Original article

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Current state of antiangiogenic therapy in neuro-oncology and own experience of its use in the radiosurgical treatment of recurrent glioblastoma

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Objective: to study the effect of antiangiogenic therapy on the quality of life and the level of headache in patients with recurrent glioblastoma who underwent radiosurgical treatment.

Materials and methods. A prospective randomized single-center study carried out at the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine in 2019-2020 involving 45 patients with GB with clinical and radiological signs of disease progression and local tumor recurrence. In this regard, patients underwent radiosurgical treatment. In the main group (BEV+) 21 patients after stereotactic radiosurgery (SRS) underwent antiangiogenic therapy with Bevacizumab (BEV). In the control group (BEV^-), 24 patients did not receive antiangiogenic therapy after SRS.

SRS with the use of a linear accelerator «Trilogy» (6 MeV) using intensity-modulated radiotherapy (IMRT). BEV was administered intravenously, once every 3 weeks at a dose of 10 mg/kg body weight. Antiangiogenic therapy was performed under the condition of preserved liver and kidney function, values of full blood count and blood biochemistry within normal range.

Global health status and headache levels were calculated according to EORTC QLQ-C30 v. 3.0 and QLQ-BN20 before and six weeks after radiosurgery in the main and control groups.

Results. There was no a statistically significant difference between the studied groups of patients' in quality of life ($p = 0.707372$) and in headache level ($p = 0.846660$) before the SRS.

Six weeks after SRS, patients in the main group had a statistically significantly higher quality of life ($p = 0.000015$) and a lower level of headache than patients in the control group ($p = 0.000035$).

During the observation period in patients of both groups there were no adverse events of III-IV degree of toxicity, in particular specific complications of antiangiogenic therapy (hypertension, bleeding, thromboembolism, leukopenia, proteinuria, gastrointestinal disorders, etc.).

Conclusions. Antiangiogenic therapy statistically significantly improves the quality of life and reduces the level of headache in patients who underwent radiosurgical treatment for glioblastoma recurrence.

Keywords: *glioblastoma; angiogenesis; anti-angiogenic therapy; bevacizumab; stereotactic radiosurgery; quality of life; headache*

Introduction

Treatment of glioblastoma (GB) - the most malignant glial tumor of the brain (IV degree of anaplasia according to the WHO classification 2016) remains one of the challenges of modern neuro-oncology. Over the last two decades, due to introduction of modern treatment standards, it has been possible to increase the overall survival (OS) of patients with GB from 4.9 to 20.9 months [1,2]. This indicates an improvement in therapy of patients with both newly diagnosed GB and tumor recurrence. A common strategy in primary GB is a surgical treatment followed by radiation therapy and chemotherapy (CT) with drugs with alkylating mechanism of action, first of all temozolomide (TMZ), nitrosourea derivatives (lomustine, carmustine, fotemustine, etc.), and in case of recurrence of GB - antiangiogenic therapy with Bevacizumab (BEV) [3].

Due to the fact that GB is characterized by an extremely high degree of vascularization, this tumor may be an ideal target for antiangiogenic therapy [4].

However, there is an ongoing discussion about the feasibility and effectiveness of BEV and antiangiogenic therapy in general in neuro-oncology.

The formation of new blood vessels (neovascularization) in mammals occurs through vasculogenesis and angiogenesis. Vasculogenesis is the process of spontaneous formation of blood vessels from endothelial progenitor cells due to their differentiation and proliferation at the stages of embryogenesis. In the adult body, vasculogenesis occurs with the development of tumors and restoration of damaged circulatory system. Angiogenesis is the formation of new blood vessels from existing ones as a result of their further branching. Endothelial cells play a main role in angiogenesis. They form new blood vessels due to migration and proliferation [5]. In adults within normal the activity of angiogenesis is very low. Its sharp activation happens during regeneration processes, in particular during wound healing, recovery after heart attack and stroke.

The importance of angiogenesis in tumor development was first discovered by J. Folkman [6]. This researcher in 1971 proposed the term «antiangiogenesis», which meant preventing the penetration of newly formed vessels into early tumor implants, because the most vulnerable period of life of a solid tumor is a short period before vascularization. At this stage of tumor formation, the microscopic population of tumor cells does not yet have its own capillaries and exists due to diffuse exchange of nutrients and waste products of tumor cells with extracellular space. Numerous studies have shown that neovascularization provides a constant need for oxygen and nutrients for continuous tumor growth [7]. In view of this, inhibition of angiogenesis should lead to tumor starvation and cell death [6,8].

The formation of new vessels in tumors, apart from angiogenesis, can be due to other mechanisms (vascular co-option, vascular intussusception, vasculogenesis with the participation of bone marrow progenitor cells, vasculogenesis due to endothelial differentiation of stem cells, vasculogenic mimicry).

Endogenous factors that affect vascular germination, depending on the effect, are divided into proangiogenic (stimulants) and antiangiogenic (inhibitors). There are more than 10 proteins that stimulate vascular growth. These include the family of vascular endothelial growth factors (VEGF), major fibroblast growth factor (FGF-2), placental growth factor (PlGF-1,2), angiopoietin (ANGPT-1,2), interleukin- 8 (IL-8), platelet-derived growth factor (PDGF), transforming growth factor (TGF-α, TGF-β), tumor necrosis factor (TNF-α), granulocyte colony-stimulating factor, epidermal growth factor, etc. [12].

