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STRATEGIC PLANNING WORKSHOP

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RESEARCH NEEDS FOR NEUTRON CAPTURE THERAPY

Williamsburg, Virginia

May 9 - 12, 1995

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Executive Summary

Key issues and questions addressed by the workshop related to optimization of Boron Neutron Capture Therapy (BNCT), in general, and to the possibility of success of the present BNCT trials at Brookhaven National Laboratory (BNL) and Massachusetts Institute of Technology (MIT), in particular. Both trials use nuclear fission reactors as neutron sources for BNCT of glioblastoma multiforme (BNL) and of deep seated melanoma (MIT). Presentations and discussions focussed on optimal boron-labeled compounds, mainly for brain tumors such as glioblastoma multiforme, and the best mode of compound delivery to the tumor. Also, optimizing neutron irradiation with dose delivery to the tumor cells and the issues of dosimetry of BNCT especially in the brain were discussed. Planning of treatment and of follow-up of patients, coordination of BNCT at various treatment sites, and the potential of delivering BNCT to various types of cancer with an appropriately tailored protocol were additional issues. The need for multicentric interdisciplinary cooperation among the different medical specialties was highlighted.

Introduction

Based on recent extensive research data obtained with thermal and epithermal neutrons and various boronated compounds from tissue cultures and tumor bearing animals, and in view of the Japanese experience and of the clinical trials that began at the Massachusetts Institute of Technology (MIT) (together with the New England Medical Center [NEMC] of Tufts University Medical School) and at the Brookhaven National Laboratory [BNL] (together with Beth Israel Medical Center [BIMC] in New York City), the workshop was convened to identify immediate needs for optimizing the clinical application of Neutron Capture Therapy (NCT).

The workshop had 52 participants, of which 36 were leading scientists and physicians directly involved in research on the clinical use of boron neutron capture therapy (BNCT) presently using nuclear fission reactors; 34 came from the United States, one from Germany and one from Japan. Also present were five representatives from the Food and Drug Administration (FDA), one from the National Cancer Institute (NCI), two from the American Brain Tumor Association, and eight from the Department of Energy (DOE).

The agenda identified six major topic areas: 1) NCT as a potential modality for treating brain tumors; 2) criteria for therapeutic boron compounds; 3) neutron sources and dosimetry; 4) planning and performing treatment trials; 5) patient selection and follow-up; and 6) program coordination.

Following short presentations of issues within the various topic areas, broad discussions informed all participants on many phases of this complex subject. The advantage of the workshop was, undoubtedly, the continuous open assessment in the plenary sessions of the evidence, pro and con, regarding the many uncertainties and possible solutions associated with the potential clinical execution of BNCT.

The presentations and discussions in each topic area were guided by designated individuals whose willingness to take on the assignment and whose contributions are gratefully acknowledged. The brief summaries given below for each topic area rely heavily on the summaries prepared by the discussion leaders.

Workshop Summary Minutes

1. NCT as a Potential Modality for Treating Brain Tumors

The *overview* presentations and discussions identified the place of BNCT in the spectrum of the many modalities of experimental and conventional treatment of brain cancer, especially glioblastoma multiforme, which causes about 7,000 deaths annually in the U.S. Boron–10 remains the only target atom being used currently for neutron capture therapy. It delivers a highly selective absorbed dose localized to targeted cells on a microscopic scale.

The overview presentations addressed the uncertainties of BNCT and the danger of wishful thinking. The evolution of treatment programs for highly malignant brain tumors began with the pioneering studies of the Brain Tumor Study Group trials about 20 years ago. Disappointingly little progress could be reported with only minor modification in the standards of treatment. Standard radiation is consistently shown to enhance survival time approximately 2.5-fold. Some additional benefit is seen with some chemotherapeutic trials, particularly for Grade III gliomas. BNCT and approaches using genetic therapy are presently considered promising.

The high LET (linear energy transfer) therapy trials, such as with neutrons, have consistently demonstrated effectiveness in eradicating glioblastoma. However, no net therapeutic gain was found since this was not achieved without severe deleterious effects on normal tissues.

BNCT is unique in offering the potential of delivering high LET radiation to individual tumor cells. The results from Japan help justify further investigation with more carefully designed protocols. The temptation must be avoided to expect a potential "home run" from present Phase I or Phase II trials or to project BNCT as a miracle cure. Major survival gains may not be seen in these initial trials. Nevertheless, it is critical to obtain the necessary information for the design of further studies.

