Effectiveness of interferon-beta therapy for recurrent glioblastoma: a case report

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ABSTRACT

Aims and background. Glioblastoma has a poor prognosis, with few therapeutic options if it recurs. We report a case in which we were able to inhibit the growth of a recurrent glioblastoma by weekly single-dose administration of interferon-beta.

Case report. A patient with recurrent glioblastoma after radiation and chemotherapy was treated with nimustine and interferon-beta. After 2 cycles of nimustine, the patient's leukocyte, neutrophil, and platelet counts showed grade 4 toxicity according to the National Cancer Institute's Common Toxicity Criteria. The patient was treated with a weekly single dose of interferon-beta at 6 × 10^6 IU. The tumor showed no remarkable changes after 18 months, and the patient's Karnofsky performance status remained at 50%.

Conclusions. The administration of interferon-beta produced long-term control in one case of glioblastoma and may be an effective therapy. Free full text available at www.tumoronline.it

Introduction

Recurrent glioblastoma usually requires surgery and/or chemotherapy because radiation therapy has already been performed. Surgical treatment may not result in the tumor's total resection. Chemotherapy is limited by side effects such as myelosuppression. Temozolomide (TMZ), a relatively new chemotherapeutic agent, has fewer side effects and rarely shows treatment-limiting toxicities. Chemotherapy with TMZ is the current standard of glioblastoma therapy established by the Stupp study. No reports so far have described an effective therapy for recurrent glioblastoma in patients with myelosuppression.

We present a case of recurrent glioblastoma in which we were able to stabilize the patient's Karnofsky performance status (KPS) and control the tumor size for 18 months by administration of interferon-beta after myelosuppression due to chemotherapy.

Case report

A 33-year-old woman presented with a 1-month history of gradually worsening speech impediments. Magnetic resonance imaging (MRI) revealed a ring-enhancing lesion in the right frontal lobe and a non-enhancing lesion in the left frontal lobe, without continuity to the right lesion (Figure 1). The Wada test revealed that her language center was in her right cerebral hemisphere. The patient underwent removal of the right frontal tumor, diagnosed as glioblastoma, under awake surgery on April 19, 2005. She experienced perseveration during tumor resection, and the tumor was too near the speech area to be completely removed. The KPS of the patient decreased from a preoperative score of 100 to a postoperative score of 80. The patient was treated by irradiation of the bifrontal lesion with 6000 cGy in daily doses of 200 cGy and by chemotherapy consisting of nimustine hydrochloride (ACNU), vincristine, and inter-
Figure 1 - Axial T2-weighted (A) and postcontrast axial T1-weighted images (B). The right frontal lesion was mixed-intense on T2-weighted images and ring-enhanced on postcontrast T1-weighted images. However, the left frontal lesion was high-intense on T2-weighted images (A) and not enhanced on postcontrast T1-weighted images (B).

Figure 2 - Axial postcontrast T1-weighted images. A) The right enhanced lesion increased after the second operation on the left frontal lesion and postoperative chemotherapy with 2 cycles of ACNU in March 2006. B) The lesion itself has not decreased, but gadolinium enhancement reveals that some cysts are present after administration of interferon-beta alone 18 months later. C) One month after interferon-beta was stopped, the center of the tumor has a large hypointense cyst at the frontal aspect and an isointense cyst (arrow) at the occipital aspect, with lateral ventricle compression.

