inoperable, previously irradiated head and neck cancer. A randomized clinical trial with a sufficiently large number of patients would be the next step.

Other types of tumors

Other extracranial tumors that have been treated include melanomas, a malignant tumor of skin, which was carried out in Japan by Yutaka Mishima and his clinical team[39] using BPA and a thermal neutron beam. Local control was achieved in almost all patients, but none were cured of their disease. Recently, several patients with cutaneous melanomas also have been treated in Argentina, but the results have not, as yet, been reported. Two patients with colon cancer that had spread to the liver have been treated by Zonta et al. in Italy.[40] The patients received an i.v. infusion of BPA, followed by removal of the liver (hepatectomy). This was treated out side of the body (extracorporeal) by BNCT and then re-transplanted into the patients. One of them did remarkably well and survived for over 4 years after treatment, but the other died within a month. Clearly, this is a very challenging approach for the treatment of hepatic metastases, and it is unlikely that it will ever be widely used. There have been several recent reports describing the possible use of BNCT to treat other solid tumors, including sarcomas of the extremities, primary lung cancer, mesothelioma, and spinal tumors,[41] but the future of these studies is in part dependent upon additional clinical studies confirming and extending the use of BNCT to treat head and neck cancer.

Summary of present experience with the BNCT type of NCT

BNCT represents a joining together of nuclear technology, chemistry, biology, and medicine to treat malignant gliomas and recurrent head and neck cancers. Sadly, the lack of progress in developing more effective treatments for these tumors has been part of the driving force that continues to propel research in this field. BNCT may be best suited as an adjunctive treatment, used in combination with other modalities, including surgery, chemotherapy and external beam radiation therapy for those malignancies, whether primary or recurrent, for which there are no effective therapies. Clinical studies have demonstrated the safety of BNCT. The challenge facing clinicians and researchers is how to move forward.

Advantages of BNCT include the potential ability to selectively deliver a radiation dose to the tumor with a much lower dose to surrounding normal tissues. This is an important feature that makes BNCT particularly attractive for salvage therapy of patients with a variety of malignancies who already have been heavily irradiated. Second, although it may be only palliative, it can produce striking clinical responses, as evidenced by the experiences of several groups treating patients with recurrent, therapeutically refractory head and neck cancers.

Problems with NCT and BNCT that need to be solved include:

- *First and foremost*, the development of more tumor-selective boron delivery agents for BNCT. Similar problems are seen with Gd-NCT and other NCTs that require deliveray of a specific neutron-absorbing nuclide selectively to tumor, but not surrounding tissues.

- *Second*, accurate, real time dosimetry to better estimate the radiation doses delivered to the tumor and normal tissues.

- *Third*, accelerator based neutron sources that can easily be sited in hospitals.

- *Fourth*, randomized clinical trials. For a more detailed discussion of these problems and their solutions in BNCT, readers are referred to the published proceedings of the 13th International Congress on Neutron Capture Therapy.[41] If these four problems can be solved, the authors in the referenced source believe that BNCT will have an important place in twenty-first century cancer treatment of those cancers that are loco-regional and that are presently concurable by other therapeutic modalities[42]

See also

- Fast neutron therapy
- Particle therapy
- Proton therapy

External links

- Helsinki University Central Hospital and Technical Research Centre of Finland BNCT Project
- Boron and Gadolinium Neutron Capture Therapy for Cancer Treatment
- MIT Nuclear Reactor Lab overview of BNCT
- Washington State University Nuclear Radiation Center BNCT Overview

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