Interstitial Hyperthermia With Intra-arterial Injection of Adriamycin for Malignant Glioma

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Abstract

A new method for treating malignant glioma by concurrent intra-arterial injection of adriamycin during thermotherapy was performed in seven patients with malignant glioma, four males and three females, with five cases of glioblastoma and two of anaplastic oligodendroglioma. Adriamycin was intra-arterially injected at a dose of 20 mg via the common carotid artery during thermotherapy. The heating procedure was repeated three times combined with chemotherapy in one therapy course, and a total of nine therapy courses were performed in the seven patients. All patients tolerated the protocol well. Based on post-therapy computed tomography, five of the therapy courses achieved partial response, one course resulted in disease progression, and the remaining three courses showed no change. The median time to progression was 3.4 months and the overall median length of survival following stereotactic biopsy was 13.2 months. Facial flushing was observed during eight therapy courses, and extensive alopecia in six therapy courses. Intracystic concentrations of adriamycin were determined in three patients, and marked increases were observed. Intra-arterial injection chemotherapy during hyperthermia is a promising therapeutic method for treatment of malignant glioma with few adverse effects.

Key words: intra-arterial chemotherapy, interstitial hyperthermia, malignant glioma, adriamycin, blood-brain barrier, tumor invasion zone

Introduction

Malignant gliomas are widely invasive tumors that rarely metastasize and generally recur locally, so local therapy is the most important. Radiation therapy is effective against de novo malignant glioma, but few therapeutic procedures are effective against recurrent tumors or tumor regrowth after irradiation. We have been developing an interstitial heating system for treatment of malignant glial tumors since 1989. Our hyperthermia treatment strategy is less invasive than excision surgery, so elderly patients or patients with deep-seated tumors are especially good candidates for the procedure. In the last 4 years, we have added intra-arterial chemotherapy during hyperthermia for the treatment of invasive tumor lesions, because of the increased drug delivery that occurs during hyperthermia.

Here we report seven cases of malignant glioma treated with intra-arterial chemotherapy during hyperthermia and discuss the therapeutic method, clinical results, and the adverse reactions, as a phase I clinical trial.

Patients and Methods

Seven patients with malignant glioma, including four males and three females, were included in the study (Table 1). One patient had a de novo tumor, and six patients had recurrent tumors. There were five cases of glioblastoma and two of anaplastic oligodendroglioma. Case 6 (first therapy) and Case 7 (second therapy) were reported previously. The six patients with recurrent tumors received thermo-chemotherapy, whereas the patient with the de novo tumor received thermo-chemotherapy with conventional radiation therapy (60 Gy, 30 fractions).

The interstitial hyperthermia system was constructed from a 13.56-MHz radio-frequency generator and needle-shaped electrodes, as described previously. Hyperthermia treatment was planned by computer simulation using a two-dimensional finite element method, as also described previously.
Table 1  Patients participating in the study

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age  (yrs)</th>
<th>Sex</th>
<th>Tumor</th>
<th>Histology</th>
<th>Adriamycin dose (mg)</th>
<th>CT evaluation</th>
<th>Alopecia</th>
<th>Facial flushing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>F</td>
<td>de novo</td>
<td>GBM</td>
<td>20</td>
<td>PR</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>recurrent</td>
<td>GBM</td>
<td>20</td>
<td>NC</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>F</td>
<td>recurrent</td>
<td>GBM</td>
<td>20 × 2</td>
<td>PR</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>4</td>
<td>47</td>
<td>M</td>
<td>recurrent</td>
<td>GBM</td>
<td>20 × 2</td>
<td>PR</td>
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<td>yes</td>
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<tr>
<td>5</td>
<td>67</td>
<td>M</td>
<td>recurrent</td>
<td>GBM</td>
<td>20</td>
<td>PR</td>
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<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>27*</td>
<td>F</td>
<td>recurrent</td>
<td>AOA</td>
<td>20 × 2</td>
<td>PR</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>M</td>
<td>recurrent</td>
<td>AOA</td>
<td>20</td>
<td>NC</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>8</td>
<td>37*</td>
<td>M</td>
<td>recurrent</td>
<td>AOA</td>
<td>20 × 2</td>
<td>PD</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Asterisk indicates the cases already reported. AOA: anaplastic oligoastrocytoma, CT: computed tomography, GBM: glioblastoma multiforme, NC: no change, PD: progressive disease, PR: partial response.

The protocol was well tolerated by all patients. Facial flushing was observed during eight therapy courses, and extensive alopecia in six therapy courses (Table 1). No other adverse reactions, such as nausea, vomiting, renal or liver dysfunction, and leukoencephalopathy, were observed.

CT showed a partial response after five thermochemotherapy courses, no change after three courses, and disease progression after one course (Table 1). The response rate was 55.6%. The time to progression was 1 to 9 months (median 3.4 months). The longest time to progression was achieved in the patient with de novo tumor treated with thermo-radio-chemotherapy. The overall median length of survival following stereotactic biopsy was 13.2 months.

