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Treatment of Glioblastoma with Intravenous Taurolidine. First Clinical Experience

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Abstract. *Background: Despite progress in diagnosis and therapy, the prognosis of patients with glioblastoma remains poor. Recently it has been found that the antibacterial agent taurolidine has a direct and selective antineoplastic effect on brain tumor cells by the induction of programmed cell death. This paper reports on intravenous taurolidine treatment in two patients with a progressive glioblastoma despite conventional therapy. Patients and Methods: Two male patients with histopathologically diagnosed glioblastoma were included. The tumors were progressive despite conventional therapy. Intravenous taurolidine treatment was initiated. Results: The neurological condition and quality of life improved in both patients such that they could be discharged for further outpatient treatment. Follow-up demonstrated partial remission of the tumor in both patients. However, both patients died about 4 months following the start of taurolidine treatment, from pneumonia and acute thrombembolism, respectively. Conclusion: Both patients achieved a transient, marked improvement in quality of life and partial tumor remission. There was a clear response to the taurolidine treatment.*

Glioblastomas are among the most devastating tumors, leading to death in most cases. Despite the "standard therapy" – removal of the tumor followed by radiotherapy – the prognosis remains poor. Because of their infiltrative growth glioblastomas tend to recur in the vast majority of cases, even after apparently complete gross resection (1-3). This results in one of the highest mortality rates of all human cancer types (4). The median survival time is reported to range from 9 to 12 months (5, 6). In a meta-analysis, reviewing the data from 12 randomized trials, a 2-month increase in median survival time by adjuvant chemotherapy had been achieved (7). However, glioblastomas remain a major cause of mortality in a relatively young population. The limited therapeutic options available for treating these tumors make it necessary to extend the search for potentially effective alternative treatment strategies.

The synthetic agent taurolidine (bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)methane) (Taurolin®,Geistlich Pharma, Wolhusen, Switzerland) has a known topical antibacterial activity (8-11). In addition, intravenous taurolidine has been used as an adjunct to treat severe infections under trial conditions. It is associated with only mild collateral effects (12-14). Recently, taurolidine was found to have a direct and selective antineoplastic effect on brain tumor cells combined with anti-angiogenetic activity (15-18). This antineoplastic effect, combined with the low toxicity known from studies with intravenous use of this substance as an adjunct for treating severe infections (19, 20), encouraged the authors to use intravenous taurolidine treatment in two patients with progressive glioblastoma despite conventional treatment following informed consent of the patients and with agreement of the local ethics committee.

Case Report I

The 66-year-old male had experienced headache, confusion, impaired concentration and a slight left-sided hemiparesis since May 2002. Magnetic resonance imaging showed a diffuse space occupying lesion right-sided in the area of the right hippocampus and the lower temporal gyrus. Stereotactic biopsy was performed in June 2002. The histopathological analysis of the specimen revealed a glioblastoma with a proliferation index of 25 %. Resection of the tumor was not indicated. A cranial radiation therapy was performed with a total dose of 49.4 Gy. After this the patient received a single cycle of BCNU, which was not continued because of tumor

