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BRIEF REPORT

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Combined high-dose intra-arterial and intrathecal chemotherapy for the treatment of a case of extraocular retinoblastoma

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Abstract

Patients with retinoblastoma and central nervous system (CNS) involvement are rarely curable with available treatments. We designed a high-dose intra-arterial regimen targeting the ophthalmic artery and chiasm combined with intrathecal chemotherapy to treat a 4-year-old patient with retinoblastoma metastasized to the CNS. After three cycles of this regimen, including carboplatin, melphalan, and intrathecal topotecan, a partial response of the orbital tumor mass and chiasmatic lesion, and complete response in the cerebrospinal fluid and bone marrow were achieved. This new treatment strategy may be explored as a treatment component for patients with overt extraocular retinoblastoma and CNS dissemination.

KEYWORDS

intra-arterial chemotherapy, intrathecal topotecan, metastatic retinoblastoma

1 | INTRODUCTION

Despite the use of systemic high-dose chemotherapy, autologous cell rescue, and radiotherapy, patients with retinoblastoma and CNS extension remain virtually incurable.[1,2]

In less developed countries, these patients usually present with concomitant massive orbital extension and occasionally distant disseminated disease.[3] As evidenced from the results of high-dose therapy in metastatic disease outside the CNS, higher exposure of the target tissues to chemotherapy likely plays a critical role in disease eradication.[2,3] Nevertheless, systemic chemotherapy fails to achieve effective drug levels in critical tissues. Preclinical studies have shown a significantly higher chemotherapy exposure in the optic nerve (the major source for CNS dissemination) after intra-arterial chemotherapy (IAC) compared to standard IV infusion[4]; however, most cases with CNS invasion have extension through the chiasm, which is not supplied by the ophthalmic artery. Thus, if this modality was to be considered for treating these cases, an alternative route of drug delivery to the optic nerve and chiasm should be developed. IAC alone would not be effective for the control of leptomeningeal dissemination, which is usually present in these cases. Intrathecal or ideally intraventricular chemotherapy would lead to pharmacologically active drug concentrations in the cerebrospinal fluid (CSF) and because of its low toxicity profile it may be administered concomitant to IAC.[5–8]

Thus, assuming that maximizing drug concentrations in the target tissues would be an option for improving tumor control in metastatic retinoblastoma in the CNS, we designed a strategy including high-dose IAC with a modified technique to administer chemotherapy to the optic nerve and chiasm plus intrathecal chemotherapy for the treatment of a

Abbreviations: CNS, central nervous system; CRX, cone-rod homeobox; CSF, cerebrospinal fluid; IAC, intra-arterial chemotherapy

