Treatment of diffuse intrinsic brainstem gliomas: failed approaches and future strategies

A review

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Diffuse intrinsic pontine gliomas constitute ~ 60–75% of tumors found within the pediatric brainstem. These malignant lesions present with rapidly progressive symptoms such as cranial nerve, long tract, or cerebellar dysfunctions. Magnetic resonance imaging is usually sufficient to establish the diagnosis and obviates the need for surgical biopsy in most cases. The prognosis of the disease is dismal, and the median survival is < 12 months. Resection is not a viable option. Standard therapy involves radiotherapy, which produces transient neurological improvement with a progression-free survival benefit, but provides no improvement in overall survival. Clinical trials have been conducted to assess the efficacy of chemotherapeutic and biological agents in the treatment of diffuse pontine gliomas. In this review, the authors discuss recent studies in which systemic therapy was administered prior to, concomitantly with, or after radiotherapy. For future perspective, the discussion includes a rationale for stereotactic biopsies as well as possible therapeutic options of local chemotherapy in these lesions. (DOI: 10.3171/2008.11.PEDS08281)

Key Words • chemotherapy • diffuse intrinsic brainstem glioma • local drug delivery • radiotherapy • stereotactic biopsy

CENTRAL nervous system tumors are the most common form of solid cancers that occur in the pediatric population. Each year, ~ 2200 children are diagnosed with primary CNS tumors, of which 10–15% are localized to the brainstem. These lesions are typically one of the most difficult pediatric cancers to treat and are recognized histologically as a heterogenic group of tumors. In the US alone, there are ~ 200–300 cases annually, of which 60–75% are classified as diffuse intrinsic brainstem tumors.33,113 Children with these infiltrating fibrillary astrocytomas often present with progressive symptoms such as ataxia and multiple deficits of the cranial nerves, long tracts, and cerebellum. The mean age at diagnosis is 7–9 years, and there is no age or sex predilection.12,70

With the advent of CT scanning and MR imaging, significant advances have been made in the classification of pontine tumors, leading to various classification schemes for brainstem tumors (Table 1, Fig. 1).3,10,21,31,32,35,106 The classic diffuse pontine lesion is characterized by diffuse infiltration and hypertrophy of the pons, and is generally > 2 cm at time of presentation. On T1-weighted MR imaging sequences, diffuse gliomas appear hypointense with indistinct margins, reflecting their infiltrative nature, while appearing hyperintense on T2-weighted MR imaging sequences, which helps to distinguish them from focal tumors (Fig. 2). At initial presentation, contrast enhancement after the administration of Gd is often absent or minimal, again distinguishing these lesions from pilocytic astrocytomas and similar tumors arising in the brainstem. The FDG-PET modality has also been used in an attempt to differentiate low-grade from high-grade brainstem gliomas.23,26,63,86 In addition, FDG-PET has been used to differentiate tumor recurrence from posttreatment effects, such as radiation necrosis.34 Diffusion tensor imaging has been investigated to assess a potential role in visualizing and quantifying white matter tract involvement in brainstem tumors.51 A recently published report in a small series of pediatric patients with brainstem tumors demonstrated changes in diffusion properties of sensory and motor tracts consistent with degeneration, which may aid in treatment planning.52

Standard treatment for diffuse pontine lesions has in-

Abbreviations used in this paper: BBB = blood-brain barrier; BCNU = carmustine; CED = convection-enhanced delivery; FDG-PET = [18F]fluorodeoxyglucose–PET.
TABLE 1: Literature review of classification schemes for brainstem tumors

