The Cooperative Group Bulletin Board

Targeted Delivery in Primary and Metastatic Brain Tumors: Summary Report of the Seventh Annual Meeting of the Blood-Brain Barrier Disruption Consortium


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Abstract

The November 2000 NIH report of the Brain Tumor Progress Review Group identified delivering and targeting therapeutic agents as a priority in the treatment of malignant brain tumors. For this reason, the seventh annual Blood-Brain Barrier Disruption Consortium meeting, partially funded by an NIH R13 Grant, focused on recent advances in targeted delivery to the central nervous system, clinical trials for primary and metastatic brain tumors using enhanced chemotherapy delivery, and strategies to lessen the toxicities associated with dose intensive treatments, using thios.

Introduction

Despite important advances in molecular characterization, malignant brain tumors remain notoriously difficult to treat with the standard tools of surgery, radiation, and chemotherapy, and outcomes remain discouraging. Recent studies using targeted delivery show promising results. Discussion topics at this meeting, which was held March 8–10, 2001 in Gleneden Beach, Oregon, included advances in immunotherapy and gene therapy in high-grade glioma, the role of chemotherapy in CNS metastases, delivery strategies, such as convection-enhanced delivery of immunotoxins and enhanced chemotherapy administered in conjunction with osmotic opening of the blood-brain barrier, the role of high-dose chemotherapy with autologous stem cell support in malignant brain tumors, and new molecular targets in childhood cancers.

Advances in Malignant Glioma

The Role of Surgery. Despite major technical advances in neurosurgery such as microsurgery and stereotaxy, malignant gliomas remain very difficult to treat, and the benefit of aggressive surgery versus biopsy on survival is unknown (1–3). Arguments in favor of radical resection include cytoreduction and the importance of decreasing tumor burden, relieving increased intracranial pressure, reversing progressive neurological deficits, including potentially eliminating seizures, obtaining large amounts of tissue for study and for therapies, such as vaccination strategies, and the limited efficacy of radiation on long-term survival.

Arguments against radical resection include the infiltrative nature and multifocal or multilobular presentation of most gliomas, and the potential for new neurological deficits from technical difficulties encountered when resecting tumors involving eloquent areas of the brain. Whether or not extensive resection is planned and in view of its limited efficacy, malignant gliomas require adjunctive therapy, and it is clear that this therapy should be multimodal.

Molecular Classification and Neuropathology. In view of the emphasis placed on modern genetic techniques in the detection and diagnosis of gliomas by the Brain Tumor Progress Review Group (4), molecular profiles of 160 snap-frozen oligodendrogliomas and astrocytomas via loss of heterozygosity analysis, multiplex polymerase chain reaction, or Southern blotting for oncogene amplification, single-strand conformational polymorphisms, and/or sequencing to detect gene mutations (mut), and comparative genomic hybridization were performed.

3 The abbreviations used are: CNS, central nervous system; BR96-Dox, BR96-Doxorubicin; OHSU, Oregon Health and Science University; 4-HPR, fenretinide; i.a. intra-arterial.
Loss of heterozygosity for 1p and 19q was seen in 34 of 45 oligodendrogliomas and 6 of 100 astrocytomas; however, comparative genomic hybridization revealed complete loss of 1p (−1p) and 19q (−19q) confined to the 34 of 45 oligodendrogliomas, whereas astrocytomas had either partial loss of 1p (n = 4) and/or 19q (n = 3) or total loss of 1p (n = 2) and/or 19q (n = 3). Forty-three astrocytomas and 9 oligodendrogliomas (classified by light microscopy) revealed loss of heterozygosity for 17p and/or p53 mut (−17p/p53mut). Among these tumors none was found to have −1p/−19q by comparative genomic hybridization concomitant with −17p/p53 mut. These data suggest comparative genomic hybridization provides strict, reproducible criteria for the identification of oligodendroglioma. The number of accumulated genetic defects in the astrocytomas revealed that patients with tumors with two or fewer abnormalities had a significantly longer survival than patients with tumors with three or more genetic defects. The survival of patients whose tumors exhibited the complete −1p/−19q defects was significantly better than patients with other gliomas, including the group with low-grade astrocytomas with partial −1p/−19q defects, regardless of therapeutic intervention. Although previous studies have suggested a therapeutic benefit to the presence of the −1p defect in gliomas (5, 6), these results may also be interpreted as demonstrating the inherent chemosensitivity of true oligodendrogliomas (7, 8). This interpretation is further supported by the insignificant survival effects of the −1p defect in tumors either microscopically diagnosed as glioblastoma or found to have three or more molecular defects. These findings lend support to the concept that molecular profiles will be useful in increasing specificity of categorization and grading gliomas.

