Long-Term Remission of Recurrent Brainstem Pilocytic Astrocytoma with Neuraxis Dissemination Using Recombinant Human Endostatin After Failure of Vincristine and Carboplatin

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Key words
- Brainstem
- Carboplatin
- Chemotherapy
- Low-grade glioma
- Pilocytic astrocytoma
- Recombinant human endostatin
- Vincristine

Abbreviations and Acronyms
CBP: Carboplatin
CNS: Central nervous system
CV: CBP and VCR
EFS: Event-free survival
KPS: Karnofsky performance status
LGG: Low-grade glioma
MRI: Magnetic resonance imaging
PA: Pilocytic astrocytoma
rh-ES: Recombinant human endostatin
RT: Radiotherapy
VCR: Vincristine

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Citation: World Neurosurg. (2018) 110:397-402. https://doi.org/10.1016/j.wneu.2017.11.150

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

BACKGROUND: **There is no standard salvage treatment for recurrent and/or unresectable brainstem low-grade gliomas after failure from carboplatin and vincristine chemotherapy. Recombinant human endostatin (rh-ES), a mild inhibitor of angiogenesis, has been used for treating lung cancer. But so far as we know, there is no experience for brainstem gliomas.**

CASE DESCRIPTION: **The authors present a pediatric case of recurrent brainstem pilocytic astrocytoma with neuraxis dissemination who experienced tumor progression with carboplatin and vincristine chemotherapy but then had a dramatic and long-term remission for at least 29 months after combined treatment of rh-ES with carboplatin and vincristine.**

CONCLUSION: **This case suggests that the addition of rh-ES to carboplatin and vincristine regimens may be synergistic and results in a long-term remission in patients with brainstem low-grade gliomas, even if the tumor is widely spread in the central nervous system.**

INTRODUCTION

Pediatric brainstem low-grade gliomas (LGGs), especially those that are recurrent or associated with neuraxis dissemination, are among the major challenges of neuro-oncology. Due to the critical location, complete surgical resection should not be achieved at the cost of impaired function.[1] Optimal adjuvant therapies after resection are needed. Radiotherapy (RT) is often effective in inducing prolonged remission and clinical improvement.[2] However, the long-term side effects are significant and severe, such as vascular complications and malignant transformation.[3] Therefore the application of RT in brainstem tumors is limited. Currently, chemotherapy is the preferred treatment, stabilizing tumor growth long enough to delay or avoid RT. Carboplatin (CBP) and vincristine (VCR) are first-line chemotherapy regimens.[4] However, there is no standard salvage chemotherapy after failure of CBP and VCR (CV) chemotherapy.

We describe a 12-year-old patient with recurrent pilocytic astrocytoma (PA) with central nervous system (CNS) metastasis, who got a tumor progression after CV chemotherapy and achieved a dramatic and sustained response after combined treatment with recombinant human endostatin (rh-ES) and CV regimen.

CASE REPORT

History and Examination

A 12-year-old girl admitted to Sanbo Brain Hospital Capital Medical University (China, Beijing) was diagnosed with a recurrent glioma in the medulla and spinal cord in October 2014. Her initial diagnosis was made in 2010, when she presented with headaches and emesia. At that time, a magnetic resonance imaging (MRI) scan revealed hydrocephalus and a gadolinium-enhanced mass in the medulla oblongata. After surgery was given, a partial tumor resection was obtained and the pathology result was consistent with a pilocytic astrocytoma (PA) (World Health Organization grade I) (Figure 1, A–F). In addition, the tumor expressed cyclin D1 strongly and vascular endothelial growth factor weakly (Figure 1, G–H). The molecular pathologic analysis revealed BRAF-KIAA1549 fusion (Figure 1, I) and no BRAF V600E mutation (Figure 1, J). Later, she received no other treatment.

