Clinical improvement of diffuse intrinsic pontine glioma treated with radiation therapy concurrent with temozolomide: A case report

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SUMMARY

Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive paediatric brain tumour and nowadays has not had satisfactory result, with most patients do not survive within 1 year of diagnosis. Due to its proximity to critical organs, surgery is avoided, and radiation is the mainstay of treatment. In this case report, we present a case of DIPG treated with radiation and concurrent temozolomide. A 7-year-old child was admitted with complaints of weakness in the eyelid, upper and lower limbs 2 months ago. Physical examination showed tetra paresis and bilateral cranial nerve palsy. Magnetic resonance imaging (MRI) scan showed intracranial tumour consistent with DIPG. Diagnosis was made based on imaging as surgery or biopsy can lead to further morbidity. The patient underwent radiotherapy with concurrent chemotherapy of temozolomide. Radiation was given by dose of 54 Gy/30 fractions (30 × 1.8 Gy) with volumetric arc therapy (VMAT). Due to technical issue after the first five irradiations resulting in 2 weeks delay, boosting of dose by 5 × 1.8 Gy was then given, hence, the total dose was 63 Gy. The booster only targeted the gross tumour volume. Following radiation, the patient felt clinical improvement. Eyelid and limb movement improved since the 15th fraction. At the last fraction, the patient's condition improved symptomatically, but experienced complaints related to post radiation oedema including dizziness and nausea. These complaints were improved upon steroids administration. The MRI evaluation will be done after 8 to 12 weeks of radiation, considering the effects of acute radiation could still occur at this period. In conclusion, a combination of radiotherapy and temozolomide could be an option for DIPG management, with tolerable acute toxicity and possible clinical improvements.

INTRODUCTION

Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive and fatal brain cancer that primarily affects children.[1] It arises in the brainstem, specifically the pons, and has a near 100% fatality rate. A previous study in the United States reported that the incidence of DIPG is estimated to be around 200 to 300 cases per year.[1] Furthermore, DIPG only constitutes approximately 10% of all paediatric brain tumour cases. The DIPGs are characterised by their unique genetic makeup, with nearly 80% of cases harbouring a K27M mutation in either the H3.3 or H3.[1] histone genes. This mutation is found in 78% of DIPGs and 14% of non-brainstem paediatric glioblastomas.[2]

The clinical features of DIPG can vary depending on the tumour location, nature, and growth pattern.3 DIPG can result in the dysfunction of multiple cranial nerves, leading to symptoms such as difficulty swallowing, changes in speech and facial weakness.[3]

DIPG often affects the cranial nerves, leading to various symptoms such as diplopia (double vision) due to abducens palsy (cranial nerve VI dysfunction). Facial weakness or asymmetry may also occur due to damage to cranial nerve VII.[4] DIPG can also cause motor deficits, including ataxia (lack of coordination), dysmetria (inaccurate movements) and dysarthria (difficulty speaking).[3]

The treatment of DIPG remains a significant challenge due to the aggressive nature of the tumour and its location in the brainstem. Focal radiotherapy continues to be the standard treatment for children diagnosed with DIPG, extending overall survival by approximately 3 months. Without radiotherapy, the median overall survival was 5 months.[4] Given the difficulty in treating DIPG, there are ongoing research efforts and clinical trials aimed at understanding the biology of the tumour and developing innovative treatment approaches. The use of concurrent radiation with temozolomide as a form of combination treatment has also been used previously.[5]

We report a case of clinical improvement in DIPG in a 7-year-old child treated with a combination of radiation and concurrent temozolomide.

CASE PRESENTATION

A 7-year-old child presented to the radiation oncology clinic with a complaint of difficulty opening the eyelids for the past 2 months. The complaint was accompanied by difficulty swallowing, occasional choking, as well as weakness and stiffness in the upper and lower extremities. The patient had no significant prior medical history.

Physical examination revealed the child appeared weak, with a condition of ptosis in the eyes, along with an impression of weakness in the upper and lower extremities.

