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 a 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 Unfortunately, this drug is not commercially available because its patent has been withdrawn in Japan, limiting its clinical usage.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.

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.
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 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.

References