The key and most studied proangiogenic factor is VEGF. The human VEGF family includes 5 members (VEGF-A, VEGF-B, VEGF-C, VEGF-D) and PlGF [13]. VEGF-A and VEGF-B are of paramount importance in blood vessels formation. VEGF-A stimulates proliferation, migration and ensures the survival of endothelial cells.

All VEGF isoforms bind to related receptors of tyrosine kinase group (VEGFR), which are predominantly localized on the surface of vascular endothelial cells and hematopoietic cells. There are three main subtypes of VEGFR: fit-1 (VEGFR-1), KDR / flk-1 (VEGFR-2) and flt-4 (VEGFR-3). The main receptor of the VEGF / VEGFR signaling pathway is considered to be VEGFR-2. When interacting with it endothelial cells are activated, their proliferation, migration and ability to survive increase, which promotes the formation of new vessels [14].

The main initiator of angiogenesis in the tumor is hypoxia. In response to hypoxia, HIF-1α (hypoxia-inducible factor-1α) is induced during tumor progression, causing increased expression and secretion of proangiogenic growth factors, primarily VEGF. The interaction of VEGF with its receptors activates the expression of proteases (matrix metalloproteinases, type IV collagenases and plasminogen activators) in endothelial cells, which destroy intercellular contacts and the basement membrane. Hypoxia also activates integrins α1β1, α2β1 and αVβ3 - transmembrane heterodimeric cell receptors that interact with the extracellular matrix, transmit intercellular signaling and play an important role in the migration and proliferation of endothelial cells [15].

In the area of new capillary formation, the vessel dilates, its permeability increases, activated endotheliocytes migrate into the surrounding space and proliferate intensively. This results in new capillary tubes formation, which are surrounded by a newly formed basement membrane and pericytes [16]. These *de novo* tumor vessels, which are anatomically and functionally abnormal, create insufficient blood flow, leading to further hypoxia and acidosis.

The molecular biology development and the focus on personalized medicine have contributed to the introduction of a fundamentally new approach in the treatment of patients - using a combination of drugs that can block tumor progression by different mechanisms of action and affect different targets.

Antiangiogenic therapy is diverse in the mechanism of action [17]:

– blocking circulating angiogenic factors in the intercellular space (BEV - an antibody to VEGF that selectively binds to VEGF and inhibits its biological activity or aflibercept, which contains extracellular domains of VEGFR-1 and VEGFR-2 receptors, acts as a receptor trap that binds VEGF);

– blockade of angiogenic factor receptors located on the surface of endothelial cells, that leads to inhibition of two or more signaling pathways involved in angiogenesis (inhibition of signaling from three known VEGF receptors, platelet-derived growth factor receptors and FGF (small molecule tyrosine kinase inhibitors - cediranib, sunitinib);

– the use of epidermal growth factor (EGFR) inhibitors, which are involved in cell growth regulation and cell differentiation (monoclonal antibody nimotuzumab);

– simulators of inhibitors of endogenous angiogenesis (angiostatin, endostatin, thrombospondin);

– inhibition of adhesion and migration of endothelial cells (integrin inhibitor - cilengitide).

One of the promising antiangiogenic drugs is EMAP II (endothelial monocyte activating polypeptide II) - a multifunctional protein first identified in malignant mammalian tumors. Proinflammatory cytokine EMAP II is a product of proteolytic cleavage of its precursor

protein proEMAP (AIMP1 / p43), an auxiliary component of the aminocyl-tRNA synthetase complex of eukaryotes [18]. Many studies have shown that EMAP II stimulates apoptosis and autophagy in tumor cells, and also has antiangiogenic properties [19,20]. One possible antiangiogenic mechanism of action of EMAP II is the ability to inhibit the binding of VEGF to VEGFR-1 and VEGFR-2 receptors, which may be a new therapeutic strategy to enhance antiangiogenic therapy [21]. In addition, EMAP II protein has been shown to bind to α5β1-integrin on the surface of endothelial cells, preventing them from adhering to fibronectin, which inhibits endothelial cell proliferation and migration, and consequently inhibits angiogenesis [22].

The widespread use of antiangiogenic therapy in oncology in general and neuro-oncology in particular is associated with BEV [23]. BEV is a genetically engineered recombinant humanized monoclonal antibody to VEGF-A. The drug action and its efficacy have been thoroughly studied since 1993, both in experiment and in clinical practice in cancer. BEV has shown high efficacy in the treatment of malignancies such as colorectal cancer, lung cancer, ovarian cancer, breast cancer, renal cell carcinoma, and in particular in unresectable, recurrent and metastatic tumors [24,25].

Normal cerebral vessels consist of endothelialcells, pericytes, and basement membrane. Together with astrocytes, these cells are part of the brain's unique structure, the blood-brain barrier (BBB), which selectively restricts the exchange of molecules between the intracerebral and extracerebral circulatory systems. Rapid invasion of tumor in the brain distorts the structure and function of BBB. This leads to the accumulation of fluid and plasma proteins peritumorally and in the surrounding areas of the brain, which is a limited space without the lymphatic vascular system needed to drain excess fluid. Interstitial hypertension develops in the tumor, fluid accumulates outside the tumor, which leads to vasogenic cerebral edema. This is the main reason for the deterioration of patients with GB [26].

