Superselective Intracerebral Catheterization for Administration of Oncolytic Virotherapy in a Case of Diffuse Intrinsic Pontine Glioma

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Summary: New therapies are needed to improve current results in diffuse intrinsic pontine glioma. We present here the initial experience of administering Celyvir, autologous mesenchymal stem cells infected with ICOVIR-5, an oncolytic adenovirus that selectively replicates in cancer cells, by means of superselective intra-arterial delivery, in a patient diagnosed of diffuse intrinsic pontine glioma. Feasibility, safety, and morbidity rates of the superselective catheterization technique are comparable with those of diagnostic angiography. The intra-arterial approach warrants a greater contact of the mesenchymal stem cells with the tumor mass, and minimizes hemorrhages or vascular disruption. The tolerance to the 2 administrations was excellent, with no acute or delayed adverse effect, underscoring the feasibility of this technique for the delivery of virotherapies and/or cellular therapies in this location.

Key Words: diffuse intrinsic pontine glioma, virotherapy, angiography

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CLINICAL REPORT

A 9-year-old girl presented with a tonic generalized seizure after traumatic head injury when playing (August 2010). In the previous 2 months she had progressively developed headaches, blurred vision, and clumsiness. Her cranial magnetic resonance (MR) was consistent with high-grade diffuse intrinsic pontine glioma (DIPG). Diagnosis was done at her hospital based on advanced MR imaging features with conventional MR (including T2-weighted MR imaging and precontrast and postcontrast T1-weighted MR imaging). Biopsy was not performed.

Radiotherapy was delivered (1.8 Gy daily in 30 fractions, a total dose of 54 Gy)[1] to the pontine area plus concomitant temozolomide (50 mg/m^2), followed by another 6 cycles of temozolomide in monotherapy. After the first 2 months of treatment, MR showed significant improvement and the patient was clinically asymptomatic. Nine months after her diagnosis (May 2011), she developed blurred vision and conjugate gaze palsy. On MR, a new cystic lesion within her DIPG, compressing the IV ventricle and without signs of hydrocephalus was identified. Upon this first progression, she received 7 cycles of chemotherapy as second-line therapy: bevacizumab (10 mg/kg/dose, days 1 and 14), and irinotecan (125 mg/m^2/dose, days 1 and 14), with 2 weeks rest between cycles. The child had no significant toxicities and her symptoms disappeared. Fourteen months after her initial diagnosis, she worsened clinically again (second progression, October 2011), chemotherapy was discontinued and she was referred to our Hospital for third-line treatment with superselective intra-arterial cerebral infusion of oncolytic adenoviruses.

Her clinical examination at this moment showed Cushingoid phenotype; adequate level of awareness; right conjugated gaze palsy, with normal convergent gaze; left VI nerve palsy; left infranuclear VII nerve palsy; mild-moderate dysarthria; mild dysphagia for solids and liquids; she had 4/5 strength in her right upper extremity and 5/5 strength in the remainder; she had bilaterally enhanced Achillian, patellar, and tricipital reflexes, without increased reflexogenic area; she had bilateral Babinski sign, without clonus response to stretch; epicritic, protopathic, and proprioceptive sensitivities were normal; thermoalgesic sensitivity was not tested; she had neither dysmetria nor dysdiadococinesia; Romberg could not be evaluated; she had a mild no-no head tremor when standing, she required assistance to walk, and her gait was unstable.

Pretreatment evaluation showed a DIPG with poorly defined borders and heterogeneous enhancement (World Health Organization grade III) (Figs. 1A, B). MR angiogram showed a dominant left vertebral artery and a hypoplastic right vertebral artery; and a fetal origin of the left posterior cerebral artery which originated from the left carotid siphon as a normal variation (Fig. 2A).

