

Administration, Marketing, Pharmacotherapy of Medicines in Neuro-Oncology

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Abstract. Primary tumors make up 1.5% of all clinical cases. The most vulnerable group is children. Brain neoplasms are the second most common after acute leukemia. According to WHO statistics, men suffer 1.5 times more often than women. Administration, marketing, and pharmacotherapy of medicines in neuro-oncology were carried out. The administration of medicines for neuro-oncology pharmacotherapy in the USA and Ukraine was analyzed. Bevacizumab, Everolimus, Lomustine, Temozolomide were found to be approved in both countries. The issue of administration of medicines for neuro-oncology pharmacotherapy other than as prescribed by a doctor has been studied. The possibility of combined pharmacotherapy in neuro-oncology is indicated. Marketing studies of medicines for neuro-oncology pharmacotherapy have been conducted. The medicines are presented in

different dosage forms: solutions for infusions, injections, capsules and lyophilisates. The manufacturers of these medicines are pharmaceutical companies from different countries: India, Germany, Austria, the Netherlands, Ukraine. The majority of medicinal products have indefinite registration in Ukraine, which indicates their availability on the pharmaceutical market for the treatment of neuro-oncological diseases. Causes of tumors, main histological groups of neoplasms, their degree of malignancy, symptoms of tumors, diagnostic methods, therapy and pharmacotherapy in neuro-oncology are given. Further research on the development of methods and preparations of pharmacotherapy for neuro-oncology is relevant and ongoing.

Keywords: neuro-oncology, medicines, administration, marketing, pharmacotherapy.

Introduction. Neuro-oncology is a branch of medicine that focuses on both primary and metastatic brain tumors, spinal cord diseases, and complications of the peripheral nervous system. This specialty is growing and constantly evolving, as new diagnostic, therapeutic and prognostic factors are discovered.

There are more than 100 different primary brain tumors, which are divided into non-malignant or benign and malignant. One of the biggest challenges in neuro-oncology is understanding the complexity of central nervous system tumors in order to develop appropriate therapeutic agents. Traditional therapy of malignant gliomas combines surgery, radiation therapy, pharmacotherapy using chemotherapeutic medicines (procarbazine, lomustine, and vincristine). The importance of the immune system in carcinogenesis has led to the development of immunotherapy using vaccination, immune checkpoint blockade, oncolytic viruses, and adaptive immunotherapy [1].

Previously, multidisciplinary case studies of neuro-oncology disorders were presented: administration, clinical and pharmacological, organizational and legal, pharmaceutical management. A plan for a multidisciplinary study of neuro-oncology disorders against the background of accompanying comorbid conditions in the conditions of military conflicts has been developed. The main directions of the research are given, including the scientific hypothesis, task, expected novelty, research design, research object, research methods, endpoints, degree of evidence, description of scientific and technical products and various aspects of project effectiveness. The scientific hypothesis is that comorbid conditions significantly affect the course and treatment of neuro-oncology disorders. This will become the basis for further research. The main tasks for further study will be the determination of the impact of comorbid conditions on the prognosis of neuro-oncology disorders, as well as the development of new approaches to their treatment. The research will contribute to the discovery of new relationships between neuro-oncology disorders and comorbid conditions, which will allow the development of innovative methods of therapy. A research design was developed: conducting a complex multidisciplinary study using modern methods of diagnosis and treatment, involving various specialists and a multi-step approach to data collection and

analysis. Indicators of treatment effectiveness were determined: assessment, diagnosis; pharmacotherapy; psychosocial support; psychocorrection; determining directions of professional reintegration. The degree of evidence and effectiveness of the research is given. It is expected that the results of the research will have a high degree of evidence and contribute to the optimization of treatment of neuro-oncology disorders, improvement of medical, pharmaceutical, social, and economic efficiency. The developed research plan provides a comprehensive approach to the study of neuro-oncology disorders against the background of accompanying comorbid conditions, defines clear steps to achieve the set goals and creates a basis for conducting further scientifically based research in this field [2].

The purpose of the study was to research the administration, therapy, pharmacotherapy, marketing of medicines in neuro-oncology.

Materials and methods. The current research was carried out using the system approach during April 2024-September 2024.

Materials: regulatory and legal framework, clinical protocols, guidelines, standards of treatment of neuro-oncology disorders associated with medicine-related conditions, medical records, medical histories, medicinal products, instructions for medical use, questionnaires (of doctors, patients, different age groups of the population) and other local documents.

