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Hypofractionated radiotherapy combined with bevacizumab plus low-dose ifosfamide, carboplatin, and etoposide as second-line chemoradiotherapy for progressing spinal diffuse midline glioma, H3K27-altered: illustrative case

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BACKGROUND Spinal cord diffuse midline glioma (DMG) is a relatively rare disease with a poor prognosis and no effective treatment.

OBSERVATIONS A 45-year-old man presented with rapidly progressive paraplegia in both lower extremities, along with bladder and bowel disturbance. Spinal magnetic resonance imaging (MRI) showed a heterogeneously contrast-enhanced mass at the T1–4 levels. A biopsy via T1–4 decompressive laminectomy with expansive duraplasty was performed. The histopathological diagnosis was DMG, H3K27-altered, World Health Organization grade 4. Radiation plus concomitant temozolomide was started; however, follow-up MRI showed tumor progression. Additional hypofractionated radiotherapy (HFRT; 24 Gy/5 fractions) was performed, with bevacizumab (BEV) plus low-dose ifosfamide-carboplatin-etoposide (ICE) as second-line treatment. One month later, MRI showed tumor regression with significant improvement in the peritumoral edema. The chemotherapy regimen was repeated every 4–6 weeks, and the patient remained stable. After 13 courses of chemotherapy, the size of the spinal DMG increased markedly, with dissemination to the temporal lobe. The patient died approximately 21 months after the initial diagnosis.

LESSONS Spinal DMG is a malignant tumor with a poor prognosis. However, treatment with additional HFRT combined with BEV plus low-dose ICE may inhibit tumor progression to prolong the progression-free period and survival.

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KEYWORDS spinal diffuse midline glioma; H3K27-altered; ICE; bevacizumab

Diffuse midline glioma (DMG), H3K27 mutant, was first described in the 2016 World Health Organization (WHO) classification[1] and corresponds to a grade 4 diagnosis, regardless of histological grade. The name was updated to DMG, H3K27-altered, in the 2021 WHO classification.[2] Originally identified in pediatric diffuse intrinsic pontine gliomas (DIPGs),[3] K27M mutations in *H3F3A* or *HIST1H3B/C*, encoding for histone 3 variants H3.3 and H3.1, respectively, are a hallmark of DMG.[4] DMG arises in midline structures, such as the thalamus, brainstem, and spinal cord. The prognosis of this disease is dismal, with a median survival of less than 1 year from the time of diagnosis.[5] Spinal cord DMG is rarer, accounting for only 4.3% of all DMGs, and fewer than 100 adult cases of spinal DMG have been reported in the literature.[6,7] Initial treatment tends to be similar to glioblastoma (GBM) treatment[8] and comprises radiation with concomitant temozolomide (TMZ).[9] No second-line treatment has been established to date.

In this report, we describe the case of an adult spinal cord TMZ-resistant DMG treated with hypofractionated radiotherapy (HFRT) combined with bevacizumab (BEV) and low-dose ifosfamide-carboplatin-etoposide (ICE) as second-line treatment, which resulted in a relatively long survival.

Illustrative Case

A 45-year-old man with a history of hypertension and diabetes mellitus was referred to our hospital because of sensory disturbance

ABBREVIATIONS BEV = bevacizumab; CTCAE = Common Terminology Criteria for Adverse Events; DIPG = diffuse intrinsic pontine glioma; DMG = diffuse midline glioma; GBM = glioblastoma; HFRT = hypofractionated radiotherapy; ICE = ifosfamide-carboplatin-etoposide; MRI = magnetic resonance imaging; PFS = progression-free survival; TMZ = temozolomide; WHO = World Health Organization.

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in his right lower extremity that had begun several months earlier. The sensory disturbance progressed to paraplegia in both lower extremities, as did bladder and bowel disturbance, within a few months. Spinal magnetic resonance imaging (MRI; Fig. 1A and B) showed a heterogeneously contrast-enhanced mass at the T1–4 levels, with multiple intratumoral hemorrhages and extensive peritumoral edema. Within days of hospital admission, the bladder and bowel dysfunction progressed rapidly. Therefore, tumor biopsy by T1–4 decompressive laminectomy with expansive duraplasty was performed urgently.

