Importance of dose intensity in neuro-oncology clinical trials: Summary Report of the Sixth Annual Meeting of the Blood-Brain Barrier Disruption Consortium[1]

Nancy D. Doolittle, Clarke P. Anderson, W. Archie Bleyer, J. Gregory Cairncross, Timothy Cloughesy, Stephen L. Eck, Paul Guastadisegni, Walter A. Hall, Leslie L. Muldoon, Sunil J. Patel, David Peereboom, Tali Siegal, and Edward A. Neuwelt,[2] for the Blood-Brain Barrier Disruption Consortium

Department of Neurology, Oregon Health Sciences University, Portland, OR 97201-3098 (N.D.D., P.G., L.L.M., E.A.N.); Childrens Center for Cancer and Blood Diseases, Childrens Hospital of Los Angeles, Los Angeles, CA 90027 (C.P.A.); Department of Pediatrics, M.D. Anderson Cancer Center, Houston, TX 99030 (W.A.B.); London Regional Cancer Center, London, Ontario, Canada N6A 4L6 (J.G.C.); Neuro-Oncology Program, University of California, Reed Neurological Research Center, Los Angeles, CA 90095-1769 (T.C.); University of Pennsylvania Medical Center, Philadelphia, PA 19104-6160 (S.L.E.); Department of Neurosurgery, University of Minnesota, Minneapolis, MN 55455 (W.A.H.); Department of Neurosurgery, Medical University of South Carolina, Charleston, SC 29425-2272 (S.J.P.); Hematology and Medical Oncology, Cleveland Clinic Foundation, Cleveland, OH 44195 (D.P.); Neuro-Oncology Center, Hadassah Hebrew University Hospital, Jerusalem, Israel 91120 (T.S.)

Therapeutic options for the treatment of malignant brain tumors have been limited, in part, because of the presence of the blood-brain barrier. For this reason, the Sixth Annual Meeting of the Blood-Brain Barrier Disruption Consortium, the focus of which was the "Importance of Dose Intensity in Neuro-Oncology Clinical Trials," was convened in April 2000, at Government Camp, Mount Hood, Oregon. This meeting, which was supported by the National Cancer Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute of Deafness and Other Communication Disorders, brought together clinicians and basic scientists from across the U.S. to discuss the role of dose intensity and enhanced chemotherapy delivery in the treatment of malignant brain tumors and to design multicenter clinical trials. Optimizing chemotherapy delivery to the CNS is crucial, particularly in view of recent progress identifying certain brain tumors as chemosensitive. The discovery that specific constellations of genetic alterations can predict which tumors are chemoresponsive, and can therefore more accurately predict prognosis, has important implications for delivery of intensive, effective chemotherapy regimens with acceptable toxicities. This report summarizes the discussions, future directions, and key questions regarding dose-intensive treatment of primary CNS lymphoma, CNS relapse of systemic non-Hodgkin's lymphoma, anaplastic oligodendroglioma,

Received 22 June 2000, accepted 24 August 2000.

[1]This conference was supported by National Institutes of Health Grant 1R13 CA 86959-01 through the National Cancer Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute of Deafness and Other Communication Disorders.

[2]Address correspondence and reprint requests to Edward A. Neuwelt, Oregon Health Sciences University, Department of Neurology, 3181 S.W. Sam Jackson Park Rd.-L603, Portland, OR 97201-3098.

[3]Abbreviations used are as follows: BBBD, blood-brain barrier disruption; BSO, buthionine sulfoxime; i.a., intra-arterial; MCT, myeloablative chemotherapy; NAC, *N*-acetylcysteine; OSG, Oligodendroglioma Study Group; PCNSL, primary CNS lymphoma; PCV, procarbazine, lomustine and vincristine; STS, sodium thiosulfate.

high-grade glioma, and metastatic cancer of the brain. The promising role of cytoenhancers and chemo-protectants as part of dose-intensive regimens for chemosensitive brain tumors and development of improved gene therapies for malignant gliomas are discussed. *Neuro-Oncology 3, 46–54, 2001 (Posted to Neuro-Oncology [serial online], Doc. 00-039, November 3, 2000. URL <neuro-oncology.mc.duke.edu>)*

Primary CNS lymphoma and anaplastic oligodendroglioma are chemosensitive brain tumors. The design of multicenter clinical trials to evaluate the role of chemotherapy dose intensity in these tumors has renewed importance. Recent advances in molecular characterization can now predict chemoresponsiveness, which when coupled with the steep dose-response curve that is characteristic of many cytotoxic drugs has important implications. Few clinical trials have addressed, in either a prospective or randomized fashion, whether increasing the chemotherapy dose by ≥3-fold (Doroshow, 1999) will translate into improved responses and survival.

In contrast to the definition of dose intensity discussed by Hryniuk and Pater (1987), the April 2000 meeting defined dose intensity more broadly to include treatments using high-dose chemotherapy with or without stem cell support, chemotherapy delivered in conjunction with osmotic opening of the blood-brain barrier, and chemoprotection to minimize chemotherapy toxicity to normal tissue. To maximize patient accrual and to determine whether safety and efficacy profiles of dose-intensive strategies are reproducible, it is critical that trials be held across multiple centers.

Dose Intensity in Neuro-Oncology

Various strategies have been explored in an attempt to improve efficacy and to overcome problems of poor drug delivery and drug resistance in malignant brain tumors. Dose intensity defined as high-dose chemotherapy with autologous stem cell rescue is one such strategy that has been used in adult patients with malignant brain tumors (Abrey et al., 1999; Fine and Antman, 1992). Abrey et al. (1999) reported results for 45 patients (26 patients had malignant glioma) treated with either a carmustine-based, carboplatin-based, or thiotepa regimen in conjunction with autologous stem cell rescue. Prolonged disease-free interval was achieved for individual patients; however, there was substantial mortality.

The effectiveness of dose intensity in pediatric neuro-oncology remains a clouded issue. Whether designated as high-dose chemotherapy, autologous bone marrow rescue, hematopoietic stem cell rescue, or MCT,[3] no absolute data exist that undeniably support the superiority of dose intensity over less aggressive consolidation regimens. Even in respected pediatric brain tumor trials that support MCT (Finlay et al., 1996; Graham et al., 1997; Mason et al., 1998), there is a potential bias toward a more favorable outcome with MCT (for example, MCT groups may have had less prior chemotherapy and more surgery). Randomized trials may be useful to settle this issue, but recent examples that either support (Matthay et al., 1999) or refute (Stadtmauer et al., 2000) the advantages of MCT demonstrate the need to accrue hundreds of patients to achieve statistical power. Despite difficulties with bias and patient numbers, it is clear that carefully designed, randomized trials must be conducted to define the role of MCT in pediatric brain tumor therapy.