Initial Chemotherapy

In October 2014, the patient experienced progressive paraesthesia, weakness in the right side of body, difficulty in walking, dysarthria, dysphagia, and coughing after drinking water. Brain MRI (Figure 2, A–B) revealed a well-circumscribed enhanced mass in medulla oblongata (2.2 cm × 2.2 cm × 2.9 cm), with a large cystic component and an enhanced mural nodule. Spinal MRI (Figure 3, A–B) highlighted multiple enhanced lesions from cervical to sacrococcygeal regions. She was diagnosed with a recurrent tumor with widespread CNS dissemination. Her

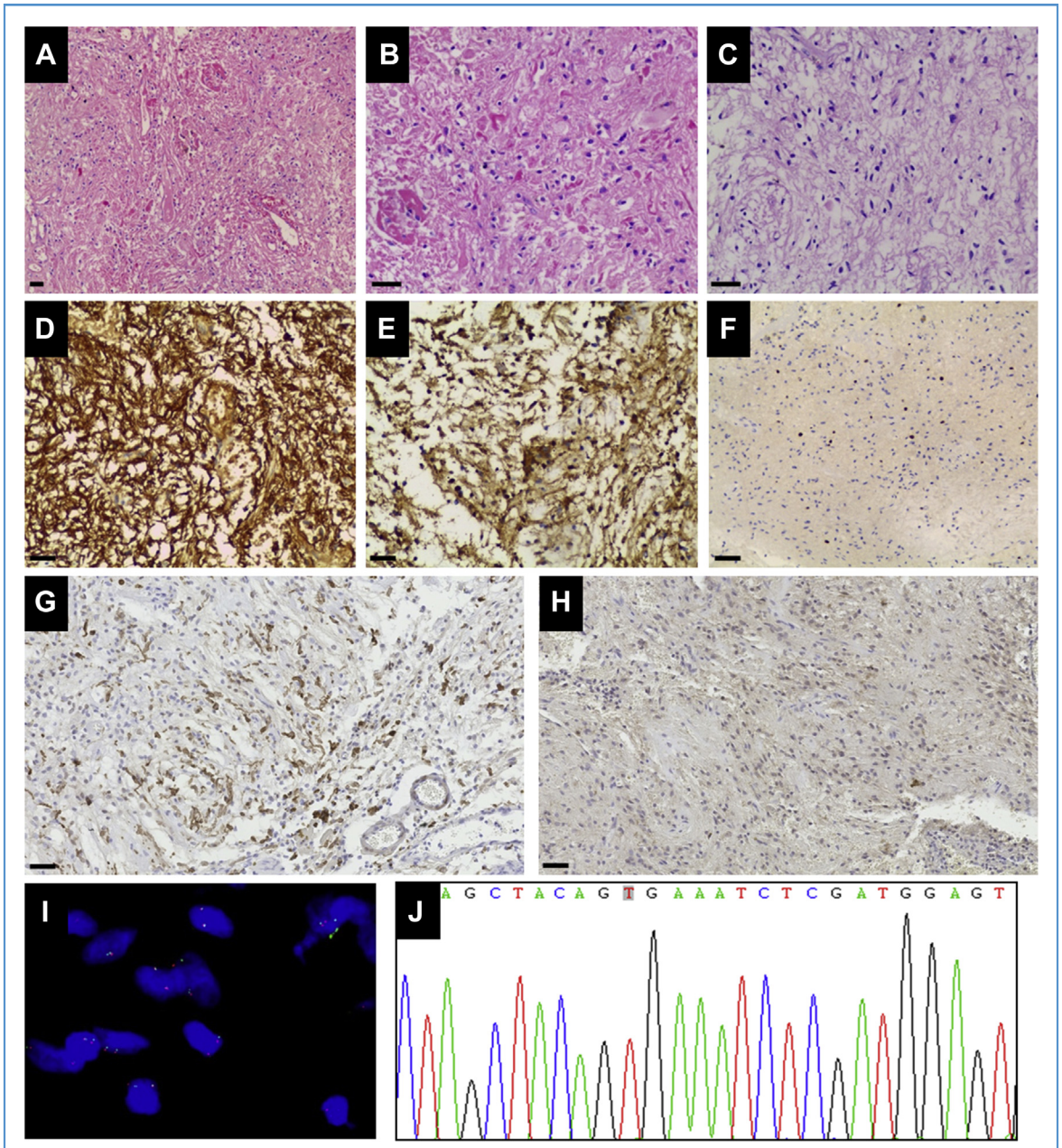

Figure 1. Typical histologic and molecular pathologic features of pilocytic astrocytoma. Routine hematoxylin-eosin staining shows abundant Rosenthal fibers and eosinophilic granular bodies. (**A**) ×100. (**B**) ×200. (**C**) Bipolar cells, ×200. Immunohistochemistry staining shows strongly expressed glial fibrillary acidic protein (**D**), S-100 (**E**), and cyclin D1 (**G**) and weakly expressed Ki-67 (**F**) and VEGF (**H**). The molecular pathologic analysis revealed *BRAF-KIAA1549* fusion (**I**) and no *BRAF* V600E mutation (**J**). Scale bars = 50 μm.

