Bevacizumab and stereotactic radiosurgery achieved complete response for pediatric recurrent medulloblastoma

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Abstract

Recurrent medulloblastoma has a very poor prognosis in children regardless of the treatment employed. We report the case of a 3-year-old child with recurrent refractory medulloblastoma who was treated with both bevacizumab and stereotactic radiosurgery (SRS). The boy was found to harbor a tumor in the cerebral posterior fossa in November 2010. Craniotomy was performed to remove the tumor completely. Postoperative pathological examination showed desmoplastic medulloblastoma. Cranial spinal radiotherapy and chemotherapy were performed. Three years later, the boy suffered from constant headache again. Magnetic resonance imaging showed seeding of medulloblastoma in the posterior fossa as four masses with diameter ranging from 2 cm to 3 cm. To avoid overdose radiation, we used SRS and anti-angiogenesis therapy. Bevacizumab was given at 10 mg/kg for four times with an interval of 1 month. Gamma Knife (Leksell Gamma Knife®, Elekta Instruments, Stockholm, Sweden) was used targeting at one lesion each time and performed for consecutive two times with bevacizumab therapy. Following this combined treatment, the lesions targeted with radiosurgery showed complete response with minimal toxicity in <1 month successively. The combined use of bevacizumab and SRS may represent a novel treatment against medulloblastoma in patients who are not surgical candidates, and should be investigated further. This is the first documented case of medulloblastoma treated with bevacizumab and SRS. Further clinical trials should be considered to evaluate the effectiveness of this strategy.

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Discussion

We present a single case of recurrent medulloblastoma in a child who responded significantly to combined treatment with bevacizumab and SRS. Complete disappearance of target lesions was observed <1 month following treatment, possibly suggesting a new and efficient therapy for medulloblastoma.

The rationale for combined SRS and antiangiogenesis therapy was based on recent clinical and preclinical observations. Medulloblastoma has been found to express VEGF ligand and cognate receptors.[7] Bevacizumab, monoclonal antibody of VEGF, has been used in patients with medulloblastoma with chemotherapeutic agents.[8],[9] It provides a wide spectrum of antitumor properties with a long half-life (20 days), so we used it at an interval of 30 days. At the same time, bevacizumab and radiosurgery may have a synergistic effect and may interact in a number of different ways.[6] Primarily, bevacizumab may normalize the formation of tumor vasculature, decreasing vascular permeability and increasing tumor oxygenation while enhancing radiosensitivity. Secondly, the hypoxic tumor cells, which are not sensitive to radiation, tend to cause recurrence through molecular signaling pathways. VEGF is one of the most important molecular signaling pathways and can be blocked by bevacizumab. Finally, radiation increases the secretion of cytokines such as VEGF in tumor cells which helps promote tumor angiogenesis. Bevacizumab can block the angiogenic response and thus enhance the efficacy of radiotherapy.

In the present case, the patient received >27 Gy whole brain radiotherapy with 57 Gy enhancement in the cerebellum after the first surgery. Thus, re-irradiation would risk overdose. As SRS can deliver local doses of >10 Gy with little radiation to surrounding structures, we selected to use a combination of bevacizumab and Gamma Knife. To date, there are no reports in literature presenting the potential efficacy of this regimen. In the literature on recurrent medulloblastoma, complete response was rarely seen following treatment with bevacizumab and chemotherapy.[10],[11],[12] In the current case, all solid tumors disappeared following combined treatment with bevacizumab and Gamma Knife, presenting a possible novel method for the treatment of medulloblastoma that warrants further investigation.

Despite intensive radiotherapy and chemotherapy, metastasis to the leptomeninges represents a major challenge in the treatment of medulloblastoma.[13],[14] Patients with diffuse meningeal dissemination generally have a poor prognosis.[15] The case presented herein developed diffuse leptomeningeal metastasis in the late stages of treatment. Since the dissemination occurred after antiangiogenic agent administration, we studied the correlation between bevacizumab and tumor dissemination. In early reports, antiangiogenic agents seemed to promote cancer cell migration and invasion leading to accelerated metastasis.[16],[17] However, recent studies have shown that antiangiogenic agents can help normalize the tumor vasculature and prevent metastasis.[18],[19] In 2014, Davare et al. found that VEGF is not involved in the modulation of the migratory properties of medulloblastoma cells in vitro.[20] Therefore, we believe that bevacizumab can be safely used in the treatment against medulloblastoma; however due to the cessation of treatment in the current case, we cannot speculate as to the effectiveness of bevacizumab on disseminated metastatic tumor cells.

This case demonstrates that bevacizumab combined with SRS may be an effective treatment for medulloblastoma and a potential new therapy for patients who are not surgical candidates. Additionally, SRS is not limited by the maximum radiotherapeutic dose and can therefore be used before or after radiotherapy which makes it especially useful for recurrent tumors. If further study indicates this to be an effective therapy, it would represent another minimally invasive option for patients with medulloblastoma. Prospective clinical trials could be considered to evaluate the effectiveness of this strategy.

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Conflicts of interest

There are no conflicts of interest.

References

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