The individual, sometimes extreme differences in the ***tolerance of the human brain to irradiation*** were also illustrated. How much x-radiation usually kills various tumor types as well as the dose that causes gray and white matter necrosis should be known. It has been generally confirmed that 60 to 70 Gray have rarely cured a patient with glioblastoma but may cause necrosis of normal brain tissue. Perhaps most germane to determining the BNCT doses are the

experiences by the radiation-therapists using higher than standard doses and had post mortem results in terms of necrosis of brain and destruction of tumor. One such study on 12 patients indicates that despite total doses of even 90 to 234 Gray in 5 cases, all 12 showed clearly viable tumor at autopsy.

Numerous reports reveal necrosis of normal brain tissue in up to 35 percent of patients following fractionated irradiation of brain tumors (total doses of circa 30 to 50 Gray). The four data bases in "Paperchase" for "human, brain, radiation injuries" list now about 207 references from 1966 to 1985 and 284 from 1986 to 1995.

Clinical trials under various protocols are necessary to assess the eventual efficacy of BNCT in the context of tolerance of normal tissue to irradiation.

2. *Criteria* for Therapeutic Boron Compounds

Potentially useful boron-containing compounds for BNCT need further research regarding their metabolic fate in the patient, optimal uptake into the tumor cell, and their general toxicity limits. Of particular importance is the requirement that the boron-containing compounds for BNCT of brain tumors be capable of traversing the blood brain barrier and of localizing selectively within tumor cells, even those dispersed throughout the gray and white matter at various distances from the surgically resected tumor. Concomitantly, it is equally important that these boron compounds be rapidly cleared from normal brain tissue. Moreover, surgical tumor resection prior to BNCT is likely to alter local brain perfusion and function of the blood brain barrier so that attention must be paid to the appropriate analyses of compound biodistribution after brain surgery and prior to BNCT.

There appeared to be general agreement that boronophenylalanine (BPA) and sulfhydrylduodecaborane (BSH), under study in humans, should not be seen as ideal or even necessarily outstanding BNCT compounds. Both were developed beginning in the late 1950s.

Compounds for NCT can be classified into three groups according to the extent of currently available information on their chemical, pharmacological, and radiobiological properties. Despite the workshop's primary focus on malignant brain tumors compounds for NCT of other cancers were considered also.

The *first group* includes the presently used compounds BPA and BSH, which are available for intravascular, intratumoral, and parenchymal

administration. BPA has a low weight percentage of boron, requiring the administration of very substantial amounts. It crosses the blood brain barrier to a significant extent and also reaches tumor cells that are within tissue with an intact blood brain barrier; it permits tumor/normal brain ratios of ~≥3:1 in humans. BPA does not appear to remain bound within tumor cells for substantial periods of time. Uptake into normal brain tissue may ultimately result in radiation damage to normal brain, particularly if it concentrates in critical substructures. Extensive discussion on BPA that is complexed to fructose (BPA-F) for enhanced solubility, restated the justification of using this drug in the present clinical BNCT trial at BNL and MIT.

BSH is essentially a blood-localized drug with a relatively poor tumor/blood ratio. Although it has proven safe in the Japanese studies, they were not at the high pharmacological amounts considered necessary for achieving a desirable boron-10 concentration of about 25–35 parts per million (ppm) in tumor tissue. BSH does not cross the blood brain barrier, but enters the tumor where the blood brain barrier is destroyed, and has uncertain tumor retention characteristics. Valuable ongoing basic research in the U.S., and a European multicenter study on biodistribution in humans will ultimately reduce these uncertainties. The pharmacologic properties of BSH show that it is usually not superior (but may be equal) to BPA or other drugs nearing trials. BSH is being (and will be) used in clinical trials both in Europe and Japan. The question was raised whether further pretreatment studies of BSH are warranted in the U.S.