New vessels formed in brain tumors gain abnormal morphological features. This is a diagnostic marker, especially for GB, the microvascular network of which has the form of «glomerular cells». The latter resemble renal glomeruli, consisting of *de novo* vessels lined with endothelial cells, which actively proliferate and are surrounded by a basement membrane and an incomplete layer of pericytes [27].

With malignancy of grade III anaplastic astrocytoma to IV grade according to the WHO there are two main changes in the biology of the tumor: 1) there are areas of necrosis due to increased hypoxia of tumor tissue, 2) microvascular hyperplasia arises as a hypoxia-induced angiogenic response [28]. Rapid proliferation of tumor cells leads to the fact that the tumor center becomes hypoxic and necrotic. In fact, hypertensive dislocation disorders that result from an increase in tumor volume cause hypoxia and necrosis. In addition, co-option of blood vessels and tumor cells increases the expression of angiopoietin-2 in involved endothelial cells [29]. Tumor cells located near the degenerated vessels begin to die, forming foci of necrosis. The latter are surrounded by tumor cells that form pseudopalisades and activate VEGF expression. This leads to vascular hyperplasia, in particular glomeruloid vascular proliferation [30].

In contrast to the above sequence, real-time data indicate that tumor evolution occurs under conditions of dynamic interaction between vascular co-option and neoangiogenesis. Invasive glioma cells have the ability to reconstruct nearby vessels [31]. At the sites of physical interaction of glioma cells and capillaries, the latter can split in two. This type of angiogenesis is called invaginal or «stratification angiogenesis» [32]. Moreover, tumor cells are able to attract vessels that come in contact with the tumor, folding them and forming vascular loops. There is the formation of chaotic and tortuous intra-tumor vascular networks, the appearance of which resembles the glomeruli. Thus, for further tumor growth and dissemination, glioma cells can reconstruct the existing vascular system in different ways [33].

Microvascular density is an indirect indicator of angiogenesis and correlates with the prognosis in astroglial tumors, in particular GB is characterized by the highest degree of microvascular density and the worst prognosis [34]. Thus, the necessary criteria for morphological diagnosis of GB, apart from necrosis area, is the presence of microvascular proliferation.

The hypothesis of action mechanism of antiangiogenic therapy due to the decrease of vascular density in the tumor under conditions of «distorted» angiogenesis was replaced by the hypothesis of influence on angiogenesis due to normalization of the vascular network of tumor under antiangiogenic medications. Functioning vessels remain intact, and the formation of immature vessels is limited by blocking VEGF, which results in a decrease of intratumoral interstitial pressure and improvement of vascular perfusion function. This enhances the permeability of chemotherapeutic agents to tumor tissue [35,36].

Angiogenesis in malignant gliomas is an extremely complex process, which is one of the factors that determine the extremely aggressive biological behavior of these tumors. Some aspects of angiogenesis of malignant gliomas have been carefully studied. However, this issue needs to be studied more thoroughly.

Antiangiogenic therapy in clinical trials in neuro-oncology patients

Numerous preclinical studies have shown that a logical approach to the treatment of malignant brain tumors may be the impact on angiogenesis. Antiangiogenic drugs have been developed and tested in clinical trials [37]. However, only BEV has shown the greatest efficacy in controlled clinical trials in patients with GB [38].

In 2009, in the United States and some countries, BEV was approved by the FDA for monotherapy of GB recurrence in accordance with promising results of radiological response to antiangiogenic treatment in phase II clinical trials [39,40].

In a randomized phase II trial of BELOB, the effect on the survival of BEV or lomustine treatment in mono-regime and in combination was studied [41]. The median OS in both types of mono-therapy was 8 months, and in combination treatment - 12 months.

However, the benefits of combination therapy have not been confirmed in phase III trial EORTC 26101 [42].

In 2017, the European Medicines Agency rejected the use of BEV for glioma therapy due to negative results of studies RTOG 0825 and AVAglio [33,43].

In 2018, the Cochrane Library published an updated systemic meta-analysis, which analyzed the results of large-scale controlled studies on antiangiogenic therapy for GB [17]. Eleven randomized clinical trials (3743 patients) were selected for analysis, of which 7 studies (2987 patients) were included in the first review (2014). The design of these studies was characterized by significant heterogeneity, especially in relation to the criteria for assessing treatment response. In all trials, only cases of GB were evaluated, without any other types of malignant gliomas involvement.

According to the results of 11 studies involved in the analysis, there was no improvement in OS with the introduction of antiangiogenic therapy (hazard ratio (HR) - 0.95 (95% confidence interval (CI) - 0.88-1.02), p = 0.16; 11 studies, 3743 patients; high level of evidence). However, in a pooled analysis of 10 studies (3595 patients) it was proved that antiangiogenic therapy statistically significantly increases the level of progression free survival (PFS) (HR - 0.73 (95% CI - 0.68-0.79), p <0, 00001; high level of evidence).