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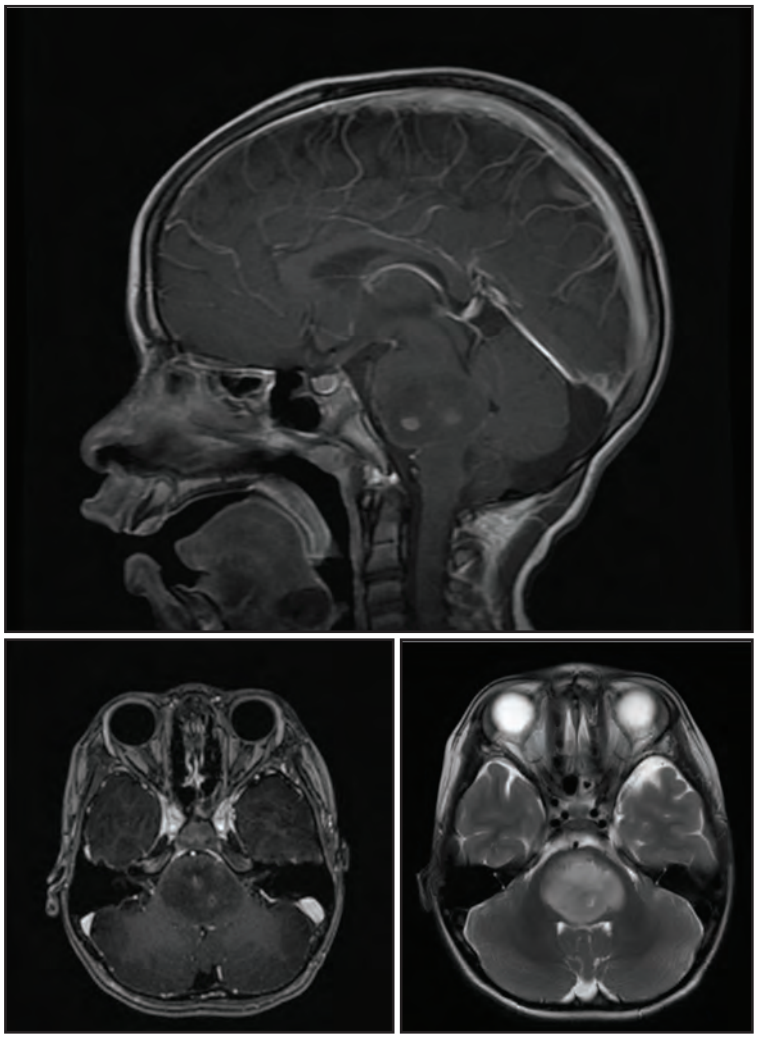

Fig. 1: Appearance of DIPG on T1 and T2 MRI sequences in sagittal and axial sections

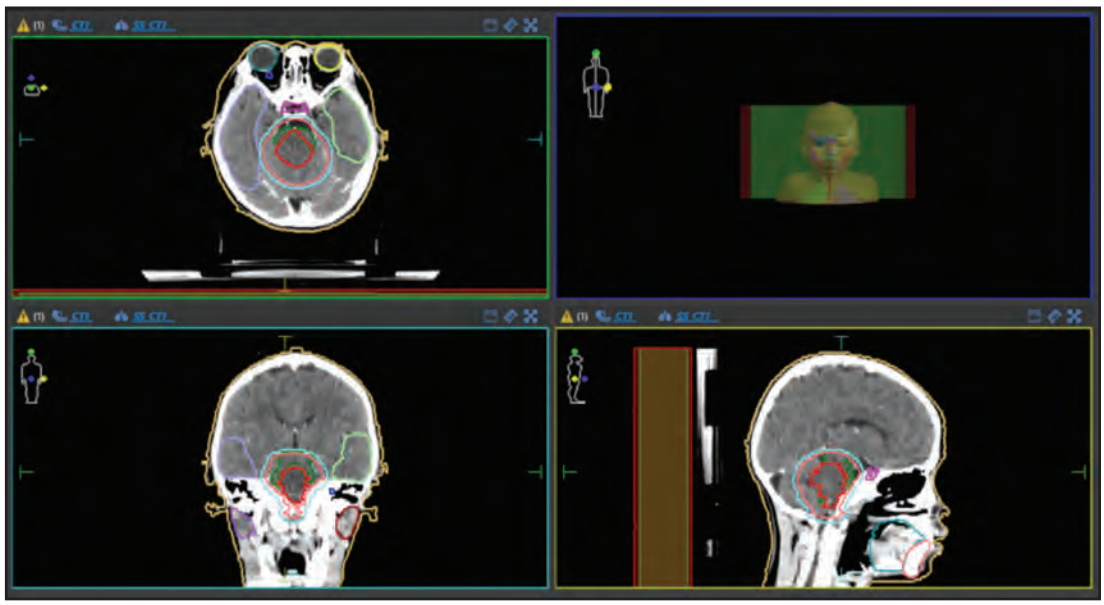

Fig. 2: Contouring in the case of DIPG. The red line indicates GTV, pink shows CTV, and light blue represents PTV