**Immunotherapy.** Recent discoveries in adoptive cellular immunotherapy, monoclonal antibodies to deliver local irradiation, cytokine gene therapy, dendritic cell vaccines, and targeted toxins offer much promise (9, 10). Anticancer vaccines stimulate the host immune system to recognize cancer as foreign. Because brain tumors do not elicit an effective immune response, brain tumor vaccines require that a tumor sample be exposed to an agent, usually a cytokine, such as granulocyte-macrophage colony-stimulating factor, that allows antigen-presenting cells to stimulate an immune response. Most preliminary work in brain tumor immunotherapy has been performed in mice and rat animal models (11, 12). The most potent antigen-presenting cells are dendritic cells, which are capable of enticing cytotoxic T cells to attack tumor cells.

Early work in a syngeneic rat flank tumor model of 9L gliosarcoma demonstrated complete tumor remission in treated animals that were vaccinated with irradiated tumor cells and a continuous infusion of granulocyte-macrophage colony-stimulating factor in the flank contralateral to the tumor (11). These animals were also resistant to rechallenge with peripheral or intracerebral gliosarcoma. In animals bearing an intracerebral 9L inoculation, peripheral challenge with irradiated 9L cells and granulocyte-macrophage colony-stimulating factor resulted in remission of the intracranial tumor in 40% of animals. In an intracerebral mouse GL261 glioma model, dendritic cell immunotherapy resulted in a cure rate of 43% (12). All treated animals that were rechallenged with intracranial GL261 glioma survived.

Under the proper conditions, T cells can cross the blood-brain barrier to attack brain tumors. Once dendritic cells have been exposed to tumor antigen in the presence of a cytokine, they can be reintroduced into an area of the body rich in lymph nodes, to generate a proliferative T-cell response to CNS tumor. Another method of stimulating an immune response is to inoculate the patient with nonviable irradiated tumor cells, which serve as a source of tumor antigen, in the presence of a cytokine. This method activates peripheral T cells to migrate into the CNS and attack the brain tumor. Numerous questions remain unanswered (13): (a) How often is vaccination necessary? (b) What is the best cytokine for T-cell activation? and (c) How long should vaccination continue? If the immune system has sufficient memory, a single inoculation should be all that is required. However, most protocols require multiple treatments because of the difficulty achieving a durable response.

**Gene Therapy.** Gene transfer or “gene therapy” offers a potentially promising treatment strategy. Tumor-selective adenoviral vectors have been developed by using an E2F-responsive promoter to express different prodrug-activating genes (14), e.g., vectors expressing the thymidine kinase gene have been successfully used to eradicate gliomas both in vitro and in vivo after ganciclovir treatment with significantly less normal tissue toxicity, compared with standard thymidine kinase-expressing viral vectors.