Boronated porphyrin (BOPP) belongs into the *second group* of compounds that may come to clinical trials next. It was shown in various animal studies to be both strongly localized to tumor over normal brain (>100:1) and cleared from blood at acceptable rates. In culture cells, BOPP localizes predominantly in the mitochondria. Various modes of labeling porphyrins permit non-invasive biodistribution studies by nuclear medical imaging techniques. Tumor boron levels of 60-80 ppm have been reported in animal models to be readily achieved. Toxicity studies are still needed, although gross non-toxicity was demonstrated in a canine experiment. Moreover, animal studies to determine the "compound factor" (relative effectiveness from preferential compound localization) are proposed in order to assess the radiobiological parameters and therapeutic efficacy of BOPP preferentially in experimental brain tumors in rodents. Depending on results of these studies, Phase I pharmacological trials will follow.

Boronated liposomes present a potentially versatile strategy for tumor targeting. Suitable boron compounds have been incorporated into either the aqueous core or the lipophilic surface lipid bilayer or both, and tumor selectivity can be enhanced by local hyperthermia, magnetic focusing, or by the addition of tumor seeking proteins to the surface of the liposomes. Boron containing liposomes are well-retained by model tumors of small animals and, thus, offer advantages of excellent tumor selectivity and uptake per injected dose. They are, however, less suited for brain tumors because of the blood brain barrier. In small animals, liposome-delivered tumor boron levels of 60 to 80 ppm are achievable with relatively rapid clearance from the circulating blood. Large animal work needs to be pursued, as do studies designed to evaluate the subcellular localization, radiobiological properties, and therapeutic efficacy of the compounds particularly for eventual clinical use when a tumor is readily accessible to the liposomes. Boronated low density lipoproteins (B-LDL) offer another attractive transport system for boron delivery to tumors. Support for further development of B-LDL has been discontinued in the U.S., but these substances are being evaluated in Phase I trials and basic research studies in Finland for eventual application to the treatment of squamous cell carcinomas of the head and neck.

The *third compound group* includes many metabolically active substrates, such as various amino acids, peptides, receptor seeking proteins, nucleosides, and other tumor DNA targeting molecules that have been labeled with boron-10 and are being proposed and/or studied for potential use for BNCT. They are currently not planned for clinical trials, but their future development may determine the long term future of BNCT.

It was proposed that the NCI play a much larger role in future *compound development* and in clinical trials. Despite many years and hundreds of millions of dollars of investment, neither chemotherapy nor hyperthermia have yielded any significant increase in survival time or improvement in quality of life in brain tumor patients above the conventional tumor control. It was suggested that a designation of some of the NCI budget for compound development to BNCT and clinical trials could lead to breakthrough results.

The problem of *compound precursor* availability was discussed and deemed noteworthy. There is currently no reliable commercial source of ^{10}B-enriched cage compounds in the U.S. Although this has not delayed targeted compound development and preclinical testing significantly, it may do so in the near future.

An additional U.S. center was suggested to complement BNL's efforts in testing new and promising boronated compounds for potential use in BNCT. The compound testing should include *in vitro* cytotoxicity and cellular uptake studies, *in vivo* screening, using implantable rodent tumors and large animal models. These models are needed for analyzing compound concentrations in critical organs and tissues in the neutron beam such as pituitary, retina, thyroid, and bone marrow. Also, the use of spontaneous tumors in large animals helps to better simulate the clinical setting and to define parameters for Phase I/II clinical trials.

Whatever boronated compound is utilized in trials of BNCT, success of the therapy in terms of tumor control depends on the *homogeneous distribution of the boron compound in the tumor* with preferential localization in, or very near, the tumor cells. The chemical and biological evaluations of new promising NCT compounds must, therefore, include their kinetics in normal tissue and tumors, following various routes of administration. Furthermore, stereotactic injections directly into the tumor, or for non-metabolizable compounds, into the ventricle system of the brain were considered promising. The knowledge of compound microdistribution in tumors and the establishment of compound quality factors in animal models, is crucial to the future of NCT, as discussed in Section 4.

3. Neutron Sources and Dosimetry

The neutron source for BNCT now and in the near future is unquestionably the nuclear fission reactor. There are three *epithermal neutron beams* available in the world, the Brookhaven Medical Research Reactor (BMRR), the Massachusetts Institute of Technology Reactor (MITR-II), and the High Flux Reactor (HFR) in Petten, The Netherlands. Clinical trials of NCT have been initiated at the BMRR and MITR-II in the U.S. Both beams have been tailored to apply the energy range from about 0.5 eV to 10 KeV, which provides greater penetration (approximately 2-3 cm) than thermal beams. Therapeutic ratios of tumor to normal tissue (about 2-4) are achievable with a compound such as BPA-F, and all parts of the brain can be irradiated with this therapeutic ratio. Considering the existing irradiation capability at the BMRR and MITR-II with current support levels, it is possible to complete NCT irradiations of 25–50 brain cancer patients in 1 to 2 years. With careful design, this number of patients may yield a statistically significant result of BNCT efficacy.