Dose intensity alone may be insufficient to treat cancer successfully. It has been reported (Keshelava et al., 1998) that for neuroblastoma, acquired resistance to cytotoxic drugs (ranging from 1 to 719 times higher than clinically achievable levels) progressively increases with the intensity of in vivo therapy delivered. Furthermore, this resistance is probably related to an expansion of tumor cells possessing stable alterations (genetic or epigenetic) that confer this high degree of resistance. To effectively treat children who have developed resistant disease, it may be necessary to use chemoenhancers to restore sensitivity.

Cytoenhancement and Chemoprotection

One way to augment dose intensity in the CNS is to increase the effectiveness of standard doses of chemotherapy. Glutathione is involved in a number of detoxification mechanisms—wherein glutathione levels are decreased by treatment with BSO—that can increase chemotherapy toxicity and efficacy. In cultured human cells, BSO increased the activity of melphalan (L-phenylalanine mustard) (Anderson et al., 1999a), carboplatin, cisplatin (L.L.M., unpublished data, 2000), and other free-radical–producing agents. BSO has been shown to enhance the antineuroblastoma activity of melphalan synergistically, leading to tumor response in pediatric patients with recurrent neuroblastoma (Anderson et al., 1999b). In drug-resistant neuroblastoma cell lines (including *p53/TP53* nonfunctional), the combination of BSO plus melphalan was highly synergistic and optimally effective (>2 to 4 logs of cell kill) when melphalan was escalated to concentrations achievable in the MCT setting (Anderson et al., in press, 2000). It was hypothesized that this combination will most likely be advantageous in patients with highly resistant disease, and a clinical trial of BSO plus melphalan in the setting of MCT is in progress (C.P.A., personal communication, 2000). Based on these data, future use of BSO to potentiate the efficacy of melphalan and carboplatin in brain tumor patients was proposed.

A major complication of chemotherapy is toxicity to normal tissues (for example, ototoxicity and myelosuppression). Stimulating factors are well known for their critical role as protectants in cancer chemotherapeutics. In terms of chemical protection, treatment with low molecular weight sulfur-containing agents that mimic one or many of the multiple activities of glutathione may provide chemoprotection against the unwanted side effects of chemotherapy. The problem is that chemoprotectants may interact with the efficacy of chemotherapy. The protectant must, therefore, be separated from chemotherapy, either in time or space. In vitro, the

thio chemoprotectants are effective against carboplatin and cisplatin if given up to 8 h after chemotherapy. In a rat model of s.c. tumor, STS decreased carboplatin efficacy if given in an aggressive regimen (2 and 6 h after chemotherapy), but did not impact efficacy if given 8 h after chemotherapy, a time interval that is still protective for ototoxicity in a guinea pig model (Muldoon et al., 2000). The blood-brain barrier provides a mechanism to spatially separate the chemoprotectant from chemotherapy by creating 2 compartments. Carboplatin is administered with osmotic BBBD, whereas the chemoprotectant (for example, STS) is administered after blood-brain barrier permeability has returned to baseline, thus excluding the chemoprotectant from brain and intracerebral tumor. Data from a clinical study using the 2-compartment model to provide STS otoprotection against carboplatin-induced high frequency hearing loss demonstrate efficacy. When STS administration was delayed from 2 h to 4 h after BBBD, the rate of ototoxicity was significantly reduced ($P = 0.0006$). With delayed administration of STS, there is potential for chemoprotection against cisplatin ototoxicity in the treatment of non-CNS malignancies.

Recent studies have targeted the protection of bone marrow from chemotherapy toxicity. Intravenous chemoprotectants have been shown to provide little myeloprotection (Gurtoo et al., 1983). A new method was proposed to administer protectants, such as NAC, via the descending aorta to increase delivery to bone marrow. In animal studies, after the infusion of NAC into the descending aorta, the kidney and the liver clear intravascular NAC so effectively that only trace amounts reach the CNS, reducing the possibility of interactions with CNS tumor. This technique provides bone marrow protection (granulocytes and platelets) against carboplatin- and melphalan-induced myelosuppression, even in the presence of BSO enhancement (Neuwelt et al., 2000). It was proposed that after osmotic BBBD, the i.a. catheter would be positioned in the descending aorta for infusion of NAC or other chemoprotectant. As of April 2000, a clinical protocol was under development to test this proposal. The hypothesis is that dose intensity can be achieved through higher CNS chemotherapy doses if unwanted systemic side effects can be reduced or prevented with chemoprotection.

PCNSL

PCNSL is a chemosensitive tumor. Protocols to treat PCNSL, sequencing methotrexate-based chemotherapy followed by whole-brain irradiation, have demonstrated improved survival compared with initial radiotherapy alone (DeAngelis et al., 1992; Glass et al., 1994; Nelson et al., 1992), with 5-year survival rates in 9% to 22% of cases (Abrey et al., 1998; Blay et al., 1998; O'Neill et al., 1999). However, combined modality therapy is associated with high rates of neurocognitive toxicity, particularly dementia and ataxia (Abrey et al., 1998).

In a recent series reporting on 74 patients who had PCNSL, with no prior radiation, and who underwent methotrexate-based i.a. chemotherapy with enhanced delivery (BBBD), the estimated 5-year survival was 42% (McAllister et al., 2000). Eighty-six percent of patients in complete remission after 1 year of BBBD chemotherapy demonstrated no cognitive loss. These 74 patients entered treatment at Oregon Health Sciences University between January 1982 and December 1997. In this series, in an attempt to correlate total dose intensity with clinical outcomes, the total number of i.a. methotrexate infusions was multiplied by the degree of BBBD achieved to derive a cumulative quality of disruption score. Both survival (using proportional hazards) and complete response rate (using logistic analysis) were significantly associated with total dose intensity (D. Kraemer et al., unpublished data, 2000), even after statistical analysis to correct for survival bias.

To evaluate the role of dose intensity in PCNSL, 2 concurrent phase II protocols developed by the BBBD Consortium were opened to patient accrual in May 2000. One protocol assesses the efficacy of i.v. methotrexate-based chemotherapy, and the second protocol evaluates the efficacy of i.a. methotrexate-based chemotherapy in conjunction with enhanced BBBD delivery. Radiation will be withheld until disease progression or recurrence occurs. Outcome measures include overall survival, progression-free survival, disease-free survival, cognitive function, and quality of life. Because no long-term toxicity data of a chemotherapy trial not employing up-front radiation are available for comparison, late treatment-related toxicity, as well as quality of life, will be assessed.

