Intensity-modulated Radiation Therapy with Hypoxic Sensitizer AK-2123 (Sanazole) for Glioblastoma Multiforme Using Simultaneous Integrated Boost Technique

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Abstract. *Background: Glioblastoma has a very poor prognosis even after incorporation into therapy of the newly-developed drug, temozolomide. Case Report: We present a case of 62-year-old woman with glioblastoma multiforme treated with tomotherapy intensity-modulated radiation therapy using simultaneous integrated boost technique (SIB-IMRT) along with a daily oral dose of a hypoxic radiation sensitizer, sanazole (AK-2123). SIB-IMRT was administered at a dose of 60 Gy in 20 fractions for high-risk planning target volume (PTV) and at 40 Gy for low-risk PTV. The patient received an oral administration of sanazole (1.0 g/day) for 10 days, 2 h before radiotherapy. She achieved a complete response without any adverse events, and remained disease-free for 3.5 years. Our study demonstrates that the higher single-dose radiotherapy combined with a hypoxic radiation sensitizer has the potential to enhance the efficacy of radiotherapy.*

Hypoxia is a major obstacle to tumor control after radiation therapy and has been studied for more than a century after Grey and colleagues (1, 2) first encountered the phenomenon. A meta-analysis of head-and-neck cancer provided evidence for improved tumor control and survival with hypoxic modification during radiotherapy (1). AK-2123 (sanazole), a nitrotriazole derivative is a hypoxic cell sensitizer that has been demonstrated to have lower neurotoxicity than most nitroimidazoles (3-8). Several phase III randomized trials, including multicenter trials, proved the efficacy of the drug for cervical and head neck cancer (6, 7). Although sanazole was initially produced in Japan, almost all data were accumulated in developing countries with the aid of the International Atomic Energy Agency (IAEA). Unfortunately, this drug is not commercially available because its patent has been withdrawn in Japan, limiting its clinical usage. We therefore initiated a clinical trial to test the toxicity of daily oral administration of sanazole (9). During this trial, we used the latest radiation therapy techniques: simultaneous integrated boost intensity-modified radiation therapy (SIB-IMRT) with tomotherapy and achieved an excellent response in a case of glioblastoma multiforme.

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Case Report

A 62-year-old woman was diagnosed with glioblastoma multiforme (GFAP+, S100+, Ki-67+ 15%–20%) by biopsy. The patient had a good performance status (ECOG PS0) but presented with aphasia. She underwent SIB-IMRT with sanazole and temozolomide administration.

High-risk clinical target volume (CTV) was generated by adding a 0.5-cm margin to the contrast-enhanced T1-weighted area, and the high-risk planning target volume (PTV) was created by adding a 0.5-cm margin to the high-risk CTV. Low-risk CTV was delineated by the addition of a 2-cm margin to the high-intensity area in T2-weighted images, and low-risk PTV was created by the addition of a 0.5-cm margin to the low-risk CTV. SIB-IMRT was administered at a dose of 60 Gy in 20 fractions for high-risk PTV and at 40 Gy in 20 fractions for low-risk PTV by D95 prescription using Helical Tomotherapy (Hi-Art System; Tomotherapy Inc., Madison, WI, USA). Organs at risk (OARs) were the eyes, brain stem, skin, and the optic tract

(bilateral optic nerve and chiasm) (Figure 1). Dose constrains were set for the optic tract, brain stem, and spinal cord. The maximal dose to the optic tract was 18.75 Gy in 20 fractions for chiasm (7.17 Gy, 10.98 Gy, 3.11 Gy, 1.75 Gy, 8.08 Gy, and 16.28 Gy for the right eye, left eye, right lens, left lens, right optic nerve, and left optic nerve, respectively). Maximal dose to other OARs were 34.54 Gy, 26.23 Gy, and 3.62 Gy for brain stem, right middle ear, and left middle ear, respectively. The spinal cord was located outside the irradiated field. Daily megavolt computed tomographic images were taken to monitor the tumor and OAR positions.