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<tr>
<th>Authors &amp; Year</th>
<th>Method Used to Create System</th>
<th>Classification System</th>
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| Epstein, 1985     | CT                           | intrinsic \                               
|                   |                              |   diffuse \                               
|                   |                              |   focal \                                 
|                   |                              |   cervicomedullary \                     
|                   |                              |   exophytic \                             
|                   |                              |   anterolat into cerebellopontine angle \     
|                   |                              |   posterolat & into brachium pontis \      
|                   |                              |   disseminated \                          
|                   |                              |   positive cytological findings \          
|                   |                              |   positive myelographic findings \         |
| Epstein & McCleary, 1986 | CT, MRI, & surgical observation | diffuse \                                 |
|                    |                              | focal \                                 |
|                    |                              | cervicomedullary \                       |
| Stroink et al., 1987 | CT                           | Group I: dorsal exophytic glioma \         |
|                    |                              | Group II: intrinsic brainstem tumors \    |
|                    |                              |   IIa: hypodense, no enhancement \        |
|                    |                              |   IIIb: hyperdense, contrast enhancing, exophytic \                  |
|                    |                              | Group III: focal cystic tumor w/ contrast enhancement \                |
|                    |                              | Group IV: focal intrinsic isodense lesion w/ contrast enhancement \   |
| Barkovich et al., 1990 | MRI                          | location (midbrain, pons, medulla) \     |
|                    |                              | focality (diffuse or focal) \             |
|                    |                              | direction & extent of tumor growth \      |
|                    |                              | degree of brainstem enlargement \         |
|                    |                              | exophytic growth \                        |
|                    |                              | hemorrhage or necrosis \                  |
|                    |                              | evidence of hydrocephalus \               |
| Albright, 1996    | MRI                          | focal (midbrain, pons, medulla) \         |
|                    |                              | diffuse \                               |
| Fischbein et al., 1996 | MRI                          | midbrain \                              |
|                    |                              | diffuse \                               |
|                    |                              | focal \                                 |
|                    |                              | tectal \                                |
|                    |                              | pons \                                  |
|                    |                              | diffuse \                               |
|                    |                              | focal \                                 |
|                    |                              | medulla \                               |
|                    |                              | diffuse \                               |
|                    |                              | focal \                                 |
|                    |                              | dorsal exophytic \                       |
| Choux et al., 2000 | CT & MRI                     | Type I: diffuse \                        |
|                    |                              | Type II: intrinsic, focal \              |
|                    |                              | Type III: exophytic, focal \             |
|                    |                              | Type IV: cervicomedullary \              |

involved the use of radiation therapy alone, which produces transient improvements in neurological function and a progression-free survival benefit but does not improve overall survival. The median onset of disease progression following irradiation is often < 6 months, with a median survival of ~ 10 months and prolonged survival (≥ 24 months) in < 10% of all patients. Evidence of transient response to radiotherapy has influenced numerous groups to attempt trials of increased radiotherapeutic dosage by using a hyperfractionated treatment regimen.\textsuperscript{30,37–39,81,82,84,85} These studies
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have shown that hyperfractionation provides a clinical response similar to that of hypofractionation or conventional radiotherapy in patients with diffuse brainstem gliomas.\textsuperscript{58,67} Moreover, toxicity is a source of major concern because intratumoral necrosis, steroid dependency, and other chronic factors are frequent. As a result, different collaborative efforts have been investigated to determine the efficacy of chemotherapy for these tumors. Many approaches have been used, including administration of chemotherapy at disease progression, concomitantly with radiotherapy, or prior to and/or after radiotherapy. Although the benefit of chemotherapy in the treatment of brainstem gliomas has not been well defined, multiple trials have been conducted to assess the efficacy of chemotherapeutic regimens.

**Chemotherapy Prior to Radiotherapy**

Several groups have tested the utility of the administration of chemotherapy prior to radiotherapy (Table 2). However, early disease progression in a substantial number of patients led to early discontinuation of chemotherapy. Results of these studies are difficult to interpret because the majority of patients often failed to receive the full course of radiotherapy and/or chemotherapy. On review of images obtained in 19 patients, Doz et al.\textsuperscript{28} reported 2 minor responses, 6 patients with stable disease, and 11 with progressive disease among patients treated with 2 courses of carboplatin prior to and during conventional radiotherapy. The median survival in their series was ~11 months. Dunkel et al.\textsuperscript{29} evaluated the use of high-dose thiotepa and etoposide-based chemotherapy regimens with autologous bone marrow rescue prior to hyperfractionated radiotherapy in 16 patients. The authors of this study concluded that the high-dose chemotherapy regimens did not prolong survival when compared with standard therapy. Kretschmar et al.\textsuperscript{62} reported 3 with partial responses, 23 with stable disease, and 6 with progressive disease among patients treated with cisplatin and cyclophosphamide prior to hyperfractionated radiotherapy at a 66-Gy dosage. The median survival was also found to be 9 months, and 3 long-term survivors (>2 years) were reported. Similar results were demonstrated in trials evaluating irinotecan and combinations of carboplatin, etoposide, vincristine, and cyclophosphamides prior to radiotherapy.\textsuperscript{17,59} Jennings et al.\textsuperscript{59} evaluated the response rates in 2 treatment groups with a combined 63 patients. In their first treatment group (A), carboplatin, etoposide,
and vincristine were administered, and the second treatment group (B) received cisplatin, etoposide, cyclophosphamide, and vincristine. In both groups, patients were treated with hyperfractionated radiotherapy after chemotherapy. The authors did not observe an improvement in the response rate, event-free survival, or overall survival in either treatment group when compared with historic controls who received radiation treatment with or without chemotherapy. In almost all cases, median survival was < 1 year, and little evidence of efficacy could be attributed to the chemotherapeutic treatment. Overall, the results of these studies demonstrate modest responsiveness of these tumors to chemotherapy, but no survival benefit when chemotherapeutic agents are given prior to radiotherapy.

