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Modern therapy of eye neoplasms

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ABSTRACT

Ocular neoplasms, despite their rarity, pose a significant problem in contemporary ophthalmic oncology. The diagnosis of a tumor in the organ of vision often causes the need to remove the eyeball. In recent years, however, the effectiveness of eye tumor treatment has markedly increased. Oncological therapy in ophthalmology is dynamically developing towards gene therapies, biotechnology and materials engineering. In addition to early detection of the disease, which plays a major role in the patient's survival, more and more attention is paid to reducing the systemic effects of therapy, preserving vision and improving the patient's quality of life. Among other things, this can be achieved through the use of nanoparticles, targeted therapy, immunotherapy as well as proton beam radiotherapy.

In this paper, we present an overview of new trends of ocular neoplasm therapies that have been researched over the last few years. On the examples of choroidal melanoma, conjunctival melanoma, retinoblastoma, primary retinovitreal lymphoma, we point out the proposed modern treatment methods dedicated to a given type of disease. Moreover, we indicate that the currently used methods of treating non-ophthalmic neoplasms, due to the similarity in oncogenesis to ocular neoplasms, may constitute a starting point for the development of new management in ophthalmic oncology. We discuss the difficulties related to the introduction of new therapies into clinical practice and justify the purposefulness of further research due to the promising results, identifying possible directions for their development.

INTRODUCTION

Oncology is one of the fastest developing fields of medicine. Currently, when planning oncological treatment, not only a given type of concoma is taken into account, but also the therapy is individually adapted to the patient, considering his age, health condition, prognosis and the characteristics of the disease itself. Advanced genetic and bioengineering technologies are developed very dynamically. Thanks to them, it is possible to determine the type of mutation precisely, its frequency and influence on the course of the disease and prognosis. Such a large amount of personalized data gives hope for the development of advanced therapies or increasing the effectiveness of those already used. Promising results of research on personalized vaccines, genetically modified T lymphocytes, interference in the genome, research on the role of the organism's microflora in the process of tumor formation are examples of the direction in which modern oncology is heading. Nowadays oncological treatment should not only be effective, but also the least burdensome and lowering the patient's quality of life.

OPHTHALMIC ONCOLOGY

Oncological therapy of ophthalmic patients is associated with many problems. The diagnosis of a maligancy of the eyesight often equals the necessity to remove the eyeball. Despite early diagnosis, the death rate is still high. However, the example of retinoblastoma shows that the effectiveness of the treatment of ocular neoplasms has increased in recent years. Currently, oncological therapy in ophthalmology is dynamically developing towards gene therapies, biotechnology, and materials engineering. In the near future, everyday clinical practice will be supplemented with new therapeutic possibilities. Traditional examination, combined with selecting high-risk groups, determining the prognosis for a given patient, and identifying specific genes responsible for neoplasms will allow for more effective diagnosis and treatment of neoplasms of the eye organ.

Ocular neoplasms are rare. They lead to significant impairment, loss of vision, and death of patients. The early detection of eyeball tumors is crucial. Their rarity results in significant difficulties in obtaining material for analysis. Nevertheless, extensive research is conducted to develop new, effective methods of treating them. Traditional radio- and chemotherapy do not always protect the patient from enucleation. The aspirations of scientists looking for new therapies are dictated by the desire to keep the

patient alive as long as possible, but also to preserve vision. The achievements of recent years give hope that eyeball tumors will no longer limit the ability to function independently, and even more so, they will cease to cause death of patients.

TUMORS OF THE EYEBALL

UVEAL MELANOMA

It makes up 80% of all melanomas of the eyeball (Krantz et al. 2017). It is derived from the melanocytes of the uveal membrane (iris, ciliary body and choroid). It is estimated that about 50% of patients metastasized when uveal melanoma was detected (Wang et al. 2020). About 30% of patients showed no symptoms. Almost 40% reported visual impairment (Damato, Damato 2012). According to the COMS study, 89% of the metastases were located in the liver. Mortality after detecting metastases reached 80% within the first year and 90% within 2 years. The survival time did not depend on the size of the primary tumor or the treatment of metastases (Diener-West et al. 2005), while the early detection and implementation of effective treatment of the primary tumor achieved a 90% survival rate (Wu et al. 2020), if metastasis did not occur.

