Case Report

Long-Lasting Partial Regression of Glioblastoma Multiforme Achieved by Edotecarin: Case Report

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We describe the response to a new chemotherapy agent, topoisomerase I inhibitor edotecarin in an 18-year-old woman with recurring glioblastoma. The therapy was administered for 17 months. The radiological partial response and clinical improvement have been achieved, with minor toxicity. Median survival of patients with glioblastoma is 10 months. With edotecarin we have achieved promising result, which should encourage further investigations to develop more efficient therapy for such a deadly disease.

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After meningioma, glioblastoma multiforme is the most common tumor of the central nervous system (CNS). Median survival of patients with newly diagnosed glioblastoma is approximately 10 months (1). Standard therapy consists of surgical resection followed by radiotherapy. Consolidation chemotherapy is usually applied to patients with good performance status, but survival benefit is minimal.

Recently, a statistically significant survival impact has been obtained by adjuvant and concomitant administration of temozolomide with external radiotherapy (2). Nevertheless, significant survival benefit was seen only in particular groups of patients, those with methylated O6-methylguanine-DNA methyltransferase (MGMT) gene promoter (3). In the event of disease progression, af-

ter radiotherapy and first-line chemotherapy, there is no standard treatment available. If nitrosourea-based chemotherapy is adjuvantly applied, second-line monotherapy with temozolomide is usually given with modest clinical efficacy (4,5). According to these clinical facts, it is obvious that more successful treatment regimens are required.

Edotecarin is a new indolocarbazole, a potent inhibitor of topoisomerase I (6). In comparison with other topoisomerase inhibitors, especially with derivatives of camptothecin, it has a broad spectrum of antitumor activity, a wider therapeutic index in preclinical models, and longer duration of action. It also seems to interact with the enzyme in a different manner. Also, unlike derivatives of camptothecin, edotecarin is active without metabolic conversion. In vitro studies have shown activity of edotecarin against some multidrug-resistant cell lines, and synergistic or additive effects in combination with other chemotherapeutic agents.

In vivo studies confirmed the synergistic effect of edotecarin in combination with both cisplatin and etoposide. Also, edotecarin was tested on a panel of malignant CNS tumor-derived xenografts growing subcutaneously and intracranially in nude mice. It demonstrated statistically significant antitumor activity against all xenografts tested in the subcutaneous site and produced an 83% increase in survival in mice bearing intracranial (D-456MG) glioma (7).

We present the case of a patient with glioblastoma progressing after surgery, radiotherapy, and first-line nitrosourea-based chemotherapy, where administration of the chemotherapy with edotecarin gave a very promising result.

Case report

In October 2003, an 18-year-old girl experienced occasional headaches localized in the occipital region, short periodical loss of vision in both eyes, flashes, flashing lights, and intolerance to odors. The patient's medical history was unremarkable. One month later, she was hospitalized in the Department of Neurology for diagnostic evaluation. Ophthalmic examination showed papill-edema in both eyes. The neurological examination showed no abnormalities except for grade 2 decreased vision in both eyes, according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (8). Magnetic resonance imaging (MRI) of the brain showed a unilateral supratentorial round mass of 2.7 cm in (largest) diameter in the right parietal-occipital region. After a stereotactic biopsy in November 2003, anaplastic oligoastrocytoma grade 3 according to the World Health Organization (WHO) classification of brain tumors (9) was diagnosed. In December 2003, the patient underwent an osteoplastic craniotomy with reduction in tumor mass as a final result. After surgery, neurological status was unchanged, and control brain MRI was not done. In January 2004, external radiotherapy was started. The patient received a planned tumor dose of 60 Gy in 30 fractions. Chemotherapy treatment with lomustine (1(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, CCNU) was started in February 2004. She received only one of 6 planned cycles of chemotherapy due to neurological and radiological disease progression. During radiotherapy she started with anticonvulsive (methylphenobarbitone) and antiedematous therapy (prednisolone). A control brain MRI in March 2004 showed enhancing supratentorial round mass of 5×4 cm in size in the right parietal-occipital region. A second stereotactic biopsy was performed in April 2004 and pathohistological findings showed a multiform glioblastoma. After the biopsy, a control brain MRI in May 2004 was performed and the largest tumor size was 5.9×2.9 cm in the transversal line.

The patient came to the Center of Oncology, Split University Hospital, in May 2004 due to neurological progression. On admission, her Karnofsky performance status was 90%. Her neu-

rological findings were as follows: grade 2 headaches, grade 1 weakness in the left arm, grade 1 weakness in the left leg, grade 2 decreased vision, and grade 1 memory impairment. Psychological exam showed anxiousness and uneasiness. Laboratory results of blood hematology and chemistry were within reference ranges.

Due to clinically and radiologically confirmed disease progression, the patient was enrolled in the EDOAGL-8725-001 study (A phase III, randomized, open-label study of IV edotecarin vs temozolomide or carmustine (BCNU) or lomustine (CCNU) in patients with glioblastoma multiforme that has progressed/recurred after alkylator-based (neo) adjuvant chemotherapy). After the patient signed the informed consent form, she was randomized to receive monotherapy with edotecarin. A central venous catheter was inserted. Chemotherapy with edotecarin was started in May 2004. Until October 2005 the patient received 24 cycles of chemotherapy with edotecarin in unchanged dose of 13 mg/m^2. Edotecarin was given in infusion over 1 hour, once every 3 weeks. Thirty minutes before edotecarin infusion, a prophylaxis consisting of 10 mg of ondansetron hydrochloride IV, 1 mg lorazepam IV, and 20 mg of prednisolone IV was administered. During the next 4 days, the patient was given oral antiemetic therapy consisting of 8 mg of granisetron and 1 mg of lorazepam every 6 hours. Antiedematous and anticonvulsive therapy with 10 mg of prednisone twice daily and methylphenobarbitone 200 mg daily, respectively, was not changed when treatment with the study protocol started. After the introduction of a central venous catheter, prophylactic anticoagulation therapy with warfarin (3 mg daily) was administered.