The authors performed an additional analysis of OS and PFS depending on the stage of the disease and compared the results of combination of antiangiogenic therapy + CT and only CT. Both in adjuvant treatment and in the treatment of recurrent GB, there was no statistically significant increase in OS when using the combination of antiangiogenic therapy + CT (respectively HR - 0.93 (95% CI - 0.86-1.02), p = 0.12, 8 studies, 2833 patients; high level of evidence and HR - 0.99 (95% CI - 0.85-1.16), p = 0.90, 3 studies, 910 patients; medium level of evidence).

The use of antiangiogenic therapy contributed to an increase of PFS in the subgroups. Combined analysis in both adjuvant treatment and treatment of recurrence of GB, showed a statistically significant increase in PFS respectively HR - 0.75 (95% CI - 0.69-0.82), p <0.00001; 8 studies, 2833 patients, high degree of evidence and HR - 0.64 (95% CI - 0.54-0.76), p <0.00001; 2 studies, 762 patients; medium degree of evidence). Analysis of PFS in antiangiogenic therapy in combination with CT compared with CT showed improvement in this indicator (HR - 0.72 (95% CI - 0.66-0.77), p <0.00001; 10 studies, 3464 patients).

As in studies of antiangiogenic therapy in other solid tumors, adverse events included hypertension and proteinuria, poor wound healing, increased risk of thrombosis, although overall class 3 and 4 adverse events were low (<14.1%) and corresponded to that described in literature.

In some studies, the impact of antiangiogenic therapy on the quality of life of patients with malignant brain tumors has been carefully analyzed [17]. Thus, one of the parameters studied in the AVAglio study was quality of life, assessed by EORTCQLQ-C30 scale and its concomitant module for brain tumors BN20. It was found that the deterioration of quality of life in patients treated with BEV occurred later than in the control group [44].

Based on a systemic analysis, it was found that BEV (as an antiangiogenic drug) increases PFS in first-diagnosed GB and has benefits in terms of survival in patients with recurrent GB. However, there is no statistically significant evidence that combination of antiangiogenic therapy and CT has an advantage in survival of patients with recurrent GB, but there is evidence that combination of antiangiogenic therapy with a particular CT compared with the treatment of the same CT in a single regimen can improve OS. The effect of antiangiogenic therapy on quality of life and clinical symptoms needs further study [17,45].

The question remains unresolved, which subtypes of GB, depending on their molecular genetic characteristics, are influenced by antiangiogenic therapy and whether such therapy is advisable for other types of malignant gliomas. In this aspect, an interesting study published in 2019 by K.E. Hovinga et al., who conducted a retrospective analysis of the results of BEV use in 80 patients with recurrent GB [4]. The obtained data indicate that the response to BEV was significantly worse in patients with the classic type of GB than in those with mesenchymal and proneural type of GB (2.7, 5.1 and 6.4 months, respectively, p = 0.011). It has been proven that the classic type of GB and amplification of the EGFR gene are associated with a negative course and a shorter period to progression both by univariate analysis (p <0.001 and p = 0.007, respectively) and by multivariate analysis (for both indicators, p = 0.010).

R.A. Manneh Kopp et al. studied the correlation between radiological and immunohistochemical parameters and the clinical course in patients with the first relapse of GB treated with BEV [46]. The following histological parameters were analyzed: vascular proliferation, mitotic index Ki-67, molecular factors (MGMT promoter methylation, EGFR amplification and EGFRvIII), immunohistochemical parameters (MET, Midkine, HIF1, VEGF-A, VEGF-R2, CD44, Olig2, microvascular areas and microvascular density), radiological (perfusion) parameters (rCBV). The investigators found no statistically significant correlation between the response to anti-angiogenic therapy and the histological, molecular, immunohistochemical, and radiological parameters. The search for predictive biomarkers of response to antiangiogenic therapy is continued. A detailed study of the issue of patients stratification in order to increase the effectiveness of antiangiogenic therapy is required.

In many countries, BEV continues to be used to treat patients with GB. Clinicians note the positive effect of the drug in prolonging survival without signs of progress and some palliative effects, in particular neurological improvement, despite the fact that in general population of patients there was no noticeable effect on OS. In particular, the use of BEV may be promising for neuro-oncology patients, since the drug has a positive effect on consequences of radiation therapy (radiation edema, radiation necrosis, and neurological dysfunction) [47].

In recent decades, approaches to the treatment of neuro-oncology patients have been acquiring patient-oriented features. This is evidenced by the fact that prolonging survival of patients without maintaining the quality of life is not considered a satisfactory result of

treatment, therefore, approaches for a comprehensive assessment of therapeutic effect using quantitative indicators of survival and an assessment of the quality of life are widely introduced. According to the decision of the American Society of Clinical Oncology (ASCO), the quality of life is more important than the level of PFS for evaluating the results of treatment of cancer patients [48].

Headache is the most common form of pain in patients with malignant gliomas. Headache is an integrated indicator of manifestations of hypertensive and dislocation syndromes, depending on the degree, it can significantly affect the quality of life and treatment strategy of patients. So, it is natural that there is a clear relationship between the headache and the quality of life of patients with GB [49].

