HISTORICAL TRENDS IN REGIONAL TREATMENT OF METASTASES OF UVEAL MELANOMA IN THE LIVER (literature review).

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Abstract:

Introduction: Choroidal melanoma is the most common primary intraocular malignancy in adults. Treatment strategies for the primary focus are well studied, but in a significant percentage of cases, distant metastases may occur.
Objective: To analyze literature sources devoted to regional methods of treating patients with uveal melanoma metastases in the liver, to determine the most effective and safe, most commonly used method, and to evaluate the results of its use.
Materials and methods: This literature review over the past 25 years describes different methods of topical treatment of liver metastases in patients with advanced uveal melanoma. Several dozen literary sources were analyzed, of which 28 are presented in this review article.
Results and discussion: In our study, transarterial chemoembolization and isolated liver perfusion proved to be effective and well-tolerated types of locoregional exposure. Regional techniques can be performed in patients with massive liver damage and concomitant diseases. At the same time, the lesion volume should not occupy a large part of the liver, and liver function should not be significantly impaired. Over a long period of time, these methods have been undergoing changes, developing, becoming more effective and safer.
Conclusion: Despite the fact that none of the available regional treatments have shown significant improvement in survival rates, they can help slow the progression of the disease. Liver chemoembolization and chemoperfusion are innovative methods that can be performed with good tolerance in almost all patients with uveal melanoma metastases in the liver.

Keywords: uveal melanoma metastases, transarterial chemoembolization, liver, isolated liver perfusion

Introduction

Uveal melanoma is the most common primary intraocular malignancy in adults, with an incidence rate of 2.3 to 13.3 cases per million (according to various sources) [1,2]. This rate in different regions of Russia ranges from 6.23 to 8 cases per million adults [3]. This tumor is rarely hereditary. Uveal melanoma develops from melanocytes of the uveal tract (which includes the choroid, ciliary body, and iris) and is of neuroectodermal origin. The choroid is a thin vascular layer between the sclera and the retina, where these tumors are most often found (up to 90%). Classic treatment methods for the primary lesion include surgery or radiation therapy. For large lesions, as well as in cases of extraocular spread, enucleation is performed [4]. According to summary data, the 5-year survival rate from the time of primary tumor diagnosis is approximately 70%, and the overall 10-year survival rate is 60%.

Treatment strategies for the primary tumor have been well studied, but distant metastases may occur in a large percentage of cases. Approximately 50% of all patients have both the primary tumor and distant manifestations of the disease. Secondary changes can occur in the bones, lungs, brain, peritoneum, and other internal organs. In over 90% of patients, the liver is the primary target for metastasis, and in half of patients, it remains the only site of distant involvement. The extent and nature of liver involvement determines the clinical course of the disease in most patients. Three types of receptors can be distinguished: IGF-1R (insulin-like growth factor receptor), cMET (hepatocyte growth factor receptor), and chemokine receptor (CXCR4) on the surface of uveal melanoma cells. This explains the tropism of uveal melanoma cells for liver hepatocytes.

The management of patients with metastatic melanoma requires a comprehensive approach, including systemic interventions, as overall survival for secondary liver disease without treatment ranges from 2 to 9 months [5].

In cases of advanced drug-resistant cells, chemotherapy currently has limited efficacy. Optimal systemic drug treatment regimens for distant lesions in uveal melanoma (unlike cutaneous melanoma) have not yet been developed. Effective adjuvant therapy for the primary lesion is lacking for patients at high risk of metastasis [6].

Genetic analysis of primary tumor samples identified two types of uveal melanoma: one with a high risk of metastasis and a poor prognosis, and one with a low risk of metastasis and a favorable prognosis. In uveal melanoma samples, following inactivation of the BAP1 gene located on chromosome 3p21, corresponding somatic mutations were described. These mutations were always associated with a poor prognosis, occurring in 40% of cases. Correlations with a favorable prognosis were found with a mutation in the gene encoding a splicing factor (SF3B1). Chromosomal aberrations in the GNAQ and GNA11 genes were also identified. Thus, using fine-needle biopsy, it is possible to analyze the tumor's genetic profile and determine the high or low risk of metastasis in specific patients. This is necessary for monitoring, as well as for planning and selecting treatment strategies [7].

