Review article

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Basic principles of contemporary chemotherapy of malignant gliomas of the brain

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The modern view on the place of antiblastic chemotherapy in clinical neuro-oncology based on NCCN 2021 clinical guidelines (The National Comprehensive Cancer Network), EANO recommendations (The European Association for Neuro-Oncology), cIMPACT-NOW (The Consortium for Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) and many years of experience of the department of adjuvant treatment for the central nervous system tumors of the State Institution "Romodanov Neurosurgery Institute, Ukraine" is presented and the basic principles of its application in the complex treatment of malignant gliomas of the brain are substantiated.

Malignant gliomas are a heterogeneous group of the most numerous primary tumors of the central nervous system, differing in both the grade of malignancy and the prognosis of the disease. The latest WHO tumors classification 2021 defines this group of tumors as "diffuse gliomas" of the brain, that is, the term itself indicates infiltrative nature of their growth, that limits the possibility of surgical removal and requires a multimodal approach to their treatment in order to maximize the reduction of tumor tissue.

The new era of chemotherapy in neuro-oncology, as well as in general oncology, began with the study of the molecular profile of tumors, which is important both for predicting the course of the disease and for choosing tactics of chemotherapeutic treatment of malignant gliomas. It's enough to give the following example: in the absence of *IDH* gene mutation and co-deletion of chromosome 1p/19q loci in grade 2 of anaplasia diffuse gliomas, the prognosis of the disease does not differ from that in glioblastoma multiforme.

For the same reason, in modern neuro-oncology, the designation of molecular genetic markers in malignant gliomas is essential for the personification of the treatment of pathology is essential to personalize the treatment of this pathology.

Key words: *malignant gliomas of the brain; chemotherapy; molecular markers; MGMT status; temozolomide; PCV polychemotherapy regimen; bevacizumab; IDH-mutation; 1p/19q co-deletion*

The use of antiblastic chemotherapy is an essential component in the treatment of malignant gliomas. The tactics of chemotherapy for gliomas is determined by their histological diagnosis, which is the main prognostic criterion for both the disease course and the effectiveness of treatment.

The morphological diagnosis of a glial tumor is established by light-optical examination of histological preparations. Mandatory immunohistochemical and molecular genetic studies of the tumor tissue make it possible to clarify the degree of malignancy, histological subtype, and identify prognostic markers.

At the present stage of development of neuro-oncology, the determination of the molecular genetic features of a tumor is of decisive importance in the prognosis of the disease and the results of adjuvant treatment, primarily chemotherapy. It is with regard to the molecular genetic profile of the tumor that the latest classifications of CNS tumors in 2016 and 2021 were constructed [1, 2].

According to multicenter randomized trials, the use of antiblastic chemotherapy is an important statistically significant factor of the favorable prognosis regarding survival of patients with malignant gliomas of grade 3-4 of anaplasia, and in certain clinical situations - with gliomas of grade 2 anaplasia [3, 4].

Factors such as patient age and radicality of tumor removal during primary surgery have a predictive value for the effectiveness of CT [5, 6]. The effectiveness of CT also depends on the physical function of the patient and the aggressiveness of its use [6].

Prognostic molecular genetic markers of gliomas included in routine clinical practice when using antiblastic chemotherapy

1. Proliferative index Ki-67 is an independent predictor of unfavorable course of the disease in malignant gliomas. Ki-67 protein is expressed in the nuclei of cells that are in active phases of the cell cycle (G1, S, G2, mitosis). Ki-67 proliferative activity index is

determined by the immunohistochemical method using monoclonal antibodies [7].

2. Co-deletion of 1p/19q (combined deletion of chromosomal loci 1p36 and 19q13) is an important prognostic marker characteristic only for glial tumors, correlates with greater survival and sensitivity to CT, occurs in 70% of grade 2 and 3 oligodendrogliomas of anaplasia. Loss of 1p/19q alleles, regardless of the grade of oligodendroglioma anaplasia, is always associated with a positive response to polychemotherapy according to the PCV scheme (lomustine–procarbazine–vincristine) [8, 9]. In case of 1p/19q co-deletion, in order to improve the quality of patient life and eliminate the side effects of polychemotherapy, the appointment of temozolomide is promising [10].