Standard therapy, such as brachytherapy, radiotherapy and enucleation, is highly effective in the treatment of the primary tumor (Ramaiya 2007). Treatment of patients with metastatic form becomes problematic. Even if metastases were not developed at the time of detection, patients with uveal melanoma are particularly at risk (Kujala, Mäkitie, Kivelä 2003).

The DecisionDx-UMTM test using PCR (Greenhaw et al. 2020), available in the USA, is used for the prognostic evaluation of a tumor sample by analyzing 15 genes and, disregarding other clinical data, assigns patients to two risk groups – class 1 UM (uveal melanoma) associated with low risk of metastasis, and a class 2 UM with a high risk of metastasis. Thanks to this division, it is possible to adjust the intensity of therapy for a particular patient (Harbour, Chen 2013).

GENETIC ANALYSIS OF THE BASIS OF NEOPLASM

Genetic analysis of the basis of neoplasm has identified a number of mutations, oncogenes, that show potential as a target for antineoplastic drugs. Differentiation of the primary tumor mutation in relation to metastatic foci gives the theoretical possibility of developing targeted therapy and systemic action, both in the topical location and in the area of metastatic foci.

Using standard biomarkers, we are able to determine the expression of diseasespecific genes responsible for tumor growth and expansion and apply targeted therapy. Such typing requires the selection of neoplastic cells. Single Cell Technology (SCIT) can help. This method allows the isolation of homogeneous tumor cells from the collected biopsy material and the separation of neoplastic cells from infiltrating cells of the immune system and cells of healthy tissues. The cells separated in this way are multiplied and typed (Li et al. 2020). The method is more effective than flow cytometry and manual selection of neoplastic cells (Wang et al. 2021).

Examples of common biomarkers are:

BAP1 – is a suppressor gene regulating cell division (Field et al. 2019). The BAP1 mutation is more commonly associated with class 2 uveal melanoma (Harbour et al. 2010).

It is believed that mutations in the GNAQ and GNA11 genes (Van Raamsdonk et al. 2010) detected in 83% of uveal melanoma tumors are associated with an increased metastatic potential. GNAQ is more common in the primary tumor, and GNA11 in the metastatic focus (Onken et al. 2008).

A mutation in the IGF-1 gene causes an increased migration of tumor cells and an increased risk of metastases in the liver and other organs (Wilky et al. 2015).

The role of the c-KIT gene in the neoplastic process of choroidal melanoma has not been definitively established (Van Poppelen et al 2021). In healthy cells, it is responsible for normal growth, increasing the number of melanocytes and their homeostasis (Grichnik et al. 1998). Limited data on the presence of an activating mutation of the c-KIT gene in uveal melanoma suggest that the mutation is extremely rare (Wallander et al. 2011). Nevertheless, it was confirmed in 78% of uveal melanoma samples taken from the Archives of the McGill University Ocular Tissue Pathomorphology Laboratory (Pereira et al. 2005).

TARGETED THERAPY

The mechanism of action of drugs in targeted therapy is to inhibit specific signaling pathways leading to neoplasia.

It has been shown that drug-targeted therapy from the group of histone deacetylase inhibitors (HDAC) used in the case of a mutation of the BAP1 gene, based on the example of valproic acid, inhibits tumor growth in vitro and reduces the number of metastases (Landreville et al. 2012).

Cixutumumab – a monoclonal antibody inhibits the activity of IGF-1 and the migration of neoplastic cells. It has been proved in an animal model that the IGF-1R inhibitor picropodophyllin is well tolerated in vivo, inhibits migration and growth of tumor cells (Girnita et al. 2008) and reduces the level of vascular growth factor in tumor cells (Economou et al. 2008).

Studies on the effectiveness of tyrosine kinase inhibitors, such as imatinib, are ongoing but its effectiveness has not yet been established (Wu et al. 2020). The use of sunitinib (in adjuvant therapy) resulted in an increase in the average survival time of patients with the cKIT mutation in choroidal melanoma (Valsecchi et al. 2018).

Mutations in the GNAQ and GNA11 genes can be neutralized by inhibiting the PKC pathway (Sagoo et al. 2014). New inhibitors of the PKC pathway – such as enzastaurin or sotrastaurin – inhibit the PKC and MAPK signaling pathway, causing apoptosis of maligant cells. When combined with an antagonist of the MEK signaling pathway, greater efficacy was obtained by acting on two different pathways simultaneously. A study conducted on 101 patients showed that the PKC inhibitor selumetinib inhibits the MAPK pathway, increasing the effectiveness of traditional temozolamide and decarbazine therapy by 14% (Goh and Layton 2016).