Regarding availability of *improved high intensity, low background, and other neutron sources*, the BMRR epithermal neutron beam will have an increased flux in 1996 following installation of a fission converter. Given funding on the order of $3M, the MITR high intensity low background fission converter beams can be completed in 2 years. The Georgia State Institute of Technology Research Reactor (GTRR) may also be converted to provide a powerful epithermal beam in 1996–1997. The conversion of the Washington State University reactor may present a new facility for animal irradiations in 1996. Moreover, during the next 5 to 10 years more than 10 university research reactors could convert for NCT applications. If BNCT proves to be safe and efficacious, then small, special purpose reactors may be constructed.

The Lawrence Berkeley National Laboratory ESQ accelerator, 10–20 mA at 3.5 MeV, can become operational in 1997–1998, although it requires lithium target development at a cost of about $5M. Compact accelerators also are potential tools for NCT but need to be demonstrated. If demand for NCT grows significantly, DOE and NCI should consider a major joint initiative.

Regarding *dose limitations to normal tissue*, currently available radiotherapy data indicate that for single doses the whole brain tolerance is about 11 Gy-equivalent or RBE Gy. Brain injury observed in NCT trials from high doses is likely to involve damage to small vessels and oligodendroglia, demyelinization, and focal and massive necrosis. The degree and spatial extent of such changes with NCT irradiations will depend on the macro- and microdistribution of the compound carrying the target nuclide and on the delivered macroscopic dose. The minimal dose needed for local *tumor control* based on available data is about 30 Gy-equivalent in 10–20 percent of patients; 70 percent require a higher dose. It follows that for effective treatment, the tumor to normal tissue ratio of absorbed doses must exceed three.

Macrodose distribution and dosimetry in the exposed tissue requires further comparison among laboratories that are involved in NCT trials. It was proposed that a standard head phantom, based on the Snyder head model, be used by all NCT clinical groups. In addition, gamma and fast neutron dose measurements and thermal flux measurements should be compared, relying on published standardized methods of dosimetry adapted for BNCT. Epithermal beams should be compared in radiobiological experiments, for example, with cell culture survival studies.

The software for planning and control of radiation exposure requires further research and development. This could lead to an efficiency

improvement of therapy and to an acceleration of treatment planning, which now requires 1 week for each patient. Benchmark validations and cross comparisons of results of planning systems should be encouraged and formalized. The information on available or to-be-developed software should be archived and accessible for post-irradiation studies. Presently, only two systems exist, one at the Idaho National Engineering Laboratory (INEL) and one at the New England Medical Center (NEMC). Private sector involvement is encouraged to support these efforts.

The success of NCT depends largely on the local *microdistribution of absorbed dose* and on optimal neutron irradiation modes of either single or fractionated exposures. It was suggested that subcellular boron (^{10}B) levels should be determined for all patients in the initial clinical trials, using high resolution quantitative autoradiography (resolution of 1–2 μm), permitting the measurement to levels of 1 ppm. Other promising approaches use surface physics and chemistry probes, such as SIMS (Secondary Ion Mass Spectrometry) or STEM (Scanning Transmission Electron Microscopy)/EELS (Electron Energy Loss Spectroscopy); these approaches need further development.

Microdosimetry in BNCT research is considered crucial for two reasons: 1) it can provide insight into how the microdistribution characteristics of boronated compounds influence their biological effects within specific cell model systems; and 2) it can be used to derive microdosimetric "transfer factors" between normal and tumor tissues in animals, where response to BNCT can be objectively measured to corresponding tissues in humans. As an example of 1), microdosimetry could provide a fast-track evaluation of new boron compounds which have been tested only for biodistribution. As an example of 2), the current set of compound-RBEs (C-RBEs) that are utilized in the ongoing BNCT glioblastoma protocol at BNL are based on experimental C-RBE determinations in rat spinal cord (50 percent paralysis endpoint) and in GS9L rat tumor (extended survival endpoint). Reproduction of these results by microdosimetric modeling and the generation of similar data in the human glioblastoma model system would strengthen the confidence in the C-RBEs being utilized in the clinical trials.