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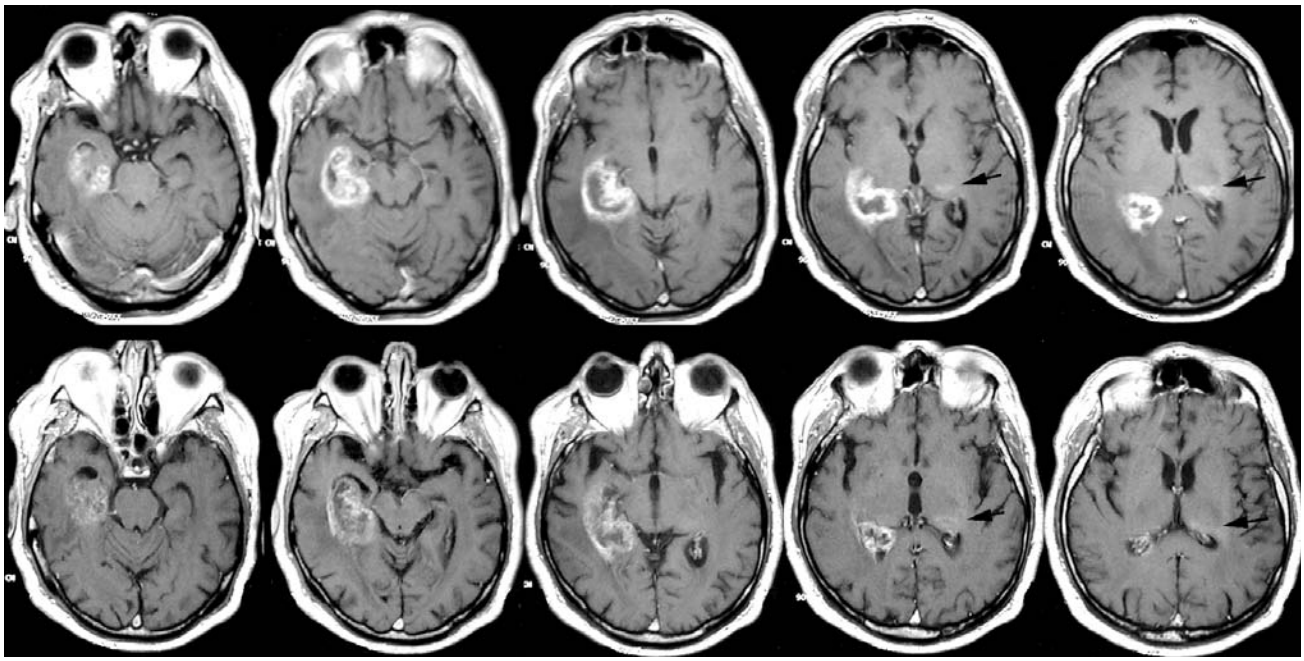

Figure 1. *Gadolinium-enhanced MRI showed contrast enhancing diffuse glioblastoma in the right hippocampal region and the right lower temporal gyrus with perifocal edema and a second focus (arrows) on the left side (upper line). Tumor size, contrast enhancement and perifocal edema were markedly decreased about 7 weeks later (lower line). The second focus (arrows) has also decreased in size.*

progression and side-effects (nausea, thrombocytopenia). The patient experienced increasing diplopia, confusion, headache and general seizures.

The patient was admitted to our department and he received taurolidine intravenously with a daily dose of 20 g from November till December 2002. In addition he received valproic acid and the corticoid regimen was continued. There were no side-effects from the taurolidine treatment and the corticoid dose could be decreased during the taurolidine treatment. After therapy the patient was discharged in a good clinical condition. Diplopia and headache were no longer apparent. The only symptom was an intermittent slight confusion, which had improved as compared to the status on admission. There was no further neurological deficit.

Follow-up using clinical and neurological examination and contrast enhanced MRI did not reveal any tumor progression. From February to March he received another taurolidine treatment with a daily dose of 20 g to a cumulative dose of 840 g. Again there were no side-effects. MRI, performed with the same parameters, showed a decreased tumor size and decreased contrast enhancement with no signs of progression (Figure 1). According to standardized criteria (21), the disease was classified as "partial remission". Shortly after finishing therapy the patient developed slight edema in both lower legs. He died from thrombembolism 4 months after the start of the taurolidine treatment. Autopsy revealed severe thrombembolism as the cause of death. The tumor had a size of 5 x 3 x 1.5 cm with only slight space occupying effect and no signs of cerebral herniation. There were no signs of side-effects from the taurolidine treatment in any organ.

Case Report II

This 40-year-old male patient suffered a generalized seizure in April 2001. Magnetic resonance imaging demonstrated a left temporal mass infiltrating the basal ganglia. Biopsy revealed a glioblastoma, which was not suitable for resection. Radiochemotherapy was initiated (60 Gy total dose, daily complemented by 0.5 mg/m^2 body-surface of Topotecan). Initial improvement was followed by deterioration in vigilance and progressive hemiparesis weeks after conclusion of the radiochemotherapy. Shortly thereafter the patient was admitted in a soporous state. Computerized tomography (CT) showed marked tumor progression with ventricular compression and midline shift (Figure 2).

