The New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium: Organization, Objectives, and Activities

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The primary goals of the NABTT CNS Consortium are to develop scientific advances and improve clinical outcomes for patients with primary brain tumors.

Background: Despite advances in neuro-imaging, neurosurgery, radiation therapy, and chemotherapy, limited progress has been made in the treatment of patients with high-grade astrocytomas. The National Cancer Institute has attempted to speed advances in this field by funding CNS consortia to conduct innovative clinical trials in this patient population since 1994.

Methods: The NABTT CNS Consortium is composed of a consortium headquarters and nine member institutions with outstanding multidisciplinary expertise, clinical and laboratory research capabilities, and access to large numbers of patients with brain tumors.

Results: The objectives of the NABTT Consortium are to improve the therapeutic outcome for adults with primary brain tumors, to conduct basic science and clinical research, and to improve the care and quality of life of adults with primary brain tumors. NABTT’s clinical studies have discovered important drug interactions between anti-convulsant and antineoplastic agents, defined the activity of paclitaxel and 9-aminocamptothecin in glioblastoma multiforme, tested a novel dose escalation strategy for brain tumor trials, and established new protocol “classes” to expedite and standardize clinical research in this field.

Conclusions: Significant progress in the care of patients with primary brain tumors is likely to result from the highly focused and multidisciplinary efforts of the NIH-funded CNS consortia.

Introduction

Primary brain tumors affect approximately 17,000 patients each year in the United States. Sixty percent of all primary brain tumors are gliomas, and the majority of these are high-grade astrocytomas. Despite the significant advances in surgery, radiation therapy, and chemotherapy during the past three decades, adults with newly diagnosed high-grade astrocytomas have a median survival of less than one year, and virtually none are cured of their illness. Chemotherapy, in particular, has had limited impact on the survival of these patients. 

The treatment of primary brain tumors is complicated by many factors. These include the apparent resistance of these tumors to conventional treatments, the susceptibility of adjacent normal brain to adverse effects of therapy, the limited capacity of brain tissue for repair, the dissemination of malignant cells through brain parenchyma, the presence of a variably disrupted blood-brain barrier that complicates drug delivery to the tumor, and leaky capillaries that result in peritumoral edema and increased intracranial pressure. In addition, clinical trials are hampered by the inability to differentiate between progressive tumor, sequelae of therapy (i.e., necrosis), or changes in blood-brain-barrier integrity due to radiation therapy or adjustments in glucocorticoid doses using clinical criteria or neuroimaging studies.

Many basic principles regarding the treatment of these malignancies stemmed from protocols conducted by several large National Institutes of Health (NIH)-funded cooperative groups. Large, randomized, comparative (phase III) studies of the Brain Tumor Study Group (BTSG) and the Radiation Therapy Oncology Group (RTOG) identified critical prognostic factors, defined optimal radiation doses and fields, and demonstrated the limited value of adjuvant chemotherapy and radiosensitizers in these diseases. However, by the mid 1980s, it was clear that little further progress was likely from large, costly, time-consuming phase III studies comparing modifications or combinations of available therapies. As a result, in 1993, the NIH solicited applications for small, innovative consortia to work with the National Cancer Institute (NCI) under the auspices of a research project cooperative agreement (UO1). This Request for Application (RFA) was designed to stimulate advances in the treatment of patients with high-grade astrocytomas by joining into one consortium those institutions with large numbers of brain tumor patients, multidisciplinary expertise in the care of these patients, a record of excellence in clinical research, and access to exciting new therapeutic approaches for these patients. It was hoped that these CNS consortia would conduct studies of toxicity, dose finding, and safety (phase I and phase II) of novel therapeutic approaches for adults with high-grade astrocytomas.

The application process for this grant required the Consortium headquarters and each institution that wished to participate in the Consortium to submit separate applications to the NCI. Each of these applications underwent peer review and was assigned a priority score. The NCI used these priority scores to determine which consortia would be funded and which institutions had priority scores that were high enough to qualify for funding.

In 1994, three CNS Consortia were funded for four years. They were headquartered at the University of California at San Francisco, the M.D. Anderson Cancer
The primary long-term objective of the NABTT CNS Consortium is to improve the therapeutic outcome for adults with primary brain tumors by fostering phase I and phase II clinical evaluations of promising new agents, biologic approaches, routes of administration, and trial design. The secondary objective of the Consortium is to share clinical and laboratory data and human brain tumor specimens in order to conduct research pertaining to the basic biology of primary brain tumors and the neuro-pharmacology of new therapies for primary brain tumors, as well as to improve the care and quality of life of adults with primary brain tumors.