Due to the negative treatment outcomes for widespread uveal melanoma, alternatives and additional treatment modalities are being sought. Various local treatment methods have long been used and actively studied for metastatic liver disease. These include chemoinfusion into the hepatic arteries, TACE, immunoembolization, and isolated liver perfusion. The latter method both causes ischemic effects on liver tissue and delivers a higher concentration of the drug than systemic chemotherapy, resulting in a pronounced cytotoxic effect on the tumor while reducing systemic toxicity. TACE can utilize various materials as embolic agents in combination with the drug, such as Lipiodol Ultrafluid, microspheres, including saturable ones, and polyvinyl particles. TACE has demonstrated a slight increase in overall survival, but further data is needed to objectively evaluate

the effectiveness of this method. An analysis of current literature on the use of various locoregional treatment methods and comparison with previously published data will enable the selection of the most appropriate solution for this complex group of patients, as a comprehensive approach incorporating various treatment modalities is necessary. Prognosis and survival outcomes in most patients with uveal melanoma metastases are most often determined by tumor control in the liver.

Objective

To analyze literature sources devoted to regional methods of treating patients with uveal melanoma metastases in the liver, to determine the most effective and safe, most commonly used method, and to evaluate the results of its use.

Materials and Methods

This literature review describes the methods of local treatment of liver metastases in patients with advanced uveal melanoma over the past 25 years. Local treatment methods include surgical interventions, ablation procedures, and direct administration of drugs to the liver, such as intrahepatic arterial infusion, immunoembolization, transarterial chemoembolization, radioembolization, and isolated liver perfusion. The analysis of literature data was conducted based on the principles of preparing modern reviews in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. Several dozen literature sources were analyzed, of which 28 are presented in this review article. The analysis included data on overall and relapse-free survival rates, the type of treatment used, drug doses, and administration details. One of the objectives was to identify prognostic factors that are consistently associated with survival and to determine which of these factors independently influence survival. If the survival rate at a specific stage exceeds the historical survival rate at a specific stage available in the staging model used, this is indirect evidence of the effectiveness of the treatment. [8]

Results and discussion

Treatment options for uveal melanoma liver metastases include systemic and regional approaches. If solitary metastatic nodes (up to 3-4) are detected in the liver, resection may be the most effective, increasing median overall survival to 40 months. The precise role of surgery has not been determined, and large randomized trials are virtually nonexistent. The data presented primarily come from retrospective case series from single medical centers. Studies typically include up to 25-45 patients, with a median overall survival of 14-39 months. Of these patients, no more than one-third can be identified as suitable for surgery. In a report by Mariani P. from the Institute Curie, data from 255 operated patients out of a total of 798 were analyzed. When comparing this

group with the group receiving systemic chemotherapy, the median overall survival was 14 and 8 months, respectively. The 5-year overall survival rate was 7%. After analyzing the resection margins, the authors recommended careful patient selection for surgery, as R0 resections were associated with longer overall survival than R1 or R2. However, recurrences were frequently observed (up to 75%) due to the nuances of the surgical technique, as well as the high biological malignancy of uveal melanoma cells [9].

Radiofrequency or cryoablation can achieve local control of up to 85–95% with minimal invasiveness. However, careful patient selection is necessary, as inclusion criteria are limited by the size, number, and location of tumor foci. Surgeon experience and precision of targeting are key. Sometimes ablation is used during open surgery [10]. Unlike cutaneous melanoma, drug treatment regimens for metastatic uveal melanoma have not yet been developed. Due to the tumor cells' pronounced drug resistance, chemotherapy has low efficacy, and for patients with a high risk of progression, there is no effective adjuvant treatment option for the primary lesion. According to the literature, various combinations of chemoimmunotherapeutic agents with varying degrees of success are possible [11].

Therefore, the search for alternatives in the form of local treatment options targeting the liver affected by metastases continues. Both internationally and in Russia, studies, including randomized trials, are being conducted to analyze the potential of interventional treatments, such as chemoimmunoembolization, isolated liver perfusion, and many others [12].