Similarly, gene transfer has been used to target tumor-associated angiogenesis (15). Both retroviral and adenoviral vectors carrying antiangiogenic genes (e.g., platelet factor 4 and angiostatin) have been constructed. These vectors mediate an antitumor effect in experimental glioma models. Finally, human and mouse endothelial progenitor cells were used as angiogen-

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**Table 1** Molecular profiles of oligodendrogliomas (n = 45) and astrocytomas (n = 100)

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of tumors</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendroglioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1p/−19q CGH*</td>
<td>II</td>
<td>16/23</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>18/22</td>
</tr>
<tr>
<td>−9p CGH</td>
<td>III</td>
<td>2/23</td>
</tr>
<tr>
<td>P53 mutations</td>
<td>III</td>
<td>11/22</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17pLOH/p53 mutations</td>
<td>I &amp; II</td>
<td>7/19</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>16/27</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>20/54</td>
</tr>
<tr>
<td>−10LOH</td>
<td>I &amp; II</td>
<td>0/19</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>14/27</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>31/54</td>
</tr>
<tr>
<td>+7CGH/−10CGH</td>
<td>I &amp; II</td>
<td>0/19</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>7/27</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>32/54</td>
</tr>
<tr>
<td>Oncogenic amplification</td>
<td>I &amp; II</td>
<td>0/19</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>2/27</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>20/54</td>
</tr>
</tbody>
</table>

*CGH, comparative genomic hybridization; LOH, loss of heterozygosity.

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esis-selective, gene-targeting vectors. Endothelial progenitor cells were isolated, expanded, and genetically engineered ex vivo to express the β-galactosidase or thymidine kinase genes using retrovirus-mediated gene transfer. Genetically labeled endothelial progenitor cells were transplanted into wild-type and sublethally irradiated mice and found to migrate and incorporate into the angiogenic vasculature of growing tumors while maintaining transgene expression. Ganciclovir treatment resulted in significant tumor necrosis in animals previously administered thymidine kinase-expressing endothelial progenitor cells. These results demonstrate the potential of using genetically modified endothelial progenitor cells as angiogenesis-selective, gene-targeting vectors and the potential of this approach to mediate nontoxic and systemic antitumor responses.

Metastases to the CNS

Is There a Role for Chemotherapy in CNS Metastases?

Although CNS metastases occur 10-fold more frequently than primary brain tumors, available treatment options are limited (16), and chemotherapy in this setting has been poorly studied. The Brain Tumor Progress Review Group noted a dearth of NIH-funded grants to investigate CNS metastases. Possible roles for chemotherapy include: (a) treatment of established brain metastases, either before or after whole brain radiation therapy; (b) treatment of leptomeningeal metastases; (c) prevention of brain metastases; and (d) prediction of patients who could benefit from whole brain radiation therapy (17).

Most trials of chemotherapy in brain metastases have been small, and almost all enrolled patients after radiation therapy. Two randomized trials of whole brain radiation therapy versus whole brain radiation therapy + chemotherapy showed a higher response rate in the combined arms but equivalent survival attributable to progression of systemic disease (17, 18). Several recent trials have used temozolomide with encouraging results as a single agent or combined with whole brain radiation therapy (19–21). Data were presented at the meeting using i.a. carbo-platin with i.v. etoposide for brain metastases. In 24 evaluable patients, 6 (25%) achieved a complete response with time to progression of 66 weeks; 11 (46%) achieved a partial response and time to progression of 39 weeks. Overall median time to progression for the entire cohort was 30 weeks.

To move forward with chemotherapy for brain metastases, the following approaches were discussed: (a) patients should be stratified/selected according to prognostic classes defined by recursive partitioning analysis to study comparable groups (22); (b) patients with controlled systemic disease should be studied as a group to allow analysis of long-term efficacy; (c) preirradiation chemotherapy trials should be performed to allow better drug penetration and more accurate assessment of response; and (d) Phase III trials must include quality of life and neuropsychometric end points. This need was identified as a priority by the NIH Brain Tumor Progress Review Group. Table 2 lists suggested trial designs for patients with CNS metastases.