Methods of the research. Administration, organizational and legal, normative, documentary, clinical and pharmacological, comparative, classification and legal, nomenclature and legal, marketing, technological, graphic analysis were used in the study.

The research of the article is a fragment of research works of Private Scientific Institution "Scientific and Research University of Medical and Pharmaceutical Law" on the topic "Multidisciplinary research of post-traumatic stress disorders during war among patients (primarily combatants)" (state registration number 0124U002540, implementation period 2024-2029); Lviv Medical Institute on the topic of "Improving the system of circulation of drugs during pharmacotherapy on the basis of evidentiary and forensic pharmacy, organization, technology, biopharmacy and pharmaceutical law" (state registration number 0120U105348, implementation period 2021-2026); Kharkiv Medical Academy of Postgraduate Education on the topic "Pharmaceutical and medical law: integrated approaches to the system of drug circulation from the standpoint of forensic pharmacy and organization of pharmaceutical business" (state registration number 0121U000031, terms 2021-2026); Luhansk State Medical University "Conceptual interdisciplinary approaches to pharmaceutical provision and availability of drugs, taking into account organizational and legal, technological, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, marketing, social and economic competencies" (state registration number 0123U101632, terms 2023-2027); Petro Mohyla Black Sea National University on the topic "Conceptual interdisciplinary approaches to the drug circulation system, taking into account organizational and legal, technological, biopharmaceutical, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, pharmacotherapeutic aspects" (state registration number 0123U100468, implementation period 2023-2028).

Results and discussion. At the first stage of the study, medicines for pharmacotherapy of neuro-oncology were administered in the USA and Ukraine. Medicines approved for the treatment of brain tumors in the USA and Ukraine are listed in Table 1.

Table 1. Medicine administration in neuro-oncology: USA – Ukraine.

INN of medicines in USA [3]	State Register of Ukraine	State form of Ukraine
Bevacizumab	+	+
Belzutiphan	-	-
Dabrafenib mesylate	+	-
Everolimus	+	+
Eflornithine hydrochloride	-	-
Carmustine	+	-

Carmustine implant	-	-
Lomustine	+	+
Naxitamab	-	-
Temozolomide	+	+
Trametinib dimethylsulfoxide	+	-

Table 1 presents a list of medicines approved for pharmacotherapy of brain tumors in the USA and Ukraine. It contains the international non-proprietary names (INN) of medicines, their status in the State Register of Medicinal Products of Ukraine, and information on availability in the State Formulary of Ukraine.

According to the results of the administration, the following was established.

- Bevacizumab, Everolimus, Lomustine, Temozolomide are approved in the USA and Ukraine.
- Belzutiphan, Eflornithine hydrochloride, Carmustine implant, Naxitamab are not registered either in the USA or in Ukraine.
- Dabrafenib mesylate, Carmustine, Trametinib dimethylsulfoxide are registered in the USA, but are not available in Ukraine.

Administration of medicines for pharmacotherapy of neuro-oncology off-prescription

At the next stage, medicines for neuro-oncology were administered without a doctor's prescription. Refers to the practice of prescribing medicines for a purpose other than that approved by the FDA. This practice is called "not for medical purposes". The medicine is used in a way that is not described in the instructions for medical use. The FDA must make sure that the medicine is safe and effective for a specific use. However, it does not control doctors' decisions about which medicines to use for their patients. This means that once the FDA approves a medicine, doctors can prescribe it for whatever purpose they deem appropriate for the patient [4].

Off-prescription use may include the use of approved medicines:

- for a type of cancer other than the one approved for treatment;
- in a different dose or frequency;
- for the treatment of a child, when it is allowed for the treatment of adults.

Off-prescription use of medicine in neuro-oncology may become an FDA-approved use. To receive additional approvals, the company must conduct research to show that the treatment is safe and effective for new uses. However, the company may choose not to invest time and money in this research.

The role of off-prescription medicines in neuro-oncology

Studies have shown that the use of medicines not prescribed by a doctor is very common in the pharmacotherapy of neuro-oncology. Often, standard care for a certain type or stage of cancer includes the off-prescription use of one or more medicines. Inappropriate medicines use is common in cancer treatment.

- Many cancer medicines are effective against several types of cancer.
- Cancer pharmacotherapy often involves the use of combined chemotherapy.