The NABTT CNS Consortium was originally funded in 1994 with six participating institutions: Brown University (Providence, RI), Columbia University (New York, NY), Henry Ford Hospital (Detroit, Mich), The Johns Hopkins University (Baltimore, Md), Massachusetts General Hospital (Boston, Mass), and Northwestern University (Chicago, Ill). Each of these institutions had an experienced multidisciplinary neuro-oncology team, a large number of adults with primary brain tumors, exceptional institutional resources, and an eagerness to try new therapeutic approaches. In addition, these centers had an abundance of high-quality, peer-reviewed, clinically relevant neuro-oncology research underway as evidenced by numerous NIH funded grants (P-20 Brain Tumor Center Feasibility Grants, National Cooperative Drug Discovery Groups, Neuro-Oncology Training Grants, R01s) and extensive publications in this field. In the 1998 grant renewal, the following institutions were awarded grants by the peer review process: Emory University (Atlanta, Ga), Henry Ford Hospital (Detroit, Mich), The Johns Hopkins University (Baltimore, Md), Massachusetts General Hospital (Boston, Mass), Moffitt Cancer Center (Tampa, Fla), the University of Alabama (Birmingham, Ala), the University of Pennsylvania (Philadelphia, Pa), the University of Texas Health Science Center (San Antonio, Tex), and Wake Forest University (Winston-Salem, NC) (Fig 1).

As the basic organizational structure of NABTT served the Consortium well during its first four years, it has been preserved with few changes. NABTT's organizational structure is shown in Figs 2 and 3. The major additions to the Consortium's structure since 1993 are (1) the Correlative Biology Center, which has been added to the Consortium headquarters to meet the specifications of the new RFA, (2) the designating Pharmacology Laboratories, which take advantage of the wide range of pharmacologic expertise within NABTT rather than designating only one location for pharmacologic studies, (3) the formal relationships with pharmaceutical companies, which did not exist when the grant was initially funded, and (4) the Conflict of Interest Committee, which has been added to the Consortium headquarters to cope with issues relating to NABTT investigators and the Consortium studies of products coming from pharmaceutical companies.
The carefully considered and well-defined organizational structure of NABTT has been instrumental in its success. NABTT has a formal constitution signed by each institution's principal investigator that specifies the rules by which these institutions will collaborate. The NABTT CNS Consortium is comprised of the Consortium headquarters and the nine participating institutions. The Consortium headquarters contains a Central Operations Office, a Scientific Research Center, a Pharmacology Center, a Correlative Biology Center, and a Biostatistics Center. Seven outstanding clinician investigators and scientists serve on NABTT's Advisory/External Review Board to help shape and steer the Consortium. In addition, there is a formal affiliation with the Eastern Cooperative Oncology Group (ECOG), with the chairman of ECOG's Brain Tumor Committee sitting as a nonvoting member of NABTT's Executive Committee to facilitate transfer of promising NABTT phase II studies to the phase III setting.

The Operations Office and Biostatistical Center work closely to ensure that the Consortium functions smoothly and efficiently. Their major efforts are to foster (1) Consortium interactions (meetings, telephone conferences, internet communications), (2) clinical research within NABTT (translate concepts into protocols and ensure that these produce accurate and complete data that is published in a timely fashion), (3) Interactions with NABTT's 11 standing Scientific Committees, Advisory/External Review Board, the NCI, ECOG, and pharmaceutical companies, (4) protocol development and submission, (4) prioritization of studies, (5) patient registration, (6) data collection and management, (7) study monitoring and analysis, (8) publication, (9) correlative studies between laboratory and clinical investigations, (10) central review and quality control, (11) audits, and (12) investigational drug management and reporting. The Scientific Research Center is responsible for the generation of new clinical research studies to be undertaken from the Consortium. As such, it draws on and consolidates the resources available throughout the Consortium. The Pharmacology Center is responsible for the design, conduct, and analysis of all pharmacologic measurements relating to research conducted by this Consortium. The Correlative Biology Center has funding to disperse each year to worthy projects that utilize the Consortium’s data and expertise to learn more about the basic biology of these malignancies.

Since 1993, a total of 31 clinical protocols have been written for the Consortium: 7 for patients with newly diagnosed high-grade astrocytomas, 19 for patients with recurrent high-grade astrocytomas, 3 for patients with non-astrocytomas, and 2 nontherapeutic protocols. A total of 178 patients have been entered on NABTT therapeutic protocols, and 669 have been registered for NABTT nontherapeutic protocols.