Regional techniques such as hepatic artery infusion, chemoembolization, immunoembolization, radioembolization, and isolated liver perfusion in various forms allow for the direct delivery of drugs of various classes to the liver. This, with limited systemic toxicity, creates advantages in the treatment of both macrometastases and clinically undetectable micrometastases. The increasing use of minimally invasive techniques leads to the refinement of indications and contraindications, expanding the scope and frequency of their use and reducing the risk of complications.

During hepatic artery infusion, catheters are inserted into the hepatic arteries either during open surgery via the gastroduodenal artery or under fluoroscopic guidance via a punctured femoral artery. Temporary catheters can be used, with 3-4 infusion courses administered, or permanent catheters can be implanted for at least 8 courses. Fotemustine is an alkylating agent with a short half-life and high first-pass extraction. Melphalan, cisplatin, and others can also be used. Intra-arterial administration creates higher concentrations of chemotherapy drugs in the liver. The effectiveness of fotemustine in the treatment of metastatic cutaneous melanoma has led to its use in uveal melanoma. According to various authors, the response rate has been 16-36%, and the median overall survival is 9-21 months [13, 14].

For several decades, isolated perfusion, a regional method for treating metastases in the liver, lungs, pelvic organs, and extremity tumors, has existed in various forms. It can be performed either in an open manner during major surgery or using X-ray-guided surgery [15,16]. The first stage involves isolating the liver vasculature, which allows for the protection of other areas of the body and the direct administration of high doses of drugs to the isolated area. Alkylating chemotherapy drugs (such as melphalan) are preferred because they have a pronounced dose-response relationship and a short action time. Isolated liver perfusion in an open surgical manner is a complex, one-stage surgical intervention lasting 7-8 hours, requiring a prolonged hospital stay of up to 2 weeks, which can be accompanied by significant complications. However, the tumor response to treatment reaches 33% - 62% with a median overall survival of 10-12 months [17, 18].
An alternative fluoroscopically administered version of isolated perfusion was developed as a more convenient and simpler option, with the ability to perform treatment multiple times. To create a closed perfusion circuit, the venous outflow of blood from the liver is isolated using a double-balloon catheter in the inferior vena cava. After passing through the circuit, the blood is filtered through sorption columns. When evaluating the effectiveness of repeated isolated liver perfusions with melphalan in the fluoroscopically administered version, the median relapse-free survival was 8.1 months versus 1.6 months with drug therapy alone. The median overall survival did not differ significantly between the groups (11.4 versus 9.9 months, respectively, $p = 0.982$). The data are presented based on the results of a randomized, controlled phase III trial [19].
Transarterial chemoembolization is a method of locoregional treatment that simultaneously delivers two treatment modalities: selective ischemia of the liver region treated with embolizing particles and prolonged high-dose chemotherapy. This allows for the creation of high drug concentrations with minimal systemic toxicity. Transarterial chemoembolization has been reported in the literature for over several decades for the treatment of various conditions, and for liver metastases from uveal melanoma since 1986. In many non-randomized studies, overall response rates and median overall survival have varied significantly. The specific blood supply to liver tumors from the hepatic artery basin makes this treatment method suitable. Transarterial chemoembolization for uveal melanoma metastases is typically used with a combination of drugs such as fotemustine, 1,3-bis(2-chloroethyl)-1-nitrosourea, cisplatin, carboplatin, doxorubicin, gemzar, and embolic particles such as lipiodol, microspheres, gelatin sponges, and others.
According to Carrasco C. et al., who used in 1986 a mixture of cisplatin and polyvinyl alcohol particles as a chemoembolic agent in patients with uveal melanoma liver metastases, relapse-free survival with significant tumor regression was achieved at 6 and 19 months [20].
Studies on the effectiveness of transarterial chemoembolization are ongoing in a series with a larger number of patients (n=30). In 1988, Mavligit G. et al. divided this group of patients into

those who responded to treatment and those who did not and analyzed the results. In the first group, overall survival was 9-54 months with a median of 14 months. In the second group, overall survival was 2-19 months with a median of 6 months. The overall result in the overall group was a median of 11 months. The overall response after treatment was 46% (n=14); a complete response was observed in 1 patient (3%), and a partial response was observed in 13 patients (43%) [21].