Administration of cixutumumab with selumetinibab is well tolerated and gives initial positive therapeutic effects of IGF (Wilky et al. 2015).

IMMUNOTHERAPY

Immunotherapy is aimed at increasing the effectiveness of a passive and active immune response by providing monoclonal antibodies and anti-cancer vaccines.

Metastatic foci of skin melanoma and uveal melanoma were compared for PDL1 ligand expression. Significant differences in the expression of the PDL1 gene within the metastatic tumor of both neoplasms have been demonstrated. Low expression of this gene may be responsible for the failure of therapy with PDL1 inhibitors and results in suppression of the immune response of T lymphocytes (Granier et al. 2017). It was found that metastatic cells of uveal melanoma less frequently present the PDL1 antigen on their surface (Javed et al. 2017). The lower expression in the metastatic tumor may account for the lower efficacy of drugs in this form of choroidal melanoma. The effectiveness of pembrolizumab in the treatment of patients with metastatic form of uveal melanoma was assessed (Ny et al. 2021). At present, the therapy has not brought satisfactory results (Rossi et al. 2019).

Tebentafusp – a drug registered in the EU in February 2021, is a drug from the group known as bispecific fusion protein, consisting of a T-lymphocyte receptor recognizing the gp100 protein and a single-chain fragment of an anti-CD3 antibody (scFv) (Liddy et al. 2012). It locates the gp100 protein on the surface of neoplastic cells and activates T lymphocytes, inducing an immune response (Wessely et al. 2020). In the study, it extended the mean survival from 16 to 21.7 months (Marseglia et al. 2021). It is an interesting therapy for patients with metastatic form of uveal melanoma (Middleton et al. 2020).

CONJUNCTIVAL MELANOMA

It clinically manifests itself as a flat or raised pigmented lesion of the conjunctiva, located either in its nasal or in its temporal part. It tends to invade surrounding tissues, including invasion of the lymph nodes. One of the risk factors here, as in skin melanoma, is exposure to UV radiation (Cancer Genome Atlas 2015). The incidence of this neoplasm ranges from 0.2-0.8 cases per million (Spatola et al. 2020) and constitutes about 2-5% of eyeball neoplasms (Isager et al. 2006). The 10-year experience represents approximately 50% of patients (Abt et al. 2019). Radical excision of the lesion, marginal cryotherapy and brachytherapy give satisfactory results (Wong et al. 2014) but as much as 30-40% of local relapses are observed (Chauhan et al. 2014). Despite the fact that treatment regimens for the local form of this neoplasm have been developed, there is no agreed consensus for the management of metastases (Grimes et al. 2020).

ANALYSIS OF ONCOGENES

Mutations in the MAP signaling pathway – RAS, BRAF, MEK, ERK, PI3K / AKT / mTOR (McCubrey et al. 2007) and the TERT mutation associated with metastatic disease (Van Poppelen et al. 2021) were found in conjunctival melanoma cells. The most common mutation is BRAF, associated with a higher risk of metastasis and worse prognosis, followed by NRAS belonging to the family of RAS kinases activated by tyrosine kinase receptors (Wallander et al. 2011). The TERT mutation, occurring together with BRAF and NRAS, increases the metastatic potential of conjunctival melanoma (Van Poppelen et al 2021) and is associated with a much worse prognosis and shorter disease-free survival. The worst form of the disease is also associated with the TERT mutation (Gandini et al. 2021). Conjunctival melanoma is genetically similar to cutaneous melanoma and mucosal melanoma. It is believed that for this reason, targeted therapies effective in treating these diseases, such as BRAF I KIT inhibitors, may be used in the future in the treatment of conjunctival melanoma. MEK inhibitors are also effective.

CHECKPOINT INHIBITORS

The cellular response of the immune system to tumor cells is regulated by multiple checkpoints. The CTLA4 checkpoint is clinically relevant (Hodi et al. 2010). It can inhibit the developing immune response of T lymphocytes. The inclusion of drugs that inhibit its action gives positive results. The PD-1 inhibitors mentioned in the context of uveal melanoma, which have not yet been reliably tested in patients with conjunctival melanoma but are used in the treatment of skin melanoma or CTLA4 (e.g. ipilimumab), reduce the number of metastases and limit local invasion also in melanoma conjunctiva (Hodi et al. 2010). The combination of the above-mentioned drugs in one treatment regimen has brought positive results. The comparison of their effectiveness with the used nivolumab or decarbazine therapy gives hope for new therapeutic regimens.