There is no consensus on the optimal treatment strategy for patients with recurrent GB. Although in most cases GB recurrence occurs in the area of the primary tumor, re-irradiation, in particular stereotactic radiosurgery (SRS), is considered as a method that increases patient survival and associated with an acceptable level of toxicity [50].

The advantages of SRS, in addition to achieving local control of tumor growth, include the possibility of precision supply a high dose of radiation to the pathological focus and minimization of radiation exposure to tissues adjacent to the radiation target. However, due to the fact that SRS is associated with the development of radiation edema, which is usually exacerbated by vasogenic peritumoral edema, steroid antiedema therapy in patients with recurrent GB is long-term and associated with serious side effects.

Objective: to study the effect of antiangiogenic therapy on the quality of life and the level of headache in patients with recurrent glioblastoma who underwent radiosurgical treatment.

Materials and methods

A prospective randomized single-center study carried out at the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine in 2019-2020 involving 45 patients with GB with clinical and radiological signs of disease progression and local tumor recurrence. In this regard, patients underwent radiosurgical treatment.

Patient acquisition criteria:

- men and women aged 18 to 76;
- pathomorphological confirmed diagnosis of GB;
- clinical and radiological signs of disease progression and local recurrence of GB;
- performance status according to the ECOG scale ≤2; Karnofsky scale ≥70;
- life expectancy >3 months;
- voluntary and informed consent of the patient to participate in the study.

The study was approved by the Commission on Ethics and Bioethics of the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine (Meeting Minutes No 3 of June 6, 2016).

Study design

In the main group (BEV^+) 21 patients after SRS underwent antiangiogenic therapy BEV. In the control group (BEV^-), 24 patients did not receive antiangiogenic therapy after SRS.

Among 45 (100%) patients there were 27 (60.0%) men and 18 (40.0%) women: in the main group - 61.9% men (13/21) and 38.1% (8/21) women, in the control - 41.7% (10/24) women and 58.3% (14/24) men. The average age of patients was 56.6 years (34-67 years): in the main group - 57.9 years, in the control - 54.3 years.

Both groups were comparable in terms of sex ratio, mean age, radiation regime and performance status.

The diagnosis of GB (IV degree of anaplasia) in all cases was verified pathomorphologically after surgical treatment of primary tumor. Molecular data on the presence of mutations of isocitrate dehydrogenase (IDH) gene in primary tumor are available in 13 (28.9%) of 45 patients (5 in the main group and 8 in the control group). In all these cases, the IDH mutation was absent (IDH-wild-type). Data on the methylation status of *MGMT* gene promoter are available in 17 (37.8%) of 45 patients (7 from the main group and 10 from the control group). Among patients of the main group in 5 out of 7 cases and in the control group in 7 out of 10 cases *MGMT* gene promoter was unmethylated. Adjuvant treatment of patients after surgical treatment of primary tumor included adjuvant radiation therapy in standard fractionation: 60.0 Gy total dose in 2.0-Gy fractions - 60.0 Gy against the background of concomitant CT TMZ (at a dose of 75 mg / m2 of body surface). Patients received maintenance CT for 5 days with a 23-day interval (28-day cycle) at a dose of 150–200 mg / m2 of body surface area (6 cycles of TMZ), which was started 4 weeks after the end of RT.

Radiosurgical treatment was performed in the presence of clinical and radiological signs of disease progression and local tumor recurrence a linear accelerator «Trilogy» with bremsstrahlung energy of 6 MeV using intensity-modulated radiotherapy (IMRT). The application of this irradiation technique makes it possible to achieve maximum uniformity of dose distribution in the irradiation target and minimum load on the tissues adjacent to the target. The following dose regimens and fractionation were used: at single- fractional irradiation the prescribed dose per target was 12.0–15.0 Gy, at irradiation for 3 fractions the dose per fraction - 7.0–9.0 Gy, total dose - 21.0–27.0 Gy , when irradiated for 5 fractions the dose per fraction - 5.0–6.0 Gy, total dose - 25.0–30.0 Gy.

The average volume of the target radiation was: Gross Tumor Volume (GTV) - 24.6 cm3 (2.5-78.9 cm3), Planning Target Volume (PTV) - 78.5 cm3 (6.8-145.4 cm3)).

BEV was administered intravenously, once every 3 weeks at a dose of 10 mg / kg body weight. Antiangiogenic therapy was performed under the condition of preserved liver, kidney function, values of full blood count and blood biochemistry within normal limits.

Steroid therapy was used as anti-edema therapy after SRS: dexamethasone intramuscularly (4.0 mg twice a day in the first week, 4.0 mg once a day in the second week).

Quality of Life and Headache Studies were conducted using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 (Quality of Life Questionnaire) version 3.0 questionnaire and its associated module specific for brain tumors QLQ-BN20,

informational content of which has been demonstrated in studies [45,51,52].

Patients were interviewed twice: the first time before SRS, the second time - 6 weeks after SRS. The results of the questionnaire were summarized according to the EORTC guidelines QLQ-C30 and QLQ-BN20.

Statistical analysis

Statistical data processing was performed using the statistical software package Statistica 10.0. Because the survey scales are discrete, the obtained rank values for the headache and global health (QoL) domains were compared in groups using the nonparametric Mann – Whitney test. The results were considered statistically significant at p-value of the criterion <0.05.