### Table 2 Clinical trial designs for chemotherapy in brain metastases

<table>
<thead>
<tr>
<th>Design</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT ± chemotherapy</td>
<td>Whole brain radiation therapy with chemotherapy</td>
</tr>
<tr>
<td>Chemotherapy ± WBRT</td>
<td>Chemotherapy without whole brain radiation therapy</td>
</tr>
<tr>
<td>Chemotherapy versus WBRT</td>
<td>Chemotherapy administered before/after whole brain radiation therapy</td>
</tr>
<tr>
<td>Chemotherapy with WBRT at progression versus WBRT</td>
<td>Chemotherapy administered before/after whole brain radiation therapy with progression</td>
</tr>
<tr>
<td>Chemotherapy: systemic versus regional (i.a.)</td>
<td>Systemic chemotherapy versus regional chemotherapy administered i.a.</td>
</tr>
</tbody>
</table>

**Immuconjugates in Primary and Metastatic Tumors.**

A great deal of research has surrounded the antitumor effects of monoclonal antibody Doxorubicin conjugate BR96-Dox (SGI-15; Seattle Genetics, Inc.; Ref. 23). BR96 binds to an extended form of the Lewis Y antigen on the surface of cells from a variety of carcinomas and on antigen binding, rapidly internalizes into endosomes and lysosomes. The bond between the drug and the monoclonal antibody is acid labile and undergoes hydrolysis within these acidic vesicles, leading to the release of active drug. BR96-Dox has pronounced activities in several preclinical models and leads to cures of established tumors at well-tolerated doses (24). Pharmacokinetic studies show that the activities are attributable to high and sustained intratumoral drug concentrations exceeding those obtainable through systemic doxorubicin administration (25). Several approaches have been devised to produce more potent immunoconjugates, including branched linkers that increase drug multiplicity (26) and peptide linkers that lead to enhanced serum stability and rapid lysosomal drug release. These new generation conjugates exhibit improved in vitro and in vivo activities over BR96-Dox.

Another approach for more effective immunoconjugates includes utilization of drugs that are significantly more potent than doxorubicin. DNA minor groove binding drugs related in structure to CC-1065, one of the prototypes for potent alkylating agents that bind to the minor groove of DNA (27, 28), and antimitotic drugs related in structure to dolastatin 10 were modified to facilitate attachment to BR96. As with BR96-Dox, the conjugates released the drug under slightly acidic conditions. The conjugates and released drugs were 50–1000-fold more potent than BR96-Dox and doxorubicin, respectively. Significant antitumor activities in preclinical in vivo models were obtained at low doses. The effects were immunologically specific, and the conjugates were well tolerated. These immunoconjugates are strong candidates for clinical development.

### Delivery Strategies

**Convection-enhanced Delivery.** Convection-enhanced delivery has also been called fluid convection or bulk flow and establishes a pressure gradient in the tissue that is being treated with the particular agent that is being delivered (29). This technique has been reported to greatly enhance the distribution of both small and large molecules that are delivered to the brain through interstitial infusion (29–31). Increasing the dose of the infused agent rather than the rate or volume of the infusion has been shown to have the greatest influence on the volume of distribution after direct intracerebral infusion (29). The volume of distribution is greatest within intracerebral tissue when the
lowest infusion rate is used compared with higher flow rates (29).

Convection-enhanced delivery is a technique for administering agents into solid tissue through infusion at very low flow rates ranging from 5 to 7 μl/min. This allows specific proteins that may have large molecular weights to be delivered directly into tumors or brain parenchyma infiltrated with tumor cells, thereby bypassing the blood-brain barrier. To date, three specific agents have been administered into malignant brain tumors by convection-enhanced delivery. The volume of infusion ranged from 5 to 180 ml with the duration of infusion lasting 2–7 days. Current infusion protocols deliver 10 ml/day for 4 days for a total volume of 40 ml. Delivery is via one to three standard ventricular catheters placed stereotactically into tumor. Concerns regarding backflow along the outside of the catheters have led to the development of a specialized parent catheter that enables four internal microcatheters to be deployed separately in different directions.

Agents that have been administered in clinical trials are targeted toxins or fusion proteins (32). These are composed of a carrier ligand that recognizes and binds to a cell type-specific antigen expressed on the surface of malignant gliomas that has been fused to a cytotoxic mutated bacterial protein. The first human Phase I trial examined transferrin attached to a mutant diphteria toxin called cross-reacting material 107. The transferrin cross-reacting material 107 conjugate demonstrated significant efficacy in a Phase II trial, and a Phase III trial is being designed. The second Phase I trial evaluated the interleukin-4 truncated Pseudomonas exotoxin (KDEL) fusion protein. A Phase II trial is anticipated. Recently, a third clinical trial was begun using the fusion protein TP-38 composed of transforming growth factor-α and a mutant form of Pseudomonas exotoxin. The increased toxicity of these agents may preclude their transvascular administration after osmotic blood-brain barrier disruption.