Interferon-beta. She received 2 courses of the following intravenous chemotherapy regimen: vincristine (1.5 g) on the first day, 2 doses of ACNU (150 mg) on the second day, followed by interferon-beta (600 × 10^4 IU) 3 times a week for 6 weeks. Tumor resection was performed for the left frontal lesion (Figure 2A) on September 22, 2005, because an enhanced lesion appeared on the MRI image in August. The pathological diagnosis of this lesion was glioblastoma. The patient then developed left hemiparesis, and her KPS decreased from 80 to 70. She showed a postoperative toxicity score of grade 4 for leukocyte, neutrophil, and platelet counts according to the National Cancer Institute’s Common Toxicity Criteria after administration of ACNU and weekly interferon-beta. Interferon-beta was tapered to a once-a-week outpatient dose. The patient then developed aphasia and hemiplegia, and her KPS decreased from 70 to 50. Follow-up MRI imaging showed an increase in size of the right tumor (Figure 2B) and ACNU was discontinued because it did not have effect. The patient’s KPS was poor, but, in view of the wishes of her family, we decided to continue chemotherapy. Since myelosuppression persisted, with the approval of the Institutional Review Board after obtaining the informed consent of the patient, we treated her with 600 × 10^4 IU interferon-beta once a week beginning in April 2006 instead of continuing with chemotherapy. Interferon-beta is a routine approved agent under Japanese health insurance. The patient continued visiting a hospital for treatment and maintained a KPS of 50. Eighteen months later, the right frontal tumor showed less enhancement (Figure 2C). Administration of interferon-beta was later stopped because the patient developed aspiration pneumonia, and her KPS decreased from 50 to 30. The residual tumor increased and the patient died 2 months after interferon-beta was stopped. The promoter methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) gene in the tumor tissue resected at the first and second operations was analyzed by methylation-specific nested PCR. MGMT promoter methylation was not detected in the 2 tumor tissues. For confirmation, immunostaining for MGMT of the paraffin-embedded sections was done, and both tumor tissues proved immunopositive for MGMT.

Discussion

We have reported a case of recurrent glioblastoma successfully treated by interferon-beta therapy. Interferon-beta facilitates radiation therapy4,5 and cell death by inductive acceleration of apoptosis6-8, decreasing cellular proliferation9,10, stimulating autoimmune cellular lysis11,12, and inhibiting angiogenesis13-15. Interferon-beta lowers the activity of MGMT and enhances the effect of chemotherapy16-18. It is effective in treating glioblastoma19,20 when used in combination with other drugs as adjuvant therapy after primary care20,21. However, there are no previous reports of treatment outcome from long-term interferon administration alone. Here, interferon-beta putatively decreased cell proliferation19,10 and induced immunocyte activation11,12 and the angiogenic depression effect13-15, which stabilized the tumor size.

Except in the case of benign astrocytoma20, there is no evidence that interferon-beta alone is effective in glioma. For the first time, we showed that interferon-beta administration could stabilize malignant glioma. Further evidence for its efficacy should be produced in a larger-scale clinical study. TMZ is one of the most effective chemotherapeutic agents for glioblastoma treatment6, and interferon-beta could be used as an adjunct to TMZ because it possibly suppresses the expression of MGMT16,22. Matsuno et al. reported the effectiveness of
the administration of interferon-beta on gliomas that are immunopositive for MGMT and resistant to chemotherapy including TMZ\textsuperscript{23}. This case supports their findings. High levels of MGMT activity in cancer cells create a resistant phenotype by blunting the therapeutic effect of chemotherapy and may be an important determinant of treatment failure. Interferon-beta may not only control the expression of MGMT but also have a direct antitumor effect. Interferon-beta gene therapy has been evaluated in a multicenter phase I clinical trial\textsuperscript{24}. The altered expression of MGMT, which is an effect of interferon-beta, has been investigated in a phase I trial in Japan\textsuperscript{25}. The possible positive effect of the combination of anticancer drugs with interferon-beta is awaiting further investigation.

In glioma patients with chemotherapy-induced myelosuppression, monotherapy with interferon-beta may be a treatment option if chemotherapy, including TMZ, cannot be continued without resulting in myelosuppression.

## Conclusion

Administration of interferon-beta alone controlled tumor size in a case of recurrent glioblastoma. This treatment may help other recurrent malignant glioma patients who experience chemotherapy side effects such as myelosuppression.

## References