Results and discussion

During the observation period (6 weeks) no fatalities were noted in both groups of patients, therefore the number of respondents did not change.

The study of patients' quality of life according to the global health level determined by the EORTC QLQ-C30 questionnaire before initiation of treatment did not reveal a statistically significant difference between the studied groups (p = 0.707372) ***(Fig. 1)***. Prior to SRS between the groups there was also no statistically significant difference in headache level calculated by QLQ-BN20 (p = 0.846660) ***(Fig. 2)***.

Statistical analysis showed that 6 weeks after SRS, patients in the main group had a statistically significantly

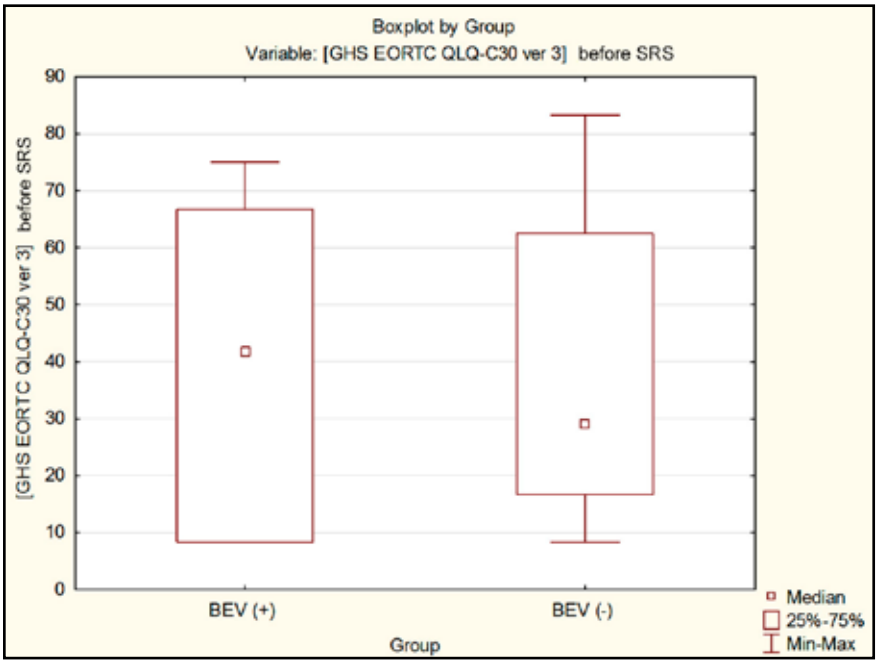

Fig. 1. The results of calculation of Global health status / QoL according to the EORTC QLQ-C30 questionnaire before radiosurgical treatment in patients of main and control groups according to the graphical model box-and-whiskers diagram

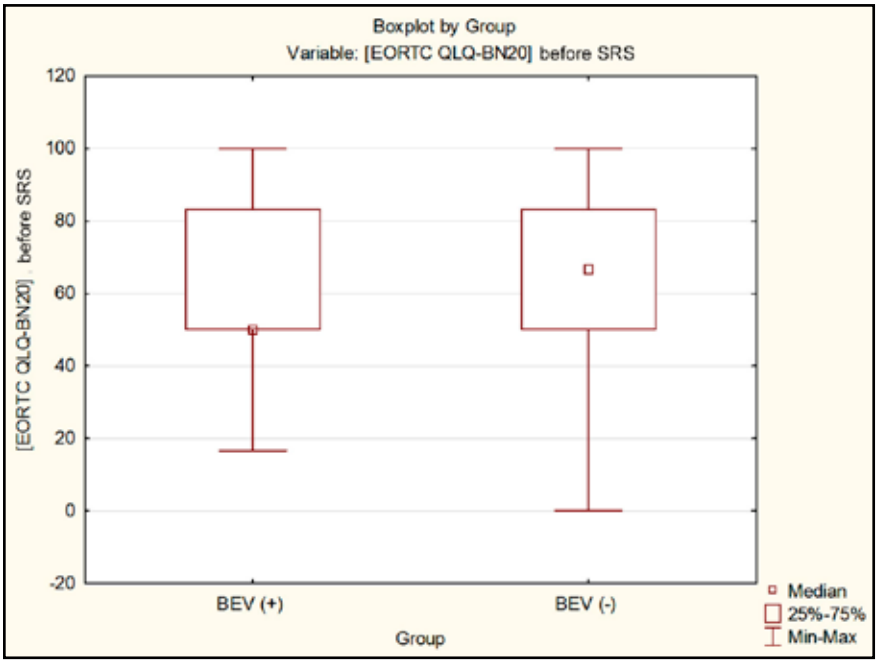

Fig. 2. The results of calculation the level of headache according to the QLQ-BN20 questionnaire before radiosurgical treatment in patients of main and control groups according to the graphical model box-and-whiskers diagram

higher quality of life (p = 0.000015) and a lower level of headache than patients in the control group (p = 0.000035) ***(Fig. 3*** and ***Fig. 4)*.**

Scores representing Global health status and headache of the interviewed patients before and after SRS were calculated according to the EORTC QLQ-C30 and QLQ-BN20 calculation recommendations ***(Table 1).***

During the observation period in patients of both groups there were no adverse events of III-IV degree of toxicity, in particular specific complications of antiangiogenic therapy (hypertension, bleeding, thromboembolism, leukopenia, proteinuria, gastrointestinal disorders, etc.).