A phase III randomized trial of PCNSL using BBBD chemotherapy has not yet been possible because it is a rare disease and because there are a small number of institutions performing BBBD. Given this situation, a novel clinical trial design will be used. The patient, in consultation with the treating physician, will decide which protocol to enter. If a patient chooses i.v. methotrexate-based chemotherapy, the patient will be treated locally. If i.a. methotrexate-based BBBD chemotherapy is chosen, treatment will be at the nearest regional BBBD center.

Because this is a nonrandomized proposal, the potential exists for selection biases (such as ability to travel) or other imbalances (such as baseline characteristics) between the 2 protocols. Therefore, potential confounding variables will be controlled for within the analyses. One approach to control for these variables is to match patients in the i.a. BBBD protocol with one or more patients in the i.v. protocol. Additional methods will be undertaken in the analysis of the baseline characteristics that differ between the 2 groups. These methods include stratification of patients and use of the Cox proportional hazards regression model for time-to-event outcomes. In spite of the challenge of potential confounding variables, the 2 concurrent protocols approach appears to be the most appropriate step at this time for evaluating the role of dose intensity in attaining a durable response in PCNSL without cognitive loss and in preparing for a conventional phase III

randomized trial once additional centers are prepared to perform BBBD.

CNS Relapse of Systemic Non-Hodgkin's Lymphoma

Metastatic involvement of the CNS is frequently diagnosed in patients with non-Hodgkin's lymphomas (Bollen et al., 1997; Keldsen et al., 1996; Lossos et al., 1999; Wolf et al., 1985). Risk factors for CNS involvement were retrospectively analyzed by univariate and multivariate analysis in 2 large, recent series (Bollen et al., 1997; Keldsen et al., 1996). The cumulative risk of CNS relapse at 4 years was 39% for high-grade, 20% for intermediate-grade, and 7% for low-grade non-Hodgkin's lymphoma (Bollen et al., 1997). CNS relapse occurred a median of 8.5 to 12 months from initial diagnosis (range, 1 month to 8 years). As a rule, CNS relapse is soon followed by systemic relapse in patients achieving a previous systemic response.

Conventional therapy for overt meningeal lymphoma consists of intrathecal or intraventricular chemotherapy (primarily with methotrexate and/or Ara-C [cytarabine]) plus radiation therapy added to the cranial, craniospinal, or symptomatic regions of the CNS. This approach is effective in clearing the cerebrospinal fluid of malignant cells and in obtaining an initial clinical response in approximately 80% of patients. However, it is limited by the short duration of remission due to successive CNS, bone marrow, and systemic relapses (van Besien et al., 1998). Review of the survival data of patients with leptomeningeal lymphomas reveals median survival ranges between 2 to 6 months, and the 1-year survival is 12% to 23% (Siegal, 1998). Death is often related to the concomitant relapse of CNS and systemic disease. Therefore, concurrent CNS and systemic therapy is needed to treat overt active disease as well as sanctuary sites inside of and aside from the CNS.

Although logical and potentially advantageous, this approach has not yet been evaluated systematically in patients with CNS relapse. Recently, a group of 23 patients with CNS relapse were treated with a protocol based on systemic high-dose methotrexate as the initial modality (Lossos et al., 1999). All patients responded (partial response or complete response), and the addition of radiotherapy did not increase the overall rate of complete response. Yet most patients relapsed systemically, and patients with brain parenchymal involvement did worse. It is clear that this approach needs to be combined with more intensive treatment to enhance drug delivery to the brain parenchyma and to eradicate systemic disease.

With the above perspective in mind, a protocol has been developed to treat adult patients with first CNS relapse of systemic non-Hodgkin's lymphoma. In principle, the regimen employs drugs that have shown effectiveness in the treatment of systemic non-Hodgkin's lymphoma and CNS lymphoma. Systemic i.v. high-dose methotrexate is cycled with conventional doses of combination chemotherapy consisting of carboplatin, cyclophosphamide, and etoposide phosphate delivered with measures to enhance drug penetration into the CNS. These measures include osmotic disruption of the blood-brain barrier induced prior to i.a. infusion of carboplatin. Weekly intraventricular Ara-C is added throughout the treatment period. After 4 cycles, patients who attain a CNS and systemic complete response will continue to receive systemic high-dose chemotherapy (1,3-bis[2-chloroethyl]-1-nitrosourea, etoposide, cytosine arabinoside, and melphalan) with peripheral blood stem cell rescue. This regimen combines intensive efforts to treat both the CNS and systemic disease.

Finally, the systemic approach for treatment of CNS relapse offers the greatest advantage to patients with isolated CNS relapse who survive for prolonged periods or may even be cured of their disease (Morra et al., 1993; Siegal et al., 1994; Siegal, 1998). In these patients, the elimination of radiotherapy from their treatment scheme may reduce the rate of delayed neuropsychological deterioration, similar to the experience gained in brain lymphoma (McAllister et al., 2000).

Anaplastic Oligodendroglioma

Oligodendroglioma study group. Oligodendroglioma is a chemosensitive brain tumor. Oligodendrogliomas that are contrast-enhancing and anaplastic usually exhibit dramatic radiographic responses to cytotoxic treatment. Although no clinical or pathologic feature confidently distinguishes a chemosensitive oligodendroglioma from a resistant one, a specific molecular alteration, allelic loss of chromosome 1p, is quickly emerging as an important marker of drug sensitivity and survival in patients with these tumors (Cairncross et al., 1998). In addition, some symptomatic, enlarging low-grade oligodendrogliomas, referred to as aggressive oligodendrogliomas, and some anaplastic mixed oligoastrocytomas, many of which also harbor chromosome 1p loss, are similarly chemosensitive.

Oligodendrogliomas respond to a variety of cytotoxic drugs, principally alkylating agents. The PCV combination is the chemotherapy of choice at present, although the new orally administered DNA methylating agent, temozolomide, holds considerable promise as an anti-oligodendroglioma cytotoxic agent (Chinot et al., 2000). Despite substantial anti-oligodendroglioma activity, however, not all responses to PCV are long lasting. In particular, oligodendrogliomas that recur postradiation are seldom controlled long term by PCV. The median duration of response to PCV in a patient with a recurrent anaplastic oligodendroglioma or oligoastrocytoma is 10 to 24 months.

