Hyperthermia in combination with ACNU chemotherapy in the treatment of recurrent glioblastoma.

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Abstract

Purpose: The glioblastoma represents a brain tumor with a extremely bad prognosis. Especially in the case of recurrent disease new therapeutic strategies are necessary to overcome the resistance of the tumor cells against cytostatic substances. The effect of a combination of ACNU chemotherapy and local radiofrequency hyperthermia should be tested in patients suffered on recurrent glioblastoma.

Patients and methods: 19 patients with recurrent glioblastoma, after primary therapy with surgery and radiation therapy, were treated in our hospital once a week with ACNU (60 mg/m^2) and local electro- hyperthermia (13,56 MHz) with a duration of 60 min. The mean temperature reached in tumor tissue was 41.6^{0}C. Treatment was given for three weeks, interrupted for three weeks and repeated until progression.

Results: Two patients (11%) showed a partial remission according to the standard criteria; 6 patients (31%) had a stable disease. 11(58%) did not respond to the therapy and showed progressive disease. The median survival time was 8.5 months, median time to progression was 7.5 months. The observed hematologic toxicity was low, only 2 patients (11%) developed a leucopenia grade 2 or 3. Thrombopenia of grade 2 and more occurred in 5 patients (26%).

Conclusion. The combined treatment is active in the therapy of recurrent glioblastoma and well tolerated. Further prospective and randomized studies are required to show significant clinical profit.

Introduction:

Malignant gliomas represent more than 50 % of newly diagnosed primary brain tumors, on the other hand, the most malignant gliomas of WHO grade IV (glioblastoma multiforme) are the most frequent with more of 50 % of the incidence. Despite of the intensive therapy including operation, radiotherapy and chemotherapy the median survival of patients of glioblastoma remains limited; it is about one year after diagnosis. In the case of recurrent disease, the median survival time is in the range of only 25- 35 weeks (Nieder et al. 2000, Wong et al., 1999).

The application of antineoplastic substances in the adjuvant therapy of glioblastoma results in a slightly enhanced median survival time (Fine et al., 1993), however, the number of long-time survivors (survival time > 5 years) increased from to 15- 20% (De Angelis, 1998; Salvati et al., 1998). Nitrosoureas belong to the most active substances in therapy of glioma and may be useful also in the case of recurrent disease, (Brandes and Fiorentino, 1996, Huncharek and Muscat, 1998).

Because of the after all disappointing results of glioblastoma treatment it is necessary to examine the impact of new treatment modalities to improve response rates and survival of newly diagnosed gliomas as well as in the case of recurrent disease. Most of the gliomas show only a low sensitivity to antineoplastic substances, therefore the effectiveness of the drugs used or the vulnerability of the cancer cells must be enhanced for better therapy results. Artificial enhancement of the tissue temperature (hyperthermia) has been integrated in medicine into an innovative anticancer treatment .To improve the effectiveness of a cytostatic therapy different forms of hyperthermia have been used in the treatment of cancer for approximately 2 decades demonstrating its effectiveness in combination with both radio- and chemotherapy. The application of hyperthermia causes manifold cytotoxic effects to tumor cells. Activation of the cell metabolism resulting by the increased temperatur induces hypoxia, ATP depletion, and acidosis *(*Bicher et al, 1980; Schäfer et al, 1993; Vaupel et al, 1980; Vujaskovic et al, 2000). Hyperthermia causes disturbance in the microcirculation of cancer tissue (Bogovic et al. 2001), results in an inhibition of the DNA repair mechanisms (Li et al, 1998; Osman et al, 1993), and induces apoptosis, as it could be demonstrated for glioma cells in vitro as well as in animal experiments (Fuse et al., 1998; Uesugi et al., 1998). The treatment modulates the activity of cytokines (Katschinski et al, 1999; Neville and Sauder, 1988) and increases the

antigenicity of tumor cells by production of heat shock proteins via an activation of natural killer cells (Multhoff, 1997; Riogas et al, 1998).
Beside of the direct heat-induced cytotoxity, increase of temperature can dramatically enhance the antineoplastic effects of cytostatics. It can be demonstrated that there is not only a relation between dose and response, but also between temperature and the response of a therapeutic substance. There are a number of factors causing temperature dependent enhancement of the cytotoxicity. The biochemical reactions of the antineoplastic substances are temperature- dependent, for example the formation of DNA adducts by platinum containing drugs is increased by hyperthermia (Hettinga et al., 1997).
Regional hyperthermia is a well- tried method for the treatment of deep-seated tumors in limited and defined areas. Locoregional capacitive hyperthermia with radiofrequencies was successfully applied in the treatment of metastatic colorectal cancer, resulting in increased survival rates (Hager et al., 1999). In the treatment of gastric or pancreatic cancer high response rates of 39% and 36%, respectively, were obtained; an increase of the survival time could be achieved (Kakehi et al., 1990, Minakuchi et al., 1990). In our study we used radiofrequency (13.56 MHz) electro-hyperthermia to enhance the temperature inside of the tumor tissue. This method combines the effects of heat treatment with the effects of electric fields on tumor growth and takes advantage of the higher conductivity (Smith et al., 1986; Dissado et al., 1995) and energy absorption especially of the extracellular matrix of the tumor tissue. The selectivity of the injuring effects of the regional hyperthermia is based not only on the higher absorption of the supplied energy but also on the reduced blood perfusion connecting with an impaired thermoregulation inside of the tumor. Both effects cause an effective and selective heating of the tumor tissue.
The aim of our retrospective analysis was to prove the effectiveness of the combination therapy including regional hyperthermia and ACNU treatment in the therapy of recurrent glioblastoma.