According to the results of our study, it was found that antiangiogenic therapy statistically significantly improves the quality of life and reduces the level of headache in patients who underwent radiosurgical treatment for recurrence of GB.

The disadvantages of the study include a relatively small number of observations. The effect of antiangiogenic therapy on patient survival and quality of life over a longer follow-up period requires further analysis.

Quality of life is an important criterion for the treatment efficcacy of neuro-oncology patients at all therapeutic stages, both in newly diagnosed and recurrent tumors. Many studies have shown a positive

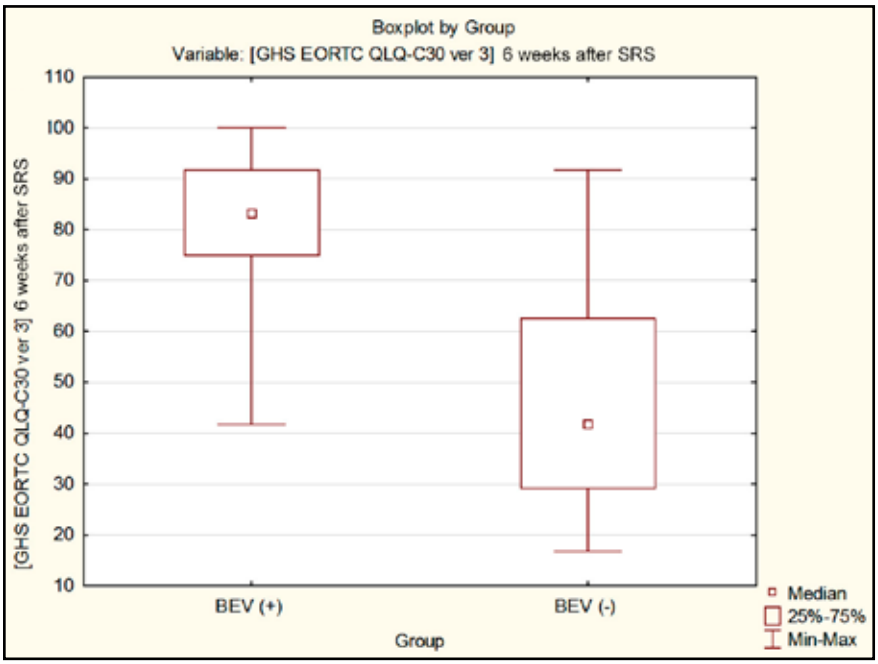

Fig. 3. The results of calculation of Global health status according to the EORTC QLQ-C30 questionnaire 6 weeks after radiosurgical treatment in patients of main and control groups according to the graphical model box-and-whiskers diagram

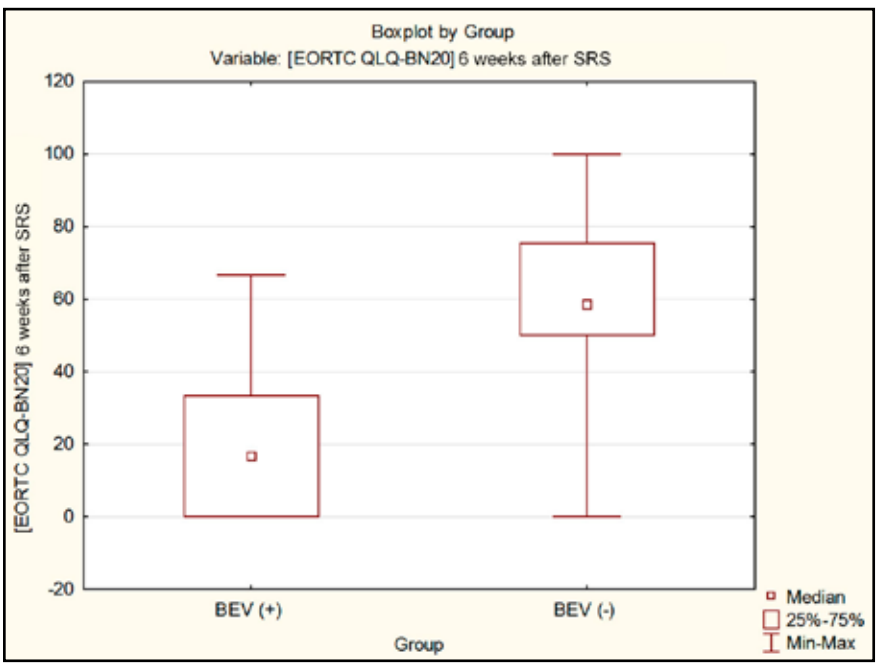

Fig. 4. The results of calculation the level of headache according to the QLQ-BN20 questionnaire 6 weeks after radiosurgical treatment in patients of main and control groups according to the graphical model box-and-whiskers diagram

Table 1. Global health status (QoL) and headache according to EORTC QLQ-C30 version 3.0 and QLQ-BN20 before SRS and 6 weeks after SRS in main and control groups