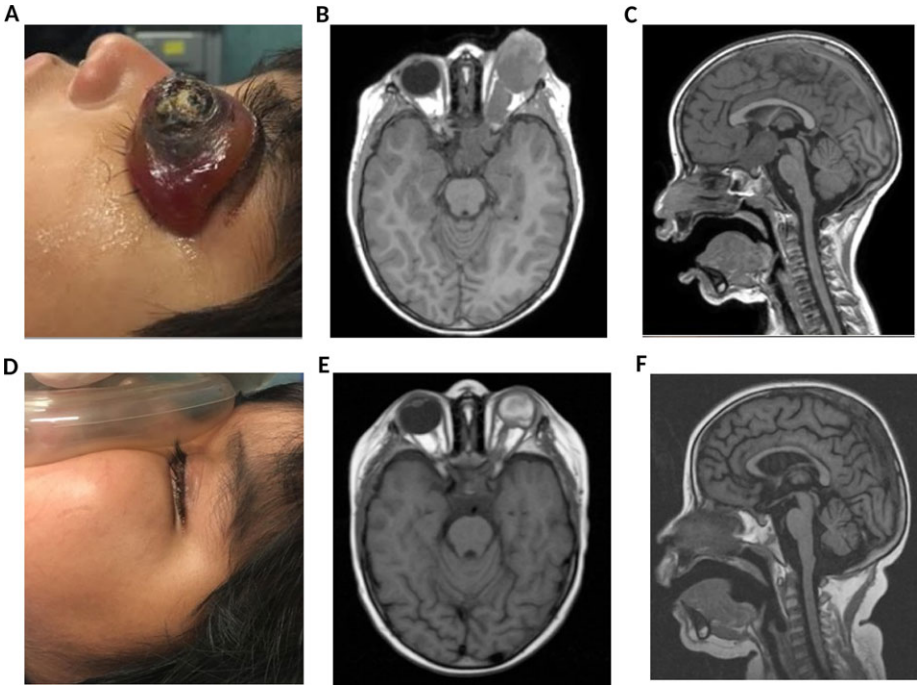

FIGURE 1 Clinical presentation of advanced retinoblastoma with orbital involvement and buphthalmos showing (A) left eye orbital involvement at clinical presentation, (B) MRI at hospitalization showing left retinoblastoma with ocular mass, enlargement of the optic nerve, and (C) chiasm and suprasellar cistern involvement. After three cycles of intra-arterial and intrathecal chemotherapy, the patient showed (D) marked reduction of the orbital tumor mass and (E, F) partial radiological response

case with limited accepted treatment options due to particular socioeconomic issues.

2 | CASE REPORT

A 4-year-old patient presented with a massive and painful unilateral orbital mass (Figure 1A). The child came from an indigenous community with a 1-year history of leukocoria treated for months with antibiotics. He showed severe general weakness, dehydration, and weight loss. During admission, he showed headache, dizziness, and progressive cognitive deterioration. Magnetic resonance imaging (MRI) showed extraocular extension of the left eye with involvement of the optic nerve and intracranial extension to the optic chiasm, suprasellar space, and interpeduncular cistern (Figure 1B and 1C).

An orbital biopsy histologically confirmed the diagnosis of retinoblastoma. Bone marrow aspirates and biopsies were negative by histopathology but positive for cone-rod homeobox (CRX) mRNA, which was considered minimal dissemination.[9] CSF cytology was positive for tumor cells and positive for ganglioside GD2 and CRX. Therefore, the patient was classified as stage IVb.[10]

Following the child's rapid clinical deterioration during diagnostic work-up, a thorough discussion of the treatment options was offered to the child's family who initially declined any therapy including high-dose systemic chemotherapy and expressed their wish to surgically resect the orbital mass so the child could be brought back home and eventually die. Orbital exenteration was not considered because of the child's poor clinical status and systemic chemotherapy was proposed but the family asked for a less toxic option to avoid myelotoxicity and transfusions.

TABLE 1 Treatment plan including drugs, doses, and routes of administration

Cycle 1	Day 1: IAC carboplatin (70 mg, 15 min) and IAC-occlusion balloon carboplatin (130 mg, 5 min) Days 2, 5, and 8: Intrathecal topotecan (0.4 mg) and intrathecal dexamethasone (4 mg)
Cycle 2	Day 1: IAC melphalan (3 mg, 15 min) and IAC-occlusion balloon carboplatin (200 mg, 5 min) Days 2, 9, and 16: Intrathecal topotecan (0.4 mg) and intrathecal dexamethasone (4 mg)
Cycle 3	Day 1: IAC melphalan (3 mg, 15 min) and IAC-occlusion balloon carboplatin (200 mg, 5 min) Days 2, 9, and 16: Intrathecal topotecan (0.4 mg) and intrathecal dexamethasone (4 mg)

Abbreviations: IAC, intra-arterial chemotherapy; IAC-occlusion balloon, intra-arterial chemotherapy using an occlusion balloon.
IAC was performed as previously reported.[14,15]

We proposed a combined treatment consisting of a modified IAC and intrathecal chemotherapy and informed consent was obtained. IAC treatment included intra-arterial ophthalmic artery infusion to target the eyeball and especially the optic nerve followed by infusion through balloon occlusion of the middle cerebral artery to target the chiasm. This procedure was favored by the fact that the patient had an aplastic A1 segment of the anterior cerebral artery, and thus the suprasellar area and optic chiasm were irrigated by the carotid artery, the posterior communicating artery, and the choroidal artery. The treatment schedule is listed in Table 1. The selected dose of carboplatin to target the chiasm was based on previous publications of

patients with glioma reporting doses of 400 mg/m^2 for intra-arterial use.[11–13]

