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Patients Report

Long-term efficacy of bevacizumab and irinotecan in recurrent pediatric glioblastoma

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Abstract

A 5-year-old boy with glioblastoma relapsed soon after postoperative irradiation in combination with temozolomide. Second-line chemotherapy was also ineffective; therefore, the bevacizumab and irinotecan were administered after a third gross-total resection of the tumor. Treatment was interrupted for 1 month due to development of posterior reversible encephalopathy syndrome, but was re-initiated at a lower dose of bevacizumab with prolonged intervals between administrations. The patient is alive and disease-free 2 years after initial diagnosis. Bevacizumab and irinotecan are a promising regimen for pediatric cases of recurrent glioblastoma after gross-total resection, although the optimal treatment schedule must be determined on a patient basis.

Introduction

Glioblastoma is the most aggressive form of primary malignant brain tumors. Local radiation therapy in combination with 6 month administration of temozolomide (TMZ) is the standard therapy for newly diagnosed glioblastoma. However, most patients discontinue adjuvant therapy due to disease progression or recurrence. The prognosis of patients with relapsed or refractory glioblastoma is extremely poor with a median survival of 3 to 6 months[1]. Furthermore, any effective second- or third-line chemotherapy has not established for such resistant cases.

Glioblastoma express high levels of vascular endothelial growth factor (VEGF), and the expression level of VEGF correlates well with prognosis[2]. Recently, bevacizumab (BV), a recombinant humanized monoclonal antibody against VEGF, was reported to be effective for recurrent or refractory glioblastoma in adults, especially in combination with irinotecan (CPT11) [3]. However, these promising results were not reproduced in a clinical study in children[4], partly because of marked differences in the molecular features of pediatric versus adult glioblastoma[5]. Moreover, given that few pediatric cases are treated by BV, there are limited data on its appropriate administration schedule and adverse effects. Here we present a pediatric patient with recurrent glioblastoma who continuously received BV and CPT11 despite the development of severe adverse effects and who is alive without disease progression 2 years after

initial diagnosis.

Case Report

A 5-year-old boy presented with a 1 month history of persistent headache and emesis. Magnetic resonance imaging (MRI) revealed a huge tumor at the left frontal lobe (Figure 1A). Partial resection of the tumor was performed (Figure 1B), and the patient was diagnosed with glioblastoma based on histological findings of the biopsied tumor tissue. The patient first received local irradiation at a dose of 59.8 Gy in 26 fractions in combination with TMZ. However, the tumor regrew locally one month after the start of irradiation (Figure 1C), and the patient underwent a second gross-total resection (Figure 1D), followed by the remaining irradiation and two courses of chemotherapy using ifosfamide, carboplatin, and etoposide. However, 2 months later, the patient developed a second local recurrence (Figure 1E) and a third gross-total resection was performed after transfer to our hospital. The first and second recurrences were confirmed by histological findings of the resected tumor tissues. The patient had a normal neurological examination before chemotherapy.

Following the third resection, the patient received BV (10 mg/kg) and CPT11 (125 mg/m^2) every 2 weeks. Grade II hypertension and grade III proteinuria occurred after the tenth cycle of chemotherapy, and the dose of BV was reduced to 8 mg/kg and enalapril was started to control hypertension. Eight days after the thirteenth cycle of chemotherapy, the patient developed grade IV hypertension (190 mm Hg systolic and 130 mm Hg diastolic pressure) with

headache and emesis. FLAIR T2-weighted images of cranial MRI at symptom onset showed multiple areas of high-intensity intensities at the putamen, thalamus, cerebellum, and brainstem (Figure 2A, B). Therefore, the patient was diagnosed with posterior reversible encephalopathy syndrome (PRES). Chemotherapy was stopped and aggressive antihypertension treatment with nifedipine and enalapril was commenced, resulting in rapid improvement of all symptoms and normalization of blood pressure 3 weeks later; however, grade I proteinuria persisted. Three weeks after the onset of PRES, cranial MRI showed complete disappearance of high-intensity areas (Figure 2C, D).

Due to the lack of appropriate alternative compounds for more effective treatment, chemotherapy was restarted 1 month after the onset of PRES with a reduction in BV dose to 7 mg/kg and extension of the treatment interval to once every 3 weeks, in combination with nifedipine and enalapril. Currently, the patient receives BV and CPT11 with no serious adverse effects or neurologic sequelae and is disease-free more than 2 years after initial diagnosis (Figure 1F).

Discussion

Previous clinical studies showed encouraging results with BV and CPT11 therapy in adults with measurable disease of recurrent glioblastoma in terms of objective response rate and progression-free survival[3]. However, few patients survived progression-free for more than 1 year. Furthermore, a recent study failed to show long-term survival in children with recurrent glioblastoma with measurable disease treated with BV and CPT11[4]. By contrast, a previous study showed that two of three pediatric patients survived more than 3 years after near- or gross-total resection with treatment consisting of conformal radiation and upfront therapy using TMZ and BV[6]. Thus, gross-total resection appears to be essential to prevent further relapses by BV-combined chemotherapy, as was reported in clinical studies on multi-drug chemotherapy[7].