Hematoxylin and eosin staining of the excised tissue (Fig. 2A and B) showed tumor cells containing small- to medium-sized nuclei and scant cytoplasm. Mitoses were observed frequently. The tissue stained positive for H3K27M (Fig. 2C), ATRX, glial fibrillary acidic protein, O-6-methylguanine-DNA methyltransferase, oligodendrocyte transcription factor 2, epithelial membrane antigen, and methylthioadenosine phosphorylase and negative for isocitrate dehydrogenase 1 R132H, NeuN, and methionine 27 mutation in histone 3 (Fig. 2D). The Ki-67 labeling index was 70% (Fig. 2E). The histopathological diagnosis was DMG, H3K27-altered, WHO grade 4.

After the diagnosis, volumetric-modulated radiotherapy (50.4 Gy/28 fractions; Fig. 3A) plus concomitant TMZ 75 mg/m^2 in accordance with the Stupp regimen[9] was started. During this first-line treatment, the patient developed Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 4 neutropenia and a urinary tract infection, which required antibiotics. After completing the initial regimen, MRI showed further enlargement of the tumor (Fig. 1C and D). Additionally, the patient became paraplegic and developed complete bowel and bladder dysfunction.

Sixty days after the first radiation treatment, additional radiation (24 Gy/5 fractions; Fig. 3B), which exceeded the tolerable dose, was administered because the patient was already paraplegic, and tumor control took precedence over the risk of spinal damage from additional radiation. After the reirradiation, BEV plus low-dose ICE (BEV 15 mg/m^2 on day 1, ifosfamide 0.75 mg/m^2 on days 1–3, carboplatin 75 mg/m^2 on days 1–3, etoposide 75 mg/m^2 on days 1–3) was started as second-line chemotherapy. One month after the second-line chemotherapy, MRI showed tumor regression with significant improvement in the peritumoral edema (Fig. 1E and F). The BEV plus ICE regimen was repeated every 4–6 weeks. No hematological problems were observed during the course of the BEV plus ICE regimen, and the tumor was stable on repeat MRI. The patient developed CTCAE grade 2 anemia after 13 courses of the BEV plus ICE regimen and grade 1 neutropenia during the first and second courses of the BEV plus ICE regimen. No blood transfusions or granulocyte colony-stimulating factor treatment was needed. The patient developed a urinary tract infection after 13 courses of the regimen, due to bladder dysfunction. Grade 3 constipation persisted during the course of the BEV plus ICE regimen, due to the bowel dysfunction caused by spinal cord damage and opioid use.

After 13 courses, the size of the spinal DMG increased markedly (Fig. 4A and B), and dissemination to the temporal lobe was noted (Fig. 4C and D). At this point, the patient and his family decided to initiate palliative care at home without further chemotherapy, requiring short-term admission to the hospital. BEV only, as outpatient chemotherapy, was administered twice at a nearby hospital. The patient died approximately 21 months after the initial diagnosis.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

DMG, H3K27 mutant was first described in the 2016 WHO classification[1] and updated to DMG, H3K27-altered in the 2021 WHO classification.[2] This neoplasia was formerly called "DIPG" and was reported to affect mostly children. The median overall survival in spinal DMG, H3K27-altered, grade 4, is dismal, at 6–16 months.[6,10] Due to the rarity of the disease, no optimal treatment and management for spinal cord DMG, H3K27-altered, has been established.[8]