RADIATION THERAPY WITH A PROTON BEAM

Proton beam radiotherapy (PBRT) is an alternative treatment for advanced conjunctival melanoma involving the eyelids and surrounding tissues. It allows for precise application of the radiation beam to the affected tissues, unlike brachytherapy, which delivers high doses of radiation also to adjacent tissues. Due to the Bragg Peak phenomenon (Lin et al. 2018), the spread of particles in tissues is inhibited by losing their velocity as they move through the tissue (Spatola et al. 2020). The technology is not new, it is an alternative to crippling surgical intervention and has positive results (Thariat et al. 2019). Currently, there are not many studies confirming the effectiveness of this therapy in conjunctival melanoma but there is evidence that it may be as effective as in the treatment of uveal melanoma (Gollrad et al. 2021).

RETINOBLASTOMA

Retinoblastoma is the most common eye tumor in children (Kivela 2009) and accounts for 3% of all childhood malignancies. It is usually diagnosed in patients under 5 years of age (Sun et al. 2020). The tumor is bilateral in 30-40% of patients. 6% of tumors are of family origin, 94% of tumors are sporadic (Dimaras, Corson 2019). The main symptoms are: visual impairment, strabismus and leukocoria (Abramson et al. 1998). The disease leads to vision loss and death. Diagnostics is based on ophthalmoscopic examination and imaging tests (ultrasonography, magnetic resonance imaging, computed tomography in older children). It is ineffective in detecting early changes.

THERAPEUTIC PROBLEMS

The initially used method of treatment was radiotherapy and enucleation (Kaewkhaw, Rojanaporn 2020). The young age of the patients, the need to remove the eyeball and the complications of radiotherapy motivated scientists to look for new methods of treatment. Systemic chemotherapy was introduced to reduce the tumor, followed by brachytherapy. Complications related to the use of radiotherapy and the fear of side effects in children have made chemotherapy the primary treatment effective in reducing tumor size, the risk of metastases and the degree of eye damage. However, aggressive treatment of a locally located tumor can lead to systemic complications affecting the developing child.

CURRENT THERAPEUTIC SCHEME

For several years, intra-arterial medications have been used to treat retinoblastoma. This therapy reduces systemic side effects and allows faster to achieve the therapeutic concentration of the drug in the tumor tissue without causing destructive systemic consequences.

Initially, they were administered into the internal carotid artery (Yamane, Kaneko, Mohri 2004), then the technique was improved and now many centers administer drugs directly into the ophthalmic artery (Abramson et al. 2008). A properly selected dose of carboplatin, melphalan, topocan (or a combination of these drugs) achieves cytostatic concentrations in the tumor, but does not suppress the immune response (Mostaghimi, Ahmadabad, Rezaei 2021). Even in the case of the so-called cavitary retinoblastoma, characterized by the presence of voids in the tumor mass (Rishi, Sharma, Sharma 2020) considered to be therapeutically resistant, spectacular successes were reported (in a small group of patients) (Zheng et al. 2021).

DIAGNOSTIC AND TREATMENT CHALLENGES IN RETINOBLASTOMA

Advances in diagnostics and treatment methods allow, in addition to saving lives, salvage the eyeball in the eye socket and often vision. Due to the fact that earlier detection is associated with a better prognosis (Sun et al. 2020), the time of appearance of symptoms until diagnosis is of a major importance (Kivela 2009). It is necessary to search for new, more sensitive and faster diagnostic methods.

The route of drug administration is problematic in the case of neoplasms of the eyeball. The water-insoluble drugs are particularly difficult to penetrate the eyeball. It should be taken into account that the application of local treatment encounters a number of anatomical barriers in the orbit and limits drug penetration into the tumor area. In addition, the administration of strong cytostatics to the eyeball area, to the orbital tissues, entails a number of complications, such as, for example, tissue necrosis in the orbit, orbital fat, atrophy of the optic nerve or impaired mobility of the eyeball (Murray et al. 1997). This has forced the development of methods for more efficient drug delivery to the tumor tissue. Considering the above, diagnostic and therapeutic methods using nanoparticles – nanotechnology are helpful (Sarwat et al. 2019).