Number of the patient in the group	Headache level on the EORTC QLQ-BN20 scale, score				Global health status/QoL on EORTC QLQ-C30 scale version 3,0, score			
	Main group, n=21		Control group, n=24		Main group, n=21		Control group, n=24	
	Before SRS	6 weeks after SRS	Before SRS	6 weeks after SRS	Before SRS	6 weeks after SRS	Before SRS	6 weeks after SRS
1	16,7	0	100	50,0	66,7	100,0	8,3	50,0
2	100	50,0	100	50,0	8,3	66,7	8,3	41,7
3	50,0	0	83,3	33,3	58,3	91,7	16,7	50,0
4	66,7	16,7	83,3	50,0	33,3	83,3	33,3	41,7
5	66,7	0	50	66,7	33,3	100,0	66,7	75,0
6	50,0	33,3	83,3	83,3	66,7	91,7	16,7	16,7
7	100,0	33,3	83,3	67,7	8,3	100,0	25,0	41,7
8	50,0	16,7	100,0	83,3	58,3	91,7	8,3	16,7
9	33,3	0	50,0	50,0	75,0	83,3	66,7	75,0
10	33,3	0	33,3	16,7	75,0	100,0	75,0	83,3
11	83,3	50,0	16,7	0	8,3	58,3	83,3	91,7
12	33,3	16,7	50,0	50,0	75,0	91,7	66,7	41,7
13	50,0	33,3	33,3	33,3	41,7	75,0	41,7	33,3
14	100,0	66,7	66,7	66,7	8,3	50,0	16,7	25,0
15	100,0	50,0	66,7	83,3	8,3	41,7	16,7	33,3
16	83,3	33,3	83,3	100,0	16,7	75,0	16,7	33,3
17	50,0	16,7	66,7	66,7	58,3	91,7	33,3	50,0
18	33,3	0	100,0	83,3	66,7	91,7	16,7	16,7
19	66,7	16,7	50,0	50,0	25,0	83,3	41,7	66,7
20	100,0	16,7	66,7	50,0	8,3	41,7	33,3	41,7
21	50,0	33,3	100,0	66,7	41,7	83,3	8,3	25,0
22			33,3	33,3			66,7	75,0
23			66,7	83,3			25,0	16,7
24			50,0	66,7			58,3	58,3

effect of antiangiogenic therapy on the quality of life of patients with malignant gliomas, primarily due to the regression of clinical symptoms caused by brain edema with tumor progression or radionecrosis, when steroids have too many side effects [17,47]. However, one of the biggest obstacles for more extensive clinical use of antiangiogenic therapy is considered to be the economic component, namely the high cost of such therapy. Recently, the staff of Mayo Clinic (USA) made an analysis of clinical and cost-effectiveness of antiangiogenic therapy [52]. A survey of 105 members of Neurooncologists Society (67% of neurooncologists and 16% of neurosurgeons from 10 countries, 82% of whom are academic staff) showed that the majority of respondents (69%) associated the use of BEV in inpatient neuro-oncology patients with a positive clinical effect namely, improving the quality of life, neurological status, reducing the length of hospital stay and faster recovery. Thus, with the timely use of antiangiogenic therapy the total cost of medical insurance payments is decreased, primarily by reducing the period of inpatient treatment and outpatient medical care.

Thus, the issues of both clinical impact and economic toxicity of antiangiogenic therapy remain controversial and need to be carefully assessed in terms of both individualization of treatment and the health care system as a whole.

Conclusions

Angiogenesis of malignant gliomas has unique properties that are likely to differ significantly from those of angiogenesis of tumors that have resulted from outside the central nervous system. Angiogenesis of malignant gliomas is an extremely complex, multicomponent cascade of various interactions, the study of which is continued. Malignant gliomas are able not only to form their own vessels *de novo*, but also to reconstruct the existing vascular network.

With the improvement of understanding of peculiarities of biological behavior of glioblastoma, the belief in the expediency of complex treatment of neuro-oncology patients with simultaneous blocking of various signaling pathways, in particular those that affect the angiogenesis of the tumor, increases.

Numerous clinical studies indicate a positive effect of antiangiogenic therapy on increased survival without signs of progression in patients with malignant gliomas and certain palliative effects, including neurological improvement, despite the fact that in general patient population there was no significant effect on overall survival.

The use of antiangiogenic therapy of bevacizumab may be promising for neuro-oncology patients, as this drug has a positive effect on the consequences of radiation therapy, including radiation edema and radiation necrosis.

Antiangiogenic therapy may be associated with a reduction in inpatient treatment, outpatient care, and faster recovery of neuro-oncology patients.

Analysis of the results of our own research showed that antiangiogenic therapy improves the quality of life ($p = 0.000015$) and reduces the level of headache ($p = 0.000035$) in patients who underwent radiosurgical treatment for glioblastoma recurrence.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical norms

All procedures performed on the patient during the study meet the ethical standards of the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine, National Ethics Committee and Helsinki Declaration of 1964 and its later amendments or similar ethical standards. The study was approved by the Commission on Ethics and Bioethics of the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine (Meeting Minutes No 3 of June 6, 2016).

Informed consent

Conscious and informed voluntary written consent to participate in the study was obtained from each patient.

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