Combined pharmacotherapy in neuro-oncology

Combination chemotherapy is a treatment using several medicines. Combined chemotherapy is effective in the pharmacotherapy of many types of cancer. Combinations may include one or more medicines.

The FDA does not usually approve chemotherapy combinations. There are many medicines combinations. It would be impractical to approve every combination.

- ❖ Research finds new ways to use already approved medicines. Research results are published in medical journals and disseminated throughout the medical community.
- ❖ Doctors then adopt a new use of the medicine. It may become an accepted and widely used treatment for other cancers, even if the FDA has not approved the medicine for that use.

Disadvantages of using off-prescription medicines in neuro-oncology

There are cases when the use of medicines not prescribed by a doctor can cause harm. Such cases:

- it has not been proven that the medicine is effective against a certain type of cancer;
- there are no reasons to believe that the medicine can be effective;
- the possible risks of using the medicine outweigh the possible benefits.

Chemotherapy uses antitumor (cytotoxic) medicines to destroy brain tumor cells [5, 6].

A detailed search for review articles related to chemotherapy and pharmacotherapy of primary brain tumors is described in Neuro-Oncology. neurological, neurosurgical, and oncological literature for fundamental scientific research, clinical research [7].

Relevant studies on tissue culture systems, animals, and humans with the study of mechanisms of action, pharmacokinetics, clinical pharmacology, and results of treatment with chemotherapeutic agents of primary brain tumors. Studies of medicines in the pharmacotherapy of neuro-oncology, used for supportive therapy and symptom control, are considered.

Primary brain tumors originate from cells in the intracranial cavity and are usually accompanied by headache, seizures, cognitive changes, and weakness. They are most effectively diagnosed using magnetic resonance imaging.

Once diagnosed, the most common supportive medications are corticosteroids, gastric acid inhibitors, and anticonvulsants. Chemotherapy is adjuvant treatment for patients with malignant tumors and selected recurrent or progressive benign neoplasms.

Marketing analysis of medicines for pharmacotherapy in neuro-oncology

Marketing analysis of medicines for pharmacotherapy in neuro-oncology by INNs, trade names, dosage forms, producing countries, registration terms is given in Table 2.

Table 2. INN, Trade names, dosage forms, country of manufacture, registration of chemotherapeutic medicines.

INN	Trade name	Dosage form	Country of manufacture	Registration
Vincristine	Vincristine-Mili	solution for injection, 1 mg/ml; 1 ml in a bottle; 1 or 10 vials in a cardboard box	Venus Remedies Limited, India	UA/6430/01/01 unlimited from 06/22/2022
Etoposide	Etopozide-Teva	concentrate for solution for infusions, 20 mg/ml in 5 ml or 10 ml bottles; 1 vial in a cardboard box	Pharmachemy B.V., the Netherlands	UA/7277/01/01 unlimited from 05/19/2017
Carboplatin	Carboplatin "Ebeve"	concentrate for solution for infusion, 10 mg/ml, 5 ml (50 mg), or 15 ml (150 mg), or 45 ml (450 mg), or 60 ml (600 mg) in a bottle; 1 bottle	Ebeve Pharma Hes.m.b.H. Nfg. KG (issue of the series), Austria; Laboratory LS SE & Co. KG (series control (additional sites), Germany; MPL Microbiologisches Prüflabor GmbH (series control (additional	UA/4960/01/01 unlimited from 07/30/2021

		in a box	sites), Austria; Fareva Unterach GmbH (full production cycle), Austria	
Carmustin	BiKNU-100 mg	lyophilisate for solution for infusions of 100 mg; 1 bottle with a lyophilisate complete with a sterile solvent (anhydrous alcohol) of 3 ml in a bottle in a cardboard package	Emkur Pharmaceuticals Ltd., India	UA/16185/01/01 unlimited from 10/30/2023
Lomustin	Lomustin Medak	capsules of 40 mg, 20 capsules in a container; 1 container per pack	Medak Gesellschaft für klinische Spezialpräparate mbH (manufacturer responsible for primary packaging labeling, secondary packaging, batch control/testing and batch release), Germany; Haupt Pharma Amareg GmbH (manufacturer responsible for the production of the medicinal product, primary packaging, batch control/testing), Germany	UA/6988/01/01 unlimited from 13.10.2017
Methotrexate	Metotrexate "Ebeve"	concentrate for solution for infusions, 100 mg/ml; 5 ml (500 mg), or 10 ml (1000 mg) or 50 ml (5000 mg) in a vial; 1 bottle in a cardboard box	Ebeve Pharma Hes.m.b.H. Nfg. KG (issue of the series), Austria; MPL Microbiologisches Prüflabor GmbH (testing), Austria; Laboratory L+S AG (testing), Germany; Fareva Unterach GmbH (full production cycle), Austria	UA/1209/02/01 unlimited from 05/08/2019
Procarbazine	Glocarbazine	capsules of 50 mg F.USA in a blister in a cardboard box	Globela Farma LTD, India	UA/17863/01/01 24.02.2020 04/01/2025

