Patterns of Recurrence After Resection of Malignant Gliomas With BCNU Wafer Implants: Retrospective Review in a Single Institution

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BACKGROUND: **Bis-chloroethylnitrosourea (BCNU) wafers have been demonstrated to be effective for prolonging survival for patients with malignant glioma and have been approved worldwide. BCNU wafers are implantable and have a unique feature of delivering chemotherapeutic drug at high concentration at tumor margin over time after resection. BCNU wafers presumably, by this mechanistic rationale, have a beneficial effect on local tumor control and thus could change the pattern of recurrence, which is most frequently local. However, no studies have demonstrated such phenomenon after BCNU wafer implants.**

METHODS: **To investigate whether the surgeries with BCNU wafers alter the predominant tendency of local recurrence pattern, we retrospectively reviewed 8 malignant glioma patients treated with BCNU wafers (BCNU wafer group), together with 22 glioma patients who did not receive BCNU wafers (no-BCNU wafer group) for comparison.**

RESULTS: **Out of 6 patients in BCNU wafer group who exhibited recurrence, 1 showed local, 2 showed diffuse, and 3 showed a distant recurrence pattern, which was away from resection cavity. On the other hand, out of 18 patients in the no-BCNU wafer group who exhibited recurrence, 10 showed a local pattern, 8 showed a diffuse pattern, and no cases showed distant pattern. Distant pattern was observed significantly more frequently in the BCNU wafer group than in the no-BCNU wafer group.**

CONCLUSIONS: **These results suggest that BCNU wafers could have a beneficial effect on local tumor control and may provide BCNU wafers with a new profile that could be considered for establishing future chemotherapeutic strategy for glioma patients.**

INTRODUCTION

Malignant gliomas are still formidable diseases despite the advancement of aggressive multimodality treatment because of their invasive characteristics.[1] Although surgical resection remains a critical component in the treatment, motile invading cells from these tumors cannot be surgically extirpated and are responsible for recurrence of the tumor following radical resection.[2] Although radiotherapy and chemotherapy, which pursue eradication of the residual tumor cells after surgery, contribute to prolonging survival, gliomas mostly return.[3,4] The majority of malignant gliomas recur at local, regional sites around original lesions,[5-8] which indicates that conventional systemic chemotherapies are insufficient even for local tumor control. Systemic toxicity, neurotoxicity, and poor central nervous system penetration secondary to passive and active blood-brain barrier mechanisms are the factors that hinder the efficacious delivery of systemically administered chemotherapeutics to gliomas.[9]

A bis-chloroethylnitrosourea (BCNU) wafer is a chemotherapeutic compound containing 3.85% carmustine, which slowly degrades to release carmustine, and one of the interstitial drug administration systems that potentially overcome the disadvantages of systemic chemotherapies.[10] During the surgical procedure, right after tumor resection or debulking, up to 8 wafers are deposited along the wall of the resection cavity. The implanted wafers are left in situ, providing a controlled release of BCNU over a period of 2–3 weeks.[11] BCNU wafers have been

Key words
- BCNU wafers
- Glioma
- Pattern
- Recurrence

Abbreviations and Acronyms
AA: Anaplastic astrocytoma
AO: Anaplastic oligodendroglioma
AOA: Anaplastic oligoastrocytoma
GBM: Glioblastoma multiforme
Gd: Gadolinium
TMZ: Temozolomide
5ALA: 5-aminolevulinic avid

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demonstrated in randomized trials to improve survival outcome when used as either multimodality initial therapy in patients with newly diagnosed malignant gliomas or as an adjunct to surgery for recurrence, which led to U.S. Food and Drug Administration approval for recurrent glioma in 1996 and subsequently for primary therapy for glioblastoma multiforme (GBM) in 2003.[12-14] BCNU wafers have also been approved in other countries. More recently, BCNU wafers were approved in Japan in 2012 and became available in 2013 as adjuvant treatment in association with surgery and radiotherapy for patients with newly and recurrent malignant glioma after a phase I/II study for Japanese population proved comparable results with those in the United States and Europe.[15] Currently, BCNU wafer treatment has become increasingly popular for treating patients with malignant glioma in Japan.

