Hypofractionated Stereotactic Radiotherapy with the Hypoxic Sensitizer AK-2123 (Sanazole) for Reirradiation of Brain Metastases: A Preliminary Feasibility Report

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Abstract. Reirradiation is a challenging field in the treatment of recurrent brain metastases. Because of the elevated risk of radiation toxicity due to previous irradiation, only a limited dose is prescribed. To enhance radiosensitivity, in the present analysis six patients received hypofractionated stereotactic radiotherapy (hSRT) with daily oral administration of the hypoxic sensitizer AK-2123 (sanazole) for progressive brain metastases after previous radiotherapy. The patients received daily oral administration of 1.0 g/day sanazole up to 2 h before radiotherapy. Three partial and three stable responses were observed, with no sanazole-related toxicity, except for a case of mild nausea. Brain failure with subsequent death occurred in one patient. The other patients maintained good performance status until disease progression in other lesions. hSRT with a hypoxic radiation sensitizer appears to have the potential to enhance the efficacy of radiotherapy.

Recent improvements in oncological therapies have prolonged survival in patients with advanced tumors. The number of cancer cases demonstrating brain metastases, as well as the possibility of recurrence in areas of the central nervous system already treated with radiotherapy, have increased (1-5). Although reirradiation can be helpful for improving neurological symptoms and extending survival, only a minority of patients receive further treatment because of iatrogenic toxicity concerns (4, 6-8). Reirradiation should thus be prescribed with prudence only for selected patients. We used multifractionated stereotactic radiotherapy (SRT), rather than a single fraction of stereotactic radiosurgery (SRS) to reduce the iatrogenic toxicity during the treatment of brain metastases. Moreover, we used a hypoxic radiation sensitizer, sanazole, to enhance treatment efficacy.

Hypoxia is one of the major obstacles to tumor control after radiotherapy and has been studied for more than a century after initial findings by Gray and colleagues (9). A meta-analysis of head and neck cancer provided evidence for improved tumor control and survival with hypoxic modification during radiotherapy (10). AK-2123, sanazole; a nitrotriazole derivative, is a hypoxic cell sensitizer. Experimental data and preliminary clinical studies have demonstrated that sanazole has lower neurotoxicity than most nitroimidazoles (11-14). Phase-III randomized trials, including multicenter trials, have demonstrated the efficacy of this drug (14). 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). Moreover, the patent of this drug has been withdrawn in Japan; therefore, it is not commercially available and its clinical usage is limited. Hence, we initiated a clinical trial to test the toxicity of convenient daily oral administration of sanazole in conventional radiotherapy (15). Following this trial, we employed a modern radiotherapy technique, namely hypofractionated SRT (hSRT) using CyberKnife, and report the results for reirradiation of brain metastases.

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Key Words: Hypoxic radiosensitizer, reirradiation, brain metastases, stereotactic irradiation, CyberKnife.
Materials and Methods

Eligibility requirements included patients of at least 18 years of age who received partial or whole-brain fractionated external beam radiotherapy three months prior to study entry. Computed tomography (CT) or magnetic resonance imaging (MRI) scans with evidence of brain recurrence were required. All patients were required to have the Eastern Cooperative Oncology Group performance status (PS) of ≤2. Patients with multiple lesions were included as long as they could be treated in one session. Six cases with recurrent brain metastases were treated by reirradiation using the CyberKnife system, and the patients’ characteristics are shown in Table I. Three patients with lung cancer and three with breast cancer with ages ranging from 44 to 75 years (four females and two males) were included. The detailed treatment procedure is described in detail elsewhere (16). In brief, a shell was first made to fit the patient’s head, and then contrast-enhanced CT and contrast-enhanced MRI scans were acquired. Next, we contoured the gross tumor volume (GTV) and organs at risk (OAR) on the CT images by fusing with the MRI images. We defined the planning target volume (PTV) as GTV-clinical target volume (CTV)=PTV or minimal CTV margin of 1-2 mm because CyberKnife can deliver radiation with sub-millimeter accuracy, even if a patient moves during treatment, by minimizing the influence of set-up error and internal motion. The dose administration was prescribed at D90 for PTV. OAR was set at the optic tract and brain stem, while the maximal dosage was restricted to the lowest range possible. The cumulative linear quadratic equivalent dose in 2-Gy fractions (EQD2) of previous, present, and accumulated radiotherapy was estimated according to the following equation: EQD2=n×d×(α/β+d)/(α/β+2), where n=number of fractions, d=fraction dose, α/β=10 for PTV, and α/β=2 for OARs.