Eighteen months after her initial diagnosis (February 2012) and given the ominous prognosis, intra-arterial cerebral infusion of oncolytic adenoviruses was considered with the IRB approval and with parental informed consent. The use of Celyvir, autologous mesenchymal stem cells (MSCs) infected with ICOVIR-5, an oncolytic adenovirus that selectively replicates in cancer cells, has been previously reported at our institution.[2]

The vascular supply for the tumor mass arised from perforators from the left posterior cerebral artery, basilar trunk, and cerebellar arteries. The left posterior cerebral artery had a fetal origin, arising from the ipsilateral internal carotid artery (Fig. 2B), therefore, the superselective infusion was performed as described below. Under general anesthesia, a bifemoral approached was performed, with both catheters placed in the left vertebral and subclavian artery, respectively. A microcatheter was placed below the origin of the right posterior inferior cerebellar artery and a balloon microcatheter (Magellan 4 × 7 mm; Balt Extrusion, Montmorency, France) was navigated into the P1 segment of the right posterior cerebral artery, which did not supply the tumor (Fig. 2C). Under temporary occlusion of the right posterior

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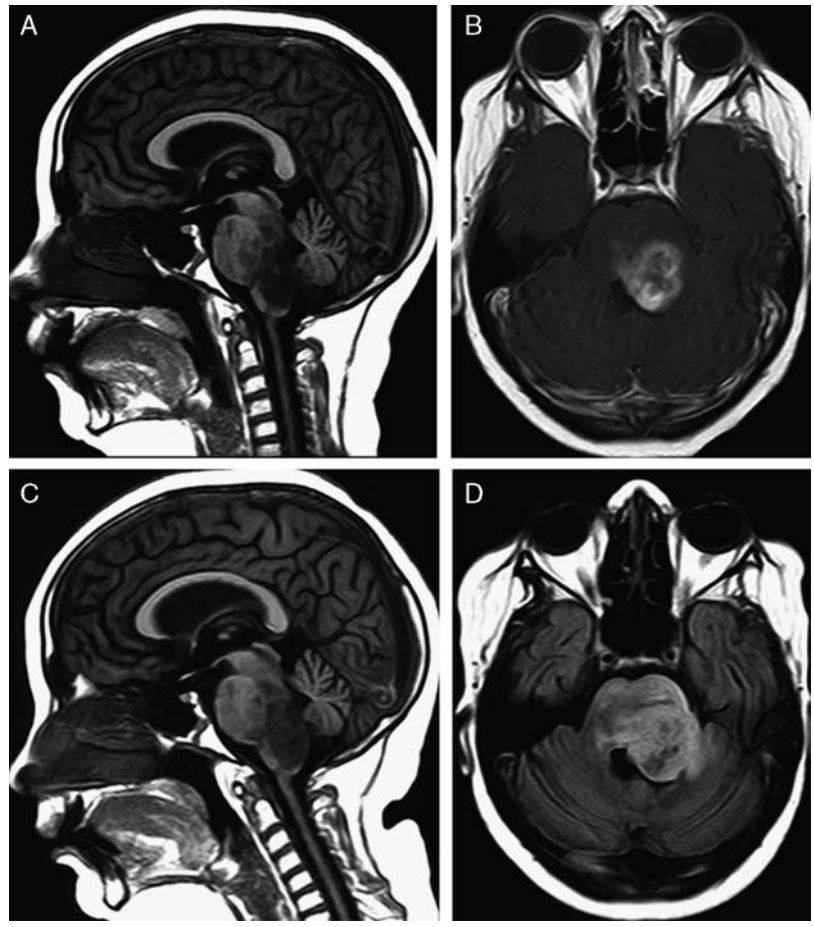

FIGURE 1. Magnetic resonance (MR) images of the tumor. A, Sagital T1-weighted MR showed diffuse infiltration with poorly defined borders and enlargement of the brainstem. B, Axial T1 postcontrast MR showed variable enhancement. The posterior portion of the tumor had moderate and heterogeneous pattern of enhancement. A and B, Pre-Celyvir therapy (October 2011). C, Sagittal T1-weighted MR showed diffuse infiltration and enlargement of the brainstem. Lack of tumor progression. D, Axial T2 FLAIR MR clearly defined the expansive pontine tumor with high signal and exophytic component that extends posteriorly. Effacement of fourth ventricle. C and D, One month post-Celyvir therapy (March 2012).

cerebral artery, 35 mL of saline solution of Celyvir (75% of the total dose) were infused through the microcatheter placed below the origin of the posterior inferior cerebellar artery (Fig. 2D). After catheterization of the left internal carotid artery and microcatheterization of the fetal left posterior cerebral artery, the remaining 15 mL of saline solution of Celyvir (25% of the total dose) were infused (Fig. 2E).