Analytical microdosimetry requires three components of analysis: (1) determination of the microscopic boron spatial distribution to be modeled; (2) determination of the tissue morphology to be modeled; and (3) the choice of the appropriate endpoint parameters (e.g., nuclear absorbed energy, nuclear hits, whole cell absorbed energy, etc.). Currently, only high-resolution

quantitative alpha-autoradiography in conjunction with 2D surrogate Monte Carlo-based microdosimetry can satisfy these requirements. This technique measures the actual boron distributions in thin frozen tissue sections, and then uses the principles of histological stereology to perform microdosimetric calculations on the actual tissue anatomy.

4. Planning and Performing Treatment Trials

At the present time, there are no experimental data that support any gain from *single vs. fractionated vs. prolonged exposure* to neutrons. Animal survival experiments at BNL and the NEMC (with MIT) have shown no statistically significant differences between single and fractionated neutron irradiation (up to four fractions) of tumors with boron compounds.

The issue of fractionated BNCT was discussed extensively. The uncertainties involved led the majority of the participants to support the single fraction mode for BNCT of glioblastoma multiforme and to postpone the option of a multiple fraction mode protocol for these tumors.

Because of the potential significance of a fractionated mode in the future, some of the arguments supporting this mode are given here:

- In conventional radiation therapy, dose escalation is used to arrive at an optimum balance of tumor control vs. risk of normal tissue damage. Fractionation is one way to optimize the differential between effects in normal tissue and tumor.
- In BNCT, in particular, it is necessary to define a safe level of exposure to the radiation field most of which is of high LET. The dose to individual cancer cells is mainly a function of the boron compound, its delivery to tumor cells, and the neutron field. The efficacy of BNCT is indeed arguable unless enough tumor cells contain sufficient amounts of boron, as the probability of therapeutic success increases with cellular amounts of boron. The aim is to achieve boron uptake in every tumor cell. The average boron concentration in the tumor is not sufficient for assessing boron distribution to cells; new populations of cells may receive boron with renewed administration. It was felt to be highly unlikely that a single administration will load enough boron into all or enough tumor cells for efficacious BNCT. Retargeting of boron compounds with each of three or four fractions may assure uptake of boron in those cells which did not take up boron after only a single delivery. Only clinical studies will answer the question of consequences of heterogeneity of boron

distribution among tumor cells.

- Fractionation in BNCT can potentially provide an additional safety margin to the radiation treatment, since there will be repair of the low LET damage to normal tissue without comprising the effect on the tumor.
- Since only a few fractions are recommended over a 1–2 week period, there should not be any detriment due to repopulation effects.
- In the literature of high LET type radiations, some normal tissue sparing is reported for even very high LET, particularly between one and two or up to four fractions. It is generally assumed that there is no further sparing of acute or late effects if more than four fractions are used.
- Tissues of the central nervous system are considered the most sensitive to application of large doses per fraction. The administration of 10 Gy-equivalent in a single dose is close to the expected tolerance but has only been tested in palliative settings.
- Investigators at the Lawrence Berkeley National Laboratory have preferred to fractionate heavy ion beams. These beams irradiate a smaller volume of the brain compared to BNCT (when multiple fields are used).
- A mathematical model showed that under consistent tolerance assumptions it is possible to escalate the dose from boron neutron capture using four fractions due to sparing of low LET effects. These modeling results have not been experimentally verified.

Boron biodistribution measurements are necessary to estimate the absorbed dose to tumor and normal tissue. These measurements are essential for spatial "macrodistribution" and "microdistribution" and their temporal changes.

Macroscopic distribution studies are well established and require sampling of tissue and blood for bulk boron analysis. Boron is analyzed by Prompt-Gamma Spectroscopy (PGS), Inductively-Coupled Plasma Spectroscopy (ICP), Direct-Current ICP (DC-ICP), or High Resolution Quantitative Alpha-track Autoradiography (QAR). The last method is ideal for the analysis of normal tissue and tumor samples following surgical resection, and can in principle handle sample sizes down to 10 μl that might be obtained by thin-needle stereotactic biopsy techniques.