Tamoxifen	Tamoxifen-Health	20 mg tablets; 10 tablets in a blister; 3 or 6 blisters in a cardboard box	Limited liability company "Pharmaceutical company "Zdorovya", Ukraine	UA/5528/01/02 unlimited from 04/23/2021
Temozolomide	Temodal	powder for solution for infusion 100 mg, 1 vial with powder in a cardboard box	Baxter Oncology GmbH (production of bulk products, primary packaging, and quality control), Germany; Organon Heist bv (secondary packaging and batch release), Belgium; Merck Sharp and Dom B.V. (Permission to issue a series), Netherlands	UA/4893/02/01 unlimited from 07/08/2021
Cyclophosphamide	Endoxan	powder for solution for injection 1 g; 1 vial with powder in a cardboard box	Baxter Oncology GmbH, Germany	UA/0027/02/03 unlimited from 08/01/2018
Cisplatin	Cisplatin-Teva	concentrate for solution for infusions, 1 mg/ml in 100 ml bottles; 1 bottle in a pack	Pharmachemy B.V. (full cycle production), the Netherlands; Pliva Hrvatska d.o.o. (series control), Croatia	UA/7552/01/02 unlimited from 17.01.2018

Table 2 contains information about medicines for neuro-oncology pharmacotherapy. It contains international non-proprietary names, trade names, dosage forms, countries of manufacture and data on registration in Ukraine. The medicines are presented in different dosage forms: solutions for infusions, injections, capsules and lyophilisates. The manufacturers of these medicines are pharmaceutical companies from different countries: India, Germany, Austria, the Netherlands, Ukraine. The majority of medicinal products have indefinite registration in Ukraine, which indicates their availability on the pharmaceutical market for the treatment of neuro-oncological diseases.

Pharmacotherapy in neuro-oncology

Pharmacotherapy in neuro-oncology can be used alone for primary lymphoma of the central nervous system. Also, as adjuvant therapy for many tumors of the central nervous system. Problems with the efficacy of chemotherapeutic or targeted agents include low concentration of medicine penetration into the tumor due to the difficulty of the agents to cross the blood-brain barrier. High binding of agents to plasma proteins makes available less free medicine, reduces the volume of distribution of agents in the brain parenchyma. Intrinsic and acquired resistance also remains an important cause of reduced effectiveness of chemotherapy for the treatment of central nervous system tumors [8].

Unique and central to the treatment of central nervous system tumors is the issue of medicine delivery across the blood-brain barrier, which is an anatomical and physiological barrier to medicine penetration. Oral and intravenous methods are usually used to deliver therapeutic agents to the CNS.

The effectiveness of pharmacotherapy in neuro-oncology depends on achieving adequate concentrations of the active form of medicines within a sufficient time. In recent years, there has been a lot of interest in researching how quickly a medicine reaches a tumor. There are a number of approaches: direct measurement of the medicine in the tumor tissue, taking samples of the cerebrospinal fluid, microdialysis.

We are very interested in the development of combined schemes of medicine treatment to enhance the effects of standard chemotherapy [9].

The priority areas of neuro-oncology are complex treatment and pharmacotherapy of brain tumors. Primary tumors make up 1.5% of all clinical cases. Children are the most vulnerable group. Brain neoplasms are the second most common after acute leukemia. According to WHO statistics, men suffer 1.5 times more often than women. Secondary (metastatic tumors) of the nervous system are more common than primary tumors. About a third of all malignant tumors metastasize in this way. Metastases to the brain are most often found in breast, lung, kidney, melanoma, and colon cancer (colorectal cancer) [10].

Causes, histological groups, degree of malignancy, symptoms. diagnosis, treatment of malignant neoplasms in neuro-oncology

The causes of tumors of the central nervous system are shown in Fig. 1.