3. *MGMT* (O^6-methylguanine methyltransferase) is a study of MGMT gene promoter methylation by polymerase chain reaction and immunohistochemical study of *MGMT* protein expression. The MGMT protein, which is a product of the MGMT gene expression, performs reparative functions and repairs DNA damage at the O6-guanine position. The MGMT gene is the first molecular marker for glioblastoma, which can be not only a prognostic factor for long-term survival, but also a predictor of effective response to chemotherapy treatment with alkylating compounds [11–13].

4. Mutation *IDH1/IDH2* is a prognostic marker for diffuse gliomas (astrocytoma *IDH*-mutant grade 2-4 and oligodendroglioma *IDH*-mutant grade 2-3). The presence of a mutation in the genes of isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) determines a favorable prognosis for these tumors to a greater extent than a histological diagnosis, but is not a predictive marker of response to chemotherapy treatment [14, 15].

Distribution of diffuse gliomas of grade 2 and 3 of anaplasia into subtypes according to molecular profile (presence of *IDH1/IDH2* mutation and 1p/19q co-deletion)

Using only *IDH1/IDH2* mutations and 1p/19q co-deletion, most diffuse gliomas of grade 2-3 of anaplasia can be classified into three molecular subtypes:

1) *IDH1* or *IDH2* mutation with 1p19q co-deletion;

2) *IDH* mutation without 1p19q co-deletion or with isolated loss of the 1p or 19q locus;

3) no *IDH1* or *IDH2* mutation (*IDH wild type*).

This distribution of gliomas into subtypes is of diagnostic and prognostic value for the indications and effectiveness of CT, and is also associated with improved progression-free survival and overall survival in patients with diffuse gliomas of grade 2-3 of anaplasia.

In general, molecular genetic characterization does not replace the standard histological evaluation, but complements it by providing additional diagnostic and prognostic information that can significantly improve the diagnostic accuracy, influence the choice of treatment and disease prognosis. Using genetic and molecular testing, histologically similar CNS neoplasms can be more precisely characterized with respect to prognosis and personalized treatment approaches for glial brain tumors.

Adjuvant chemotherapy of diffuse gliomas of grade 2 of anaplasia (low-grade glioma)

Specific markers used to determine the molecular subtypes of diffuse gliomas of grade 2 of anaplasia have been found to be important (1p/19q co-deletion and *IDH* gene status) [2, 15, 16].

A differentiated approach to CT in patients with diffuse gliomas of grade 2 of anaplasia depending on the presence of prognostically favorable and unfavorable factors is mandatory [17].

Risk factors, in addition to well-known unfavorable factors, such as age >40 years, physical function according to the Karnofsky scale (Karnofsky index (KI)) <70 points, tumor size >6 cm with spread to subcortical formations or beyond the midline, preoperative neurological deficit including increased perfusion during neuroimaging, absence of 1p/19q co-deletion, absence of *IDH1* and *IDH2* gene mutation.

The presence of two risk factors significantly affects the recurrence-free period and patient survival [18].

With visually complete tumor removal in low-risk patients, dynamic follow-up without additional methods of treatment is possible.

In the presence of 1p/19q co-deletion, polychemotherapy in the PCV mode is prescribed. In case of oligodendrogliomas with *IDH1* and *IDH2* gene mutations, the determination of co-deletion 1p/19q is not mandatory, since these mutations are related in most cases. PCV polychemotherapy is also prescribed.

The use of CT alone can be considered as an option at the risk of long-term cognitive impairment in patients with large (>6 cm) tumors, for which the prognosis is more favorable [19].

In patients over 40 years of age with a high risk of unfavorable course of the disease, especially in case of partial resection or tumor biopsy, PCV polychemotherapy after prior radiotherapy (RT) is mandatory in the presence of 1p/19q co-deletion in oligodendrogliomas and *IDH*-mutant in astrocytomas of grade 2 of anaplasia. In the absence of 1p/19q co-deletion in oligodendrogliomas and *IDH*-mutant in grade 2 of anaplasia astrocytomas, CT with temozolomide (TMZ) is prescribed in a concomitant regimen (in addition to RT) followed by adjuvant TMZ therapy according to the protocol [19–21].

In elderly patients or those with a burdened somatic status, the appointment of polychemotherapy according to the PCV scheme should be avoided due to its greater toxicity. The drug of choice is TMZ with/without RT.

In recurrent gliomas of grade 2 of anaplasia, CT can be prescribed immediately after reoperation, if patients received only RT after primary operation. In case of disease progression, it is possible to use another CT regimen after determining the molecular profile of the tumor. TMZ is most often preferred.