Results

Four patients received second- and two received third-radiotherapy with sanazole (Table I). The median tumor diameter was 20 mm (3-38 mm), and the period from previous radiotherapy was a median of seven months (2-15 months). The median prescribed dose in EQD2 was 58 Gy (30-78 Gy; α/β=10) and 83 Gy (40-136 Gy; α/β=2), whereas the median prescribed dose by CyberKnife hSRT was 31 Gy (28-33 Gy) in five fractions (3-7 fractions) at D90 prescription with EQD2 at 42 Gy (33-58 Gy; α/β=10) and 59 Gy (33-71 Gy; α/β=2). The accumulated EQD2 was 101 Gy (33-58 Gy; α/β=10) and 129 Gy (107-196 Gy; α/β=2) and 50 Gy or less for the optic tract. All patients demonstrated good performance status (0 or 1) and completed hSRT without interruption. The median administered dose of sanazole was 5 g (1-7 g) in five days, with no toxicity except for mild nausea in patient 5 (Table II). The patient experiencing nausea stopped sanazole administration but completed SRT. After treatment, three partial and three
stable responses were observed (100% response ratio, Table II). Four out of six irradiated tumors were controlled until the patient’s last visit or death, as in the case of one patient who had brain failure which resulted in death (patient 2). All patients maintained good PS until disease progression in other sites, and the median survival time was five months.

**Discussion**

Reirradiation is a challenging field in treating recurrent brain metastasis. Because of the elevated risk of radiation toxicity, patients who have received previous irradiation are prescribed a limited dose for reirradiation. A recent systematic review documented several studies addressing the role of SRS for recurrent and progressive brain metastases in patients whose initial management included whole-brain radiotherapy (17). Data from published series with an accrual of over 50 cases (4, 5, 7) are summarized as follows: previous whole-brain radiotherapy was primarily administered with a median dose of 30 Gy in 10 fractions, the median dose of SRS was usually 20 Gy, and both one-year local control rates (65-91%) and median survival after SRS (7.8-10 months) reached significant values. Although making definitive comparisons is difficult since our study population had a poorer medical background, our data is nonetheless similar to the results of the previously reported results.

Sanazole was developed 24 years ago and was shown to be beneficial in a number of *in vitro* experiments. Sanazole accumulates in hypoxic areas (18), acting as a radical enhancer (electron-affinic sensitization) (19). Under hypoxic conditions, the sensitizer enhancement ratio determined at the 1% cell survival level was 1.55 at 1 mM and 1.40 at 0.5 mM *in vitro* (20). Furthermore, in rats, sanazole only accumulates in tumors with hypoxic lesions and not in the normal rat brain (21). The drug was initially developed for use in developing countries with the aid of the IAEA and had demonstrated positive outcomes, including phase III trials of cervical cancer. However, there is a problem associated with the distribution of the drug. It is a cheap product with an expired license in Japan, making its potential marketability quite limited. We initiated a precedent oral administration trial to determine the toxicity of convenient daily usage of this drug (15). We found that administration of 1-9 g sanazole is safe without neurological toxicity, which is a major side-effect of radiation sensitizers; however, approximately 20% of patients suffered neurological toxicities after administration of 10 g. Therefore, we chose to administer up to 9 g of sanazole in addition to a modern radiotherapy technique. Since the total prescribed dose of hypoxic sensitizers is limited, these agents are expected to be more effective when administered with larger single doses of radiation than with conventional 1.8-2 Gy fractionation. Therefore, procedures that require large doses per fraction, such as SRT, high-dose brachytherapy, or intensity-modulated radiation therapy with simultaneous integrated boost technique (SIB–IMRT) are suitable applications for modification by sanazole. To our knowledge, this is the first report to use the hypoxic radiation enhancer sanazole in combination with hSRT. Although it is difficult to draw any definitive conclusions regarding the efficacy of sanazole, we previously reported on excellent outcome after using this drug in preoperative radiotherapy for Ewing’s sarcoma (22) and glioblastoma using SIB–IMRT (15). These results including those of the present study, imply the potential of sanazole in radiotherapy, which warrants for further research.

**References**