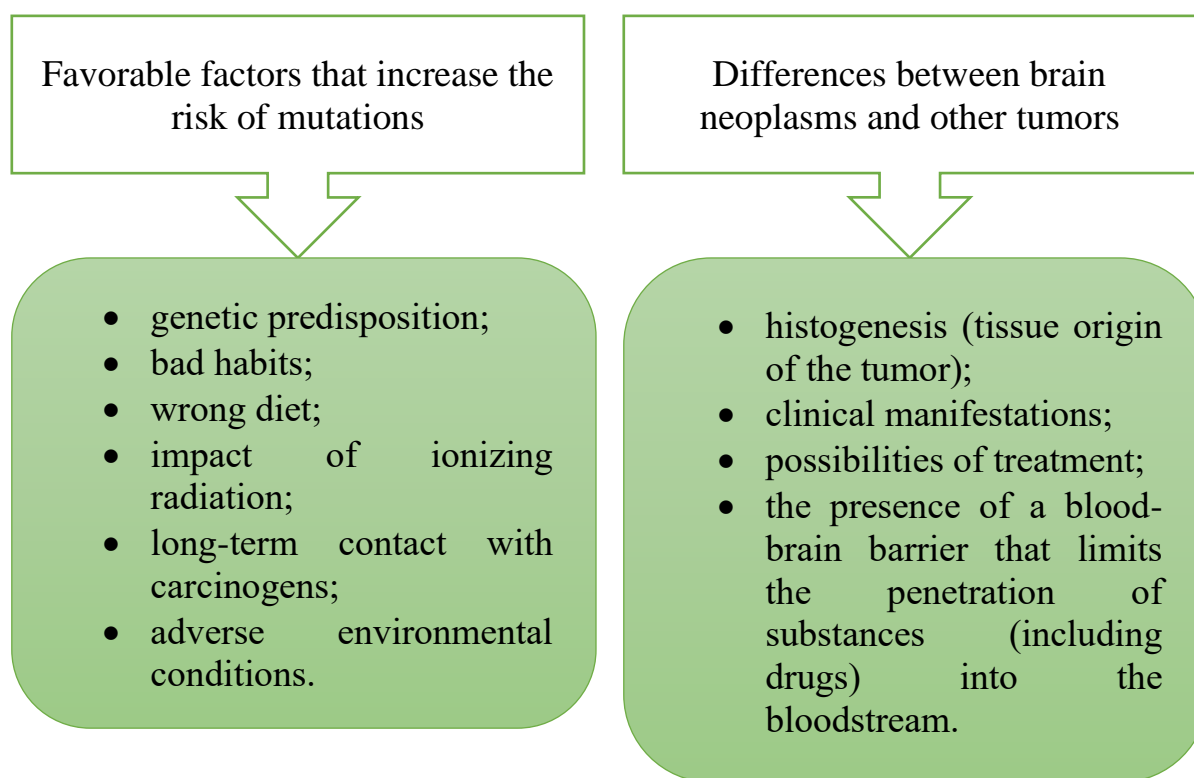


Fig. 1. Causes of tumors of the central nervous system.

The main histological groups of neoplasms of central nervous system are shown in Fig. 2.

The main histological groups of neoplasms of the central nervous system

1. Neuroepithelial (derived from brain tissue).
2. Tumors formed from the membranes of the spinal cord or brain.
3. Neoplasms developed from pituitary cells.
4. The formation of nerves that leave the brain.
5. Tumors of the central nervous system that arose at the stage of embryonic development of the fetus.

Fig. 2. Main histological groups of neoplasms.

Tumors of the central nervous system are divided according to the degree of malignancy, which also includes benign neoplasms (Table 3).

Table 3. Degree of malignancy of tumors in neuro-oncology.

Degree of malignancy	Description
I degree	Benign tumors that develop slowly. Treatment is surgical, a "wait and scan" tactic is possible. Given the surgical inaccessibility of the tumor, as well as the potentially high risk of gross dysfunction of the affected nerves after surgery, neurosurgeons prefer not to operate, but to observe tumors that are asymptomatic and have been diagnosed incidentally.
II degree	Formation of intermediate, uncertain, and low degree of malignancy. Tumors grow slowly and can transform into neoplasms of high malignancy. Also, these tumors are prone to relapse after treatment due to the infiltrative nature of development (germination into healthy tissue).
III degree	High-malignancy tumors requiring radiation therapy and (or) chemotherapy.
IV degree	Formations of high malignancy that develop rapidly despite treatment.