Follow-up posteroanterior and lateral projections of the left vertebral artery and the left posterior cerebral artery demonstrated normal anterograde flow without evidence of vascular injury. Dexamethasone was initiated to prevent brainstem edema. The dose was tapered every 3 to 4 days. There were no procedure-related complications and the follow-up MRI 10 days later showed no signs of edema.

One month later, her MR showed stable tumor size (Figs. 1C, D). At physical examination, the clinical picture was worse due to fixed gaze to her left side; increased difficulties in swallowing; 3/5 strength in her right upper extremity; lack of epicritic sensitivity in her right hemibody and hemiface; dysmetria and intention tremor in her right upper extremity; and a no-no head tremor with postural changes. A second superselective intra-arterial cerebral infusion of Celyvir was performed, total dose of 2.5×10^6 infected cells, following the same procedure as described above without procedure-related complications. Dexamethasone dosing remained unchanged after the procedure. The following days there were no changes in the clinical examination and cranial MR 4 days later showed no signs of brainstem edema. Two weeks later the patient was discharged.

One month after the second oncolytic adenovirus infusion, the cranial MR showed signs of progression with increased tumor size and triventricular hydrocephalus. The child underwent palliative care and passed away 6 weeks later, 21 months after her initial diagnosis.

COMMENTS

DIPG have a dismal prognosis under current therapeutic strategies based on radiation, chemotherapy,[3] immunotherapies,[4,5] or convection enhanced/convective drug delivery.[6,7] End-stage progressive disease invariably occurs after the initial response, with no long-term survival. Therefore, new therapies are needed to improve current results. We present here the initial experience with an experimental approach we have used in other pediatric tumors,[2] autologous MSCs infected with ICOVIR-5, an

