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Sono-Photodynamic Therapy for Glioblastoma- A New and Promising Area of Research in Clinical Neurooncology

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ABSTRACT

The aim of this study is to evaluate the antitumor efficacy and safety of intraoperative sono-photodynamic (iSPDT) therapy with photosensitizer photolon in patients with recurrent glioblastoma. The study included 25 patients with histologically verified recurrence of glioblastoma (grade IV). The main group included 15 patients who received treatment under the scheme «surgery + iSPDT + chemotherapy»; in the control group-10 patients receiving treatment under the scheme «surgery + chemotherapy». The first stage of the treatment was total/subtotal tumor resection followed by intravenous administration of photolon; then tumor bed was consecutively exposed to ultrasound (1.04 MHz; 1 W/cm^2; 10 min.) and photoirradiation (50-100 J/cm^2) 0.5 h. after the start of photolon infusion. Within 3-4 weeks after discharge from hospital all patients underwent chemotherapy. The toxicity of anticancer therapies was evaluated on the basis of frequency and severity of adverse reactions accounted in accordance with CTCAE (Version 4.0). The criteria for assessing antitumor efficacy were: MRI images at 3 and 6 months after iSPDT treatment, median OS and post-iSPDT median times. The revealed adverse reactions (headache – n=6, 40%; convulsions – n=2, 13%) corresponded to I/II degrees and did not affect the terms of hospitalization. The median OS of died patients from first diagnosis was 23.9 months in iSPDT and 14.1 months in control group, respective (p=0.004). The post-iSPDT median survival was 8.2 month, while in the control group (without iSPDT) it was 5.8 month (p=0.012). iSDDT is a well-tolerated and potentially effective option in the treatment of glioblastoma. However, to evaluate the antitumor efficacy of this method of treatment, randomized trials are necessary.

Key words: Sono-photodynamic therapy, Photosensitizer, Photolon, Glioblastoma

INTRODUCTION

Glioblastoma is a serious health and social problem and is one of the most malignant types of central nervous system tumors. The main treatment for this nosologic form of tumor is surgery in combination with external beam radiation therapy and chemotherapy with temozolomide [1, 2]. Despite advances in treatment modalities it remains largely incurable. According to epidemiological studies, 5-year survival in patients with this pathology is an average of 3-5%, and the median overall survival from the time of histological verification varies from 12 to 17 month [3]. In many countries there is an intensive search and development of new methods of treatment of malignant gliomas allowing to increase the overall survival of patients with this disease.

One of these is sono-photodynamic therapy (SPDT), which is a treatment method based on the significant increase of the cytotoxicity of drugs (photosensitizers, PS) combined with ultrasound (US) and photoirradiation of the tumor tissue. According to numerous studies of sono-photochemical reactions include a direct interaction of excited molecules with the help of ultrasonic radiation, the PS on the substrate and forming transient radicals that react with oxygen. Interaction initiates a complex cascade of free radicals, such as singlet oxygen, hydroxyl radical, hydrogen peroxide and superoxide anion radical, causing the development of oxidative stress

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syndrome. As a result, SPDT effectively induced glioma-cell apoptosis and necrosis. The two possible mechanisms might be:

- promoting mitochondria to release Cyto-C and activate Caspase-3, then to initiate apoptosis;
- the destroying of microvessels, inhibition of angiogenesis and the induction of ischemia and anoxia of glioma cells, resulting in ischemic necrosis [4,5].

At the moment, this area in experimental and clinical neurooncology is actively developing in Japan, South Korea, China and Republic of Belarus. Scientists from a number of scientific centers have published the results of experimental studies (*in vivo*) that indicate a high antitumor efficacy of SPDT in the treatment of various glioma cell lines (glioma C6, glioma F98, etc.) [6-9]. Approbation of the SPDT in clinical conditions in patients with malignant gliomas within I/II phases of clinical trials is a very relevant and necessary option.

The aim of our study was to evaluate the results of phase I clinical testing method intraoperative SPDT (iSPDT) with PS photolon in patients with recurrent glioblastoma.

MATERIALS AND METHODS

The work is based on the analysis of treatment results of 25 patients with recurrent forms of malignant gliomas (glioblastoma grade IV, GBM) who received treatment in Department of Neurooncology and Neurosurgery of N.N. Alexandrov National Cancer Centre (Lesnoy, Republic Belarus).

Ethical aspects: The study was started after approval by the local ethics committee. All patients were informed of treatment methods, follow-up and possible adverse reactions, and signed informed consent to participate in the study. All studies were conducted in accordance with the requirements of the Helsinki Declaration of the World Medical Association, which was adopted at the 18th General Assembly of the World Medical Association (1964) and Law of the Republic of Belarus № 2435-XII (June 18, 1993) «On Health Care» as amended by the Law of the Republic of Belarus № 433-3 (October 21, 2016).