Karnofsky Performance Status (KPS) score was 50.

Failure from Initial Chemotherapy

In November 2014, the girl accepted chemotherapy of weekly CV regimen according to the previous studies described.[5-6] CBP and VCR were administered at doses of 300 mg/m^2 and 1.5 mg/m^2 (max dose 2 mg), respectively. Three weeks later, she experienced acute pneumonia without decrease of leukocytes. During that time, her symptoms of walking unsteadily, dysphagia, and coughing progressed. Her KPS score was 40. After she recovered from pneumonia, MRI obtained in December 2014 revealed a further increase of the overall size of the enhanced mass in medulla oblongata (2.9 cm × 2.2 cm × 3.6 cm) and the masses in the spinal cord were stable (Figure 2, C—D and Figure 3, C).

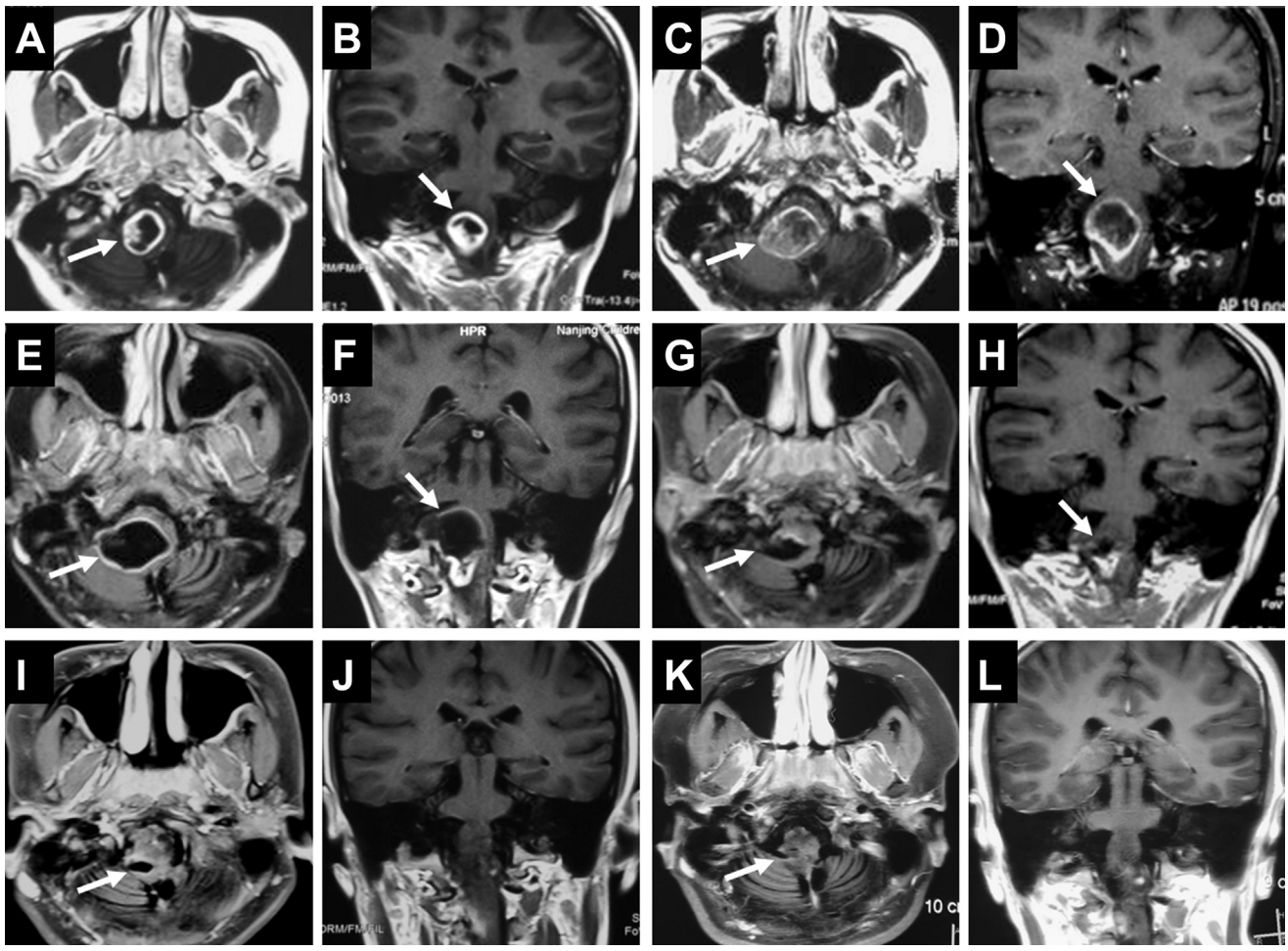

Figure 2. Brain T1-weighted magnetic resonance images. (**A**–**B**) Baseline images showed a well-circumscribed enhanced mass in medulla oblongata with a large cystic component and an enhanced mural nodule (*arrows*). (**C**–**D**) 3 weeks after carboplatin and vincristine chemotherapy (before rh-ES treatment), the tumor had progressed (*arrows*). (**E**–**F**) 2 months after addition of rh-ES, the enhanced intensity of the tumor was decreased while the cystic component was increased (*arrows*). (**G**–**H**) 4 months after addition of rh-ES, the enhanced intensity and the cystic component of the tumor were significantly decreased. A partial response was achieved (*arrows*). (**I**–**J**) At the end of treatment, there are only a few residual abnormal signals (*arrow*). (**K**–**L**) Sixteen months away from stopping treatment, it shows no signs of recurrent or progressive disease (*arrow*).