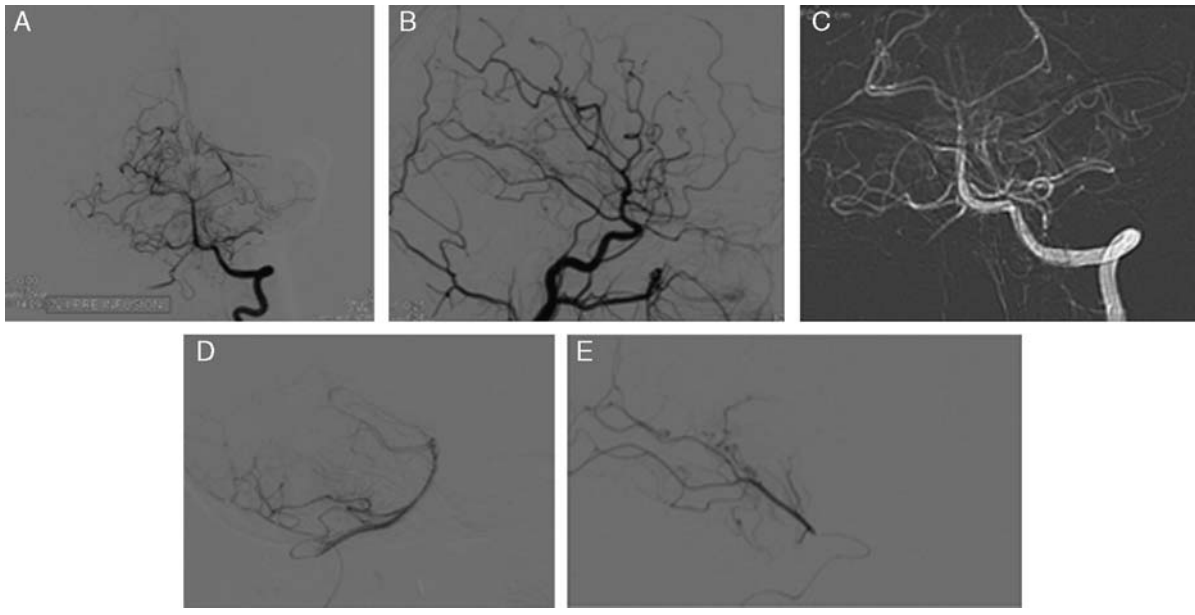

FIGURE 2. Images of the supraselective intracerebral catheterization procedure. A, Left vertebral artery catheterization (posteroanterior projection) showing a fetal origin of the left posterior cerebral artery. B, Left internal carotid artery catheterization showing fetal origin of the left posterior cerebral artery, arising from the carotid artery. C, Left vertebral artery catheterization under roadmapping. The right posterior cerebral artery shows no opacification due to an indwelling balloon, intended to block the anterograde flow. D, Selective microcatheterization of the basilar artery. The microcatheter is placed in the basilar artery and mesenchymal stem cell were infused under balloon inflation. E, Superselective catheterization of the origin of the fetal left posterior cerebral artery.

oncolytic adenovirus that selectively replicates in cancer cells. ICOVIR-5 is a conditionally replicative adenovirus, with replication restricted to cells with an activated RB pathway, a hallmark of human cancers. ICOVIR-5 was developed and tested initially for glioma therapy.[2] Celyvir combines ICOVIR-5 with MSCs, to take advantage of the capacity of MSCs for targeting the tumor stroma.

Superselective intracerebral catheterization was first used in the mid 80s and is widely used for the treatment of vascular diseases. In the late 80s, microcatheters were used to selectively infuse chemotherapy for malignant gliomas.[8,9] Feasibility, safety, and morbidity rates of the superselective catheterization technique are comparable with those of diagnostic angiography. We decided to administer Celyvir through superselective catherterization due to the limitations imposed by the brainstem localization of the glioma. The intra-arterial approach warranted a greater contact of the MSCs with the tumor mass compared with that of the intravenous approach. In contrast, intra-arterial infusion minimizes hemorrhages or vascular disruption which might happen with stereotaxic MSCs implantation. In this case, there was no edematous reaction following the intra-arterial infusion of MSCs, as compared with reported cases after stereotactic implantation. The tolerance to the 2 administrations was excellent, with no acute or delayed adverse effect, underscoring the feasibility of this technique for the delivery of virotherapies and/or cellular therapies in this location. We did not see any clinical benefit in the patient, suggesting that further improvements are needed.

REFERENCES

1. Freeman CR, Suissa S. Brain stem tumors in children: results of a survey of 62 patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys*. 1986;12:1823–1828.
2. Garcia-Castro J, Alemany R, Cascalló M, et al. Treatment of metastatic neuroblastoma with systemic oncolytic virotherapy delivered by autologous mesenchymal stem cells: an exploratory study. *Cancer Gene Ther*. 2010;17:476–483.
3. Recinos PF, Sciubba DM, Jallo GI. Brainstem tumors: where are we today? *Pediatr Neurosug*. 2007;43:192–201.
4. Okada H, Pollack IF. Do we need novel radiologic response criteria for brain tumor immunotherapy? *Expert Rev Neurother*. 2011;11:619–622.
5. Maes W, Van Gool SW. Experimental immunotherapy for malignant glioma: lessons from two decades of research in the GL261 model. *Cancer Immunol Immunother*. 2011;60:153–160.
6. Bartels U, Hawkins C, Vézina G, et al. Proceedings of the diffuse intrinsic pontine glioma (DIPG) Toronto Think Tank: advancing basic and translational research and cooperation in DIPG. *J Neurooncol*. 2011;105:119–125.
7. Nduom EK, Walbridge S, Lonser RR. Comparison of pulsed versus continuous convective flow for central nervous system tissue perfusion: laboratory investigation. *J Neurosurg*. 2012;117:1150–1154.
8. Théron J, Villemure JG, Worthington C, et al. Superselective intracerebral chemotherapy of malignant tumours with BCNU. Neuroradiological considerations. *Neuroradiology*. 1986;28:118–125.
9. Tyler JL, Yamamoto YL, Diksic M, et al. Pharmacokinetics of superselective intra-arterial and intravenous [11C] BCNU evaluated by PET. *J Nucl Med*. 1986;27:775–780.