Given their unusual chemosensitivity, and in light of the steep dose-response curve for many cytotoxic drugs, the OSG hypothesized that induction chemotherapy followed by myeloablative doses of thiotepa, an alkylating agent with excellent CNS penetration, might result in long-term control of previously irradiated recurrent oligodendrogliomas. To test the feasibility of this approach, the OSG designed a multicenter pilot study in which

patients with visible tumors who had major responses to induction PCV or cisplatin plus etoposide received thiotepa 300 mg/m^2 i.v. 3 times a day followed by marrow or stem cell reinfusion (Cairncross et al., 2000). Thirty-eight patients began induction treatment, and 20 (53%) proceeded to the high-dose phase of the trial. Four patients (20%) had fatal toxic complications attributable to thiotepa, and 4 others (20%) had long-term tumor control. The median event-free survival was 17 months. After patients who died from toxicity were excluded, the median time to tumor progression was only 20 months, a disappointing result. At this juncture, the OSG is no longer pursuing studies of dose-intensive chemotherapy for recurrent oligodendrogliomas.

The OSG will continue to explore the role of dose-intensive chemotherapy for patients with newly diagnosed tumors in an upfront multicenter trial of similar design. One might argue that early aggressive treatment is illogical given the poor tumor control and serious toxicity observed in recurrent cases, but in the initial study, serious toxicity was neurologic in nature and could be traced to prior cranial irradiation. The study for newly diagnosed patients utilizes high-dose chemotherapy but delays radiation therapy. Patients receive induction PCV chemotherapy followed by high-dose thiotepa, as described above. Responders to induction PCV, and patients with complete surgical resections whose tumors do not recur during the induction phase, are eligible for the high-dose phase. Those with partially resected lesions that do not respond to induction PCV are ineligible to receive high-dose treatment. Seventy-one patients have entered the study, 11 are currently receiving PCV, and 33 received transplantations. Data on tumor control are not yet available, but to date there have been no toxic deaths.

Currently, the OSG is discussing a second pilot study for newly diagnosed patients in which the induction regimen is temozolomide (not PCV) and the high-dose therapy is either busulfan plus thiotepa or busulfan plus melphalan plus thiotepa.

BBBD Consortium. The BBBD Consortium proposes a study for patients with anaplastic oligodendroglioma in which the induction chemotherapy is temozolomide. In this trial, which was under development as of April 2000, patients receive 3 cycles of temozolomide and then are evaluated radiographically. If patients obtain a complete response, they may continue to receive temozolomide, or they may undergo a dose-intensive regimen with i.a. carboplatin, i.a. cytoxan, and i.v. etoposide phosphate given in conjunction with BBBD. Patients with partial response, stable disease, or progressive disease will advance to a phase I i.a. melphalan, i.a. carboplatin, and i.v. etoposide-phosphate trial given in conjunction with BBBD. The primary goal of this trial is to determine the maximum tolerated dose of melphalan that can be safely administered in conjunction with carboplatin. An additional question that will be addressed is whether NAC, when administered i.a., can reduce granulocytopenia and thrombocytopenia, allowing for dose escalation of melphalan.

High-Grade Glioma

Modern molecular biology is allowing researchers to identify molecular characteristics of various cancer types. Doing so has allowed the pursuit of treatment development with single molecular pathways in mind. We have seen successes with the blocking of the HER2-neu receptor in breast cancer (Cobleigh et al., 1999) and blocking of the Bcr/Abl receptor in chronic myeloid leukemia (Deininger et al., 2000). Additionally, studies using targeted delivery in the treatment of high-grade glioma show promising results. For example, targeted delivery using monoclonal antibodies to deliver local radiation (such as antitenascin antibodies) appears to prolong survival for patients with glioblastoma multiforme (Bigner et al., 1998).

Malignant gliomas have been notoriously difficult to treat with the standard tools of surgery, radiation, and chemotherapy. Intensifying the treatments has, for the most part, been frustrating. Aggressive resections, high-dose radiation, and high-dose chemotherapy with stem cell or bone marrow rescue have not improved survival for patients and are fraught with serious toxicities (Abrey et al., 1999). Yet investigators continue to investigate these approaches based on individual patients who have shown dramatic responses through these intensive therapies.

Our endeavors may be more successful by marrying our clinical observations with molecular characterization. Thirty-five percent of anaplastic astrocytomas respond to temozolomide (Yung et al., 1999), roughly 70% of anaplastic oligodendrogliomas respond to PCV (Paleologos et al., 1999), and 15% of patients with glioblastoma multiforme are alive at 18 months with adjuvant treatment consisting of 1,3-bis(2-chloroethyl)-1-nitrosourea, whereas none are alive at 18 months without adjuvant treatment with 1,3-bis(2-chloroethyl)-1-nitrosourea (DeAngelis et al., 1998; Walker et al., 1980). Molecular characterization should allow us to identify the groups demonstrating homogenous favorable responses. Improved characterization of anaplastic oligodendrogliomas has been achieved by using comparative genomic hybridization, fluorescence in situ hybridizations, or other methods. The coincidental loss of 1p and 19q identifies an oligodendroglioma that is likely to show significant shrinkage with chemotherapy compared with an anaplastic oligodendroglioma without this molecular signature that responds infrequently (Cairncross et al., 1998). Are there markers that predict anaplastic astrocytoma or glioblastoma multiforme responses to chemotherapy? Even though we consider these tumors to have genetic heterogeneity, we are seeing homogenous responses. Molecular characterization of these tumors should provide for improved stratification to answer difficult questions more accurately regarding treatment effects in malignant gliomas including dose intensification.

The BBBD Consortium proposes a study for patients with high-grade glioma analogous to the proposal for treatment of anaplastic oligodendroglioma. After 3 cycles of temozolomide, patients will be evaluated radiographically. If a complete response is obtained, patients may continue treatment with temozolomide or undergo i.a.

carboplatin, i.a. cytoxan, and i.v. etoposide phosphate in conjunction with BBBD. Patients with partial response, stable disease or progressive disease after temozolomide would enter the phase I i.a. melphalan, i.a. carboplatin, and i.v. etoposide phosphate trial, with administration of a chemoprotectant to allow for dose escalation of melphalan.

CNS Metastases

Dose-intensive regional chemotherapy for CNS metastases was discussed with several possible approaches. Results were reported using i.a. carboplatin and i.v. etoposide (without BBBD) for 22 patients with brain metastases from solid tumors (primarily lung or breast cancer) treated at the Ohio State University (H. Newton, unpublished data, 2000). The potential advantage of this approach is delivery of chemotherapy to tumor and brain around tumor in a dose-intensive manner, with simultaneous treatment of systemic disease. All patients had prior whole-brain radiotherapy. Fourteen of 19 evaluable patients had radiographic responses or stable disease, with an overall time to progression of 30 weeks. Toxicity was mainly hematologic with no grades III and IV neurological toxicity. Several patients experienced progression of systemic disease. It was concluded that this regimen was well tolerated with efficacy for some patients especially those for whom systemic disease was controlled. Additionally, Doolittle et al. (2000) summarized data on 13 patients with brain metastases treated between 1994 and 1997 by the BBBD Consortium. All patients achieved stable disease or better.