Symptoms of tumors are shown in Fig. 3.

The appearance of symptoms of brain tumors depends on their anatomical location and size. They are divided into focal and general brain.

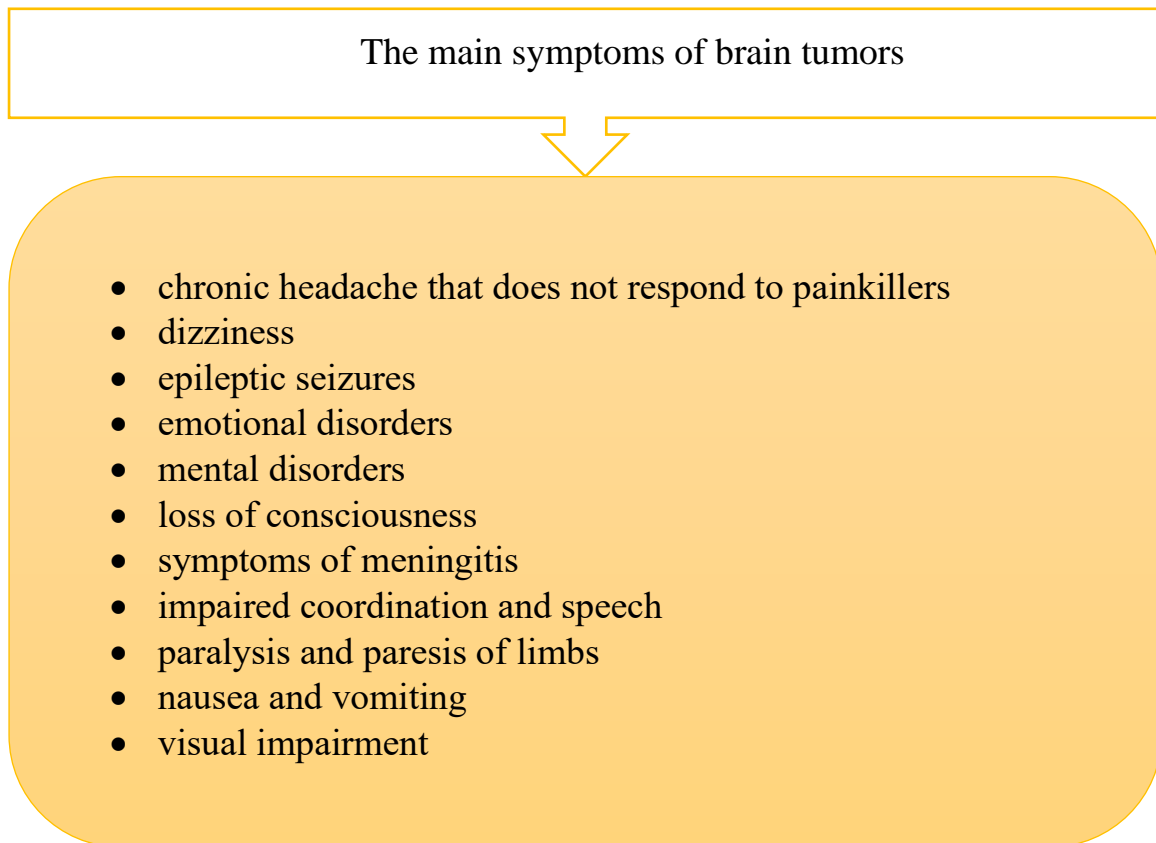


Fig. 3. The main symptoms of brain tumors.

Diagnostic methods are shown in Fig. 4.