Magnetic Resonance Imaging (MRI) of boron–11 is still under development, but shows great promise for noninvasively assaying the spatial boron distribution in tissue. Presently, spatial resolution of MRI is limited to 1-2 cm with boron–11 concentrations of at least a few tens of ppm. Necessary hardware and software upgrades to GE Sigma MRI scanners are commercially available.

Positron Emission Tomography (PET) uses ^{18}F-labelled boron compounds (e.g., 1,BPA-fructose) and shows promise for quantitatively measuring spatial boron compound distributions. Preliminary data using 1,BPA-fructose appear to validate similar macrodistributions of labelled and unlabelled compounds. Spatial resolution is approximately 8–10 mm and the method is quite sensitive to low concentrations of boron compound. Access to this technology is presently limited by the need to synthesize the labelled compound for each specific use and by the relatively small number of PET centers in the U.S.

Scanning by Single Photon Emission Computer Assisted Tomography (SPECT) is widely available in the U.S. and can utilize either positron emitting ^{18}F-labelled boron compounds with special high-energy collimators or single gamma emitters such as ^{123}I-labelled boron compounds with conventional collimators. Although ^{123}I-labelled boron compounds have not yet been fully studied, conventional radiopharmaceutical experience suggests that they should be easy to synthesize and would probably demonstrate the same relative macrodistribution as the unlabelled compound. Advantages include the substantially longer half-life of ^{123}I and easier access to SPECT equipment. However, SPECT images are not as easy to quantitate as PET images at this time; research to improve SPECT in this area is ongoing.

Regarding *microdistribution* of boron-10 labelled compounds in tissue, QAR requires that tissue samples be prepared carefully to prevent the translocation of the boron compound post-biopsy. QAR uses thick tissue sections and thick track detectors, where neutron-induced alpha exposure generally is measured by examination of the resulting increase in optical density following etching of the detector. "Thick detector QAR" has a non-linear response to boron-10 concentration, a relatively small dynamic range, and poor spatial resolution (>20 μm). In addition, the track detectors used (commonly LR115 or CR39) are sensitive to charged particles other than alpha and lithium-7 (e.g., protons) and, thus, manifest a significant background.

The SIMS, EELS, and STEM also require tissue sample preparation to avoid compound translocation after biopsy. Once this has been achieved, these methods have the potential to measure boron distributions with extremely fine spatial resolution (sub-micron) and high sensitivity. Currently, however, absolute quantitation of boron concentrations has not been achieved but may be possible in the future with further development.

High-resolution QAR uses thin (1 μm) frozen tissue sections and a thin (1 μm) Lexan based detector and relies on track counting rather than optical density. This accomplishes a spatial resolution of approximately 1 μm with

excellent linearity and satisfactory dynamic range. Because the Lexan detector is insensitive to LET characteristic of protons, background tracks are virtually absent, sensitivity is greatly enhanced down to single ppm levels of boron-10, and the measurements are highly accurate. The laboratory and image-processing requirements for this technique are well established. The HRQAR is presently considered to be a benchmark method for microscopic spatial boron analysis.

Methods for *temporal measurement of boron concentrations* in tissue are critical as prerequisites to accurate physical dosimetry, since the boron time-concentration curves in tumor and normal tissues determine the dosimetry. The methods that are able to measure temporal boron distributions noninvasively are essentially those used for macro- and microdistribution studies. The methods enhance tumor dosimetry, particularly where blood boron levels cannot be used as surrogate measurements for tumor boron levels.

For the *diagnostic follow-up* of patients after BNCT, various methods are routinely available and should be used:

MRI is presently the leading diagnostic modality for follow-up. Under suitable conditions it can measure tumor volume and has been shown to be useful as an endpoint of radiation effect in normal brain following BNCT. However, MRI is ineffective in distinguishing tumor regrowth from reactive gliosis in normal brain.

PET, using readily available ^{18}F-labelled compounds such as ^{18}F-deoxyglucose (FDG), has been shown to differentiate between regrowth of some brain tumors and reactive tissue scarring or necrosis in patients. Even more promising are ^{18}F-labelled amino acids that are taken up by tumor cells. PET has a lower accessibility and a higher cost than MRI, limiting its use.

SPECT imaging with ^{123}I-labelled amino acid analogues readily differentiates between tumor and normal tissue during the diagnostic follow-up of patients after BNCT.