Based on these data and the encouraging preclinical and clinical data using chemoprotectants, a hypothesis was proposed that patients with CNS metastases who are treated with increased dose intensity and chemoprotectants such as NAC and STS may achieve improved response rates and overall survival, without additional neurotoxicity. A proposal for a phase I trial was discussed in which patients with brain metastases would receive i.a. melphalan, i.a. carboplatin, and i.v. etoposide phosphate before radiation (Cormio et al., 1998; Franciosi et al., 1999) with the addition of i.a. NAC and i.v. STS for those with grade II hematologic toxicity. This dose-finding study would potentially lead to Phase II studies in a variety of tumor types including chemotherapy sensitive tumors, such as small-cell lung cancer, breast cancer, and germ cell malignancies. Several key questions were raised during this discussion: Can whole brain radiotherapy be postponed in certain patients with brain metastases? What is the role of BBBD in patients with brain metastases? Could such an approach be used prophylactically for patients with limited stage small-cell lung cancer who achieve complete response?

Preclinical data using several immunoconjugates in a rat model were reviewed. The doxorubicin-conjugated antibody BR96 (BR96-Dox; Bristol-Myers Squibb, Princeton, N.J.) delivered i.a. with BBBD, increased survival in a rat model of brain metastases from small-cell lung cancer. In addition, BBBD delivery of immunoconjugates appears to be more efficacious when given before radiation rather than concurrent with or after radiotherapy. Other conjugates for which early preclinical data were discussed include Herceptin and rituximab. These encouraging preclinical data will likely lead to clinical trials of i.a. delivery of these immunoconjugates.

Neuropsychological and Quality-of-Life Assessment

Important outcome measures in dose-intensive clinical trials include tumor response, survival, and performance status. Likewise, the patient experience, including cognitive functioning and quality of life, must be primary outcome markers. In a review of brain tumor studies and quality of life, assessment of psychosocial and cognitive functioning was found to be more appropriate than other functional measures such as the Karnofsky score (Giovagnoli et al., 1996). Some of the main issues identified with decreasing quality of life in brain tumor patients have been memory loss, fatigue, and decreased attention/concentration (Lovely, 1998). Due to the potential for neurotoxic effects from brain tumor treatments, cognitive functioning is a critical issue. Detailed neuropsychological assessment of the effects of cancer treatments on the brain has been recommended as an important treatment accompaniment (Ahles et al., 1998).

Cognitive decline and dementia have been unfortunate but prevalent side effects of many brain tumor treatments in the past and present (Abrey et al., 1998). A key question must be asked—"Is the extended survival produced from new therapies meaningful for the patient?" This question can be answered by incorporating a comprehensive assessment of cognitive functioning through standard neuropsychological tests and quality of life through validated and reliable cancer-specific quality of life questionnaires. Clinical trials can longitudinally evaluate the effect of prolonged and intensive treatment effects on quality of life and cognitive functioning, as the trial proceeds and after the trial is completed.

The ability to conduct detailed assessment of cognitive functioning in patients undergoing BBBD has been demonstrated (McAllister et al., 2000). The BBBD consortium has developed a test battery which can be administered in 45-60 min, and captures both cognitive function and quality of life. The information gained from this battery will provide useful information for the health care team in evaluating effectiveness of treatment and side effects, but more importantly, this information will provide a sense of comfort and confidence to patients as they undergo intensive treatment for a potentially disabling and life-threatening illness.

Gene Therapy

Gene-based therapies for malignant gliomas have attracted considerable attention in the last decade. To date, 6 phase I trials have been completed and 3 are

ongoing, enrolling more than 150 patients (Alavi and Eck, in press, 2000). These trials have employed retrovirus, adenovirus, and more recently herpes simplex virus vectors. Most of the trials have been designed to deliver the herpes simplex virus–thymidine kinase gene (*HSVtk*) in combination with systemically administered ganciclovir. Although the entry criteria, study design, and measured endpoints varied considerably among these trials, several common findings emerged. First, all of these trials have shown that gene therapy is a relatively safe procedure given the condition of patients with malignant gliomas (Eck et al., 1996; Izquierdo et al., 1996, 1997; Klatzmann et al.,1998; Ram et al., 1997; Shand et al., 1999; Trask et al., 2000). Second, a few significant clinical responses have occurred with long-term freedom from disease in patients with relapsed high-grade gliomas (Ram et al, 1997; Trask et al, 2000). Although this has yet to be reproduced in significant numbers and in a systematic fashion that would allow comparison to conventional therapies, these anecdotal findings do underscore the potential of this developing treatment modality.

A major problem facing cancer gene therapies is the delivery of the therapeutic agent uniformly throughout the tumor. The data available from the brain tumor clinical trials suggest that distribution of the genetic vector after local injection is limited and is unlikely to reach islands of tumor cells that have migrated away from the central tumor mass. While newer approaches-such as the use of replicating vectors (herpes simplex vectors, for example) (Martuza, 2000) or vectors that produce secreted agents (such as interferon-β) (Eck et al., in press, 2000). may address this issue, vascular delivery remains a physiologically attractive option. Experiments using artificial particles that simulate viral vectors (for example, iron oxide particles), or the vectors themselves, have demonstrated in rodents that this approach is technically feasible. With increased clinical experience using BBBD to deliver chemotherapeutic agents, the two approaches will likely be combined to provide a selective vascular administration of a genetic vector after barrier opening.

Summary

It is expected that rapid strides will continue to be made in discovering genetic signatures in additional brain tumor histologic groups, therefore identifying tumors most responsive to chemotherapy and predicting prognosis. Key questions discussed at the meeting and yet to be answered include the following: Which dose-intensive regimens will show greater efficacy, with the least toxicity, in chemosensitive malignant brain tumors? To what degree will cytoenhancement and chemoprotection permit dose intensification while preserving quality of life? Can preradiation dose-intensive chemotherapy improve clinical outcomes that include quality of life? It is hoped that these important questions will be addressed in the near future by multicenter clinical trials.