Patients and Methods:

Patients

19 patients (Table I) with a median age at beginning of therapy of 55.3 years (range 33.0-67.3) with a histologically or radiographically verified recurrent glioblastoma

multiforme (WHO grade IV) were treated in our hospital with hyperthermia and ACNU chemotherapy. All patients were pretreated with surgery and radiation therapy, 8 had prior chemotherapy.

Treatment regimen

6 hours before hyperthermia treatment 20 mg of dexamethasone were orally applied; 30- 60 min. before a solution of 500 ml mannitol (20%) was injected. The systemic chemotherapy consisting of ACNU (60 mg/m^2) was given once a week to the patients 30 min. before beginning of hyperthermia.

Local electro- hyperthermia with modulated waves (13.56 MHz) was applied twice a week (with and without chemotherapy) using a oncotherm EHY 2000 device. The electro- hyperthermia equipment uses the principles of capacitive coupling to induce an electric field and enhance the temperature of the tissue. The frequency and intensity are chosen in that manner that the energy is absorbed mainly in tumor tissue. The electrodes were placed so that the tumor location inside the brain was heated to a maximum. The temperature control was performed using a non-invasive method calculating the temperature from measured energy absorption and impedance data. Mean temperature of tumor tissue during treatment was 41.6^{0}C. Duration of hyperthermia was 60 minutes, the interval between two treatments was 72 hours. The treatment was given for three weeks, interrupted for three weeks and then repeated until progression.

Clinical response and assessment

Only patients with measurable lesions were included our analysis. Responses were assessed according to the criteria of Macdonald (1990). A complete remission (CR) was defined as the disappearance of all tumor lesions on two consecutive imaging studies taken at least 1 month apart. The patient is off corticosteroids and the neurologic status is stable or improved. A partial response (PR) was defined as greater than or equal to 50% decrease in the sum of the products of perpendicular diameters of all measured lesions for at least 1 month, with stable or reduced corticosteroid dose and stable or improved neurologic status. No lesions should increase in size and no new lesion should appear. Stable disease (SD) was defined as a steady state or a response less than a PR, but with no disease progression for at least 1 month. No new lesions could appear and no symptoms could worsen. Progressive disease (PD) was defined as any increase of 25% or more in the sum of the products of perpendicular diameter of any measurable lesion or new tumor

lesions were detected, or the neurologic condition had deteriorated and/or the dose of corticosteroids was stable or increased. Time to progression and overall survival time were measured from beginning of therapy to the time of disease progression and death, respectively. The Kaplan-Meier method was used to calculate survival probabilities for all patients.

Results

19 Patients were treated with ACNU chemotherapy and hyperthermia. 10 patients received one cycle of the combined therapy, one patient 2 cycles, 3 received 3 cycles and 5 were treated with 4 and more cycles of hyperthermia and chemotherapy. 11 (58%) of the patients suffered from progressive disease (PD) after combination therapy, 6 patients (31%) had a stable disease (no change, NC), partial remission (PR) could be observed in two cases (11%). Median survival time determined for all patients using the Kaplan-Meier method (Fig. 1) was 8.5 months (range 1 to 32 months); a median time to progression of 7.5 months (range 3 to 21 months) was observed. The two patients with partial remission to the therapy had survival times of 12 and 32 month, the time to progression was 21 and 4 months, respectively (Table II).

Toxicity

6 patients (32%) developed a leucopenia grade 1, 2 (11%) grade 2 and 3, respectively, and one patient had a leucopenia grade 4. Thrombopenia grade 1 occurred in 5 (26%) patients, grade 2 in one patient. 3 patients (17%) had thrombopenia grade 3 and one thrombopenia grade 4.

Discussion

Malignant gliomas remain a form of cancer with high rates of morbidity and mortality, and there are only few documentation of improved survival resulting of therapy modifications. Analyses of clinical trials for gliomas show that the survival depends mainly on several prognostic factors. The histology (glioblastoma vs. anaplastic astrozytoma), the age (younger or older than 50 years) and the performance status of the patients represents the most important factors for survival time and for the frequency of long time survivors (more than 3 years after diagnosis) (Curran et al., 1993, Scott et al., 1999).