Dramatic clinical improvement was seen during treatment (Figure 1D) and the child evolved from not being able to get out of bed to regaining his normal play activity. Disease status was assessed after three treatment cycles. MRI showed partial resolution of the orbital tumor mass and the chiasmatic lesion (Figure 1E and 1F) and complete remission was documented in the CSF. Minimal disease measured by CRX mRNA was negative in the bone marrow and the CSF. No grade 1–4 hematological toxicity was observed throughout treatment.

The eye was enucleated and histopathologic analysis showed complete tumor necrosis without choroid, scleral, or optic nerve involvement. After recovering from enucleation, the family asked to go back to their community and was lost to follow-up.

3 | DISCUSSION

The treatment used in this case may provide preliminary evidence for a future strategy to treat extraocular retinoblastoma with CNS invasion with high-dose IAC and intrathecal chemotherapy as putative treatment components. We applied the rationale that was used to improve results in metastatic retinoblastoma without CNS invasion based on the concept that maximum doses of chemotherapy at target tissues are the key components for disease control.[1] However, for these cases, maximum chemotherapy exposure in critical tissues such as the optic nerve, the chiasm, and the CSF would not be optimal with systemic chemotherapy so we designed an alternative strategy. The results from two previous studies were used as a background for this strategy. First, the 80-fold higher exposure attained in the optic nerve, retina, and vitreous with IAC compared to the same intravenous dose in an animal model would be critical to obtain a higher chemotherapy exposure.[4] The marked response to treatment in this child cannot be explained only by direct exposure of the affected tissues after IAC. Exposure after systemic distribution of chemotherapy and intrathecal treatment may also have played a role. Second, according to minimally disseminated disease evaluations, CSF dissemination occurs as an isolated event with no relation to concomitant systemic dissemination. Thus, intensive therapy targeting the CSF with intrathecal or intraventricular chemotherapy might be important for tumor control.[3,7,9] Here, we faced the challenge of targeting the chiasm, which is not supplied by the ophthalmic artery but shows a complex irrigation. The use of a local balloon occlusion method shows benefits for improving local drug exposure in the chiasmatic areas.[12] An advantage in this case was the existence of an aplastic anterior cerebral artery allowing for the placement of only one balloon in the middle cerebral artery to occlude blood flow and expose the optic chiasm to the infused chemotherapy. In patients with a normal A1 segment, the injection technique can be performed by using two low-profile balloons, one placed in the M1 segment of the middle cerebral artery and the other in the A2 segment of the anterior cerebral artery.[16,17] Nonetheless, safety concerns in terms of neurological complications and systemic and local adverse events should not be disregarded and we emphasize the role of a trained neurointerventionist in performing the interventional procedure. Also, as IAC was not intended for sight saving, a higher and close to systemic dose of chemotherapy could be given. This may enhance the antitumor effect by systemic distribution, which was evident by the clearance of minimally disseminated disease in the bone marrow after three cycles. Systemic chemotherapy may also achieve a comparable clinical response but the high dose needed would have caused severe and life-threatening toxicity in these severely affected children.

Finally, as previously published, we highlight the activity and safety of intrathecal topotecan for high-risk retinoblastoma with CSF involvement included in this multimodality treatment.[7] We selected intrathecal topotecan based on its activity in retinoblastoma and previous reports for intrathecal use.[5–7,18]

Our patient abandoned therapy for social reasons, so it is highly likely that treatment was insufficient and further treatment would have been needed for tumor control.

Based on these encouraging results, we propose that combined high-dose intra-arterial and intrathecal treatment may be further explored as components of the treatment of children with retinoblastoma and CNS invasion in a multimodal strategy.

ETHICS STATEMENT

Informed consent has been properly obtained from parents.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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