A review of the *Japanese experiences* of a prolonged (4-7 hours) irradiation with thermal neutrons of the exposed brain in the open skull of the anesthetized patients led to inconclusive results, mainly because the variations in the histological tumor type and treatment conditions. The patients who developed delayed damage to the normal brain in the form of necrosis suffered nausea and vomiting shortly after the treatment. No emergency treatment was, however, required.

The participants discussed the question of expanding the *referral base for* BNCT *patients*. Physicians referring patients from long distances to the sites of

BNCT should be assured that a proper care infrastructure is available at those sites. In addition, these physicians should be prepared to conform to strict follow-up and reporting protocols following BNCT. This is crucial for maintaining the scientific objectivity of BNCT clinical trials.

Whether *tumors other than glioblastoma multiforme and melanoma* will eventually receive BNCT depends on their relevant ability to concentrate boronated compounds relative to normal tissue, and on additional factors, including their location, the feasibility of intraoperative techniques, and the success of conventional therapeutic approaches. Two types of tumor that are believed to be strong candidates in these respects are squamous cell carcinomas of the head and neck and metastatic melanoma. Of these, BNCT of melanoma is currently at the stage of Phase I clinical trials at MIT-NEMC.

5. Patient Selection and Follow-up

The *selection of patients* must adhere to the approved protocols for biodistribution studies as well as for safety and efficacy studies. The minimal number of patients required for a statistically significant answer varies with the degree of response to therapy and may be based on matched pairs or on randomized trials, for a given degree of expectation of efficacy.

The BNCT *protocol* that is presently being followed at BNL for glioblastoma multiforme evaluates: (1) the maximum tolerated dose below toxicity of BPA-F that will give a favorable biodistribution of the boron; the BPA-F dose escalation study is carried out at the time of the scheduled craniotomy; (2) the safety of BNCT using BPA-F and the epithermal beam; and (3) the impact of treatment results as to survival, time to tumor progression, quality of life, and neurological findings (Karnofsky score). The use of existing protocols for follow-up investigations will provide useful documentation of alternative approaches.

The attendees suggested that investigators at MIT and NEMC, who are in the process of developing a BNCT protocol for brain tumors, work in collaboration with the investigators at BNL and BIMC in New York City, so that the design and objectives of the two studies are complementary.

Future clinical trials will seek: (1) neutron dose escalation and a fixed BPA-F loading of the tumor; (2) escalation of BPA-F loading and a fixed neutron dose; (3) BNCT of brain metastases from melanoma; (4) BNCT for tumor types other than glioblastoma multiforme and melanoma; and (5) evaluation of imaging techniques in tumor diagnosis before and after BNCT. This last

procedure may also determine the ratio of boron compound concentration in the tumor to the concentration in normal tissue for individual patients. The consensus among the clinicians was that BNCT should not be permitted as a retreatment after a full course of chemotherapy and radiation therapy, at least until the safety and toxicity of BNCT as a primary treatment is evaluated.

As a guide to determining future regulatory and resource needs, FDA suggested that the investigators involved outline a developmental program for BNCT clinical trials to FDA.

Some participants commented that the study at BNL and BIMC in New York City had an initial low *patient accrual*. The implementation phase of such a study is necessarily time consuming and significant regulatory and institutional clearances are required prior to accepting patients. This led eventually to an average patient acceptance of one per month. There are, also, at least 53 ongoing clinical glioblastoma trials that are competing for patients. Nevertheless, necessary steps for disseminating information on the ongoing trials should be taken in accordance to FDA regulations, such as listings in the Physicians Desk Querier (PDQ) and through organizations such as the American Brain Tumor Association, as is discussed in Section 6.

Regarding *funding*, the clinicians present proposed developing an infrastructure to support clinical trials. There was a strong plea for seeking outside (to DOE) funding for support of the clinical arm of BNCT trials. The clinicians voiced concern and asked for a balanced allocation of resources between the basic research and clinical studies in order to prevent a slow-down of clinical trials. If preliminary results from the current clinical study are encouraging, it was suggested that additional support and recognition for BNCT as a treatment modality may be obtained through appropriate funding agencies, especially the NCI.