Besides the survival benefit, one tangible effect that would be expected to be exerted by BCNU wafers is more obvious local tumor control due to the advantage of mechanistic rationale over systemic chemotherapies. A demonstrative consequence following such effect would be a change of recurrence pattern, that is, a delay of the appearance of recurrence at a local site where BNCU wafers are implanted, which subsequently leads to the increase of recurrence at distal areas. However, previous studies have reported that local recurrence remained dominant even under the usage of BCNU wafers and denied the effect of BCNU wafers on changing patterns of recurrence.[16,17] Nonetheless, the number of studies investigating that issue is still small, and recurrence pattern is one of the intriguing concerns related to BCNU wafers.

In this study, we retrospectively reviewed patients with malignant gliomas treated with and without BCNU wafers at our hospital and analyzed radiographic recurrence patterns to investigate whether BCNU wafers affect the tendency of the failure pattern after glioma resection. Our results demonstrated that BCNU wafer implants led to a significantly higher rate of distant recurrence pattern compared with no BCNU wafer treatment. We also presented cases showing unique distant failure patterns after BCNU wafer implants.

MATERIALS AND METHODS

Patient Population

Institutional review board approval was obtained for this study, with waiver of informed consent for retrospective review of medical record.

The record of all patients treated for pathologically diagnosed World Health Organization (WHO) Grade III and IV gliomas at Kariya Toyota General Hospital, Aichi, Japan, between January 2007 and October 2014, were retrospectively assessed. This review included only patients who underwent surgical tumor resection. Three patients who were lost to follow-up before recurrences appeared were excluded from analysis.

Treatment and Follow-up

The patients underwent maximal safe tumor resection using standard microsurgical techniques with preoperative magnetic resonance imaging (MRI)-based navigation. After BCNU wafers became available in Japan in January 2013, they were implanted to the resection cavity at surgery for all patients except 3, for whom intraoperative pathologic diagnosis or BCNU wafers were not available at surgery. The number of BCNU wafers used depended on the size of resection cavity up to 8.

For patients newly diagnosed with WHO grade III or IV gliomas, radiotherapy (RT) and concurrent/adjuvant TMZ treatment were performed with the dose of TMZ 75 mg/m^2/day during RT and 150–200 mg/m^2/day for 5 days every 28 days as adjuvant treatment.

Extent of resection was assessed on the basis of T1-Gd enhanced sequences within the 2 weeks postoperative period. Then the patients were followed up with MRI after the completion of RT and every 2 to 3 months thereafter, or according to clinical symptoms.

Analysis of Recurrence Patterns

Recurrence is defined as the new appearance of T1-Gd enhancement after complete resection, or as an enlargement of T1-Gd enhancement of residual enhanced lesion observed on postoperative MRI. The analysis of recurrence pattern focused on whether the areas of recurrence were directly connected to the resection cavity for the purpose of evaluating local tumor control. Next, the patterns were classified into 4 different groups according to the criteria for patterns of recurrence reported previously.[16,17] Within the recurrences that were in continuity with the wall of resection cavity, "local" pattern was assigned if the contrast enhancement was within 1.5 cm from the resection cavity and "diffuse" pattern was assigned if the recurrence was extending more than 1.5 cm from the margin of resection cavity. "Distant" pattern was assigned for all the recurrences that were not contiguous with the resection cavity. "Multifocal" pattern was assigned if the recurrences have the mixture of "distant" and "local" or "diffuse."

In patients who received BCNU wafers, a thin contrast-enhancing ring surrounding resection cavity was identified as a reactive disruption of the blood-brain barrier induced by the BCNU wafers.[16,17] The possibility of pseudoprogression was denied by follow-up MRI in patients showing recurrences at early time point after initial adjuvant therapy.

RESULTS

Patient Characteristics

During the inclusion period, 30 patients who underwent glioma resection were identified. Of those, 8 patients received BCNU wafers during tumor resection (BCNU wafer group) and 22 patients did not (no-BCNU wafer group). Patient characteristics, histopathologic glioma subtypes, and resection rate are shown in **Table 1**. The number of BCNU wafers implanted was also shown in **Table 1**.

Median age was 57.5 years (range 40–74 years) in no-BCNU wafer group and 65 years (range 50–78 years) in BCNU wafer group. Resection rate ranges from 50%–100%. Gross total resection (>95%) was achieved in 6 patients in the BCNU wafer group (75%) and 16 patients in the no-BCNU wafer group (73%). In other patients, partial resection was opted because of tumor location.

There were 4 patients with recurrent glioma. In case #19, the initial tumor resection was performed at other hospitals and was