Acknowledgments

We gratefully acknowledge the following meeting attendees who participated in and facilitated group discussions: Clarke P. Anderson, W. Archie Bleyer, R. Hunt Bobo, Felix Bokstein, Mark Brunvand, Joseph Bubalo, J. Gregory Cairncross, Kathleen Campbell, Timothy Cloughesy, Jamie Cohen, Maurice Collada, Johnny Delashaw, James Doroshow, Todd Dunaway, Stephen L. Eck, David Fortin, Reinhard Gabathuler, Michael Goodman, Paul Guastadisegni, Mary Kay Gumerlock, Stephen Haines, Walter A. Hall, Jerry Hanson, Jim Henry, Michael Horgan, Thomas Jacobs, Himed Kherbache, Grzegorz Kiwic, Dale Kraemer, Todd Kuether, Michael Miner, Leslie L. Muldoon, Gary Nesbit, Herb Newton, H. Stacy Nicholson, Randy Nixon, Alfred Nuttall, Sunil J. Patel, David Peereboom, Darryl Peterson, Lilian Pubols, Timothy Ryken, Stephen Sagar, Gary Sexton, Tali Siegal, Justine Smith, Glenn Stevens, Lode Swinnen, Pam Trail, John Trusheim, Mike Walker, Clark Watts, Roy Wu, and Byron Young. Finally, we send special thanks to Gail Campagna for organizing the meeting, and to Jennifer Quipotla, Rose Marie Tyson, Cindy Lacy, and Emmy Tyson for key assistance during the meeting.

References

Abrey, L.E., DeAngelis, L.M., and Yahalom, J. (1998) Long-term survival in primary CNS lymphoma. *J. Clin. Oncol.* **16**, 859-863.

Abrey, L.E., Rosenblum, M.K., Papadopoulos, E., Childs, B.H., and Finlay, J.L. (1999) Highdose chemotherapy with autologous stem cell rescue in adults with malignant primary brain tumors. *J. Neurooncol.* **44**, 147-153.

Ahles, T.A., Silberfarb, P.M., Herndon, J., II, Maurer, L.H., Kornblith, A.B., Aisner, J., Perry, M.C., Eaton, W.L., Zacharski, L.L., Green, M.R., and Holland, J.C. (1998) Psychologic and neuropsychologic functioning of patients with limited small-cell lung cancer treated with chemotherapy and radiation therapy with or without warfarin: A study by the cancer and leukemia group B. *J. Clin. Oncol.* **16**, 1954-1960.

Alavi, J.B., and Eck, S.L. (2000) Gene therapy for malignant gliomas. *Expert Opin. Biol. Ther*. In press.

Anderson, C.P., Tsai, J.M., Meek, W.E., Liu, R.M., Tang, Y., Forman, H.J., and Reynolds, C.P. (1999a) Depletion of glutathione by buthionine sulfoxine is cytotoxic for human neuroblastoma cell lines via apoptosis. *Exp. Cell Res.* **246**, 183-192.

Anderson, C.P., Seeger, R.C., Matthay, K.K., Neglia, J.P., Bailey, H.H., Meek, W., and Reynolds, C.P. (1999b) Buthionine sulfoximine (BSO) and melphalan (L-PAM) are active against recurrent neuroblastoma. *Med. Pediatr. Oncol.* **33**, 158. (Abstract)

Anderson, C.P., Keshelava, N., Meek, W.H., Satake, N., Reynolds, C.P. (2000) Buthionine sulfoximine (BSO) synergises the action of melphalan (L-PAM) for neuroblastoma cell lines established after disease progression in intensively treated patients. *Med. Pediatr. Onco.* In press.

Bigner, D.D., Brown, M.T., Friedman, A.H., Coleman, R.E., Akabani, G., Fried-

man, H.S., Thorstad, W.L., McLendon, R.E., Bigner, S.H., Zhao, X.G., Pegram, C.N., Wikstrand, C.J., Herndon, J.E., Vick, N.A., Paleologos, N., Cokgor, I., Provenzale, J.M., and Zalutsky, M.R. (1998) Iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with recurrent malignant gliomas: Phase I trial results. *J. Clin. Oncol.* **16**, 2202-2212.

Blay, J.-Y., Conroy, T., Chevreau, C., Thyss, A., Quesnel, N., Eghbali, H., Bouabdallah, R., Coiffier, B., Wagner, J.P., Le Mevel, A., Dramais-Marcel, D., Baumelou, E., Chauvin, F., and Biron, P. (1998) High-dose methotrexate for the treatment of primary cerebral lymphomas: Analysis of survival and late neurologic toxicity in a retrospective series. *J. Clin. Oncol*. **16**, 864-871.

Bollen, E.L., Brouwer, R.E., Hamers, S., Hermans, J., Kluin, M., Sankatsing, S.U., A-Tjak, R.V., Charvat, M.V., and Kluin-Nelemans, J.C. (1997) Central nervous system relapse in non-Hodgkin lymphoma: A single-center study of 532 patients. *Arch. Neurol.* **54**, 854-859.

Cairncross, J.G., Ueki, K., Zlatescu, M.C., Lisle, D.K., Finkelstein, D.M., Hammond, R.R., Silver, J.S., Stark, P.C., MacDonald, D.R., Ino, Y., Ramsay, D.A., and Louis, D.N. (1998) Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J. Natl. Cancer Inst.* **90**, 1473-1479.

Cairncross, G., Swinnen, L., Bayer, R., Rosenfeld, S., Salzman, D., Paleologos, N., Kaminer, L., Forsyth, P., Stewart, D., Peterson, K., Hu, W., Macdonald, D., Ramsay, D., and Smith, A., for the Oligodendroglioma Study Group (2000) Myeloablative chemotherapy for recurrent aggressive oligodendroglioma *Neuro-Oncology* [serial online], **Doc. 99-54**, March 22, 2000. URL http://neuro-oncology.mc.duke.edu. *Neuro-Oncology* **2**, 114-119.

Chinot, O.L., Jr., Honore, S., Barrie, M.F., Jr., Dufour, H., Braguer, D., and Grisoli, F. (2000) Temodal (Temozolomide, TMZ) in second line treatment after PCV in oligodendroglioma tumors. *Pro.* Am. Soc. Clin. Oncol. **19**, 159. (Abstract)

Cobleigh, M.A., Vogel, C.L., Tripathy, D., Robert, N.J., Scholl, S., Fehrenbacher, L., Wolter, J.M., Paton, V., Shak, S., Lieberman, G., and Slamon D.J. (1999) Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J. Clin. Oncol.* **17**, 2639-2648.

Cormio, G., Gabriele, A., Maneo, A., Zanetta, G., Bonazzi, C., and Landoni, F. (1998) Complete remission of brain metastases from ovarian carcinoma with carboplatin. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **78**, 91-93.

DeAngelis, L.M., Yahalom, J., Thaler, H.T., and Kher, U. (1992) Combined modality therapy for primary CNS lymphoma. *J. Clin. Oncol.* **10**, 635-643.