Considerable attention has been focused on issues of quality assurance within the Consortium. All fully participating NABTT institutions have undergone an external review of their NABTT studies. The quality of NABTT’s research data is excellent. For example, recent audits of NABTT studies of 9-aminocamptothecin have demonstrated that over 94% of the 61 patients accrued were eligible for the studies and 97% were evaluable. Furthermore, 87% of all data was available to the Central Operations Office in one month or less. Central reviews of pathology and radiologic studies have been performed for all patients who were believed to be responders to protocol therapy. Central biostatistical input has been included in all protocols, and reports and the pharmacologic studies have been successful and informative.

Accrual to therapeutic protocols has also been impressive. Although it was originally anticipated that most of NABTT's protocols would be phase II studies, the pharmacologic observations described below have transformed most of these into phase I studies. These are slower and more labor intensive. A small cohort of patients is accrued, and then a pause of at least one month follows to accumulate toxicity information before reopening the protocol at a higher dose. As a result, the protocol becomes unavailable for long stretches of time. However, accrual has been rapid when these protocols are open. For example, in the dose-escalation carbustine (BCNU) wafer protocol that NABTT is conducting, available patient slots are routinely filled or reserved within days of opening, and patients are oftend in anticipation of the protocol's reopening. NABTT is now running several protocols at the same time to ensure that protocols are usually available to eligible patients who wish to participate in clinical trials. The NABTT CNS Consortium has impressive potential to accrue patients with primary brain tumors. In 1996, our member institutions saw a total of 2,116 patients with primary brain tumors, which is a sizable percentage of the national total. Over 1,000 of these were patients with high-grade gliomas, and 472 were placed on an NABTT, cooperative group, pharmaceutical, or institutional trial.

NABTT Accomplishments

Although the NABTT CNS Consortium is a relatively young cooperative group, its early years have been productive. Its primary strengths lie in its outstanding institutions, investigators, and organizational structure, its access to large numbers of patients with primary brain tumors, and its firm commitment to multidisciplinary research. Furthermore, it is committed to novel systemic and local treatment approaches, unique trial designs, thoughtful pharmacologic correlations, and meticulous clinical research. These features of the Consortium have made NABTT an ideal setting to test new agents and to make important observations regarding the therapy of patients with primary brain tumors. Some of NABTT's early findings and novel approaches are outlined below.

1. Important Drug Interactions Between Anticonvulsant and Antineoplastic Agents

NABTT investigators were the first to note that anticonvulsants have a major effect on the pharmacology of several chemotherapeutic drugs. NABTT's initial clinical trial used paclitaxel at a dose of 140 mg/m² as a 96-hour continuous intravenous infusion. This was the maximum tolerated dose (MTD) in phase I studies and resulted in considerable myelosuppression and alopecia in patients with breast cancer and lymphomas. However, in the NABTT study that treated patients with newly diagnosed glioblastoma multiforme, this dose was not associated with significant toxicity, and plasma paclitaxel levels were approximately one fifth of those seen in patients with other solid tumors. As all of the early patients on this study were also taking phenytoin, a P450 activator, it was hypothesized that this increased the degradation of paclitaxel. For this reason, NABTT's phase II trial was converted to a dose-escalation study, and the MTD was noted to be 200 mg/m² in patients receiving enzyme inducing anticonvulsant drugs.8

The second agent studied by the NABTT was of 9-aminocamptothecin. As there are no known hepatic metabolites of this drug, the concomitant use of hepatic enzyme-inducing anticonvulsants was not expected to affect the pharmacology of this agent. However, once again at the MTD, which was determined in patients with systemic neoplasms, no toxicities were observed at a dose of 850 µg/m² per day for three days. This trial was also converted to a dose-escalation study. The dose-escalation portion of these trials has recently been completed, and the MTD for newly diagnosed patients on enzyme-inducing anticonvulsants is 1776 µg/m² per day.9 These studies suggest that using an MTD obtained in patients not on anticonvulsants could result in significant underdosing in patients with brain tumors, and that careful pharmacologic studies are required in new drug development in this patient population.

2. Paclitaxel and 9-Aminocamptothecin in Patients With Glioblastoma

Several unique trial designs are being tested within the NABTT CNS Consortium. One of these utilizes pre-irradiation chemotherapy to screen new agents (paclitaxel, 9-aminocamptothecin, and CI-980) for activity in patients with newly diagnosed glioblastoma multiforme who have measurable residual disease after surgery. These previously untreated tumors are the most likely to respond, and their responses are the easiest to assess radiologically. Thus, new agents can be screened for efficacy with relatively few patients using a two-stage design. This approach was used to determine that, even at the proper MTD, systemically...
administered paclitaxel and 9-aminoacoptethcin have minimal efficacy in patients with glioblastoma multiforme.\textsuperscript{7,10} Studies with CI-980 are currently underway. NABTT is also studying the potential risks and benefits of this trial design. To date, the use of preirradiation paclitaxel does not appear to have adversely affected survival.