**Dose Intensity with Osmotic Blood-Brain Barrier Disruption.** We previously defined dose intensity to include high-dose chemotherapy with or without stem cell support, chemotheraphy delivered in conjunction with osmotic opening of the blood-brain barrier, and chemoprotection to minimize chemotherapy toxicity to normal tissue (33). These approaches offer important advantages for patients with chemoresistant primary brain tumors, such as primary CNS lymphoma. Although the prognosis for patients with primary CNS lymphoma has improved dramatically with combined modality chemotherapy and radiation, >50% of patients relapse, and the risk of neurotoxicity (i.e., dementia) approaches 90% in older patients. Dose intensity offers the possibility of eliminating cranial radiotherapy and the associated treatment-related neurotoxicity.

A recent series of 74 primary CNS lymphoma patients, with no prior radiation, treated with methotrexate-based i.a. chemotherapy with osmotic blood-brain barrier disruption was reported (34). The estimated 5-year survival was 42%, with 86% of patients in complete response after 1 year demonstrating no cognitive loss. Kraemer et al. (35) assessed the association of total dose intensity and survival in the above series. The number of disruptions and the cumulative quality of disruption scores demonstrated longer survival with increased total dose intensity.

At the meeting, Guastadisegni et al. (36) reported the relationship between magnetic resonance imaging changes and cognitive function, in a subset of primary CNS lymphoma patients treated with blood-brain barrier disruption who were in complete response after a year of treatment (34). Neuropsychological testing and imaging performed before, at completion of, and in follow-up was available on 16 patients. Neuropsychological test results and T2 magnetic resonance signal abnormalities improved from baseline to end of treatment. A significant association between neurocognitive data and T2 signal abnormality was found at baseline, but there was no correlation at the end of treatment. By the end of treatment, all patients’ cognitive function improved, and T2 signal abnormalities associated with enhancing tumor decreased or resolved in 15 of 16 patients.

Tyson et al. (37) reported results of 37 patients with relapsed primary CNS lymphoma treated with i.a. carboplatin-based chemotherapy in conjunction with blood-brain barrier disruption. Most patients failed prior frontline methotrexate-based chemotherapy, and 9 patients had prior radiation therapy. Thirty-five patients were evaluable for response. Nine patients had complete remission (25.7%), 4 patients had partial remission (11.4%), and 12 had stable disease (34.3%). The median survival from first i.a. carboplatin with blood-brain barrier disruption treatment was 6.7 months (range: 1.1–91 months). Seven patients survived ≥27 months. In view of the limited therapeutic options available for relapsed primary CNS lymphoma, additional studies of i.a. carboplatin as a treatment alternative are indicated.

Smith et al. (38) reported 16 patients with intraocular B-cell lymphoma treated with intravitreal methotrexate (400 μg/0.1 ml). Patients were monitored by serial examinations, including visual acuity, slit lamp biomicroscopy, and dilated fundoscopy. Twenty-six eyes (100%) were cleared clinically of malignant cells after a maximum of 12 methotrexate injections. The initial site of primary CNS lymphoma malignancy was brain (n = 9) and eye (n = 7). Complications of treatment included cataract, corneal epitheliopathy, and maculopathy. The results suggest that intravitreal chemotherapy using methotrexate can induce a remission of intraocular lymphoma, with acceptable ocular morbidity. Additional studies are needed to determine whether clinical remission improves survival.