Following initial improvement by antiedematous treatment, taurolidine was administered intravenously at a daily dose of 20 g for a total of 2 x 21 days. The neurological condition improved after the first taurolidine treatment period. The patient was discharged for further outpatient

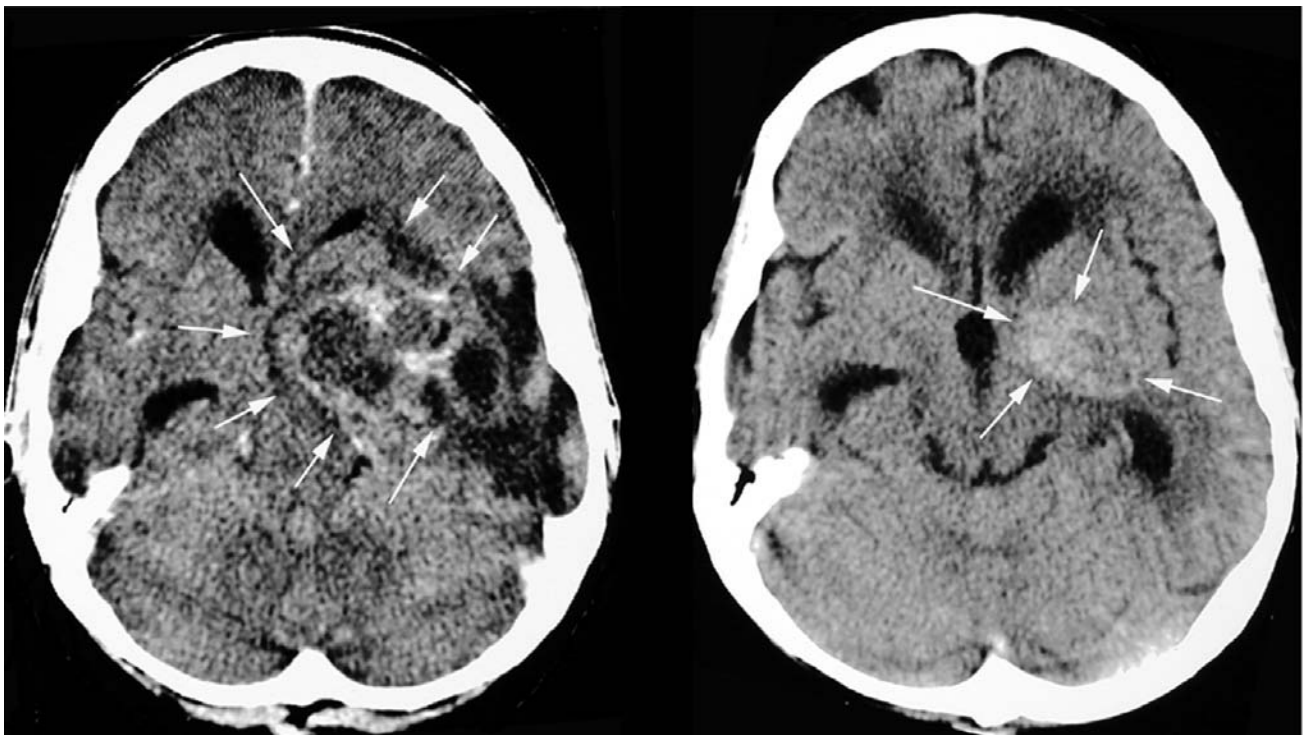

Figure 2. *CT scans obtained following radiochemotherapy prior to the taurolidine treatment (left) demonstrate a large left temporal glioblastoma with cystic components and marked perifocal edema. Note the ventricular compression and midline shift. CT with contrast medium scans following taurolidine treatment (right). Marked regression of the solid and cystic tumor components and disappearance of the perifocal edema.*

treatment 3 weeks following the beginning of taurolidine therapy. During a subsequent break in treatment (about 3 months following the start of taurolidine treatment), the patient suffered an acute diabetic decompensation as a result of a latent diabetes mellitus and prolonged corticoid intake. CT on re-admission showed a marked size-reduction of the tumor as well as disappearance of perifocal edema (Figure 2). According to standardized criteria (21), the disease was classified as "partial remission". Because of the diabetic decompensation the taurolidine treatment was interrupted. Six weeks later, the patient developed a severe pneumonia. He died about 4 months following the beginning of taurolidine treatment due to progression of pneumonia.