Chemotherapy Before and After Radiotherapy

Not many studies have been performed to assess the efficacy of chemotherapeutic agents administered prior to and immediately following radiation for diffuse brainstem gliomas in children. Broniscer et al. assessed treatment in patients with brainstem gliomas in which some received optional window therapy with irinotecan prior to conventional radiotherapy. All patients in the study, including those not treated with optional window therapy, were treated with radiotherapy and subsequent administration of temozolomide. All of the patients in their study experienced disease progression and died.

Concomitant Chemotherapy and Radiotherapy

Multiple studies have been conducted to evaluate the response of patients with brainstem gliomas to treatment with chemotherapy during radiotherapy (Table 3). One of these, a study that included 6 patients with diffuse brainstem gliomas, investigated concurrent radiotherapy and dose-intensive chemotherapy with procarbazine, lomustine, and vincristine. The median overall survival was 11 months. Packer et al. assessed the concurrent administration of radiotherapy and chemotherapy with RMP-7 and carboplatin in 13 patients in a Phase I study. The median survival was 328 days. Survival was not improved in a group of 9 patients treated with hyperfractionated radiotherapy and chemotherapy with carboplatin and etoposide. Allen et al. found a median overall survival of 12 months in 34 patients treated with carboplatin and hyperfractionated radiotherapy. Disappointing results were obtained by Bernier-Chastagner et al., in which 32 patients

<table>
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<th>TABLE 2: Literature review of clinical trials of chemotherapy administration prior to radiotherapy*</th>
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<tr>
<td><strong>Authors &amp; Year</strong></td>
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<tr>
<td>Doz et al., 2002</td>
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<tr>
<td>Dunkel et al., 1998</td>
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<tr>
<td>Kretschmar et al., 1993</td>
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<tr>
<td>Jennings et al., 2002</td>
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<tr>
<td><strong>Group A</strong></td>
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<td><strong>Group B</strong></td>
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* ABMR = autologous bone marrow reinfusion; MR = minor response; PD = progressive disease; PR = partial response; SD = stable disease.
† The 3 patients with partial response were long-term survivors (>38, 40, and >44 months).

<table>
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<th>TABLE 3: Literature review of clinical trials of concurrent chemotherapy and radiotherapy*</th>
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<tr>
<td><strong>Authors &amp; Year</strong></td>
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<tr>
<td>Jakacki et al., 1998</td>
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<td>Packer et al., 2005</td>
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<td>Walter et al., 1998</td>
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<td>Allen et al., 1999</td>
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<tr>
<td>Bernier-Chastagner et al., 2005</td>
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<tr>
<td>Turner et al., 2007</td>
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<td>Wagner et al., 2006</td>
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* HIT-GBM = Hirntumor-Glioblastoma multiforme; PBSC = peripheral blood stem cells; TTD = time to death; TTP = time to progression.
treated with conventional radiotherapy and topotecan had a median survival of 8.3 months. A recent study by Turner et al.\textsuperscript{109} did not demonstrate an increase in survival in 12 patients treated with thalidomide and conventional radiotherapy. These reports provide data that are not encouraging in regard to the prolongation of survival in patients treated concomitantly with radiation and chemotherapy.