**High-dose Chemotherapy with Autologous Stem Cell Support.** High-dose chemotherapy with autologous stem cell support allows very high doses of chemotherapy to be administered, and *in vitro* studies demonstrate a logarithmic increase in tumor cell kill (39). Soussain et al. (40) reported 22 patients with recurrent primary CNS lymphoma treated with high-dose chemotherapy/autologous stem cell support with an excellent response rate and a 64% overall survival at 3 years. Unfortunately, a third of the patients had significant neurological complications. Successful allogeneic peripheral blood stem cell transplantation with graft versus lymphoma effect has been reported in 1 patient with recurrent primary CNS lymphoma (41). An ongoing multicenter study is exploring the role of high-dose chemotherapy/autologous stem cell support for patients with newly diagnosed primary CNS lymphoma (42).

Anaplastic oligodendrogliomas with loss of heterozygosity on chromosome 1p are uniquely chemo-sensitive. The Oligodendrogioma Study Group conducted a Phase II trial of high-dose chemotherapy/autologous stem cell support for recurrent ana-
plastic oligodendrogliomas (43). Although the median overall survival was promising at 49 months, there was significant neurological morbidity. Recently, a similar study was completed in newly diagnosed patients. The preliminary survival analysis is excellent; neither median progression free or overall survival have been reached. To date, no significant neurological morbidity has been reported.

Patients with medulloblastoma or primary CNS germ cell tumors may benefit from high-dose chemotherapy/autologous stem cell support strategy. In a retrospective review of all adult brain tumor patients treated with high-dose chemotherapy/autologous stem cell support at Memorial Sloan-Kettering Cancer Center, 11 patients with recurrent disseminated medulloblastoma achieved a median survival of 34 months (44). Several small series have reported success using high-dose chemotherapy/autologous stem cell support in nongerminomatous germ cell tumor or recurrent germinoma in the brain (45). High-dose chemotherapy/autologous stem cell support can be safely administered; however, the risk of significant neurological morbidity may be increased in patients with recurrent tumors or prior cranial radiotherapy. Until clinical efficacy is demonstrated, high-dose chemotherapy/autologous stem cell support should be limited to prospective clinical trials.

New Molecular Targets in Childhood Cancers. Many children with cancer are now cured, often requiring complex, multiagent chemotherapy. For high-risk neuroblastoma, intensive chemoradiotherapy with autologous bone marrow transplantation, followed by maintenance therapy with 13-cis-retinoic acid, has improved event-free survival, but >50% of the patients still die from recurrent, drug-resistant tumors (46). Neuroblastoma cell lines can manifest a sustained high-level drug resistance acquired during therapy that correlates with the intensity of the therapy received and is mediated in many cases by a loss of p53 function (47, 48).

Depletion of glutathione with buthionine sulfoximine is cytotoxic to neuroblastoma cell lines (49) and enhances the activity of melphalan against neuroblastoma cell lines (50), and buthionine sulfoximine/melphalan achieved responses in patients with recurrent neuroblastoma (51). Buthionine sulfoximine can overcome high-level resistance to melphalan in neuroblastoma cell lines if melphalan levels obtainable using hematopoietic stem cell support are used (50, 52). Buthionine sulfoximine/melphalan appears to be p53 independent, as it was effective against cell lines that had lost p53 function (50, 52). An ongoing Phase I trial in the New Approaches to Neuroblastoma Therapy consortium is determining the maximal tolerated dose of melphalan when given together with buthionine sulfoximine and hematopoietic stem cell support.

Another approach to p53-independent therapy is the synthetic retinoid, 4-HPR. Neuroblastoma cell lines selected for resistance to retinoic acid become collateral hypersensitive to 4-HPR (53), which kills by both apoptosis and necrosis in a p53-independent manner (54). One mechanism by which 4-HPR achieves tumor-specific cytotoxicity is via generation of large quantities of ceramide in tumor cells but not in normal cells (54, 55). Combining 4-HPR with ceramide modulators (especially safingol) results in a striking synergistic enhancement of cytotoxicity at drug levels that are nontoxic for normal cells (55).