Inclusion criteria: All patients who were included in the study met the following criteria:

- histologically verified diagnosis–glioblastoma grade IV (according to the three-degree system in the modification of St. Anne-Mayo);
- physical status by the Karnovsky index > 50%;
- the expected life expectancy is not less than 6 months;
- the age of patients is from 18 to 70 years;
- absence during the last 3 weeks of chemotherapy sessions and during the last 4 weeks – radiotherapy sessions;
- complete recovery of patients from acute toxic effects of all previous chemotherapeutic interventions.

The control group (retrospective control) included 10 patients with recurrent GBM grade IV with mean age 55.4 ± 9.9 years. All patients included in the control groups had previously undergone surgical intervention in the volume of total/subtotal resection of the tumor focus with courses of adjuvant chemotherapy with carmustine (2 mg, intravenously) and/or lomustine (40 mg, orally) 3-4 weeks after completion of surgical intervention (number of chemotherapy courses: 3-7).

The main group included 15 patients with recurrent GBM grade IV with mean age 49.5 ± 9.7 years. Patients included in main group were performed (**Table 1):**

- total or subtotal removal of tumor recurrence;
- 0.5 hours before the end of the operational phase the PS photolon (RUE «Belmedpreparaty», Minsk, Republic of Belarus) was intravenously administrated in a dose of 2 mg/kg;
- local ultrasonic treatment of the bed and walls of the removed tumor was performed on ultrasound therapy unit «Phyaction USTH 91» (Gymna Uniphy N.V., Bilzen, Belgium)» at a frequency of 1.04 MHz, intensity of radiation 1 W/cm^2 and power 3 W for 10 minutes;
- photoirradiation of the bed and walls of the removed tumor was performed on semiconductor laser «UPL PDT» (LEMT, Republic Belarus, λ=660±5 nm) at the exposure doses 50 J/cm^2 (n = 5), 75 J/cm^2 (n = 5), 100 J/cm^2 (n = 5) with power density – 0.17 W/cm^2 and time of photoirradiation of 10-30 minutes.
- 3-4 weeks after treatment (surgical intervention + iSPDT), patients received chemotherapy as patients of control group.

Follow-up and evaluation of treatment effects: all patients were performed brain MRI with contrast enhancement to monitor the effectiveness of the treatment and after 3 and 6 months. Assessment of tolerability and safety of the treatment was carried out for 1 month after the treatment on the basis of data on adverse events and reactions revealed in the course of treatment, their nature, frequency and severity. Given the specific characteristics of the disease and the treatment, the following side effects were assessed (*CTCAE, Version 4.0, http://www.meddramsso.com*).

Statistical analysis: to estimate the patients' survival rates, Kaplan-Meier method was used. The comparative survival analysis was performed with non-parametric log-rank test.

Differences were considered statistically significant at a significance level of $p<0.05$. The following parameters were studied: frequency and severity of complications and adverse reactions after treatment (%); median overall survival (OS; month); post-iSPDT median survival (month); indicators of 6-, 12-, 18- and 24-month survival rate after diagnosis verification (%). The calculation of statistical indicators was performed with «STATISTICA 8.0» software.

RESULTS

Assessment of safety and tolerability of iSPDT: PS administration was not accompanied by violations of vital functions in any case. In all patients, the postoperative period was favorable, no serious complications were found. 3 out of 5 patients from group 100 J/cm^2 has been noted moderately severe headache (*CTCAE, version 4.0; grade II*) in the early postoperative period. According to multi-slice computed tomography 24 hours after treatment, no signs of intracranial bleeding in the postoperative cavity were identified. No manifestations of cutaneous phototoxicity (itching, pasty skin) were noted.

Assessment of antitumor efficacy of iSPDT: Frequency evaluation of tumor stabilization based on MRI data. In order to evaluate the immediate results after exposure in patients in the study group, intravenous contrast MRI was performed in 3 and 6 months after the treatment. In MRI studies at 3 and 6 months after iSPDT no signs of local recurrence were found in 60% of cases (in 9 of 15 patients). The most effective treatment regimen included surgery, photolon administration at a dose 2 mg/kg, local ultrasound (1.04 MHz; 1 W/cm^2; 3 W) and photoirradiation at an exposure dose of 75 J/cm^2. In MRI studies at 3 and 6 months after iSPDT with this parameters no signs of local recurrence were found in 100% of cases (in 5 of 5 patients) and there was a regression of residual tumor lesions in 2 patients (**Table 1).**