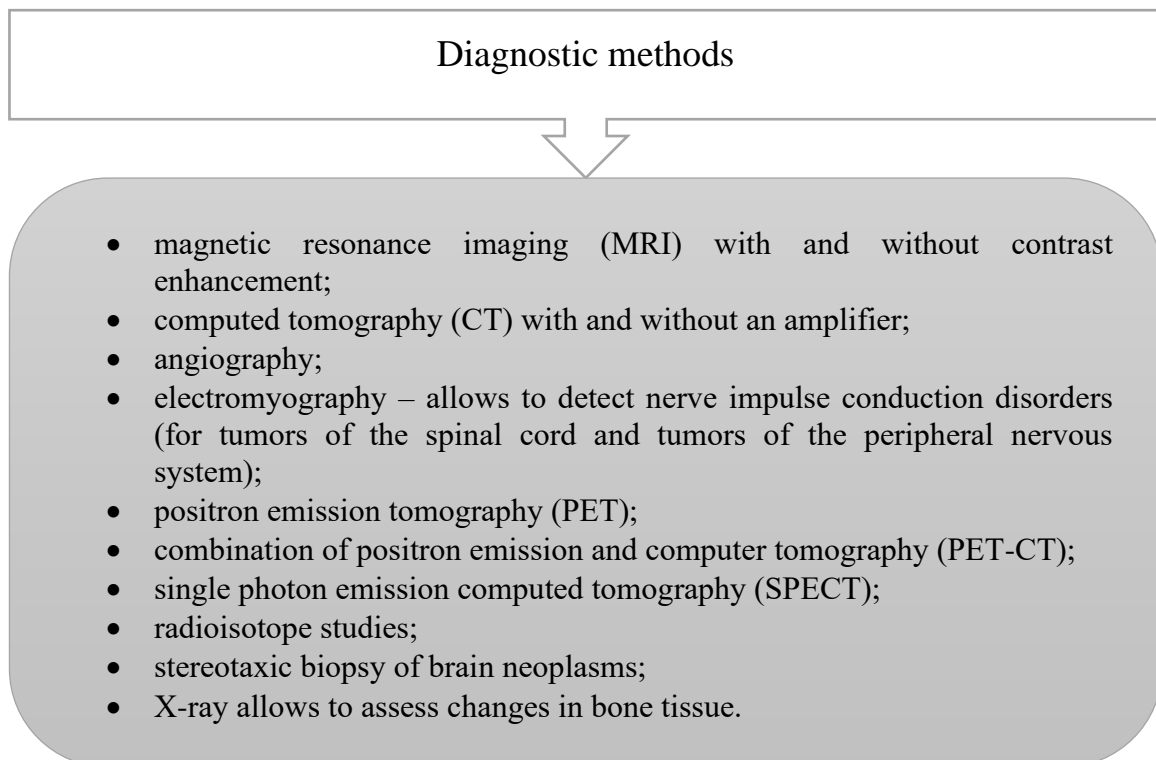


Fig. 4. Tumor diagnosis methods in neuro-oncology.

Therapy and pharmacotherapy of tumors in neuro-oncology is shown in Fig. 5.