Radiotherapy with temozolomide CT (concomitant and adjuvant mode) is a treatment option for patients with recurrent or progressive gliomas who have not previously received RT. RT with adjuvant polychemotherapy in the PCV regimen and RT with adjuvant TMZ may be prescribed.

Adjuvant chemotherapy of diffuse astrocytomas of grade 3 of anaplasia

Molecular and genetic characteristics of these tumors provide additional information that improves diagnostic accuracy and helps with the choice of CT.

For postoperative treatment of grade 3 of anaplasia astrocytomas, especially with *IDH*-mutant in patients

with KI ≥60 points, a concomitant regimen of TMZ has an advantage over RT with simultaneous appointment of nitrosourea drugs. Lomustine, carmustine, fotemustine and other nitrosourea drugs are highly toxic, leading to premature discontinuation of such CT in a large number of cases. TMZ concomitant therapy regimen followed by TMZ adjuvant therapy according to the protocol or TMZ adjuvant administration after RT remains a priority [22, 23]. As an option, the adjuvant mode of monochemotherapy with nitrosourea drugs is possible.

Combined use of TMZ and RT increases survival only in patients with grade 3 of anaplasia gliomas with *IDH1* and *IDH2* gene mutations. In patients with gliomas with/without *IDH* gene mutation, the combined use of TMZ and RT has no effect on survival [23].

In patients with KI >70 points in primary grade 3 of anaplasia astrocytomas without *IDH* gene mutation, adjuvant mode of PCV after RT is the option of choice. In case of progression of grade 3 of anaplasia astrocytomas after RT, CT with alkylating compounds, both TMZ and nitrosourea drugs, should be used [24, 25].

Adjuvant chemotherapy of grade 3 of anaplasia oligodendrogliomas

Multiple randomized studies have found that for grade 3 of anaplasia oligodendrogliomas, co-deletion of 1p/19q and *IDH1* and *IDH2* gene mutations correlate with longer recurrence-free period and overall survival [26]. In addition, these features distinguish them from glioblastomas when making a histopathogenetic diagnosis.

The addition of polychemotherapy in the PCV regime to RT for newly diagnosed oligodendrogliomas of grade 3 of anaplasia in case of detection of 1p/19q co-deletion is a generally accepted standard in their adjuvant treatment [27, 28]. Usually 6 cycles of PCV should be planned. If acute hematological toxicity occurs and cannot be corrected, the number of courses may be reduced.

In young and middle-aged patients with 1p/19q co-deletion, high KI (>70 points) and normal hematological indicators, it is possible to conduct up to 4 courses of polychemotherapy in the PCV regime before RT [28].

In case of KI <60 points and the presence of comorbidities, regardless of the age of patients, and especially in those over 70 years old, RT with TMZ in the concomitant regimen followed by the use of TMZ in the adjuvant mode is recommended [22].

In the presence of grade 3 anaplasia oligodendrogliomas without co-deletion of 1p/19q, PT with TMZ in the concomitant regimen, followed by the use of TMZ in the adjuvant mode (6–12 courses) is also recommended. The number of courses depends on the tolerability of therapy and severity of myelosuppression [29].

In patients over 70 years of age with low KI (<60 points) in the presence of methylation of the MGMT gene promoter, an alternative to RT may be the use of TMZ alone in an adjuvant mode according to the protocol.

It should be noted that for all subtypes of diffuse gliomas of grade 2–3 anaplasia with *IDH1* and *IDH2* gene mutation, in case of disease progression after surgery and RT, TMZ CT should be the standard of treatment.

The use of antiangiogenic therapy with bevacizumab in recurrent gliomas of grade 2-3 anaplasia does not increase both overall and recurrence-free survival, in the absence of 1p/19q co-deletion [30].

Adjuvant chemotherapy for IDH wild type glioblastomas

Combined chemoradiation therapy (concomitant use of drugs with an alkylating mechanism of action, primarily TMZ) has become a new standard of care for young and middle-aged patients with glioblastoma, if KI >70 points, regardless of *MGMT* gene status. To continue TMZ CT in the adjuvant mode for at least 6 courses [11]. The number of TMZ courses 6 or 12 is a matter of debate [31]. Tactics are chosen individually depending on tolerability and the level of myelosuppression in CT. In the absence of tumor progression, the number of courses can be more than 12 [6].