PRES is a clinical-radiological entity that includes clinical symptoms such as headache, nausea, emesis, visual loss and seizures, all of which are generally reversible. Cranial MRI typically shows white matter abnormalities predominantly in the parietooccipital posterior regions, but involvement of white matter of the anterior and posterior regions as well as of the cerebellum and brain stem has also been reported[8]. In our case, interruption of therapy was inevitable due to development of PRES, although no risk factors for this disorder, such as renal dysfunction and hypertension were initially identified prior to commencement of BV and CPT11.BV occasionally causes PRES in both adult and pediatric patients, especially when

hypertension and proteinuria are poorly controlled, which was seen in the clinical course of the present case[8, 9].

Re-initiation of BV-combined therapy is feasible under close blood pressure monitoring and aggressive management of hypertension[8]. In our case, we decided to reduce the dose of BV and extend the treatment interval in combination with aggressive antihypertension treatment, because of persistent proteinuria after interruption; as a result, re-initiation of therapy was possible without exacerbation of adverse effects.

In conclusion, BV and CPT11 exerted beneficial effects for recurrent pediatric glioblastoma after gross-total resection, although no definite conclusions can be drawn from the small number of cases with relatively short periods of follow-up periods currently in the literature.

Figure legends

Figure 1. (A-F) Radiographic findings of our case. Gadolinium-enhanced T1-weighted images of cranial magnetic resonance imaging (MRI) reveal a huge tumor at the left frontal lobe at initial diagnosis (A). After a first partial resection (B), first recurrence occurred during local irradiation in combination with temozolomide (C). Despite a second gross-total resection (D), the patient developed a second local recurrence (E). After chemotherapy with bevacizumab and irinotecan, the patient is alive and disease-free more than 2 years after initial diagnosis (F). Arrows show tumors at the left frontal lobe.

Figure 2. (A-D) Radiographic findings after development of posterior reversible encephalopathy syndrome. FLAIR T2-weighted images of cranial MRI demonstrate multiple high-intensity areas at the putamen, thalamus, cerebellum, and brainstem at symptom onset (arrows) (A, B). Three weeks later, all high-intensity areas completely disappeared (C, D).

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Fig. 1

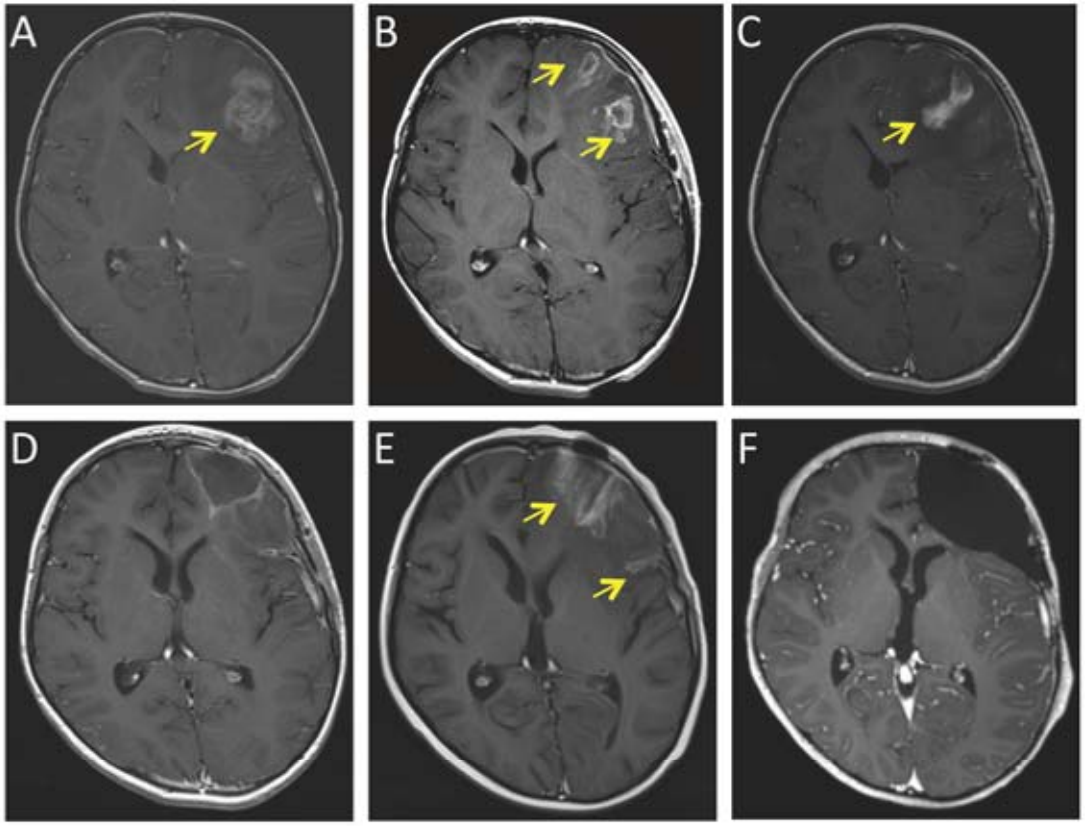

Fig. 2