A general problem of assessment of clinical advance in therapy of recurrent glioma is the lack of clinical trials. Because of the relative small number of patients, it is not

possible to realize an unlimited number of randomized, prospective clinical studies. It must be taken into consideration, that the response to the antineoplastic therapy is depending on the histology of the brain tumor, anaplastic astrocytoma are generally more sensitive to cytostatics than glioblastoma multiforme. Therefore, a comparison of clinical trials is difficult and outcome measures of clinical trials as overall survival and time to progression may reflect patient selection. Also the response criteria for chemotherapy in the treatment of malignant glioma has to be tested with regard to its suitability. Macdonald et al. (1990) described response criteria for glioma, which includes the neurologic status of the patients and the application of steroids. Further, in the palliative therapy it should be shown consideration to the improvement of quality of life.

In the preclinical research a lot of evidence could be gathered for the effectiveness of hyperthermia in brain tumor treatment. In human glioblastoma cell culture as well as in a rat glioma model heat treatment induced apoptosis (Fuse et al., 1998, Uesugi et al., 1998). The enhancement of the cytotoxicity of antineoplastic drugs using hyperthermia could be also demonstrated. So it could be shown a temperature-dependent sensitivity of glioma cells against a number of cytostatics (Hermisson et al., 2000). It has been demonstrated in vitro as well as in vivo that also the activity of nitrosoureas an be enhanced by an increased temperature. In animal experiments local hyperthermia increased the cytotoxicity of ACNU to glioma and resulted in an enhanced survival time (Schem et al., 1995).

Hyperthermia is used in the therapy of malignant brain tumors since several years, the safety and effectiveness of the application is proved in clinical trials. In a phase I trial noninvasive localized hyperthermia in combination with chemotherapy resulted in increased temperature up to 42 ^{0}C selectively in tumor tissue (Silbermann et al., 1985). Clinical trials with radiofrequency (13,56 Hz) capacitive local hyperthermia combined with ACNU chemotherapy also caused high temperatures inside of the tumor tissue (Tanaka et al., 1987).

In our retrospective study we examined the effect of a combination of a chemotherapy with nitrosourea (ACNU) and locally applied radiofrequency hyperthermia. All patients suffered on recurrent glioblastoma and were pretreated with surgery and radiation therapy. We observed a response rate of 11% and stable disease of 31%, respectively. The median survival time was 8.5 months; the hematologic toxicity was low and no serious complications were observed. The

observed remission rate seems to be low, but malignant gliomas are not much sensitive to cytostatic drugs, so the therapeutic effects of chemotherapy are limited. Our response rate after the combined therapy is comparable with the described therapy results of treatment with nitrosoureas. Other studies using nitrosoureas (alone or in combination with other cytostatics) in treatment of recurrent glioblastoma resulted in response rates of 10-12% (Hildebrandt et al., 1998; Kappelle et al., 2001). Our median survival time was high compared to other studies. Application of nitrosoureas results in survival time up to 32 weeks (Huncharek et al., 1998). Taken together, the therapy results of seems to be good compared with other studies, but is difficult to demonstrate significant higher effects that obtained with chemotherapy alone. Further randomized trials with hyperthermia and different chemotherapy regimens are necessary to study the clinical profit of this new treatment modality.

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Table I Individual data and therapy results of patients entering the retrospective analysis a combined therapy with hyperthermia and chemotherapy.

No.	Age (a)	Karnofsky index	Survival since first diagnosis (months)
1	50,6	90	39+
2	57,4	30	4
3	62,7	40	10
4	37,7	80	24
5	60,6	80	8
6	56,5	60	12
7	55,3	70	36
8	39,9	90	27
9	61,3	60	59
10	50,7	80	33
11	33	70	13+
12	67,3	40	14+
13	50,8	80	29
14	50,4	40	11
15	58,6	80	12
16	59,7	60	13
17	39,1	70	55
18	52,7	80	16
19	62,5	62,9	15

Table II Individual data and results of therapy given to patients

No.	No. of therapies	Response	Survival (months)	Leucopenia NCI grade	Thrombopenia NCI grade
1	4	NC	31+	1	1
2	1	PD	1	0	3
3	1	PD	1	0	2
4	1	PD	12	2	3
5	1	PD	2	0	1
6	3	PD	6	0	0
7	3	PD	2	0	0
8	1	PD	12	1	0
9	7	PR	32	1	0
10	1	PD	6	0	0
11	1	PD	1+	4	4
12	3	NC	4+	0	0
13	1	NC	24	0	0
14	1	NC	6	1	0
15	2	PD	1	1	1
16	6	PR	12	2	1
17	1	PD	11	3	3
18	4	NC	13	1	0
19	4	NC	11+	3	1

Abbreviations: PD, progressive disease; NC, no change; PR, partial remission; CR, complete remission