The patient received daily oral administration of 1.0 g/day sanazole up to 10 g for a period of 10 days, 2 h before radiotherapy. Temozolomide was administered thereafter at 200 mg per day after radiotherapy five days a week for four weeks, which induced mild nausea (grade 1) transiently, but which disappeared without medication. No other side effect was observed. The patient was enrolled in the study after providing written informed consent prior to treatment. The consent was obtained in accordance with the guidelines of the Institutional Review Board. The patient achieved complete response (Response Evaluation Criteria in Solid Tumors version 1.1) and remained disease-free at her 3.5-year follow-up visit (Figure 1).

Discussion

Sanazole was developed 24 years ago and has been shown to be beneficial in a number of *in vitro* experiments. It accumulates in hypoxic areas (10), acts as a radical enhancer (electron-affinic sensitization) (11), and induces apoptosis (12). The drug was initially developed for use in developing countries with the aid of the IAEA and has demonstrated positive outcomes in clinical trials, including phase III trials of cervical cancer under the directions of the IAEA. The total prescribed dose of hypoxic sensitizers is limited and these drugs are expected to be more effective when administered with larger single-doses of radiation than with conventional 1.8-2 Gy fractionation. Therefore, they are suitable for use with procedures requiring large doses per fraction, such as stereotactic radiation therapy, high-dose brachytherapy, or SIB–IMRT.

To our knowledge, this is the first report evaluating the hypoxic radiation enhancer sanazole in combination with modern modalities. Although it is difficult to draw any definitive conclusions regarding the efficacy of sanazole, this result may show the potential merit of this drug when used in combination with SIB–IMRT. In addition, we have previously reported an excellent outcome of this use of drug in preoperative radiotherapy for Ewing sarcoma (13).

Glioblastoma multiforme has an extremely poor prognosis. Our patient was classified as a patient of recursive partitioning scoring class III (age >50 year, Karnofsky performance status 100) (14), whose expected median survival time is only 17.9 months (2-year survival rate 35%). However, she now enjoys disease-free status without any adverse reaction or symptoms. The limited confined lesion without extension to contralateral side and without dissemination could be one reason for this positive outcome. In addition, temozolomide administration is also an important factor in improving treatment efficacy.

There are several drawbacks to the use of for sanazole. As previously described, wide commercial distribution of this drug is difficult because the patent has been withdrawn. This drug does not belong to the class of newly-developed drugs, but is rather old and enthusiasm for new financial funding for further clinical trials is limited. It is unknown whether the application of such drugs requires quantitative analysis for hypoxic fractionation before administration. Such analyses have included studies of hypoxic markers, for example, direct oxygen measurement (15), detection of pimonidazole by immunohistochemistry (16), and, most recently, identification of proteins and hypoxia-related genes (17). Such quantitative estimations should precede the administration of hypoxic radiation modifiers.

In conclusion, our study demonstrates that the higher single-dose radiotherapy combined with a hypoxic radiation sensitizer has the potential to enhance the efficacy of radiotherapy.