However, the appointment of TMZ therapy in the adjuvant mode alone for up to 6 courses does not improve survival results even in the case of methylation of *MGMT* gene promoter [32].

It should be taken into account that in young and middle-aged patients with KI >70 points, even in the absence of methylation of *MGMT* gene promoter, concomitant CT with adjuvant TMZ therapy for up to 6 courses under the control of magnetic resonance imaging once for 3 months is mandatory in the presence of residual tumor sites. In the absence of tumor progression, the number of courses of TMZ adjuvant therapy should be increased to 12, in some cases, taking into account the level of CT toxicity, more courses may be possible [6].

In patients with newly diagnosed glioblastoma with KI <60 points regardless of age, TMZ CT in mono regimen with delayed RT or without RT is possible.

In older and elderly patients, treatment tactics depend on the physical function of the patient:

– for patients aged <70 years with newly diagnosed glioblastoma in a satisfactory physical function (KI ≥70 points), standard RT in the course of treatment TMZ as a radiomodifier (concomitant therapy) followed by adjuvant TMZ therapy according to the protocol is prescribed [11];

- for patients aged ≥70 years in a satisfactory physical function in the absence of methylation of the *MGMT* gene promoter, TMZ therapy is used in concomitant and adjuvant modes in combination with hypofractionated radiotherapy. In case of methylation of the *MGMT* gene promoter, TMZ monochemotherapy with delayed hypofractionated RT is possible [33];

- in elderly patients with methylation of the *MGMT* gene promoter, TMZ monochemotherapy can be an alternative to RT even with poor physical function (KI <60 points) to prevent cognitive impairment [34].

In the treatment of grade 3-4 anaplasia recurrent diffuse gliomas and IDH wild type glioblastomas, if the period duration from initiation of CT to tumor progression is more than a year, the drugs that the patient received during the initial treatment can be a reasonable second line of CT. In the case of methylation of the *MGMT* gene promoter, drugs with an alkylating mechanism of action, such as TMZ, are prescribed. The lack of methylation of the *MGMT* gene promoter justifies CT regimens based on nitrosourea drugs (lomustine, carmustine, fotemustine) or polychemotherapy in the PCV regimen [35–37].

If in malignant gliomas with an oligodendroglial component, in particular with glioblastoma, TMZ was used during the primary therapy, then polychemotherapy according to the PCV scheme is prescribed as the second-line of therapy. Its appointment is mandatory in the absence of methylation of the *MGMT* gene promoter.

In case of recurrence of diffuse astrocytomas of grade 3-4 of anaplasia and a pronounced vascular network of the tumor (according to MRI-perfusion data), antiangiogenic therapy bevacizumab in combination with TMZ is prescribed. If *MGMT* gene promoter methylation is absent, irinotecan is used [38–40].

A treatment option for malignant glioma recurrence is the intraoperative use of biopolymer plates containing such drugs as carmustine, cisplatin, etc. [41]. Local application of chemopreparations through the Ommaya reservoir is possible [42].

Support therapy

Support therapy involves the use of antiemetic and anticonvulsant therapy, antihistamine blockers and hematopoietic stimulations. Antiemetic therapy (if necessary) with drugs osetron, ondansetron, etc. is carried out before, after or simultaneously with CT.

In case of anticonvulsant therapy, anticonvulsants inducing hepatobiliary enzymes (for example, Finlepsin® or carbamazepine) should be avoided. It is possible to use such drugs as Keppra®/Levicitam®, Depakine®, Lamotrin®, Lamictal®, Epileptal® [43].

In the presence of myelosuppression, colony-stimulating factor stimulators (filgrastim, lenograstim, methyluracil, Revolade™, etc.) are prescribed to correct thrombocytopenia and leukocytopenia. The use of alkylating agents with other bone marrow suppressants (e.g., carbamazepine) may increase the risk of myelosuppression.

Antihistamine blockers (histamine H_1-, H_2-receptor blockers) omeprazole, ranitidine, loratadine, famotidine, etc. are often used for CT.

When conducting CT, chemotherapy – related toxicity criteria should be taken into account, primarily hematotoxicity, in some cases - hepatotoxicity, nephrotoxicity, neurotoxicity, cardiotoxicity, dermatotoxicity, etc.

Indications for CT are determined only by clinical oncologists, chemotherapists and "neuro-oncologists".

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This article is a literature review, therefore no ethics committee approval was required.

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