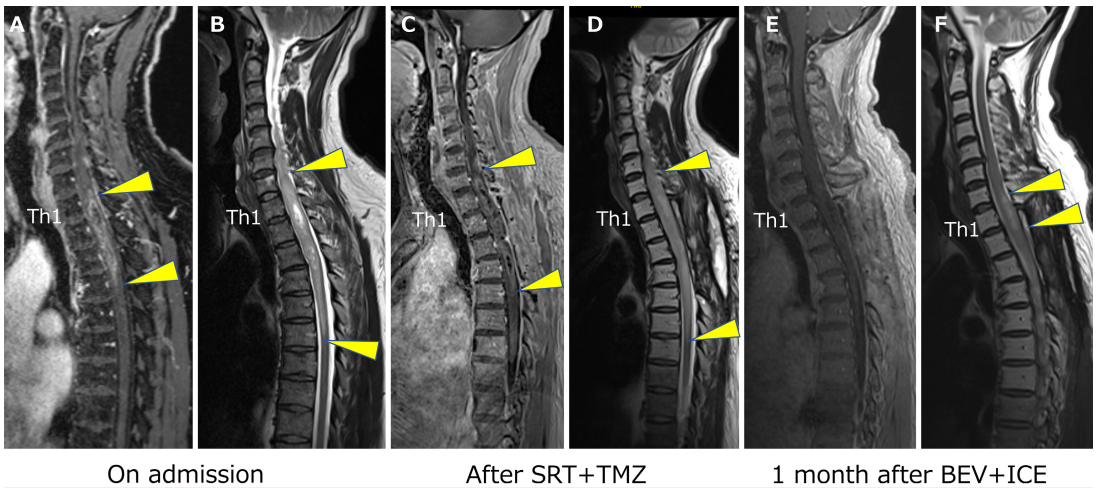

FIG. 1. Changes over time on spinal MRI. The extent of the gadolinium-enhanced area and peritumoral edema is outlined by the *yellow arrowheads*. **A:** Contrast-enhanced T1-weighted imaging on admission showing a heterogeneously enhanced mass at the T1–4 levels. **B:** T2-weighted imaging showing a high-intensity area at the C7–T6 levels on admission. **C and D:** After stereotactic radiotherapy (SRT) and TMZ, the mass increased in size to encompass the C7–T5 levels, and the peritumoral edema extended to the C7–T7 levels. **E and F:** After irradiation and 1 course of the BEV plus ICE regimen, the mass showed no contrast enhancement, and the peritumoral edema had decreased markedly.

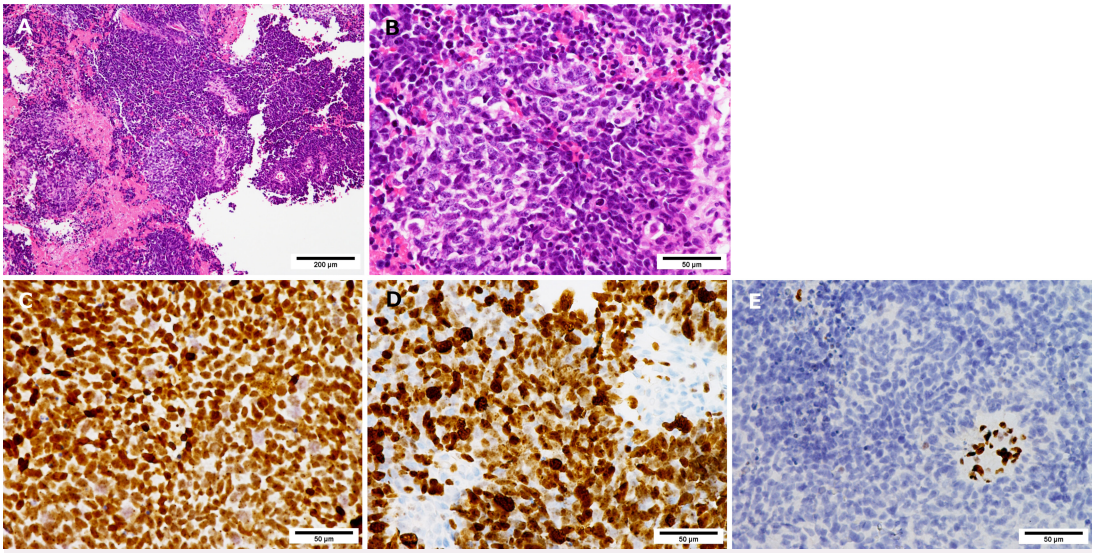

FIG. 2. Histological and immunohistochemical findings. **A:** Hematoxylin and eosin staining showing tumor cells containing small- to medium-sized nuclei and scant cytoplasm. **B:** Mitoses were observed frequently (5/mm^2). **C:** On immunohistochemical staining, the tumor cells were positive for H3p.K28 (K27)–mutant protein. **D:** Tumor cells were negative for H3pK28me3 (K27me3). **E:** The Ki-67 labeling index was 70%.