3. Novel Dose Escalation Strategy for Brain Tumor Trials

A second novel trial design being used by NABTT involves a modified continuous reassessment method for phase I dose escalation. This was implemented when it became clear that many NABTT trials would require dose escalation because of drug interactions associated with anticonvulsant medications. In NABTT studies of 9-aminoacoptothcin, the MTD was reached using far fewer patients using the continual reassessment method than if conventional phase I dose-escalation techniques had been employed.\textsuperscript{11,12} To our knowledge, this is the first time this dose-escalation method has been employed in a cooperative group setting.

4. Multisite Phase I Trials in Brain Tumors

Phase I studies are typically restricted to one institution because of the need for real time reporting of patient toxicities. Furthermore, patients with central nervous system involvement are usually excluded from these trials. For these reasons, it was expected that NABTT would conduct primarily phase II studies. However, as a result of the unexpected drug interactions noted with paclitaxel and 9-aminoacoptothcin and the availability of novel agents from pharmaceutical companies, as many as two thirds of NABTT studies have been multisite phase I studies. Furthermore, additional data collection to meet pharmaceutical company and FDA requirements are required for two of these dose-escalation studies (RSR-13 and BCNU polymers). NABTT's Central Operations Office has demonstrated its ability to conduct these studies and collect and process the appropriate data simultaneously at all member institutions.\textsuperscript{13,14} The success of these undertakings is evident as an increasing number of pharmaceutical companies are requesting NABTT to evaluate their novel approaches to the treatment of primary brain tumors.

5. New Protocol "Classes" for Brain Tumor Trials

NABTT is also experimenting with a new classification of protocols for patients with primary brain tumors to speed protocol development and to standardize eligibility and response criteria. This should allow them to crudely compare treatments. Each protocol class has a different objective, set of eligibility criteria, and protocol design (Table). Class A protocols are designed to screen new agents for efficacy in the preirradiation setting with response as the endpoint. Class B are conventional protocols that assess response in patients with recurrent disease. Class C are conventional protocols that assess response in patients with recurrent disease. Class D protocols are designed for patients with local recurrences who are eligible for regional therapies, such as direct local injections of chemotherapy or radiation or gene therapy trials. Class E protocols are for patients with histologies other than high-grade astrocytomas, and Class F protocols are for nontherapeutic protocols.

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<th>Clinical Protocol Classifications of NABTT CNS Consortium</th>
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The standardization of entry criteria is already paying dividends with the creation of the NABTT Glioblastoma Database.\textsuperscript{15} This database currently contains over 104 adults with newly diagnosed glioblastoma multiforme who were treated with preirradiation paclitaxel, 9-aminoacoptothcin, or CI-980 chemotherapy or RSR-13 with radiation. This cohort provides 75 patient years of survival experience and yields a reasonably precise historical estimate of the failure (death) rate in this NABTT population. This can be used to estimate the efficacy of novel cytotoxic and noncytotoxic approaches to GBM in relatively small phase II studies. Although decision rules will depend on therapy-related toxicities, in general, a > or = 25% reduction in the failure rate compared to this historical series would be considered strong evidence in favor of proceeding to a formal comparative trial, while a <25% reduction would not be considered reliable or promising enough to initiate a phase III trial.

6. New Sources of Therapeutic Agents

Patient accrual during the early months of the NABTT CNS Consortium was slow for several reasons. First, the planned phase II studies became phase I studies. This required that accrual be limited to cohorts at each dose level, followed by a mandatory pause while toxicity data at that dose matured. Thus, a larger number of active protocols were needed to ensure steady and higher accrual. Furthermore, NABTT was relying entirely on the NCI to provide new agents, and sometimes this process took longer than anticipated. With the support of Cancer Therapy Evaluation Program (CTEP)/NCI, we sponsored the first NABTT Industrial Meeting in the spring of 1996 in conjunction with our biannual NABTT Meeting. We had senior management and scientists from six pharmaceutical companies making presentations to our investigators. Two of those companies (Guilford Pharmaceuticals and Allos Therapeutics) have subsequently entered into formal agreements with NABTT, and their products are currently in trials within the NABTT CNS Consortium. These protocols were written by NABTT investigators in cooperation with the pharmaceutical company. They underwent review within NABTT and were then sent to the NCI/CTEP for formal review and approval before they were activated.