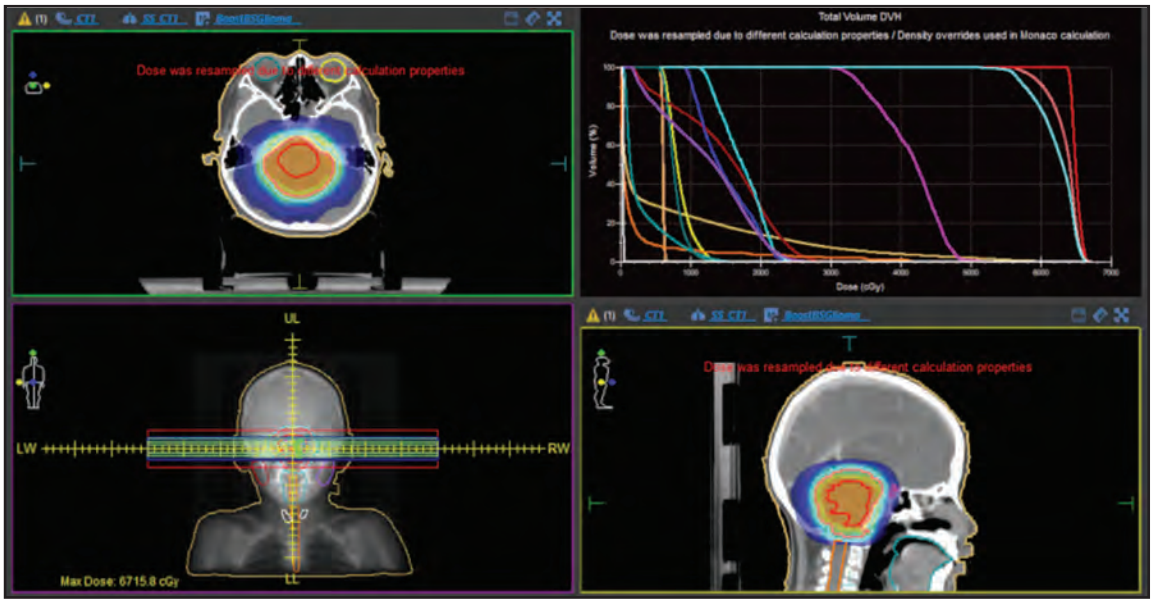

Fig. 3: The result of the TPS dose calculation displayed in the form of a colour wash. The orange or reddish colour indicates the prescription dose/higher dose, while the green or tendency towards blue shows the spread of a lower dose

The patient presented with visual acuity of 6/19 in the right eye (OD) and 6/15 in the left eye (OS) with nystagmus was present. The patient exhibited free ocular movement in both eyes, indicating normal mobility of the eyes without restriction or weakness in extraocular nerves. Examination revealed clear corneas, positive light reflex and clear lenses in both OD and OS. Fundus examination showed clear media in both eyes (OD and OS), papillary diameter measured 0.3-disc diameters in both eyes, and retinal arteriovenous ratio was 2/3 in both eyes. The patient exhibited grade 2 movement in both upper and lower extremities, as per the Medical Research Council (MRC) scale. The child also appeared inactive and difficult to engage in communication but was still seemingly aware of his surroundings.

MRI examination showed an enlargement of the pons due to a mass filling in the brainstem, measuring 3.5 × 3 × 2.3 cm, hypointense on T1 sequence and hyperintense on T2 (Fig. 1). Upon administering gadolinium contrast, there appeared to be several areas that enhanced the contrast heterogeneously. These findings are consistent with a DIPG. No lesions were found in the spinal cord.

The parents have already consulted with a neurosurgeon and a paediatric oncologist and based on the signs and symptoms as well as the MRI findings, a diagnosis of DIPG was established. The neurosurgeon did not recommend performing a biopsy or excision due to the potential morbidity that may be caused. The patient was then referred to a radiation oncologist to undergo radiotherapy. Meanwhile, the paediatric oncologist considered administering temozolomide chemotherapy concurrently with radiotherapy.