Stupp Protocol for DMG

In this study, we initially treated the patient using TMZ with radiotherapy in accordance with the Stupp regimen.[9] Conventional radiotherapy is the only effective modality for DMG or traditionally DIPG. Doses and fields similar to those used for DIPG are recommended for DMG, with a total dose of 54–60 Gy using conventional fractionation (1.8–2.0 Gy daily).[8,11]

Although TMZ has become part of standard therapy for most adult patients with high-grade gliomas, several trials have demonstrated no improvement in activity compared with radiation alone. Furthermore, TMZ is associated with an increased risk of adverse effects and toxicity in the treatment of DMG.[12] Nevertheless, TMZ is the most common chemotherapeutic agent for DMG in the absence of other proven chemotherapeutics and is partly effective within a short period.[8,9]

Additional Irradiation as HFRT

Although evidence for repeat irradiation for spinal DMG is scarce, Wolff et al. reported that repeat radiation to the primary tumor resulted in tumor shrinkage in 4 of 7 patients compared with 5 of 52 patients treated with protocols not including radiation to the primary tumor.[13] The repeat radiotherapy dose (20 Gy/10 fractions)

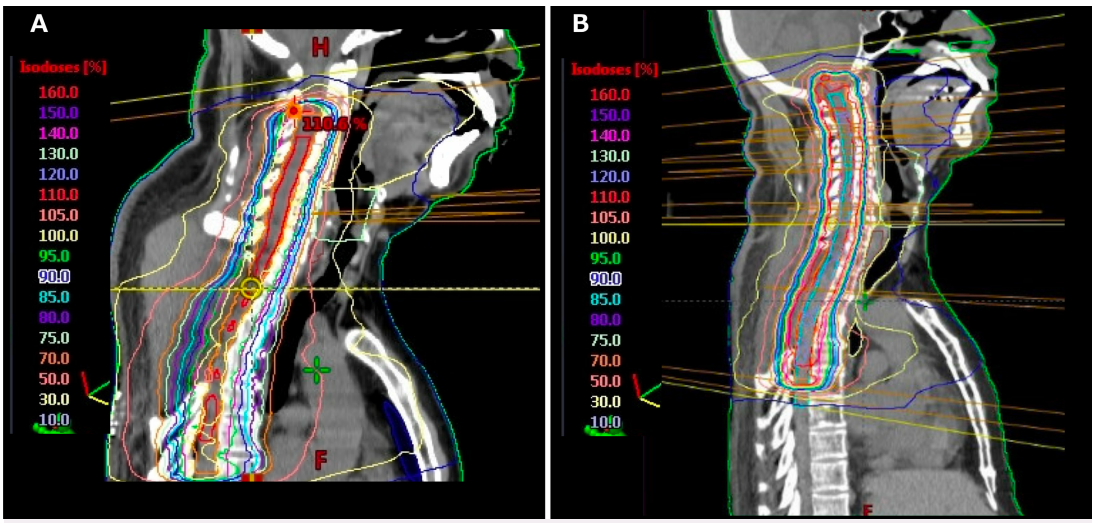

FIG. 3. Isodose plots of the volumetric-modulated radiotherapy dose distribution in the sagittal plane at the first irradiation (50.4 Gy/28 fractions, **A**) and additional irradiation (24 Gy/5 fractions, **B**). The *colored lines* represent various isodose lines as indicated in the guide on the left in each panel.