Thiols As Chemoprotectants. Glutathione is a naturally occurring endogenous antioxidant that is cytoprotective (56). Thus, treatment with glutathione or its precursors may protect normal cells during cancer chemotherapy. Exogenous administration of glutathione, especially glutathione esters, has been shown experimentally to impart limited cytoprotection. Precursors of glutathione synthesis, including N-acetylcysteine and methionine, also appear to offer a potential source of therapeutic cytoprotection. Conversely, pharmacological inhibition of glutathione synthesis (i.e., using L-buthionine-SR-sulfoximine) makes cells sensitive to oxidative damage, which has been used as a strategy to make certain tumors more susceptible to chemotherapeutic agents.

However, cancer cells may be resistant to selected cytotoxic drugs because of cellular protective mechanisms (57). An array of multidrug-resistant proteins was discussed that impairs cytoprotection to various cell types, including certain tumors. These plasmalemmal transporters extrude drugs, including chemotherapeutic agents, from protected cancer cells. Thus, a strategy to circumvent this naturally occurring cytoprotective mechanism may be beneficial during chemotherapy.

Dose-intensive strategies necessitate minimizing CNS and systemic toxicities and protecting patients against side effects that impact quality of life. Carboplatin, a DNA-alkylating agent, is effective in malignant brain tumors. However, carboplatin causes myelosuppression, and when administered with blood-brain barrier disruption, carboplatin is ototoxic. Thiols, such as sodium thiosulfate and N-acetylcysteine, protect against in vitro chemotherapy cytotoxicity (58, 59). A clinical study using delayed high-dose sodium thiosulfate was reported and showed a clear otoprotective effect against carboplatin-induced hearing loss when carboplatin is administered in conjunction with blood-brain barrier disruption (60, 61).

The potential role of delayed high-dose sodium thiosulfate in protecting against carboplatin-induced thrombocytopenia is under investigation. Preliminary results from a retrospective review of patients treated with carboplatin, cyclophosphamide, and etoposide phosphate with or without delayed high-dose sodium thiosulfate suggest that thiosulfate protects against severe thrombocytopenia, decreasing the number of patients and chemotherapy courses requiring platelet transfusions, as well as dose reductions of carboplatin (62).

In results of animal studies presented at the meeting, N-acetylcysteine was protective against chemotherapy-induced myelosuppression, particularly if given by a new aortic infusion technique 30 min before chemotherapy (63). A Phase I dose escalation study was presented to assess toxicity and determine maximum tolerated dose of N-acetylcysteine administered with carboplatin-based chemotherapy in patients with malignant brain tumors. The N-acetylcysteine will be administered in the descending aorta, 30 min before blood-brain barrier disruption and i.a. carboplatin. Blood/bone marrow toxicity associated with dose escalation of N-acetylcysteine will be evaluated.

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8 Internet address: http://www.nant.org.
Future Directions

New clinical trials are being developed by the Blood-Brain Barrier Disruption Consortium using thiols as chemoprotectants, with the goal of decreasing dose reductions and ultimately permitting dose escalation of carboplatin. In one such proposal, patients with primary malignant brain tumors or CNS metastases treated with i.a. carboplatin-based chemotherapy will be randomized to receive or not receive delayed high-dose sodium thiosulfate, to determine the effect of this agent on severe carboplatin-induced thrombocytopenia.

A clinical trial for patients with anaplastic oligodendroglioma, aggressive oligodendroglioma, and oligoastrocytoma is being developed. The chemotherapy regimen will consist of carboplatin, melphalan, and etoposide phosphate in conjunction with blood-brain barrier disruption, and patients will receive delayed high-dose sodium thiosulfate for otoprotection.

The long-term goal is utilization of N-acetylcysteine administered in the descending aorta, in conjunction with carboplatin-based chemotherapy with blood-brain barrier disruption. High-dose thiosulfate will be administered i.v. 4 and 8 h after carboplatin. N-acetylcysteine may protect against neutropenia, whereas delayed thiosulfate may protect against severe thrombocytopenia. Further details on chemotherapeutic dose intensification strategies for the treatment of malignant brain tumors are discussed by Kraemer et al. (64).

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References


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