Data were analyzed from 153 pooled patients with diffuse brainstem gliomas from different prospective multicenter studies by the German language group of the Pediatric Oncology and Hematology Society collected in the “Hirntumor-Glioblastoma multiforme” (also known as HIT-GBM) database from 1983 to 2001. Ninety of these patients received chemotherapy in addition to radiotherapy. Radiotherapy and chemotherapy had prognostic relevance in univariate analysis.\textsuperscript{111} The 1-year overall survival rate was 45.8% in patients treated with both radiotherapy and chemotherapy, compared with 34.4% for patients treated with radiotherapy only. In addition, positive prognostic factors for survival were age younger than 4 years and tumor size. However, no patient in this database was documented as living longer than 3.9 years. These data from a significant cohort of patients demonstrate a small effect on survival with chemotherapeutic regimens, and provide a promising perspective for chemotherapy with better chemotherapeutic agents and/or techniques of delivery.

**Chemotherapy Immediately Following Radiotherapy**

The role of chemotherapy administration after radiotherapy has been investigated (Table 4).\textsuperscript{58,112,120} In 1 study, investigators explored the role of the administration of high-dose busulfan and thiotepa after conventional radiotherapy in 35 patients with diffuse pontine gliomas.\textsuperscript{15} The median survival time was 10 months, which was no better in comparison with radiotherapy alone. Jenkin et al.\textsuperscript{58} performed a prospective randomized trial that included 74 children, in which patients received either a combination of carmustine, vincristine, and prednisone or no treatment after conventional radiotherapy. Survival was not prolonged with the adjuvant chemotherapy regimen. Wolff et al.\textsuperscript{120} assessed the efficacy of a combination of trophosphamide and etoposide during and after conventional radiation treatment in 20 patients with diffuse pontine gliomas, and found no prolongation in survival. Cumulatively, these studies do not provide any evidence for an alteration in the natural history of the disease when chemotherapy is administered after radiotherapy.

**Discussion**

At present, there is little that suggests that chemotherapy provides substantial impact in the prognosis of disease progression in children with diffuse intrinsic brainstem gliomas; single-dose or multiagent chemotherapy regimens have provided only transient effects at best. Regardless of scheduling parameters for chemotherapy in relation to radiotherapy, whether given as adjuvant therapy, pre- or postradiotherapy, concomitantly with radiotherapy, or with other exogenous agents, time to progression and survival remain unchanged. As a result, standard treatment for patients with these invasive neoplasms remains conventional radiotherapy to a total dose of 54–59.4 Gy.\textsuperscript{7} These tumors generally respond to radiotherapy, with minimal side effects and improvements in neurological function; however, the duration of response is not lasting, with disease progression within 1 year. Given the poor response to current systemic therapies, new drugs and delivery methods warrant investigation.

**Does the Diagnostic Regimen Need to be Changed?**

Current opinions pertaining to the technique of diagnosing diffuse brainstem gliomas are mainly directed toward MR imaging modalities. Advances in the imaging technique and the restricted surgical options have led many practitioners to avoid interventional biopsy procedures and to use MR imaging findings alone for the diagnosis. Barkovich and colleagues\textsuperscript{9} first described MR imaging criteria for brainstem tumors. These criteria were rated highly sensitive and allow good identification of different subsets of tumors to anticipate growth characteristics and prognosis. Albright and colleagues\textsuperscript{4} reviewed the Children’s Cancer Group experience and had already questioned the necessity of biopsies in pontine gliomas. The German Pediatric Oncology and Hematology group reviewed 110 cases with MR imaging and histological diagnosis of brainstem tumors.\textsuperscript{98} In a blinded manner, 3 observers were able to identify tumors and nonneoplastic lesions correctly, with a sensitivity of 94%. However, assigning the correct WHO grade in these lesions varied between 12 and 74%. Based on these findings, the authors suggested only a rare need for biopsy procedures in these patients. A recent report by Roujeau et al.\textsuperscript{92} provided data in favor of stereotactic biopsy sampling of diffuse pontine lesions that have imaging characteristics suggestive of a malignant astrocytoma. A suboccipital trans cerebellar approach was used in 24 patients, without any deaths and with minimal morbidity. One patient had a transient cranial nerve palsy, and a second patient had both a transient cranial nerve palsy and an exacerbation of a preoperative hemiparesis. A histological diagnosis was made in all patients, according to which 22 had a malignant astrocytoma, 1 had a low-grade astrocytoma, and 1 had a pilocytic astrocytoma. These results are significant because the initial therapy would be affected