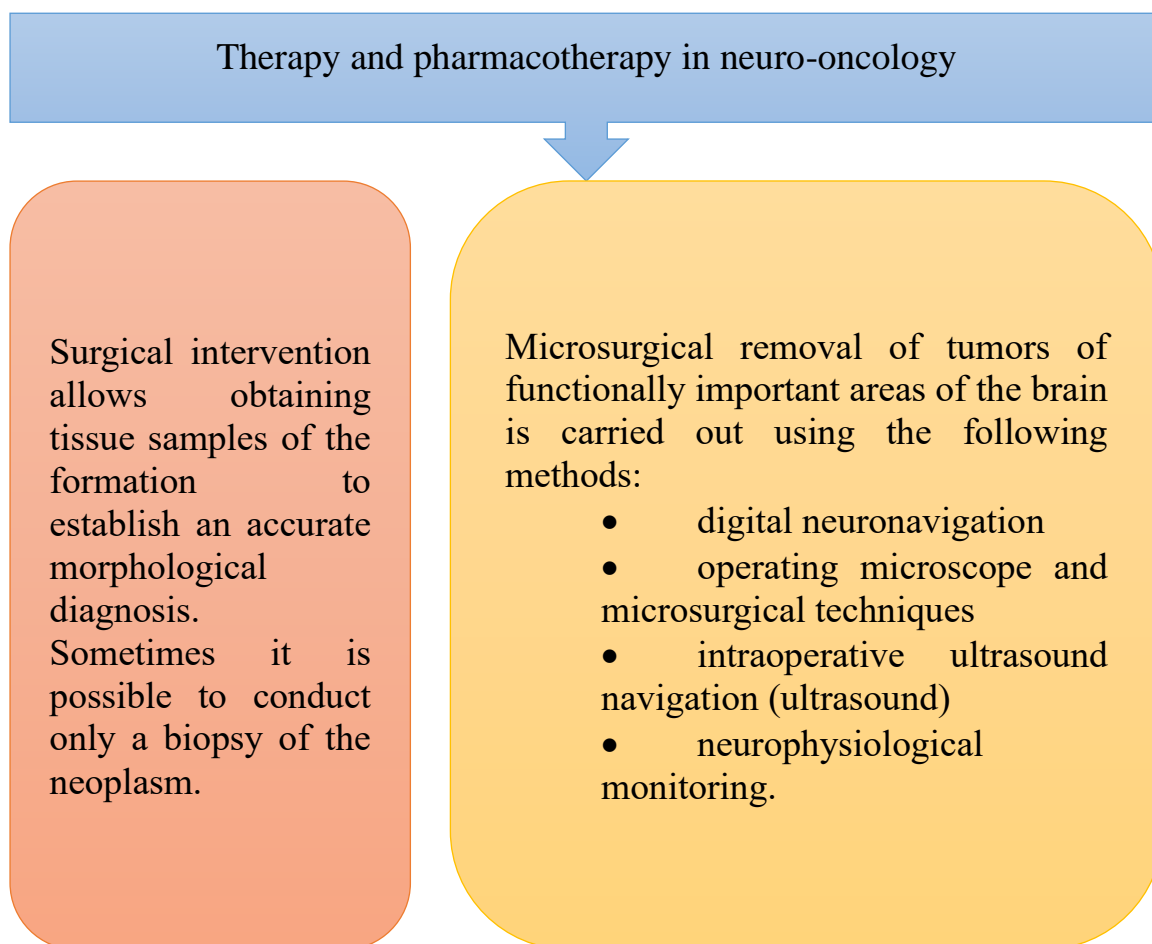


Fig. 5. Therapy and pharmacotherapy of tumors in neuro-oncology.

Radiation treatment is prescribed after a histological examination of the structures of the neoplasm and after a brain biopsy. In the treatment of highly malignant tumors, after surgical intervention, a control study (X-ray computer and magnetic resonance imaging with intravenous contrast enhancement) is performed. Depending on the morphological structure of the neoplasm, its bed (residual tumor) is irradiated with adjacent parts of the brain, cerebrum, head and spinal cord (simultaneously). The beginning of radiation therapy - 8 weeks after the surgical operation.

In the treatment of tumors of low malignancy, therapy and pharmacotherapy are carried out if it is impossible to completely remove the neoplasm.

In the treatment of benign tumors, radiation therapy is performed if surgical intervention is not possible.

Radiation therapy is used in the treatment of neoplasms of high malignancy. In neoplasms of a low degree of malignancy, chemotherapy is used when it is impossible to carry out surgical intervention and radiation therapy. Traditionally, chemotherapy is supplemented with surgical and radiation methods of treatment.

Patients with tumors of the central nervous system undergo complex treatment and pharmacotherapy. Side effects and complications from these interventions pose significant challenges in clinical practice. They affect the function and quality of life of patients [11, 12].

Further research on the development of new methods of stimulating the immune system to attack the tumor, new medicines for the destruction of tumor cells [13-16] is relevant.

Conclusions. Administration, marketing, and pharmacotherapy of medicines in neuro-oncology were carried out. The relevance of research in neuro-oncology is given. In a comparative aspect, the administration of medicines for pharmacotherapy of neuro-oncology in the USA and in Ukraine was analyzed. Bevacizumab, Everolimus, Lomustine, Temozolomide were found to be approved in both countries. The issue of administration of medicines for neuro-oncology

pharmacotherapy other than as prescribed by a doctor has been studied. The role of non-prescription medicine use in neuro-oncology is given. The possibility of combined pharmacotherapy in neuro-oncology is indicated. Emphasis is placed on the disadvantages of using medicines not prescribed by a doctor in neuro-oncology. Marketing studies of medicines for neuro-oncology pharmacotherapy have been conducted. The medicines are presented in different dosage forms: solutions for infusions, injections, capsules and lyophilizates. The manufacturers of these medicines are pharmaceutical companies from different countries: India, Germany, Austria, the Netherlands, Ukraine. The majority of medicinal products have indefinite registration in Ukraine, which indicates their availability on the pharmaceutical market for the treatment of neuro-oncological diseases. Causes of tumors, main histological groups of neoplasms, their degree of malignancy, symptoms of tumors, diagnostic methods, therapy and pharmacotherapy in neuro-oncology are given. Further research on the development of methods and preparations of pharmacotherapy for neuro-oncology is relevant and ongoing.

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