NANOTECHNOLOGY IN THE TREATMENT OF RETINOBLASTOMA

Increasing the resolution of imaging eyeball tumors in magnetic resonance imaging (Gold NPs (nanoparticles) (Kozenkova et al. 2020), increasing the sensitivity of neo-plastic tissues to laser radiation (Silver NPs) (Park et al. 2020) or the use of nanoparticles to detect DNA methylation characteristic for retinoblastoma (Carbon nanomaterials) are examples of a new technology that shows promising results in the phase of research on in vivo models.

The challenge is to develop new ways and methods of drug administration. Modern methods of treatment using nanoparticles, such as: Nanocarrier, Melaphalan NPs, Galactose NPs, Hyaluronic acid NPs, Folic acid NPs, LipidNPs, SilverNPs, Gold NPs, are used for delivering drugs to the tumor tissue more effectively in the eyeball environment. The most commonly used are multi-functionalized NPs and lipid-based NPs, and metallic NPs.

Material bioengineering plays a significant role in obtaining the desired physicochemical properties of drugs, which, when administered to the inside of the eyeball, enable better penetration of drugs. An example is the coating of DNA molecules with hyaluronic acid which allows the complex to move more easily inside the vitreous body (Martens et al. 2017). The discovery of over-expression of lectin receptors on the surface of retinoblastoma tumor cells paved the way for research into new galactose-coated nanoparticles (Godse et al. 2021). This combination increases the affinity of the drug to neoplastic cells, saving healthy tissue. Lipid nanocomplexes formed from the combination of melphalan and miR-108 also allow the treatment to be concentrated in the tumor area (Su et al. 2015).

The biotechnological successes in the field of producing new drugs give hope for a wider application of the above-mentioned technologies in clinical practice. The use of selective therapy makes it possible to limit the effect of the drug to the tumor affected area, reduce the systemic toxicity of antineoplastic drugs and increase the effectiveness of the treatment.

TARGETED THERAPY

MLN4924 is an inhibitor of neddylation, the post-translational modification of a protein responsible for neoplasia. There are currently numerous studies on pevonedistat (clinical name MLN4924) in the treatment of malignant neoplasms. Intravitreal administration of MLN4924 was effective in animal studies in which the target was SKP2 oncogene found in retinoblastoma cells (Wang et al. 2010). Due to its low toxicity, this therapy shows promising results. In vitro studies showed that three-hour exposure to the drug resulted in a 50% reduction in tumor mass and extending this time had positive anti-tumor effects but increased toxicity to retinal cells. This gives hope for the development of therapeutic regimens for the use of intravitreal injections of MLN4924 (Aubry, Yu and Bremner 2020).

The protein kinase PLK1 plays the role of a cycle regulator in healthy cells (Bouhlal et al. 2016). Overexpression of the PLK1 protein kinase is observed in many malignancies such as melanoma, non-small cell lung cancer, esophageal cancer (Yim and Erikson 2014) and also in retinoblastoma (Singh et al. 2015). Rigosertib, and more specifically ON-01910.Na, is a PLK1 kinase inhibitor used in the treatment of lung cancer (Medema, Lin, Yang 2011). Tumor weight reductions have been reported in the eye with subretinal retinoblastoma in an animal model. The study is the starting point for the development of PLK1 targeted therapy in retinoblastoma (Ma et al. 2021).

PRIMARY VITREORETINAL LYMPHOMA

Primary vitreoretinal lymphoma – PVRL is a rare subtype of lymphoma and 20% coexists with central nervous system lymphoma – PCNSL. Initially, it involves the vitreous body, the retina, subretinal tissues, and the optic nerve with or without central nervous system involvement (Soussain, Malaise, Cassoux 2021). The ocular manifestation of this neoplasm precedes the symptoms of the central nervous system by an average of 29 months (Baron et al. 2020). Older people are more common to become ill. It may be initially confused with chronic uveitis due to the observed inflammatory cells in the anterior chamber and yellow subretinal infiltrates. The diagnosis is made on the basis of physical examination, imaging examinations (Yang et al. 2021) and the presence of lymphoma cells in the vitreous after biopsy (Wang et al. 2021). Research is ongoing into the possibility of diagnosing this disease through the analysis of the aqueous humour (Wang et al. 2011). Its inflammatory mediators, IL-10 / IL-6 (Shi et al. 2021), are to become a less invasive method of disease confirmation in the future (Wang et al. 2011).