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**Table 4: Literature review of clinical trials of chemotherapy administration after radiotherapy**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Bouffet et al., 2000</td>
<td>35</td>
<td>busulfan, thiotepa, ABMR</td>
<td>median survival 10 mos</td>
</tr>
<tr>
<td>Jenkin et al., 1987</td>
<td>74</td>
<td>BCNU, vincristine, prednisone</td>
<td>overall 5-yr survival 20%</td>
</tr>
<tr>
<td>Wolff et al., 2002</td>
<td>20</td>
<td>trophosphamide &amp; etoposide</td>
<td>median survival 8 mos, 5-yr survival 0%</td>
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</table>
in tumors that are not considered malignant. Therefore, stereotactic biopsy sampling of pontine lesions may be of benefit in a minority of cases in which imaging characteristics are atypical.

Recent discussions deal with the fact that modern molecular biological diagnostic tools for tumor specimens might justify stereotactic biopsy sampling in diffuse brainstem gliomas, the better to investigate tumor identities for future therapeutic options. Comprehensive profiling of each respective tumor through cataloging of its individual characteristics may be of high value. Using techniques such as digital karyotyping and high-throughput sequencing of genes, researchers can identify specific genetic anomalies and analyze each mutation’s function with regard to the tumor expression and/or proliferation. On a larger scale, the analysis of the expression of brainstem tumor genes as a whole may also be effective. Through highly advanced techniques, such as serial analysis of gene expression, scientists can observe all the expressed genes in a cell at one time and study the patterns of expression during tumor formation. In doing so, genes can be isolated that are activated during key processes of tumor formation, such as those involved in protection against hypoxia, promotion of angiogenesis, and the proliferative nature of the tumor itself. By targeting a combination of these genes, we may be able to inactivate key processes, which will ultimately help prevent tumor growth, while also developing small-molecule drugs that can interact specifically with the tumor at intracellular levels. However, it should be kept in mind that although some progress has been made at the molecular level in studying supratentorial high-grade astrocytomas, the underlying molecular pathophysiological mechanism remains elusive, and the same challenges confront the elucidation of molecular mechanisms underlying diffuse brainstem gliomas.

Regardless of possible diagnostic options, the decision whether a biopsy should be performed depends, furthermore, on weighing risks as well as the benefits of possible treatment options resulting from the biopsy findings. In terms of risks, a literature review of brainstem tumor biopsy procedures performed in 378 patients showed a diagnostic rate of 94.8%, with a complication rate of 6.6% for transient and 1.5% for persisting neurological deficits. 84 Approximately 0.5% of patients suffered fatal consequences after intervention. In a single-center experience with biopsy sampling exclusively performed in 10 children with atypical brainstem lesions, 1 patient suffered biopsy-related persistent diplopia, although the diagnostic rate in this series was 100%. 88 In the same study, 157 pediatric cases of brainstem tumor biopsy sampling reported in the literature were reviewed, revealing 0.5% mortality and 5.1% morbidity rates, with a diagnostic rate of 93.6%. With these available data, the low morbidity associated with stereotactic biopsy procedures in brainstem gliomas may be acceptable, if new treatment modalities are discovered for these children.

New Therapeutic Perspectives Strategies

In light of the lack of evidence for improved outcomes or prolonged survival in patients with diffuse brainstem gliomas, it is difficult to imagine that any of the currently available drugs, even when used in novel combinations, will prove useful in enhancing the dismal outcome of this disease. The restricted accessibility of the BBB to systemic infusions of chemotherapeutic compounds, especially at conventional doses, may be a factor, compounded by its poor distribution in the tumor cells. Several strategies have been explored to circumvent the poor solubility of chemotherapy at the BBB, so as to allow direct access to tumors, while avoiding the adverse effects of standard systemic drug therapy. Products such as Gliadel, an FDA-approved biodegradable polymer loaded with the chemotherapeutic agent BCNU, have been successfully implanted in the resection cavity after tumor extirpation in the treatment of glioblastoma multiforme; however, the implantation of similar products for patients with brainstem tumor is not technically feasible. 86,88,96,106,107 Therefore, regional strategies, such as injection of the drug into a carotid artery, or the coadministration of a second compound, have been used to increase the permeability of the BBB temporarily, and intratumoral (local) approaches such as the use of surgically implanted catheters from infusion pumps have been implemented for long-term release of a drug directly into brainstem tissue. The latter local delivery strategy has shown safety and efficacy in animal models. 19,20,47,55,65,76,95,96,104,108

