Regression of recurrent glioblastoma infiltrating the brainstem after convection-enhanced delivery of nimustine hydrochloride

Case report

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This 13-year-old boy with a history of cranial irradiation for the CNS recurrence of acute lymphocytic leukemia developed a glioblastoma in the right cerebellum. Resection and chemo- and radiotherapy induced remission of the disease. However, recurrence was noted in the brainstem region 8 months later. Because no effective treatment was available for this recurrent lesion, the authors decided to use convection-enhanced delivery (CED) to infuse nimustine hydrochloride. On stereotactic insertion of the infusion cannula into the brainstem lesion, CED of nimustine hydrochloride was performed with real-time MR imaging to monitor the co-infused chelated gadolinium. The patient’s preinfusion symptom of diplopia disappeared after treatment. Follow-up MR imaging revealed the response of the tumor. The authors report on a case of recurrent glioblastoma infiltrating the brainstem that regressed after CED of nimustine hydrochloride. (DOI: 10.3171/2011.2.PEDS10407)

Key Words • convection-enhanced delivery • glioblastoma • brainstem • nimustine hydrochloride • gadolinium

Abbreviations used in this paper: ACNU = nimustine hydrochloride; CED = convection-enhanced delivery; Gd-DOTA = gadoterate meglumine.

Gliomas diffusely affecting the brainstem have 2 different origins: one is the so-called brainstem glioma, and the other involves infiltration from gliomas originating in surrounding structures. Brainstem gliomas account for approximately 20% of all CNS tumors among children younger than 15 years of age. Among adults, brainstem gliomas are less common but have been reported in individuals up to the age of 70 years. Surgery no longer plays a role in diffuse brainstem glioma treatment. Meaningful resection is not possible, as the diffuse tumor is interwoven within white matter tracts traversing the brainstem, and resection does not confer a survival advantage. Radiotherapy was previously the recommended treatment for all brainstem gliomas, leading to transient improvements in neurological function and a progression-free survival benefit, but it does not improve overall survival. Currently, there is little, if any, evidence to suggest that chemotherapy has affected the outcome in patients with diffuse brainstem gliomas. Consequently, the prognosis for diffuse brainstem glioma is very poor, with a median survival of less than 1 year. The median onset of disease progression following radiation is often less than 6 months, median survival is approximately 10 months, and less than 10% of patients are alive at 2 years. Gliomas originating from surrounding structures such as the thalamus or cerebellum also infiltrate the brainstem, often at the time of recurrence. In this setting, it is more complicated because radiotherapy has already been administered in many cases at the time of initial therapy. Therefore, novel treatment modalities are required.

In the present report, we describe a case of recurrent glioblastoma affecting the brainstem that regressed after local ACNU-based chemotherapy. The local chemotherapy was administered using CED, aided by real-time MR imaging monitoring.
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Case Report

History. This 13-year-old boy developed truncal and right cerebellar ataxia, and he visited the department of pediatrics at our hospital in October 2008. He had a history of acute lymphocytic leukemia (French-American-British Class L1) and underwent chemotherapy at the age of 2 years. Recurrent disease in his testis and CNS was detected when he was 5 and 8 years of age, respectively. Both recurrent lesions were treated with combined chemo- and radiotherapy including 18-Gy whole-brain and whole-spine irradiation at 8 years of age. After these treatments, complete remission of the acute lymphocytic leukemia was achieved without any systemic or neurological deficits. However, in October 2008, T2-weighted MR imaging of the brain revealed a massive high-intensity lesion in the right cerebellar hemisphere (Fig. 1A). Contrast-enhanced T1-weighted MR imaging revealed spotty enhancement within the lesion (Fig. 1B). Magnetic resonance spectroscopy detected an elevated choline peak in the lesion. With a diagnosis of malignant glioma, he was referred to our department.

Treatment. The tumor was subtotally resected in November 2008 (Fig. 1C and D). After surgery, the patient underwent local radiotherapy (50 Gy) and concomitant temozolomide therapy. Exhibiting just slight ataxia, he was discharged from the hospital to home and enjoyed his school life until May 2009 (Fig. 1E and F). During this period, temozolomide-based chemotherapy was continued on an outpatient basis. On follow-up outpatient chemotherapy in June 2009, slight enhancement was noted in the brainstem (Fig. 2A). Considering a differential diagnosis of tumor recurrence and radiation necrosis, we conducted further examinations. A methionine-based PET study revealed a high uptake (maximal standardized uptake value = 4.2) (Fig. 2B), suggesting a tumor recurrence, and MR images obtained simultaneously depicted the enlargement of the enhanced tumor (Fig. 2C). At this point, we decided to perform CED of ACNU. During the preparation period of only 16 days, we observed additional enlargement of the enhanced tumor (Fig. 2D). The patient developed diplopia due to right-side medial-longitudinal-fasciculus syndrome. After planning the route for the catheter (iPlan stereotactic software, Brainlab), an 18-gauge 30-cm single-lumen central venous catheter (UNITIKA) was inserted via the left frontal lobe with stereotactic assistance (Fig. 3A–C). Ni-mustine hydrochloride solution, which contained 0.25 mg/ml of ACNU and 1 mM Gd-DOTA in saline, was infused over 2.5 days through the inserted catheter, using the CED method. Briefly, using a microinfusion pump, the infusion rate was controlled and gradually increased from 1.0 to 5.0 µl/min, resulting in a total infusion of 7020 µl after 2.5 days. Oral temozolomide at 200 mg/m²/day was used simultaneously for 5 sequential days starting from the day of catheter insertion. Intravenous dexamethasone was also used during infusion. Magnetic resonance images were obtained during and after infusion. Noncontrast T1-weighted MR images revealed the delivery of Gd-DOTA that was mixed in the infusion solution (Fig. 3D–G). The volume of distribution was plotted against the volume of infusion (Fig. 3H). We calculated the volume of distribution as the volume of distribution from MR images containing at least 10% of the total increase in signal intensity due to the addition of contrast agent as reported previously. The images in Fig. 4 (A–D) demonstrate the relationship of the tumor and distribution of Gd-DOTA at the end of the infusion.
CED. During the infusion, when infusion reached 2000 mll, slight aggravation of right-side medial-longsitudinal-fasciculys syndrome was observed. Development of mild right hemiparesis was noted 4 days after the termination of infusion, which fully recovered within a week. On a diffusion-weighted MR image obtained when hemiparesis was recognized, we noted a spotty high-intensity lesion in the left corona radiata (Fig. 4E). As Gd-DOTA was also found at this site in the image obtained at the end of infusion (Fig. 4F), we considered this to represent a side effect of the delivered ACNU. Otherwise, the clinical course after CED was uneventful. The diplopia and right hemiparesis resolved. The patient returned to normal school life with the continuation of monthly temozolomide. Contrast-enhanced T1-weighted MR imaging revealed the shrinkage of the brainstem lesion (Fig. 5). Unfortunately in December 2009, the patient was readmitted to our hospital with the rapid progression of multiple disseminated diseases. In late January 2010, he died.