CURRENT THERAPEUTIC REGIMENS

Two treatment regimens are available to clinicians. The first is high-dose methotrexate therapy with or without radiation therapy to the central nervous system. Another approach is topical treatment – radiotherapy, intravitreal injections of methotrexate or in combination, and systemic chemotherapy. Currently, there are studies on the effective treatment of lymphoma confined to the eyeball (Zhang et al. 2021).

In patients with newly diagnosed PVRL, the efficacy of intravitreal injections of methotrexate with rituximab (which is used to treat B-cell lymphoma and is effective in treating PVRL in ophthalmic monotherapy (Rishi et al. 2021)) and with lenalidomide has been studied. This treatment regimen was shown to be effective in 10 out of 11 patients. In one patient new lesions were found in the central nervous system during the course of therapy. This treatment has not been shown to be more effective than systemic chemotherapy. More research is needed on the efficacy of lenalidomide in PVRL therapy (Zhang et al. 2021).

Diffuse large B-cell lymphoma (DLBCL) is a subtype of vitreoretinal lymphoma (Miserocchi et al. 2019). Bruton's tyrosine kinase (BTK) plays a mediating role in the B-cell cycle (Vogel et al. 2021). A set of mutations characteristic for the above-mentioned lymphoma (Hiemcke-Jiwa et al. 2018) gave the direction to the study that showed that the BTK inhibitor ibrutinib has the ability to cross the blood-brain barrier and its use gives positive results in the treatment of DLBCL (Soussain et al. 2019).

Temozolomide (TMZ) is a well-tolerated second generation antineoplastic drug with good pene-

tration into the central nervous system and the cerebrospinal fluid. Its effectiveness in PCNSL has been confirmed in several small studies (Soussain, Malaise, Cassoux 2021). A retrospective study of the efficacy of this drug was conducted in patients with relapsed, refractory and ineligible for first-line treatment form of PVRL. Interestingly, the use of TMZ shows a good pricebenefit ratio compared to other therapies already used in the treatment of PVRL (Baron et al. 2020).

A therapeutic strategy for the treatment of this type of oncoma requires development. Presently, there is a lack of big and reliable studies providing knowledge about the effective treatment of isolated PVRL.

SUMMARY

Due to the large amount of research carried out, in the last two decades significant progress has been made in the diagnosis and treatment of neoplasms. Modern therapy of eye neoplasms presents researchers with a number of challenges, combining many branches of modern medicine. In uveal melanoma the DecisionDx-UMTM test using PCR enables to assess the risk of metastases and as a result to adjust the intensity of the therapy. Single Cell Technology helps to isolate neoplastic cells which are multiplied, typed and undergone targeted therapies. Furthermore, in metastatic form, new drug tebentafusp extends the survival by inducing immune response. In conjunctival melanoma, due to genetic similarity to cutaneous and mucosal melanomas, targeted therapies effective in treating these neoplasms, such as BRAF I KIT inhibitors, may be used in the future in the treatment of conjunctival melanoma. Checkpoint inhibitors, for example iplimumab, also give positive results. Moreover, proton beam therapy, thanks to its accurate application, may be a safer solution than brachytherapy. In retinoblastoma new techniques and ways of administration of the drugs are developed. Currently medications may be given directly to ophthalmic artery, increasing the concentration of the drug and reducing systemic side effects. What is more, the usage of nanoparticles enables better penetration of the drug in the inside of the eyeball. Targeted therapy, using PLK1 kinase inhibitor gives hope to be effectively used in the future. In primary vitreoretinal lymphoma there are studies on the treatment confined to the eyeball, limiting systemic side effects during chemotherapy or radiation to the central nervous system. Targeted therapy gives positive effects. A significant problem in the diagnosis and treatment of eye tumor is the relatively small number of affected patients. This results in limited access to data, so the effectiveness of the therapies described can be easily questioned. Nevertheless, the presented results give hope for the development of new therapeutic regimens and demonstration of their actual effectiveness. Hence the need for more studies on bigger number of patients. Another important problem is the high cost of the diagnosis and treatment. It is necessary to involve many highly specialized entities in the process of comprehensive diagnostics. Their coordinated operation gives positive results, but is a big organizational problem. These are relevant problems, the overcoming of which will result in faster, more accurate diagnosis and more effective treatment of oncological diseases in ophthalmology.

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