Irradiation for this patient was planned with a conventional dose of 54 Gy delivered in 30 fractions (30 × 1.8 Gy). Simulation was conducted with a CT simulator, Canon Aquilion Prime. Image acquisition was performed on the head and neck area. From the CT simulator results, an image was obtained and then exported to the Treatment Planning System (TPS) Monaco Sim version 5.11. Contouring was performed on the target volume, with the outlining of the gross tumour volume (GTV), followed by a radial expansion of 1 cm to form the clinical tumour volume (CTV), and further expansion of 0.5 cm to form the planning target volume (PTV) (Fig. 2). The PTV area will receive radiation of 54 Gy.

Radiation planning was performed using volumetric arc therapy (VMAT) technique with TPS Monaco Plan software version 5.11 (Fig. 3). After the dose calculation by medical physicist with TPS was completed, and constraints were met, the radiation planning data was sent to the LINAC Versa HD machine for the execution of radiation.

Radiation was administered five times a week, every Monday to Friday, so the radiation would be completed in 6 weeks. During the radiation, the patient also received oral temozolomide administered daily throughout the treatment. However, after five sessions, the LINAC machine broke down, requiring extensive repairs, causing a 2-week delay in radiation. After that, the radiation proceeded smoothly without any hindrances until the completion of 30 fractions. At the end of the fractions, considering the radiation gap after the initial five sessions, and to achieve the maximum therapeutic effect, we attempted to escalate the dose by administering a booster for five fractions, so the total dose delivered was 63 Gy/35 fx. The area receiving this radiation booster was only the GTV, without any expansion at all, to minimize radiation effects.

During the radiation, the patient experienced improvement. There was notable enhancement observed in upper and lower extremity strength, as well as improvements noted in swallowing and opening the eyelids. This improvement occurred after receiving about 15 fractions of radiation.

Towards the end of the radiation and up to 2 weeks post-radiation, the patient complained of headaches and nausea, but these conditions improved when administered steroids.

Clinical evaluation is still ongoing, which will be followed by a repeat MRI of the head 8 weeks post-radiation, with the goal of determining the response to radiation.

DISCUSSION

Radiation is currently the primary treatment option for cases of DIPG. The general dose given is 54 to 60 Gy, delivered conventionally. We escalated the dose to 63 Gy to compensate for the radiation delay that occurred at the beginning of the fractions. A previous study has tried to escalate the dose to 70 Gy.[6] This dose escalation certainly has the potential to cause more severe acute effects, but in this case, those effects were relatively controlled with the administration of steroids.

The radiation technique used is the VMAT technique. VMAT is a radiation therapy technique that has been used in the treatment of paediatric brain tumours. It offers advantages such as highly conformal dose distribution and reduced radiation dose to adjacent normal tissue compared to conventional photon radiation therapy.[7] This will reduce excessive radiation to the surrounding normal brain tissue.

Temozolomide is an alkylating agent that has been investigated as a potential treatment for DIPG. A phase II study conducted by the Children's Oncology Group (COG) tested the efficacy of chemoradiotherapy with temozolomide followed by adjuvant temozolomide in children with newly diagnosed DIPG.[5] The study enrolled 63 children, and all patients received temozolomide at a dosage of 90 mg/m²/day for 42 days in combination with radiation therapy with median times to progression and death were 6.1 and 9.6 months. A previous study reported that the median onset of disease progression following irradiation is < 6 months, with a median survival of 10 months.[8] Nevertheless, there was no significant improvement in event-free survival or overall survival compared to single therapy.

Although some trials have not shown significant benefits in terms of survival, in this certain case, temozolomide is the only currently available agent in our region Indonesia for DIPG. Its administration to this patient was relatively well-tolerated, with minimal haematological side effects.

As for the clinical symptom improvement that occurred, it is not yet known whether it is the effect of radiation, temozolomide, or a combination of both. However, this agent is often used in cases of brain tumours in both paediatric and adult patients, as an adjunct to radiation therapy, as it is believed to have synergistic effects and act as a radiosensitiser.[9]

The clinical improvement experienced by the patient, such as increased muscle strength and improvement in cranial nerve palsy, is certainly something to be pleased about. However, it is unknown how long this will continue. As is already known, radiation therapy has not yet been able to provide a curative effect on DIPG. It may be that the improvement experienced is only temporary. As of the writing of this article, the patient is still under clinical observation and will be followed by radiological evaluation with MRI.

CONCLUSION

The combination of radiotherapy with concurrent temozolomide may be an alternative therapy in improving clinical symptoms in DIPG. The long-term effects and their impact on survival still require further follow-up, and more extensive data is also needed.

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