Combined Chemotherapy

On 5 December, 2014, we updated the chemotherapy regimen by adding with rh-ES. Rh-ES was administered intravenously once daily, 2 weeks on and 2 weeks off. CBP and VCR were administrated as usual. Two months later, brain MRI (January 2015) revealed a decrease in enhanced intensity of the tumor in the medulla oblongata while the cystic component was increased (Figure 2, E–F). The masses in the spinal cord were stable (Figure 3, D–E). Her clinical symptoms remained unchanged and KPS score was 40. The combined chemotherapy was continued.

Four months later, the patient's clinical symptoms were significantly improved in walking ability, swallowing function, and dysarthria. She could walk by the support of someone and eat by herself. Her KPS score was 60. MRI (April 2015) showed the tumor in the medulla oblongata was significantly decreased, though the masses in the spinal cord had no change (Figure 2, G–H and Figure 3, F–H). According to the MacDonald criteria, a partial response was achieved.

On 25 December 2015, treatment was stopped. MRI revealed no change of the residual abnormal signals compared with the former (Figure 2, I–J and Figure 3, I–J). The lesions were controlled. She was capable of speaking intelligibly, walking while holding the wall, eating, writing, and drawing by herself. The KPS score was 80. Follow-ups occurred at 3-month intervals.

Follow-Up

The last follow-up was on 5 May, 2017, sixteen months away from stopping treatment. The latest MRI showed no signs of recurrent or progressive disease (Figure 2, K–L and Figure 3, K–L). The girl was in good health and could walk alone without help. She achieved effective and sustained control of tumor and stable