Discussion

Taurolidine, a derivative of the non-essential aminoethyl-sulfonic acid taurine, has been used as an adjunct to treat bacterial infections for many years (8-10, 22-25). In addition, taurolidine was reported to suppress the activity of interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) in humans (26-28). Furthermore, taurolidine was observed to reduce the severity of postoperative and inflammatory peritoneal adhesions (26, 27, 29). Considering these effects, taurolidine has been applied by lavage to reduce postoperative adhesions and for treatment of peritonitis (30-33). In contrast to other antibacterial agents, taurolidine acts by a chemical reaction. Active hydroxymethyl-groups formed by degradation of taurolidine seem to react with components of the bacterial cell wall. As a result the adhesion of the bacteria to biological surfaces is prevented (34-36).

In 1990 Monson *et al.* (37, 38) noticed a direct growth inhibition of intestinal tumor cell lines following exposure to taurolidine. An influence on the adhesive properties of the tumor cells, similar to that of bacteria, was thought to be the mechanism of this antineoplastic effect (37-39). In agreement with this assumption, it has been reported that intraperitoneal administration of a taurolidine-heparin-CO_2 mixture to rats receiving simultaneous intraperitoneal injections with colon adenocarcinoma cells prevented adhesion of the tumor cells (40).

In contrast, it has been recently found that taurolidine exerts a direct and selective antineoplastic effect on brain tumor cells (15-18). The results of these studies suggest that not simply an inhibition of cell adhesion but the induction of programmed cell death, probably of a mixed type of autophagy and apoptosis (41), is the underlying mechanism of the direct antineoplastic action of taurolidine. Furthermore,

the induction of the programmed cell death following exposure to taurolidine was found to be specific for tumor cells. Surprisingly, the taurolidine concentration required for this antineoplastic effect was about two orders of magnitude lower than its antibacterial concentration, which has been reported to be in the range of some milligrams per milliliters (19, 32, 34, 42).

The results of the described therapeutic trials using intravenous taurolidine treatment in patients with a progressive glioblastoma seem encouraging. Both patients achieved a transient, marked and surprising improvement in quality of life during and after taurolidine treatment. Both patients could be discharged after therapy. There was a clear response to the taurolidine treatment. The aggressive tumor growth was stopped in both cases, achieving a partial remission of the tumors.

The survival time was limited to about 4 months in both cases, caused by a thrombembolism in the first and pneumonia in the second patient. A meta-analysis investigating patients with recurring malignant glioma revealed a progression-free interval of 9 weeks and a progression-free survival rate following 6 months of 15 % (43). In patients with anaplastic astrocytoma or anaplastic oligoastrocytoma treated with temozolomide, the progression-free interval was 11 weeks and the progression-free survival rate following 6 months 21 % (44). However, it is well known that glioblastoma is much more aggressive and causes shorter survival times as compared to anaplastic astrocytoma or anaplastic oligoastrocytoma (45-48). Thrombembolism is a known and frequent complication in patients with advanced malignant glioma. It is reported to occur in about 18 % of the cases and to have a more severe course as compared to patients without glioblastoma (49-51). Severe infections such as pneumonia in the second patient may have been promoted by long corticoid intake and the latent diabetes mellitus.

Taking into account the results of these cases, a clinical trial was prepared to study the effect of taurolidine in patients with recurrent or progressive glioblastoma following standard treatment.

Conclusion

The results of the described therapeutic trials using intravenous taurolidine treatment in patients with a progressive glioblastoma seem encouraging. Together with the *in vitro* results, these cases suggest that taurolidine may constitute a promising antineoplastic agent for treatment of glioblastoma that warrants future examination.

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