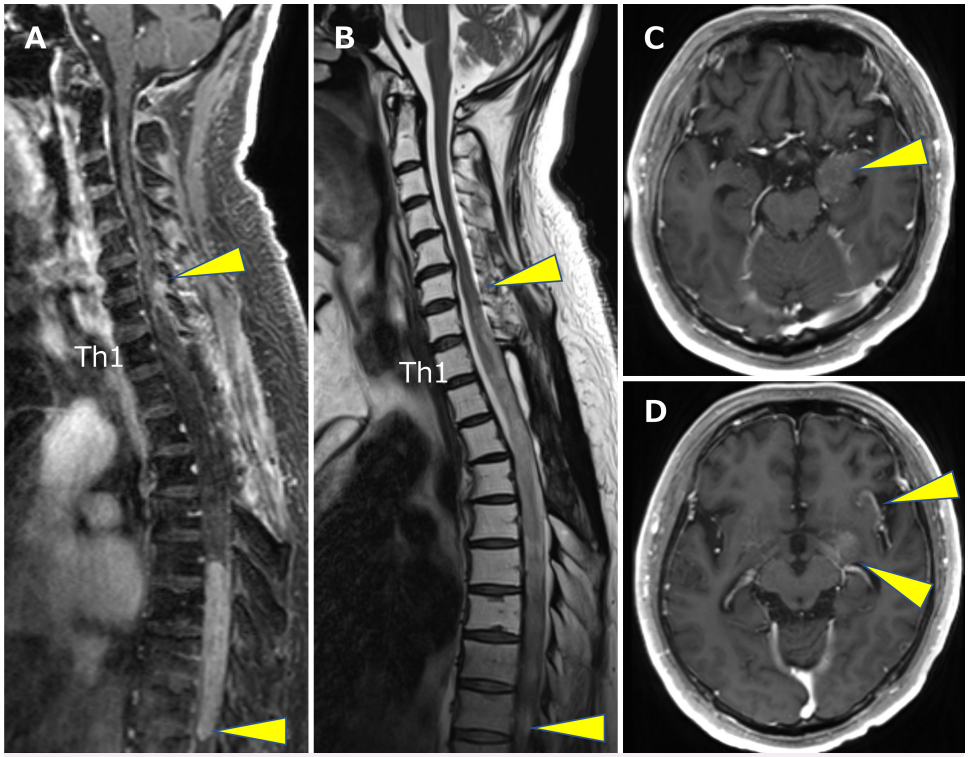

FIG. 4. Spinal MRI findings after 13 courses of the BEV plus low-dose ICE regimen. **A:** Compared with the initial MRI, the mass is markedly increased in size at the C7–T9 levels (outlined by *yellow arrowheads*), especially at the T6–9 levels. **B:** The degree of peritumoral edema (outlined by *yellow arrowheads*) has also increased. **C:** Dissemination to the medial temporal lobe is visible (*yellow arrowhead*). **D:** Dissemination to the insula and the optic tract is also demonstrated (*yellow arrowheads*).

was much lower than the initial radiation dose (54 Gy/30 fractions) in the study. The efficacy of additional radiation, especially as HFRT, has been suggested for recurrent GBM. RTOG 1205 was the first prospective randomized phase II trial evaluating additional irradiation and showed an improvement in 6-month progression-free survival (PFS) with HFRT of 35 Gy in 10 fractions.[14] Kazmi et al. also showed the efficacy of additional irradiation for recurrent GBM and found that patients who received less than 5 fractions of radiotherapy had improved 6-month PFS.[15] We performed additional HFRT of 24 Gy in 5 fractions and obtained relatively long survival in our patient. Additional irradiation such as HFRT may also improve PFS in recurrent DMG.