DeAngelis, L.M., Burger, P.C., Green, S.B., and Cairncross, G.J. (1998) Malignant glioma: Who benefits from adjuvant chemotherapy? *Ann. Neurol.* **44**, 691-695.

Deininger, M.W., Vieira, S., Mendiola, R., Schultheis, B., Goldman, J.M., and Melo, J.V. (2000) BCR-ABL tyrosine kinase activity regulates the expression of multiple genes implicated in the pathogenesis of chronic myeloid leukemia. *Cancer Res.* **60**, 2049-2055.

Doolittle, N.D., Miner, M.E., Hall, W.A., Siegal, T., Hanson, E.J., Osztie, E., McAllister, L.D., Bubalo, J.S., Kraemer, D.F., Fortin, D., Nixon, R., Muldoon, L.L., and Neuwelt, E.A. (2000) Safety and efficacy of a multicenter study using intraarterial chemotherapy in conjunction with osmotic opening of the blood-brain barrier for the treatment of patients with maligant brain tumors. *Cancer* **88**, 637-647.

Doroshow, J.H. (1999) Pharmacological basis for high-dose chemotherapy. In: Thomas, E.D., Blume, K.G., and Forman, S.J. (Eds.), *Hematopoietic Cell Transplantation.* Second edition. Malden, Mass.: Blackwell Science. pp. 103-122.

Eck, S.L., Alavi, J.B., Alavi, A., Davis, A., Hackney, D., Judy K., Mollman, J., Phillips, P.C., Wheeldon, E.B., and Wilson, J.M. (1996) Treatment of advanced CNS malignancies with the recombinant adenovirus H5.010RSVTK: A phase I trial. *Hum. Gene Ther.* **7**, 1465-1482.

Eck, S.L., Alavi, J.B., Judy, K., Phillips, P., Alavi, A., Hackney, D., Cross, P., Hughes, J., Gao, G., Wilson, J.M. (2000) Treatment of recurrent or progressive malignant glioma with a recombinant adenovirus expressing human interferon-beta (H5.010CMV*hIFN*-β): A phase I trial. *Hum. Gene Ther.* In press.

Fine, H.A., and Antman, K.H. (1992) High-dose chemotherapy with autologous bone marrow transplantation in the treatment of high grade astrocytomas in adults: Therapeutic rationale and clinical experience. *Bone Marrow Transplant.* **10**, 315-321.

Finlay, J.L., Goldman, S., Wong, M.C., Cairo, M., Garvin, J., August, C., Cohen, B.H., Stanley P., Zimmerman, R.A., Bostrom, B., Geyer, J.R., Harris, R.E., Sanders, J., Yates, A.J., Boyett, J.M., and Packer, R.J. (1996) Pilot study of high-dose thiotepa and etoposide phosphate with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. *J. Clin. Oncol.* **14**, 2495-2503.

Franciosi, V., Cocconi, G., Michiara, M., Di Costanzo, F., Fosser, V., Tonato, M., Carlini, P., Boni, C., and Di Sarra, S. (1999) Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: A prospective study. *Cancer* **85**, 1599-1605.

Giovagnoli, A.R., Tamburini, M., and Bioardi, A. (1996) Quality of life in brain tumor patients. *J. Neurooncol.* **30**, 71-80.

Glass, J., Gruber, M.L., Cher, L., and Hochberg, F.H. (1994) Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: Long-term outcome. *J. Neurosurg.* **81**, 188-195.

Graham, M.L., Herndon, J.E., II, Casey, J.R., Chaffee, S., Ciocci, G.H., Krischer, J.P., Kurtzberg, J., Laughlin, M.J., Longee, D.C., Olson, J.F., Paleologos, N., Pennington, C.N., and Friedman, H.S. (1997) High-dose chemotherapy with autologous stem-cell rescue in patients with recurrent high-risk pediatric brain tumors. *J. Clin. Oncol.* **15**, 1814-1823.

Gurtoo, H.L., Marinello, A.J., Berringan, M.J., Bansal, S.K., Paul, B., Pavelic, Z.P., and Struck, R.F. (1983) Effect of thiols on toxicity and carcinostatic activity of cyclophosphamide. *Semin. Oncol.* **10** (Suppl. 1), 35-45.

Hryniuk, W.M., and Pater, J.L. (1987) Implications of dose intensity for cancer chemotherapy. *Semin. Oncol*. **14** (Suppl. 4), 43-44.

Izquierdo, M., Martin, V., de Felipe, P., Izquierdo, J.M., Perez-Higueras, A., Cortes, M.L., Paz, J.F., Isla, A., and Blazquez, M.G. (1996) Human malignant brain tumor response to herpes simplex thymidine kinase (HSVtk)/ganciclovir gene therapy. *Gene Ther.* **3**, 491-495.

Izquierdo, M., Cortes, M.L., Martin, V., de Felipe, P., Izquierdo, J.M., Perez-Higueras, A., Paz, J.F., Isla, A., and Blazquez, M.G. (1997) Gene therapy in brain tumours: Implications of the size of glioblastoma on its curability. *Acta Neurochir. Suppl. (Wien)* **68**, 111-117.

Keldsen, N., Michalski, W., Bentzen, S.M., Hansen, K.B., and Thorling, K. (1996) Risk factors for central nervous system involvement in non-Hodgkins- lymphoma—a multivariate analysis. *Acta Oncol.* **35**, 703-708.

Keshelava, N., Seeger, R.C., Groshen, S., and Reynolds, C.P. (1998) Drug resistance patterns of human neuroblastoma cell lines derived from patients at different phases of therapy. *Cancer Res.* **58**, 5396-5405.

Klatzmann, D., Valery, C.A., Bensimon, G., Marro, B., Boyer, O., Mokhtari, K., Diquet, B., Salzman, J.L., and Philippon, J. (1998) A Phase I/II study of herpes simplex virus type 1 thymidine kinase "suicide" gene therapy for recurrent glioblastoma. *Hum. Gene Ther.* **20**, 2595-2604.

Lossos, A., Lossos, I.S., Bokstein, F., and Siegal, T. (1999) CNS involvement by systemic non-Hodgkin's lymphomas: Results of treatment with high dose methotrexate-based combination therapy. *Neurology* **52** (Suppl. 2), A281p. (Abstract)

Lovely, M.P. (1998) Quality of life in brain tumor patients. *Semin. Oncol. Nurs.* **14**, 73-80.

Martuza, R.L. (2000) Conditionally replicating herpes vectors for cancer therapy. *J. Clin. Invest.* **105**, 841-846.