Adriamycin concentrations in cyst fluids during thermo-chemotherapy were higher than those in chemotherapy in the three cases in which these concentrations were measured (Fig. 1). The maximum concentrations of adriamycin were 4.5-fold and 3.6-fold greater than the baseline values in Cases 6 and 7, respectively. The adriamycin concentration in the cyst fluid was too low to be detected during chemotherapy in Case 1.

### Results

**Representative Case**
Case 1 was a 35-year-old female who presented with a 10-day history of severe headache. CT revealed a cystic and well-enhanced tumor in the right putamen and deep white matter (Fig. 2). She was treated with thermo-chemotherapy and conventional radiation therapy (60 Gy). Histological examination showed the tumor to be a glioblastoma. CT after thermo-chemo-radiotherapy showed partial...
response, and no symptoms were associated with the treatment. Tumor regrowth occurred 9 months later, and the patient underwent three tumor excision surgeries, but died of central herniation 24 months after onset.

**Discussion**

Our hyperthermia treatment strategy involves heating of the lesion to 42.5–43°C, after identification of the lesion by CT or MR imaging with contrast medium. Direct thermal killing of glioma cells is expected under these conditions. Glioma cells infiltrate the blood-brain barrier (BBB) and surrounding brain tissue, but these structures may remain functional. Computer simulations suggest that the outside of the contrast-enhanced lesion, which is considered to be the tumor invasion zone, overlaps well with the region raised to 40–42°C during heating. Therefore, we added intra-arterial chemotherapy for the treatment of invasive tumor lesions. Our strategy for thermo-chemotherapy is shown schematically in Fig. 3.

Numerous investigations of hyperthermia-
induced BBB disruption in normal brain tissue have mainly concluded that threshold temperatures above 43°C are required. However, BBB or tumor-blood barrier disturbance in glioma patients during hyperthermia is little understood. Investigation of hyperthermia-induced permeability of the BBB using bovine brain microvessel endothelial cells found that mild hyperthermia (40°C for 20 min) can enhance drug penetration through the BBB.

We selected adriamycin as the chemotherapeutic agent because this agent has a high dose-dependent antitumor effect against malignant glial tumors in vitro. Study of uptake of intravenous injection of adriamycin in eight malignant gliomas found that the tumor tissue concentration of adriamycin was far below cytotoxic levels. The presence of the BBB was considered to be one of the major reasons for this result. Disturbance of the BBB during hyperthermia is one approach to this problem. We previously reported the efficacy of combined infra-arterial chemotherapy and interstitial hyperthermia in a Wistar rat model, in which a high concentration of adriamycin in the tumor was achieved. Clinical and laboratory studies have also shown that hyperthermia enhances the cytotoxic effects of several chemotherapeutic drugs. For example, the cytotoxic effect of adriamycin in malignant glioma cells is improved with hyperthermia, even in adriamycin-resistant cells.

In the present series, the CT response rate was 55.6%. Tumor regrowth occurred within 6 months in all patients, except for the patient with de novo tumor, for which radiation therapy was also used. This outcome is not satisfactory, but the dose of adriamycin can be increased, as the dose used in this series was small and few adverse reactions were noted. Therefore, further studies are required to determine the optimal dose of adriamycin infusion during hyperthermia. The effectiveness of this treatment should be considered with caution regarding Cases 6 and 7, because oligodendroglial tumors are considered to be more chemosensitive than astrocytic tumors.

Determination of the intracystic concentrations of adriamycin showed marked increases in all three patients. BBB or blood-tumor barrier disturbance due to hyperthermia is likely to have been the major factor resulting in these increased concentrations. The adriamycin concentrations of the cyst fluid varied greatly, possibly due to differences in temperature distribution during hyperthermia and to the different locations of the cysts.

Facial flushing was observed in eight therapy courses and extensive alopecia in six therapy courses. Facial flushing is classified as a grade 1 adverse reaction and alopecia as a grade 2 adverse reaction, according to the Common Toxicity Criteria of the National Cancer Institute. Therefore, intra-arterial chemotherapy during hyperthermia causes only relatively minor side effects while allowing the amount of antitumor agent to be reduced, so we conclude that this approach is a promising therapeutic method for the treatment of malignant glioma.

References

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Commentary

The authors present a novel form of combination therapy for the treatment of malignant glioma. They have utilized this in the number of patients and although the results are impossible to determine and are not obviously better than other modes of therapy, the idea is intriguing and further development is certainly desirable.

In their study, the authors utilized interstitial hyperthermia delivered by RF electrodes, to treat not only solid tumor using the modality of hyperthermia, which has long been known to be moderately effective, but also they imply that the hyperthermia will produce a breakdown of the blood/brain barrier, thereby making much more effective the intra-arterial delivery of chemotherapy compounds such as adriamycin that do not ordinarily cross the blood/brain barrier. They present some evidence that their theory is validated in that concentrations of adriamycin that were measured in tumor and cyst fluid were significantly elevated using this technique. It will be of interest to learn how their future applications of this concept develop.

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