Guilford Pharmaceuticals, Inc, is providing escalating doses of BCNU in their controlled-release polymeric implants. Laboratory data suggest that wafers containing higher doses of BCNU than in the currently FDA-approved Gliadel polymer implants (3.9% BCNU) might be more effective. NABTT has conducted dose escalations in patients eligible for the commercially available 3.9% polymer in conjunction with an independent Safety Monitoring Committee. To date, the BCNU loading in the wafers has been studied at 6.5%, 10%, and 14.5%. Patients have recently been accrued to 20% BCNU wafers. The total amount of BCNU delivered regionally to the brain is 73 mg in the 3.9% polymer and 320 mg in the 20% formulation.\textsuperscript{14}

Allos Therapeutics, Inc, is providing RSR-13, an allosteric modifier of hemoglobin that shifts the oxygen dissociation curve promoting oxygen release to tissues. This is currently being evaluated using short-term infusions to relieve tissue hypoxia in myocardial infarction and strokes. However, it may be possible to dramatically improve oxygenation within glioblastomas and thereby improve the results of radiotherapy and chemotherapy. Preclinical work in this regard is encouraging. NABTT is now conducting the first and only study of this compound in patients with newly diagnosed glioblastoma multiforme in conjunction with radiation therapy. Dosing was
initially begun every other day during radiation therapy and then escalated to every day. The toxicity of these therapies is still under evaluation.

A second NABTT Industrial Meeting occurred in June of 1997 in conjunction with the regularly scheduled biannual NABTT Meeting in Detroit. Five pharmaceutical companies participated sharing a wide range of therapeutic compounds suitable for clinical trials in primary brain tumors. Negotiations are well along, with several of these companies to begin trials of their products within NABTT. Isis Pharmaceuticals, Inc, has asked NABTT to test an antisense oligonucleotide against protein kinase C alpha in patients with recurrent high-grade astrocytoma, and Schering-Plough Corp is working with the Consortium to develop an ad-p53 gene therapy trial. These efforts involve pharmaceutical companies have provided new opportunities for NABTT to test a wide variety of novel compounds. They have also provided innovative surgery- and radiotherapy-based protocols that have helped to solidify support for NABTT within our member institutions. However, it is important to note that the primary source of new agents for NABTT clinical trials remains the NCI.

The NABTT CNS Consortium is funded by the NIH to conduct innovative clinical trials. Thus, for these trials, the pharmaceutical companies are only assessed costs to NABTT headquarters and member institutions that are above and beyond typical NABTT protocols. These funds are paid to the NABTT Operations Office and are channeled into program income to this NIH grant through arrangements that have been made with the NCI. These funds are allocated by the Executive Committee based on each institution's accrual to NABTT's therapeutic protocols and the need for additional funding. Thus, there is no preferential reimbursement to a participating institution for placing patients on a trial that tests an agent from a pharmaceutical company over one that originated from the NCI. Funding also goes to the NABTT headquarters to cover additional costs at the central offices.

Conclusions

When NABTT investigators responded to the original RFA in 1993, they believed that this Consortium could provide an exciting framework to advance clinical brain tumor research. Our growth and experience over the past four years make us even more optimistic about NABTT's potential to contribute. Currently, NABTT has clinical protocols chaired by medical oncologists, neurologists, radiation oncologists, and neurosurgeons. These are evaluating the toxicity and efficacy of local and systemic therapies including cytotoxic and noncytotoxic drugs, an antisense oligonucleotide, a radiation enhancer, and gene therapies. In addition, the Consortium has large numbers of patients with brain tumors, an increasing number of novel therapeutic approaches from the NCI and from the pharmaceutical industry, and a basic science effort to learn more about the biology of these tumors. All of these focused multidisciplinary efforts are directed toward NABTT's primary goal, which is to provide significant scientific advances in the treatment of patients with primary brain tumors in the near future.

Drs Brem and Piantadosi are consultants to Guilford Pharmaceuticals, Inc. Dr Brem is also a consultant to Rhone-Poulenc Rorer, and Guilford Pharmaceuticals, Inc., has provided a gift for research in Dr Brem's laboratory. The Johns Hopkins University and Dr Brem own Guilford stock, the sale of which is subject to certain restrictions under University policy. The terms of this arrangement are being managed by the University in accordance with its conflict of interest policies.

References