Mason, W.P., Grovas, A., Halpern, S., Dunkel, I.J., Garvin, J., Heller, G., Rosenblum, M., Gardner, S., Lyden, D., Sands, S., Puccetti, D., Lindsley, K., Merchant, T.E., O'Malley, B., Bayer, L., Petriccione, M.M., Allen, J., and Finlay, J.L. (1998) Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. *J. Clin. Oncol.* **16**, 210-221.

Matthay, K.K., Villablanca, J.G., Seeger, R.C., Stram, D.O., Harris, R.E., Ramsay, N.K., Swift, P., Shimada, H., Black, C.T., Brodeur, G.M., Gerbing, R.B., and Reynolds, C.P. (1999) Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation and 13-cis-retinoic acid. *N. Engl. J. Med.* **341**, 1165-1173.

McAllister, L.D., Doolittle, N.D., Guastadisegni, P.E., Kraemer, D.F., Lacy, C.A., Crossen, J.R., and Neuwelt, E.A. (2000) Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. *Neurosurgery* **46**, 51-61.

Morra, E., Lazzarino, M., Brusamolino, E., Pagnucco, G., Castagnola, C., Bernasconi, P., Orlandi, E., Corso, A., Santagostino, A., and Bernasconi, C. (1993) The role of systemic high-dose cytarabine in the treatment of central nervous system leukemia: Clinical results in 46 patients. *Cancer* **72**, 439-445.

Muldoon, L.L., Pagel, M.A., Kroll, R.A., Brummett, R.E., Doolittle, N.D., Zuhowski, E.G., Egorin, M.J., and Neuwelt, E.A. (2000) Delayed administration of sodium thiosulfate in animal models reduces platinum ototoxicity without reduction of antitumor activity. *Clin. Cancer Res.* **6**, 309-315.

Nelson, D.F., Martz, K.L., Bonner, H., Nelson, J.S., Newall, J., Kerman, H.D., Thompson, J.W., and Murray, K.J. (1992) Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *Int. J. Radiat. Oncol. Biol. Phys.* **23**, 9-17.

Neuwelt, E.A., Muldoon, L.L., Pagel, M.A., Walker, S., and Hasler, B. (2000) Enhancing CNS chemotherapy cytotoxicity using BSO with systemic thiol chemoprotection against myelosuppression. *Neuro-Oncology* **2**, 283. (Abstract 152)

O'Neill, B.P., Wang, C.H., O'Fallon, J.R., Colgan, J.D., Earle, J.D., Krigel, R.L., Brown, L.D., and McGinnis, W.L. (1999) Primary central nervous system non-Hodgkin's lymphoma (PCNSL): Survival advantages with combined initial therapy? A final report of the North Central Cancer Treament Group (NCCTG) Study 86-72-52. *Int. J. Radiat. Oncol. Biol. Phys.* **43**, 559-563.

Paleologos, N.A., MacDonald, D.R., Vick N.A., and Cairncross, J.G. (1999) Neoadjuvant procarbazine, CCNU, and vincristine for anaplastic and aggressive oligodendroglioma. *Neurology* **53**, 1141-1143.

Ram, Z., Culver, K.W., Oshiro, E.M., Viola, J.J., DeVroom, H.L., Otto, E., Long, Z., Chiang, Y., McGarrity, G.J., Muul, L.M., Katz, D., Blaese, R.M., and Oldfield, E.H. (1997) Therapy of maliganant brain tumors by intratumoral implantation of retroviral vector-producing cells. *Nat. Med.* **3**, 1354-1361.

Shand, N., Weber, F., Mariani, L., Bernstein, M., Gianella-Borradori, A., Long, Z., Sorensen, A.G., and Barbier, N. (1999) A Phase I/II clinical trial of gene therapy for recurrent glioblastoma multiforme by tumor transduction with the herpes simplex thymidine kinase gene followed by ganciclovir. *Hum. Gene Ther.* **10**, 2325-2335.

Siegal, T. (1998) Leptomeningeal metastases: Rationale for systemic chemotherapy or what is the role of intra-CSF-chemotherapy? *J. Neurooncol.* **38**, 151-157.

Siegal, T., Lossos, A., and Pfeffer, M.R. (1994) Leptomeningeal metastases: Analysis of 31 patients with sustained off-therapy response following combined-modality therapy. *Neurology* **44**, 1463-1469.

Stadtmauer, E.A., O'Neill, A., Goldstein, L.J., Crilley, P.A., Mangan, K.F., Ingle, J.N., Brodsky, I., Martino, S., Lazarus, H.M., Erban, J.K., Sickles, C., and Glick, J.H. (2000) Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer: Philadelphia Bone Marrow Transplant Group. *N. Engl. J. Med.* **342**, 1069-1076.

Trask, T.W., Trask, R.P., Aguilat-Cordova, E., Shine, D.H., Wyde, P.R., Goodman, J.C., Hamilton, W.J., Rojas-Martinez, A., Chen, S.H., Woo, S.L.C., and Grossman, R.G. (2000) Phase I study of adenoviral delivery of the HSV-tk gene and ganciclovir administration in patients with recurrent malignant brain tumors. *Mol. Ther.* **1**, 195-203.

van Besien, K., Ha, C.S., Murphy, S., McLaughlin, P., Rodriguez, A., Amin, K., Forman, A., Romaguera, J., Hagemeister, F., Younes, A., Bachier, C., Sarris, A., Sobocinski, K.S., Cox, J.D., and Cabanillas, F. (1998) Risk factors, treatment, and outcome of central nervous sytem recurrence in adults with intermediate-grade and immunoblastic lymphoma. *Blood* **91**, 1178-1184.

Walker, M.D., Green, S.B., Byar, D.P., Alexander, E., Jr., Batzdorf, U., Brooks, W.H., Hunt, W.E., MacCarty, C.S., Mahaley, M.S., Mealey, J., Jr., Owens, G., Ransohoff, J., II, Robertson, J.T., Shapiro, W.R., Smith, K.B., Jr., Wilson, C.B., and Strike, T.A. (1980) Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N. Engl. J. Med.* **303**, 1323-1329.

Wolf, M.M., Olver, I.N., Ding, J.C., Cooper, I.A., Liew, K.H., and Madigan, J.P. (1985) Non-Hodgkin's lymphoma involving the central nervous system. *Aust. N. Z. J. Med.* **15**, 16-21.

Yung, W.K., Prados, M.D., Yaya-Tur, R., Rosenfeld, S.S., Brada, M., Freidman, H.S., Albright, R., Olson, J., Chang, S.M., O'Neill, A.M., Friedman, A.H., Bruner, J., Yue, N., Dugan, M., Zaknoen, S., and Levin, V.A. (1999) Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. *J. Clin. Oncol.* **17**, 2762-2771.