Convection-enhanced delivery is a treatment modality that is being investigated as a method to circumvent the BBB to deliver therapeutic agents for brainstem gliomas. 14,77 The CED modality is based on a positive pressure gradient and the principle of bulk flow to drive an infusate through parenchyma, which is in contrast to other local delivery techniques, such as drug-impregnated biodegradable polymers, which rely on diffusion rather than bulk flow. The safe and reliable targeted homogeneous distribution of infusate can be achieved over large or small volumes through the use of the bulk-flow properties of CED, and local drug concentrations several orders of magnitude over systemic administration can be achieved. 86 Similar to glioma cell invasion, CED has a distribution that occurs preferentially along white matter tracts. 45 Implantable cannulas have been used to study the continuous infusion of chemotherapeutic agents into the brainstems of rodents and primates. 20,47,55,66,79,95,96,102,103,108,122 Sandberg et al. 84 reported the first safe application of CED with the stereotactically guided implantation of a cannula into the rat brainstem, which provided the basis for further studies on the local delivery of therapeutic agents for brainstem gliomas. A subsequent study by this group demonstrated that prolonged CED can safely achieve large volumes of distribution in the rat brainstem. 79 Slow infusion rates are generally used because high flow rates may increase intracranial pressure and may disrupt tissue architecture. 83,89 Brainstems harboring a tumor may not be able to accommodate a transient increase in intracranial pressure in the same capacity that normal tissue may be able to, and a direct relationship between increasing flow rates and morbidity in a rodent brainstem model has been demonstrated. 20

Furthermore, studies have shown that local perfusion of the rat brainstem with chemotherapeutic agents, such as BCNU, carboplatin, and gemcitabine, is safe. 25,103 Distribution studies with CED have demonstrated that carboplatin can reach therapeutic levels in the brainstem, although it
was shown that the drug diffused up to 4 mm around the tip of the cannula. Thus, larger tumors may need the placement of more than 1 cannula. Thomale et al.\(^\text{108}\) reported on the safe placement of up to 3 cannulas in the brainstems of rats for local drug delivery, and the drug distribution was greater in the 3-cannula group than in the 1-cannula group. Because CED can be used for the delivery of large macromolecules, such as targeted toxins or monoclonal antibodies, Souweidane et al.\(^\text{102}\) showed that the tumor-specific chimeric cytotoxin IL13-PE38QQR can be safely delivered into the rat brainstem via interstitial infusion. This recombinant cytotoxin is a combination of the cytokine interleukin-13 and the modified *Pseudomonas* exotoxin moiety PEA, and this chimeric cytotoxin has been shown to be highly selective for glioma cells, with proven cytotoxicity in experimental studies.\(^\text{24}\) Brainstem glioma models have been developed to simulate diffuse pontine gliomas (Fig. 4).\(^\text{56,57,65,123}\) Wu et al.\(^\text{122}\) demonstrated that carboplatin could be locally delivered to neoplastic cells in a rat brainstem tumor model with mini-osmotic pumps, which resulted in a prolongation of survival. Moreover, Lonser et al.\(^\text{71}\) documented the safety of locally infused Gd-bound albumin via stereotactically implanted cannulas into large areas of the primate midbrain and pons, followed by other reports showing the safety of CED of chemotherapeutic agents, such as gemicitabine and carboplatin, infused into the primate brainstem, although dose-dependent toxicity has been found with carboplatin.\(^\text{58,104,105}\)