Table 1. The results of MRI studies in main group

Pat.	Patient information						
	Sex	**Diagnosis**	**extent of surgery**	**ultrasound frequency/intensity, MHz; W/cm^2**	**ED[1], J/cm2**	**MRI scans (3 months)**	**MRI scans (6 months)**
K.	M	GBM[4]	PR[2]	1-Jan	50	progression	progression
R.	M	GBM	PR	1-Jan	50	stabilization	stabilization
P.	M	GBM	PR	1-Jan	50	progression	progression
C.	F	GBM	PR	1-Jan	50	progression	progression
X.	M	GBM	PR	1-Jan	50	stabilization	stabilization
Z.	F	GBM	CR[3]	1-Jan	75	stabilization	stabilization
I.	M	GBM	PR	1-Jan	75	stabilization	regress
A.	M	GBM	CR	1-Jan	75	stabilization	stabilization
Y.	M	GBM	PR	1-Jan	75	stabilization	regress
G.	F	GBM	CR	1-Jan	75	stabilization	stabilization
M.	F	GBM	PR	1-Jan	100	progression	progression
K.	F	GBM	CR	1-Jan	100	stabilization	stabilization
S.	M	GBM	CR	1-Jan	100	progression	progression
G.	M	GBM	CR	1-Jan	100	progression	progression
S.	F	GBM	CR	1-Jan	100	stabilization	stabilization

[1]ED – exposure dose; [2] PR – partial resection; [3] CR – complete resection; [4]GBM – glioblastoma grade IV.

Overall survival: The median OS for main group patients amounted to 23.9 month [95% CI=12-35 month], it being 14.1 month in the control group (without iSPDT) [95% CI=5.5-21 month] (p=0.004) **(Figure 1).**

The post-iSPDT median survival was 8.2 month [95% CI=5.5-23 month]; it being 5.8 month [95% CI=1.5-12 month] in the control group (without iSPDT) (p=0.012) (**Figure 2).**

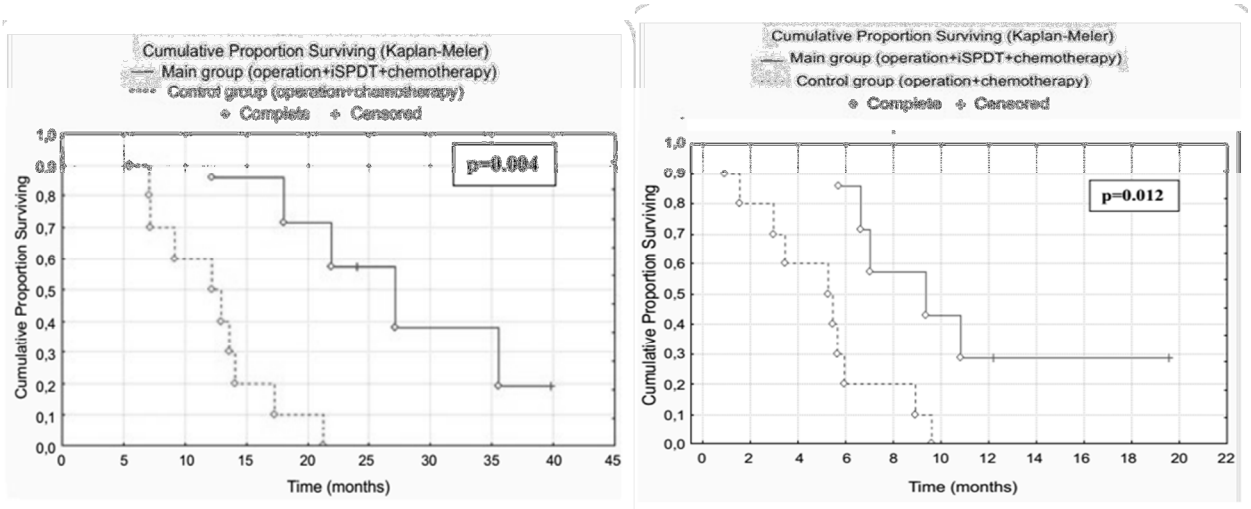

Figure 1 & 2. Indications of overall and post-iSPDT survival in control and main groups

Survival rates are presented in Table 2.

Table 2. Indicators of patient survival in control and study groups

Variable	Control group	Main group
Median overall survival (days)	320	632
Overall survival (%)		
6 months	88	90
12 months	44	80
18 months	10	30
24 months	0	30
Progress free survival (%)		
6 months	10	50
12 months	0	10

CONCLUSION

In our opinion, the combination of different technological solutions allows practitioners to choose an adequate scheme of laser and ultrasonic irradiation of the resected tumor bed of any location and, in the long term, to make the developed method an integral part of the scheme of complex treatment of patients with primary and recurrent forms of malignant gliomas.

Despite a small number of observations in our study, we can draw a preliminary conclusion about good tolerability and antitumor efficacy of iSPDT in the treatment of recurrent forms of GBM. In our opinion, the inclusion of the method of treatment developed by us into combined and complex treatment regimens will improve the results of treatment of this severe pathology. And further study of the mechanisms underlying the antitumor response of the SPDT, will allow to find the optimal regimens of exposure to cells of glial tumors.

In order to determine the antitumor efficacy and SPDT in the near future, we plan to continue our studies within the framework of a randomized study.

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