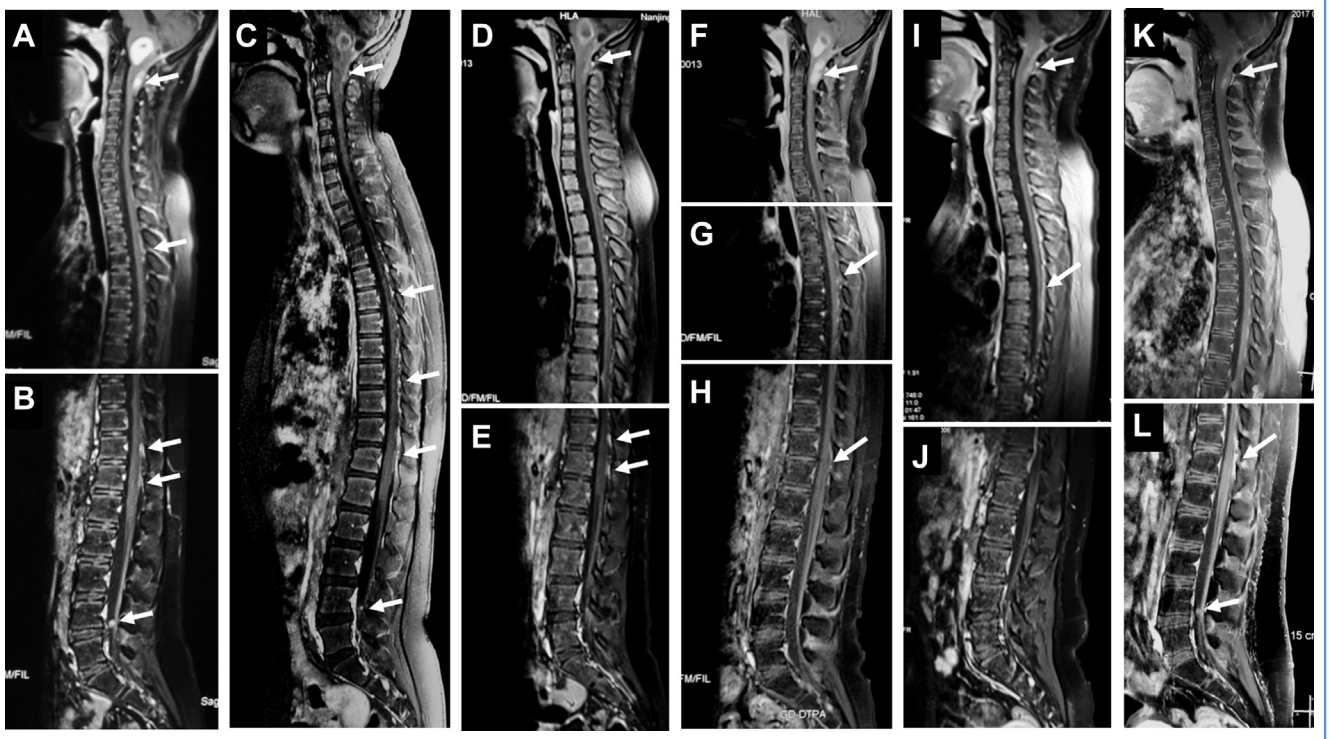

Figure 3. Spinal T1-weighted magnetic resonance images showed few changes among the treatment and follow-up. (**A**–**B**) Baseline images reveal multiple enhanced lesions from cervical to sacrococcygeal regions (*arrows*). (**C**) 3 weeks after carboplatin and vincristine chemotherapy. (**D**–**E**) 2 months after addition of rh-ES. (**F**–**H**) 4 months after addition of rh-ES. (**I**–**J**) At the end of treatment. (**K**–**L**) Sixteen months away from stopping treatment.

physical status. Her KPS was 90. Since the addition of rh-ES, this patient had a progression-free survival of 29 months.

Side Effects

The main side effect in the course of chemotherapy was hematologic toxicity, which was well tolerated.

DISCUSSION

CV Regimen—Well-Studied Chemotherapy Treatment for Recurrent LGGs

Currently, chemotherapy is the preferred treatment for recurrent brainstem LGGs with widespread CNS dissemination.

A prospective, randomized clinical trial (the children's oncology group trial A9952) compared the outcomes of newly diagnosed LGGs treated with CV with those with TPCV (thioguanine/procarbazine/lomustine/VCR) regimen in 2012. The 5-year event-free survival (EFS) rates were 39% ± 4% for CV and 52% ± 5% for TPCV ($P = 0.1$). However, the difference in EFS did not reach significance based on the stratified log-rank test. TPCV had slightly more toxicity, such as weakness, reduction of platelets, increase of ALT, and potential risk of second neoplasms.[7]

A retrospective observational study confirmed the efficacy of CV chemotherapy regimen in progressive or recurrent unresectable brainstem LGGs. Among the 16 children, 11 had a positive response, 4 had stable disease, and only 1 suffered disease progression. After a median follow-up of 57 months from initiation of chemotherapy, 11 out of 16 patients (68.8%) remain progression free.[4] Weekly vinblastine monotherapy has shown promising outcomes in treating pediatric progressive/recurrent or refractory LGGs in 2 phase II studies. The 5-year EFS was about 40%–50%, comparable with CV therapy. Nevertheless, the effect of vinblastine on the brainstem LGGs was not especially mentioned.[8-9] CV regimen was considered as the primary chemotherapy for the recurrent brainstem LGGs currently.

However, in our report, the patient experienced tumor progression at 3 weeks while on CV chemotherapy. Currently, there is no standard salvage chemotherapy for children with recurrent LGGs who have failed from the CV regimen.