The *uncertainties of therapy results* must, of course, be known to the patients entering such studies. The thorough discussion of ethical questions in this regard stimulated a short review of the beginning of the clinical BNCT trial at BNL. The political pressure for starting clinical application of BNCT at BNL was viewed as a consequence of the social pressure that had arisen over the past few years. Compassion for patients and realistic assessment of potential benefit of therapy must be carefully balanced.

6. Program Coordination

The discussion of program coordination initiated a detailed description of the situation of BNCT *research in Europe* where biodistribution studies of BSH have just been completed. Regarding data on toxicity of BSH, the long term clinical and laboratory findings from Japan are helpful. In Europe, fractionated therapy is planned for glioblastoma multiforme (three to four BNCT sessions per patient), at the reactor in Petten, The Netherlands. Drug approval and development of standards and clinical protocols are still pending with BNCT applications foreseen to commence in 1996.

In view of the ongoing trials of BNCT for glioblastoma multiforme in the U.S., it will be difficult to conduct a BPA-F biodistribution according to the Phase I trial, i.e., without following up with BNCT. *However, multi-centered biodistribution studies* are expected to be initiated in the U.S. and each trial center would likely conduct the biodistribution of BPA-F at the time of the primary surgery. Patients with an acceptable distribution would be included in the protocol with follow-up at the original institution. This approach should increase the number of patients entered in the protocol for executing BNCT at BNL and MIT-NEMC.

Concern was raised about the supply of BPA-F, with the suggestion that the material be prepared at each institution, rather than making the solutions at BNL and distributing them to each site. Currently, the "shelf life" of the BPA-F solution is considered to be 48 hours, but may be increased after additional stability studies.

Workshop participants felt that *communications between the various groups* at universities and National Laboratories involved in the BNCT studies have improved significantly. The overall impression was that increased interactions among the various groups resulted in better understanding of the clinical study objectives. Moreover, improved communication among the BNCT groups, DOE, and FDA contributed to a beneficial collaboration.

The *patient information flow* needs to be improved and the contacts with the neurosurgical and radiation oncology community need to be enhanced. The physicians will be contacted through the PDQ that BNL is preparing, while the patient contact should work through established patient information and counseling services such as the American Brain Tumor Association, Des Plaines, Illinois, and the National Brain Tumor Foundation, San Francisco, California (in collaboration with the University of California, San Francisco). In this context, it was suggested that acceptance of patients for trial BNCT

should consider the treatment regime especially when the quality of life is important. The duration of conventional radiation therapy is 6 weeks and of chemotherapy about 8 weeks. Thus, the 1-3 day BNCT protocol can be an important factor, if BNCT provides at least the life extension of conventional therapy.

Regarding *development of standards*, it was reemphasized that, as the clinical trials are initiated at various reactor sites, an agreed method should be used at all sites to report the radiation biophysics and medical physics information. First and foremost, the characterization of the epithermal neutron beams should use a common set of measurements. It was suggested that the methods used (developed at INEL) to measure the energy spectrum of neutron beams at BNL and in Petten, The Netherlands, be also used for measuring the MIT beam. The commonality of measurement and dosimetry so far has facilitated the intercomparison and combination of the large animal model data. However, as suggested in Section 3, direct dosimetric measurements in phantoms as carried out at MIT and BNL are believed to be more valuable than direct measurements of the epithermal neutron beams.

The *validation of the treatment planning* codes was again addressed, as in Section 3, with the plea for reporting the dosimetry in a standardized fashion and in an understandable format, for making treatment plans comparable, for permitting reconstruction of the actual doses at later times, and also for decreasing the computation time. In this context it was confirmed that the current practice of using Gray-equivalent does not completely define the dosimetry. It was reiterated that a standard of reporting the dose be focused on the sum of the three components (total gamma, fast neutron-recoil proton + nitrogen-capture proton, and boron capture) in terms of physical dose, dose rate, and RBE for each component, rather than the summation of doses and RBEs.

Eventually, *multi-center trials* of BNCT are envisaged in the U.S., Europe, and Japan, with well standardized dosimetry procedures. In time, better modes of administration of a chosen boron-labeled drug are foreseen to treat a variety of tumors by specialized physicians in a coordinated effort. Patients need to be informed about the different treatment schedules, but this will require coordination and cooperation by the institutions providing the BNCT. Workshop participants also discussed the distinction between recruiting patients for clinical trials and advocating an unimproved therapy, such as BNCT.

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