Discussion

We have been working toward the CED of ACNU to treat malignant gliomas. In our first article published in 2007, we demonstrated the efficacy of ACNU in a rodent intracranial xenograft tumor model. The subsequent publication demonstrated the efficacy of combination therapy using CED of ACNU and systemic temozolomide. We then concluded a toxicity study in nonhuman primates (unpublished data). Histological examination revealed minimum tissue damage after a 1-mg/ml infusion of ACNU, which was the safety dose detected in our previous rodent study. Based on these results, we started a pilot clinical study in 2008 on the CED of ACNU in patients with recurrent high-grade glioma after being granted approval from our institutional ethical committee. To treat recurrent high-grade gliomas, we used a mixture of ACNU and Gd-DOTA in CED. Starting from the day of infusion, temozolomide was also given orally for 5 consecutive days according to the protocol for recurrent disease. The present case was a patient involved in the study.

The treatment of a recurrent glioma affecting the brainstem is challenging. No effective therapy is available for patients in whom chemo- and radiotherapy have already been given for the initial disease. In the present case, the rapid progression of recurrent disease was detected on
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MR imaging together with the rapid deterioration of diplopia. Methionine-based PET scanning detected a region of high uptake corresponding to the brainstem lesion, which suggested “recurrence” rather than radiation necrosis. We observed that CED of ACNU demonstrated the efficacy against this lesion. Regression of the lesion was documented together with the disappearance of diplopia. Although dissemination developed 5 months after CED, our patient was able to resume his school life until then. An important motivation for the development of CED has been the desire to offer a new treatment to children with diffuse pontine gliomas. In the present case the patient did not have diffuse pontine glioma, but the condition treated is similar. Thus, results in this case indicate a promise for future development of this delivery strategy.

Visualization of drug distribution during CED is also of importance in the future development of CED. The Gd-DOTA used in this study provided important information on drug delivery. Although it is not clear if the Gd-DOTA distribution directly reflects that of ACNU, there were findings that suggested a similarity in the distribution. Magnetic resonance imaging detected the backflow of Gd-DOTA through the catheter tract. The backflow was detected at the catheter tract penetrating the corona radiata of the left hemisphere. During infusion, we were anxious about this because, if the distribution of ACNU was the same as that of Gd-DOTA, this might cause some damage to the left corona radiata. Actually, the patient developed mild right hemiparesis after infusion. On diffusion-weighted MR imaging, performed when hemiparesis was

**Fig. 4.** Relationship between the enhanced tumor mass and distribution of CED Gd-DOTA. **A–D and F:** Images produced using the iPlan stereotactic software. The contrast-enhanced T1-weighted MR image are overlapped with the T1-weighted MR images obtained at the end of CED. The tumor is indicated by the red and the distribution of Gd-DOTA by yellow. The images in **A–D** demonstrate the relationship between the tumor and distribution of Gd-DOTA at the end of CED. Diffusion-weighted MR images obtained when the patient developed mild right hemiparesis (**E**), showing a high-intensity lesion in the left corona radiata where there was a reflux of infused Gd-DOTA at the end of infusion (**F**).

**Fig. 5.** Axial contrast–enhanced T1-weighted MR images obtained 1 week after CED (**A**), 1 month after CED (**B**), and 3 months after CED (**C**).
recognized, we observed a spotty high-intensity lesion in the left corona radiata. Fortunately, this symptom fully resolved soon after termination of the CED. However, this suggested the importance of monitoring the drug distribution during CED.

Based on these experiences, we are now planning a Phase I study on the MR imaging–monitored CED of ACNU for recurrent brainstem gliomas. Although the treatment of this disease is challenging, the present case suggests the possibility of using CED against this devastating disease. We can only treat localized disease with CED, and we still need to develop an effective treatment against disseminated disease. However, localized disease should be cured beforehand. Together with imaging guidance, this platform of therapy may provide an alternative therapeutic strategy to brainstem gliomas in the future.13,15

Conclusions

The present case of recurrent glioblastoma affecting the brainstem suggests the efficacy of local chemotherapy aided by CED. Regression of the enhanced tumor as well as symptoms was achieved even with the recurrent, rapidly progressing disease. Although the patient finally died of disseminated disease, the CED of ACNU facilitated local control of the disease even in the brainstem region. Based on these experiences, we are now preparing a Phase I study on the MR imaging–monitored CED of ACNU for recurrent brainstem gliomas.

Disclosure

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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