Salvage Chemotherapy After Failure from CV Regimen

Activation of the RAS-RAF-MEK-ERK signaling pathway is thought to be the key driver of pediatric LGG growth. BRAF is typically activated in PA, through either an activating mutation or a fusion.[10] In our case, the tumor harbored *BRAF-KIAA1549* fusion. Sorafenib is a multikinase inhibitor targeting BRAF, VEGFR, PDGFR, and c-kit. A first multicenter phase II clinical trial conducted to determine the response rate to sorafenib in patients with recurrent or progressive LGGs was terminated because of an unexpected acceleration of tumor growth. This disappointing result is likely related to paradoxical ERK activation.[11]

Promising Results of rh-ES-Combined Chemotherapy in Our Case

Angiogenesis is critical for growth, invasion, and metastasis of solid tumors. Antiangiogenic therapy may be an alternative strategy in the treatment of recurrent brainstem LGGs. Rh-ES (commercial name Endostar), a new recombinant human endostatin developed in China, is an endogenous broad-spectrum angiogenesis inhibitor. A number of randomized, double-blind, and placebo-controlled phase II/III trials have revealed that a combination of rh-ES with conventional chemotherapy agents can significantly improve the therapeutic efficacy for several tumors, such as non–small-cell lung cancer,[12] breast cancer,[13] and melanoma.[14] But rh-ES, as a single agent, yielded a poor objective response rate compared with a standard second-line therapy of advanced tumor.[15] In our case, when the patient failed from the CV chemotherapy, we added rh-ES to the CV regimen. The patient got a sustained improvement of clinical status and radiographic response.

The effect of our case is better than that of vemurafenib in LGGs. A previous case report revealed a child with brainstem ganglioglioma was successfully treated with vemurafenib and vinblastine.[16] However, the follow-up time on treatment was only 3 months. Moreover, it was difficult to attribute the partial response solely to vemurafenib as it was given in combination with vinblastine at the beginning. Aguilera D et al[17] described a case that was treated with vemurafenib as a single agent. That patient with brainstem ganglioglioma received sustained single vemurafenib treatment for 1 year, resulting in >70% tumor reduction, but significant tumor progression occurred 3 months after vemurafenib terminated. In contrast, in our case report, rh-ES was added after failure from CV chemotherapy. The patient achieved an obvious response at the end of treatment and got a long-term remission for 29 months at least. Combining rh-ES with CV regimen dramatically improved the therapeutic efficacy without increasing adverse effects for pediatric brainstem LGGs.

Possible Underlying Mechanisms of Response of rh-ES

The addition of rh-ES results in significantly and clinically meaningful improvement. Several studies were being conducted to explore the underlying mechanisms of antiangiogenic efficacy of rh-ES.

Rh-ES could inhibit vascular endothelial growth factor (VEGF), metalloproteinases, integrins, c-myc, cyclin D1, and even Wnt signaling, thus inhibiting endothelial cell proliferation and migration, suppressing tumor vascularization and blocking the nutrition and oxygen supply to tumor cells.[18-20] Xu X et al[21] discovered that rh-ES suppressed angiogenesis through down-regulating beta-catenin and its downstream molecules cyclin D1 and VEGF. In our case, the tumor expressed cyclin D1 protein strongly and VEGF protein weakly (**Figure 1, G–H**), indicating that rh-ES could exert its function by targeting cyclin D1 and VEGF. The broad-spectrum antiangiogenic activity of rh-ES could help to reduce drug resistance and act synergistically with other cytotoxic drugs.[22]

In addition, blocking VEGF signaling decreases interstitial fluid pressure and promotes vascular normalization, thus inducing a pressure gradient across the vasculature and improving drug penetration in tumors.[23] This may be another underlying mechanism of rh-ES effective response. More studies are required for full understanding of the mechanisms of rh-ES.

In conclusion, our single experience suggests that combining rh-ES with CV regimen is a possible effective salvage treatment program for children with recurrent brainstem LGGs after failure from conventional CV chemotherapy. However, a larger clinical trial is necessary.

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Conflict of interest statement: This work was supported by Beijing Municipal Science & Technology Commission (Z151100004015165). The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Received 28 June 2017; accepted 25 November 2017

Citation: World Neurosurg. (2018) 110:397-402.
https://doi.org/10.1016/j.wneu.2017.11.150

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