BEV Plus ICE for DMG

BEV is a humanized monoclonal antibody against vascular endothelial growth factor and is currently the most common chemotherapeutic agent for recurrent GBM and is expected to be effective for DMG.[6] BEV is generally combined with cytotoxic agents in studies of solid malignancies, and regimens comprising BEV and carboplatin have been suggested to be effective in recurrent malignant GBM.[16,17] For DMG, Yabuno et al. reported that BEV reduced edema and improved the ability to perform activities of daily living in 2 patients with spinal cord DMG.[6] The authors used BEV as second-line chemotherapy in one patient and BEV combined with stereotactic radiotherapy plus TMZ for the other patient. Kumar et al. also reported the effect of BEV combined with TMZ plus stereotactic radiotherapy for a pediatric patient with spinal DMG.[18] Although 2 phase III studies, AVAglio and RTOG 0825, failed to show improved overall survival in newly diagnosed GBM patients when BEV was added to standard TMZ therapy, the addition of BEV improved the patients' performance statuses.[19,20] It would be reasonable to add BEV to the standard Stupp protocol or start BEV when patients show neurological deterioration in the treatment of DMG.

In our patient, we chose BEV plus ICE for second-line therapy. The use of ICE alone or ICE plus BEV has been our practice to treat recurrent GBM. The ICE regimen has been suggested to be effective for high-risk or relapsed medulloblastoma and pediatric high-grade astrocytoma.[21,22] Although some reports suggest that ICE is not effective in patients with recurrent high-grade glioma,[23] a phase II study of ICE for recurrent GBM at our institution showed that the 6-month PFS was 35%, with mild adverse events.[24] After BEV was approved for GBM, we also showed that combination treatment with BEV plus ICE can be safe and beneficial in patients with second-recurrence GBM.[16] Although there are no reports, to our knowledge, on the effect of BEV plus ICE for DMG, our patient showed relatively prolonged survival of 21 months, compared with reported rates of 6–16 months.[6,10] The BEV plus ICE regimen is a reasonable option for recurrent or refractory DMG.

Tolerability and Safety of BEV Plus ICE Therapy

Our patient experienced no serious hematological problems during the course of BEV plus ICE, with only CTCAE grade 2 anemia after 13

courses of the BEV plus ICE regimen and grade 1 neutropenia during the first and second courses of the BEV plus ICE regimen. In our previous analysis of BEV plus ICE for second-recurrence GBM,[16] BEV plus ICE did not result in acute toxic events. Hematological toxicities, namely anemia, lymphopenia, and thrombocytopenia, were identified in 7 of 8 patients; all were grade 2 or 3 adverse events. Grade 2 hypoalbuminemia and constipation were also observed in 2 patients. Cerebral hemorrhage, hypertension, proteinuria, and venous thromboembolism > grade 3 were not identified in the series. Considering these findings, BEV plus low-dose ICE therapy is a well-tolerated and safe chemotherapy regimen.

Future Perspectives

Recently, the underlying molecular mechanisms of DMG tumorigenicity and biology have been studied extensively,[25] resulting in the identification of novel drug targets and the development of potential therapies. These advancements are promising, but currently there is no established clinically proven treatment for DMG, H3K27-altered.

The results of our retrospective analysis suggest that additional HFRT combined with BEV plus low-dose ICE can be safe and beneficial in patients with recurrent or refractory spinal DMG as second-line chemoradiotherapy.

Lessons

We present the case of an adult with spinal TMZ-resistant DMG, who experienced relatively long survival with additional HFRT combined with BEV plus low-dose ICE. DMG is a malignant tumor with a poor prognosis. However, treatment with additional HFRT combined with BEV plus low-dose ICE may inhibit tumor progression to prolong the progression-free period and survival. Additional case series and studies are needed to confirm our results.

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Author Contributions

Conception and design: Tanji, Nakayasu, Uto, Sano. Acquisition of data: Tanji, Nakayasu, Takeuchi, Sano. Analysis and interpretation of data: Tanji, Nakayasu, Uto, Mineharu, Arakawa. Drafting the article: Tanji, Nakayasu, Arakawa. Critically revising the article: Nakayasu, Uto, Takeuchi, Makino, Hattori, Sano, Mineharu, Mizowaki, Arakawa. Reviewed submitted version of manuscript: Nakayasu, Uto, Hattori, Terada, Sano, Mineharu, Mizowaki, Arakawa. Approved the final version of the manuscript on behalf of all authors: Tanji. Study supervision: Arakawa.

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