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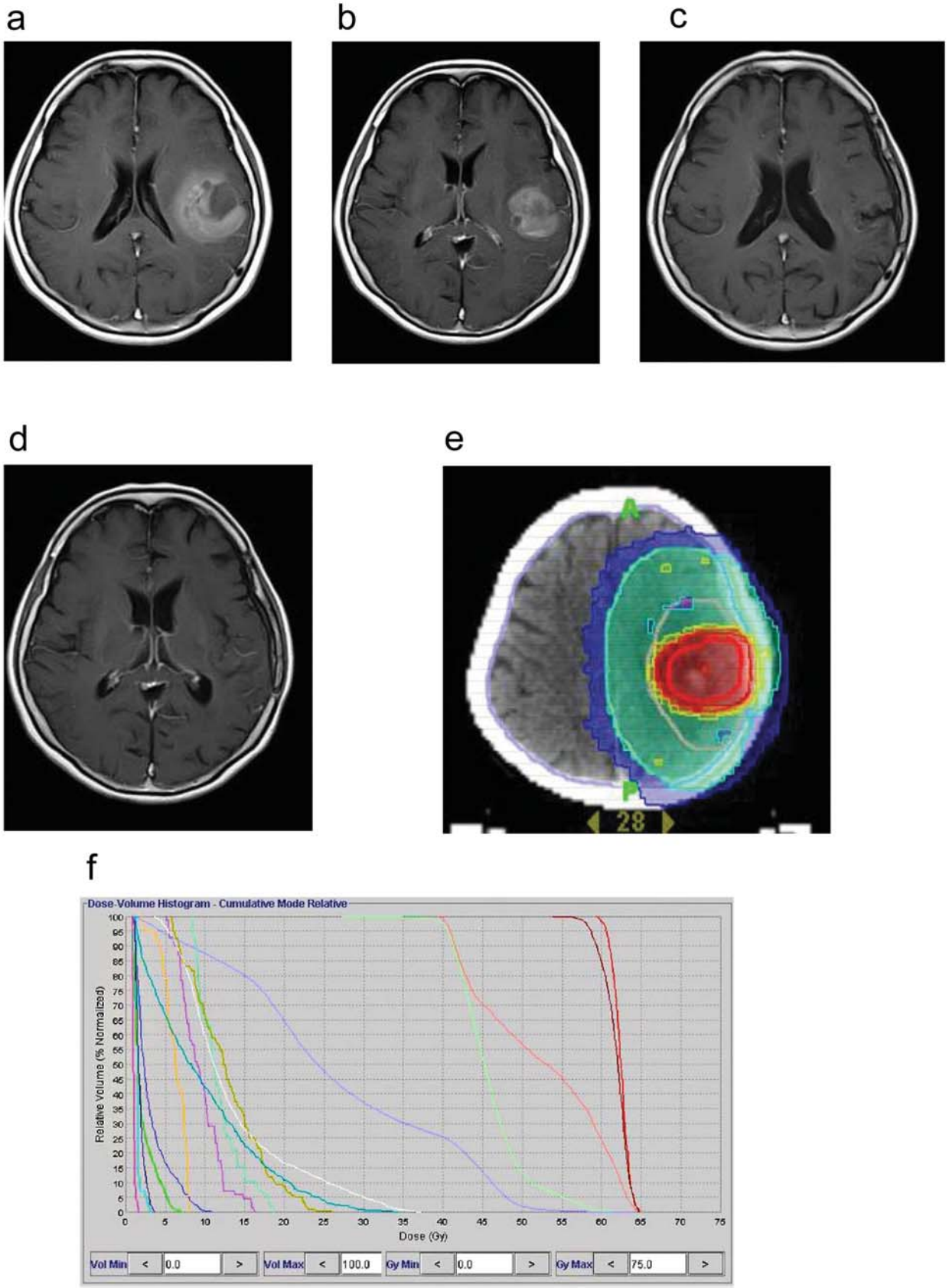
Figure 1. *A 62-year-old woman with glioblastoma underwent simultaneous integrated boost intensity-modified radiotherapy (SIB-IMRT). a, b: Contrast enhanced (MRI) (T1w) images before treatment. c, d: MRI (T1w) 3.5 years after treatment. e: SIB–IMRT dose distribution. The red line represents the contrast-enhanced lesion in T1w images, and the white line represents the high density area in T2w MRI images. High-risk clinical target volume (CTV) was generated by adding a 0.5-cm margin to the contrast-enhanced T1w area, and the high-risk planning target volume (PTV) was created by adding a 0.5-cm margin to the high-risk CTV. Low-risk CTV was delineated by the addition of a 2-cm margin to the high-intensity area in T2w images, and low-risk PTV was created by the addition of 0.5 cm to the low-risk CTV. Radiotherapy was administered at a dose of 60 Gy (red area) in 20 fractions for high-risk PTV and at 40 Gy (green area) in 20 fractions for low-risk PTV. f: Dose-volume histogram. Red line, high-risk CTV; gray, high risk PTV; vermilion, low risk CTV; light green, low risk PTV; green, right eye; dark bluenavy blue; left eye, light blue, left lens; pink, left lens; orange, right optic nerve; purple, right optic nerve; yellowish green, chiasma; dark blue, brain stem; dun, left middle ear; and azure, right middle ear.*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Dose-Volume Histogram - Cumulative Mode Relative
Relative Volume (% Normalized)
Dose (Gy)
Vol Min
0.0
Vol Max
100.0
Gy Min
0.0
Gy Max
75.0

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