With every second cycle of chemotherapy (6 weeks apart) a control brain MRI was done and the tumor response was evaluated by modified Response Evaluation Criteria in Solid Tumors (RECIST) (10). After 8 cycles of chemotherapy, clinical improvement was observed on neurological examination, which was normal except for grade 1 decreased vision.

Partial radiological tumor response was achieved after the 16th cycle of chemotherapy, with a 62% reduction in size from the baseline. The best radiological tumor response was recorded after the 20th cycle of chemotherapy, with 66.7% reduction in tumor size in comparison with the baseline MRI findings (Figure 1).

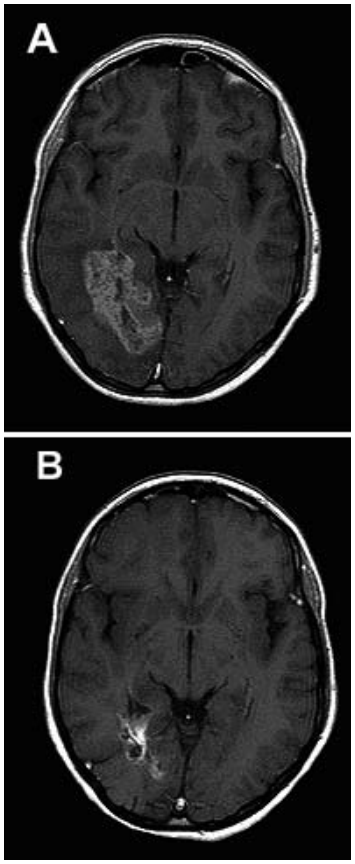

Figure 1. Transverse magnetic resonance imaging (MRI) brain scans revealed the tumor mass in right parietal-occipital region in the 18-year-old woman with glioblastoma multiforme. **A.** Largest size of tumor mass at baseline, 5.9 × 2.9 cm. **B.** Largest size of tumor mass after 20 cycles of chemotherapy with edotecarin, 3.8 × 1.5 cm.

The patient has been using anticonvulsive and antiedematous therapy in unchanged dose. Although there were no major toxic effects that would require discontinuation of chemotherapy, there were some mild to moderate toxic effects present in the patient during the treatment. The severity and type of observed toxic effects accord-

ing to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, were as follows: grade 2 headaches, grade 2 fatigue, grade 1 leucopenia, grade 1 constipation, grade 1 vomiting, and bloody diarrhea (8).

In consensus with the patient, we are planning to continue with edotecarin chemotherapy, sponsored by Pfizer Pharmaceutical Company, until the disease progression or development of unacceptable toxicity.

Discussion

Despite numerous investigations, the role and time of application of chemotherapy in patients with glioblastoma has not been clearly defined. Statistically significant improvement in survival was achieved with radiotherapy treatment after surgical resection (11), whereas studies investigating chemotherapy after surgical resection followed by radiotherapy did not show a statistically significant survival benefit (12). However, meta-analysis of the results of 12 studies detected small but statistically significant survival benefit achieved by chemotherapy after radiotherapy, with a 2-month increase in survival median (13). Although polychemotherapy is usually administered, it did not show statistically significant benefit in comparison with monochemotherapy in the treatment of patients with glioblastoma (14). The most commonly used agents are nitrosourea derivatives. Recently, promising results have been achieved with temozolomide in concomitant chemoradiotherapy setting followed by adjuvant chemotherapy (2).

Beside previously known prognostic factors (age, extent of surgical resection, mental status, and Karnofsky performance status), it is important to emphasize the molecular characteristics of the tumor, which determined existence and expression of the chemotherapy benefit (3).

Chemotherapy achieves even less effects in patients with recurrent glioblastoma. Survival of such patients rarely exceeds 6 months. The aim of the treatment is palliation with improvement in quality of life. Temozolomide is the most recognized agent for the treatment of this patient population, because it has modest clinical efficacy, acceptable safety profile, and measurable improvement in quality of life (4,5).

Edotecarin, after promising results in the preclinical and early clinical studies, has been evaluated in the phase III trial. Phase III study was terminated early due to the results of the interim analysis that showed no statistically significant benefit obtained with edotecarin. Nevertheless, we decided to present success of chemotherapy with edotecarin in a patient with nitrosourea refractory disease enrolled in the study. There were also 3 more patients enrolled in this phase III trial at our institution. Two of them have received edotecarin. One had disease progression after the first cycle. In the second patient the therapy was discontinued after the second cycle due to granulocytopenia grade IV and seizures grade III, despite stable disease according to the modified RECIST criteria (10). During a one-year follow-up period, this patient was without neurological worsening and with partial disease regression according to modified RECIST criteria (10). The third patient received temozolomide and her best tumor response was stable disease; however, after 8 cycles disease progression occurred.

Knowing the nature of the glioblastoma and its chemoresistance, we believe that every patient should be approached individually and treated with the best available anticancer modalities. No drug should be dismissed as inactive for all patients and better tests of in vivo or in vitro chemosensitivity should be developed to help us select the best drug or drug combination in the treatment of such deadly disease.

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