Recently, the cases of 2 patients with intrinsic brainstem lesions have been published, in which they received frameless stereotactic placement of cannulas into the brainstem for CED.\(^\text{72}\) One patient with progressive Gaucher disease received glucocerebrosidase with Gd–diethylenetriamine pentaacetic acid contrast medium, whereas in the second case, involving a diffuse pontine glioma, interleukin-13 bound to *Pseudomonas* exotoxin was administered with Gd–diethylene-triamine pentaacetic acid at a rate of 0.5–10 μl/minute, with a total volume of 2 and 1.4 ml in the first and second cases, respectively. The tissue distribution of Gd after delivery in the first and second cases reached a total volume of 4.2 and 3 ml, respectively. It is reported that both patients were neurologically stable during and immediately after infusion. The patient with the pontine glioma, whose treatment started 10 months after diagnosis, showed slight, progressive neurological signs 5 days after treatment, and tumor progression was observed after 8 weeks. These preliminary findings suggest that local delivery for a limited volume and period of time is feasible in patients with intrinsic brainstem lesions. However, further investigation of such approaches is needed over longer periods of time and at earlier stages of tumor growth to enhance the conditions producing a better response. Furthermore, it will allow analysis of associated neurological deficits, and it will allow us to assess the highest possible degree of efficacy with the least amount of toxicity.

Intranasal delivery of therapeutic agents to the brain has been investigated as a noninvasive method for bypassing the BBB. Hashizume et al.\(^\text{49}\) treated rats harboring intracerebral human tumor xenografts intranasally with daily administration of fluorescein-labeled GRN163, a telomerase inhibitor. It was demonstrated that GRN163 accumulation peaked at 4 hours after intranasal delivery. A 12-day course of GRN163 delivery resulted in a significant prolongation of survival, in which the median survival was 35 days in the control group, compared with 75.5 days in the GRN163-treated group. There was no toxicity shown in normal brain tissue, which provided evidence for the selective killing of tumor cells. Although further studies are
needed, this treatment modality may serve as an alternative to systemic delivery and CED of therapeutic agents.

Through exploration of different alternative devices and delivery methods, such as microspheres, endovascular injection, or stereotactic injection, which are capable of locally delivering drugs in precisely timed regimens, we may attain the critical advantage of being able to control targeted delivery with new therapeutic agents, which needs to be further defined.

New Compounds for Local Delivery

An additional factor leading to such a poor prognosis in patients with brainstem glioma is the tumor’s ability to grow without significant impedence from the immune system. Although the immune system attempts to attack and remove the glioma, the body’s T cells are incapable of sufficiently infiltrating the areas of tumor proliferation. Gliomas have been found to express a protein called Fas ligand, which, when in contact with immune cells, causes them to undergo apoptosis. Inhibition or downregulation of the expression of Fas ligand could facilitate a more effective immune response toward these highly aggressive tumors. Through the incorporation of molecular techniques in animal models, virus-based immunotherapies and retroviruses can be engineered to deliver various agents and small interfering RNA to the site of tumor growth. Small interfering RNA is an innovative technology that allows the highly specific inhibition of the expression of particular genes. These techniques will allow us to understand better how tumor cells avoid attack by the immune system, and also to uncover new avenues for tumor vaccine development.

Local delivery models that increase efficacy of agents, including RNA interference sequences, cytokine-targeted adenoviruses, anticancer RNAses, and other site-specific agents will also need to be investigated, because angiogenesis, lack of apoptosis, and uncontrolled cellular proliferation are the chief processes that make these tumors so difficult to treat. Therefore, the effectiveness of chemotherapy in combination with agents possessing differing and complementary mechanisms of action, such as angiogenesis inhibitors (for example, statins), resistance modifiers, apoptosis and immune stimulators (for example, p53 and herpes simplex virus thymidine kinase), and other agents that intervene in critical pathways of tumorigenesis and tumor growth will also need to be explored.

Conclusions

Diffuse intrinsic brainstem gliomas are generally considered to be surgically inoperable lesions that display heterogenous pathological features. Standard treatment for these high-grade neoplasms has consisted of conventional fractionated radiotherapy, and the response to these ancillary therapies has been transient at best, providing a progression-free survival benefit with no effect on overall survival. Multiple trials investigating a potential role for systemic therapies in combination with radiotherapy in the treatment of these lesions have been predominantly disappointing. More well-designed prospective randomized trials are needed to assess the efficacy of chemotherapeutic agents in the treatment of this disease, because the prognosis continues to be so dismal.

Furthermore, adjuvant approaches that incorporate local delivery techniques to bypass the BBB are now under investigation. Therefore, new therapeutic options such as immunotherapy and gene therapy techniques need to be evaluated for efficacy and toxicity. Further exploration and innovation will be critical to the improvement of prognoses and future management of these infiltrative lesions.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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89. Prabhu SS, Broadus WC, Gillies GT, Loudon WG, Chen ZJ, et al:...
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