A 1995 study by Bedikian A. et al. compared the results obtained with chemoembolization, intra-arterial chemoinfusion, and systemic therapy. The analysis included a group of 201 patients with uveal melanoma liver metastases. The immediate response rate varied: up to 36% with chemoembolization and less than 1% with systemic drug therapy. When comparing the median overall survival, no statistical significance was observed in the regional treatment and systemic therapy groups (6 and 5 months, $p = 0.2$). However, in those who responded to chemoembolization, the median overall survival was significantly higher (14 months; $p = 0.003$). Based on the obtained effectiveness of locoregional therapy compared with other treatment methods, the authors propose using this technique as the primary one in patients with uveal melanoma liver metastases [22].

In 2007, Vogl T. and colleagues used transarterial chemoembolization to treat 12 patients using a combination of mitomycin 10 mg/m2, lipiodol (with monitoring of its distribution and accumulation in the liver), and absorbable microspheres.

As in previous studies, in the group of patients with a partial response, the median overall survival was significantly higher (21 and 16.5 months, respectively, $p < 0.01$) than in the group of non-responders. Furthermore, when analyzing the accumulation of the embolic agent in the liver, it was noted that patients with relatively hypovascular tumors and those that do not accumulate lipiodol progressed more often than those with hypervascular tumors [23].

In 2010, Gupta S and colleagues, in a study of overall survival in patients with varying degrees of liver metastasis from uveal melanoma, observed a decrease in the median with an increasing degree of liver parenchyma replacement by the tumor: 2.4 months for a spread of > 75%, 5.5 months for a spread of > 50%, and 14.0 months if ≤ 25%. Moreover, if the tumor is represented by single nodes with clearly defined feeding vessels, rather than multiple scattered, even small, metastases, the median overall survival increases from 3.7 months to 12.7. The authors thus conclude that the degree of liver damage is a key prognostic factor in patients undergoing transarterial chemoembolization treatment [24].

In 2015, literature data on a 5-year follow-up of patients with isolated liver disease after regional treatment with transarterial chemoembolization were presented [25]. In 2016, Russian authors analyzed a small group of patients (n=31) with uveal melanoma metastases to the liver using transarterial chemoembolization, achieving a local response in the form of tumor nodule reduction or stabilization in 67% of patients. Patient follow-up after treatment lasted up to 60 months. Overall

survival in this group of patients was 51% at 1 year and 34% at 2 years (according to Kaplan-Meier). The median survival was 12.9 months [26].

Transarterial chemoembolization involves several stages. After patient preparation in a specially equipped operating room, a main artery, most commonly the femoral artery, is catheterized in the right or left lower limb. Sometimes, access through the arteries of the upper limb is used. To facilitate simple and convenient manipulation of catheters, including microcatheters, an introducer is inserted into the vessel puncture. Due to differences in vascular architecture, various catheters and guidewires may be used to adequately access the liver vessels. Their material, diameter, length, stiffness, tip configuration, and hydrophilicity vary. Next, a diagnostic phase is performed, during which a series of images are taken to determine the vascular anatomy, location, and blood supply of the tumor nodes. After a decision has been made on the target liver area, the catheter or microcatheter (if highly selective) is positioned in the vessel feeding the tumor. Following further diagnostic procedures, a chemoembolizing mixture is administered. This mixture is prepared in advance from a combination of a chemotherapy drug and an embolizing component, such as carboplatin, doxorubicin, mitomycin C, cisplatin, mitomycin C, saturable microspheres, gelatin sponges, Lipiodol Ultrafluid, and others. The microspheres are saturated with the drug within an hour, and the Lipiodol mixture is ready almost immediately. Infusion of the resulting mixture is performed under X-ray television guidance. Before completion of the procedure, a control angiographic examination is performed, implanted catheters and associated devices are removed, and careful hemostasis is ensured [27].

Recently, with the advent of new drug substances and delivery methods, immunotargeted drugs and radiopharmaceuticals can be used. Immunoembolization is a combination of embolization of targeted vessels with the simultaneous local administration of drugs to stimulate the immune system, which leads to the development of a systemic immune response. Intra-arterial administration of granulocyte-macrophage colony-stimulating factor in an emulsion with lipiodol stimulates macrophages, increases the production of myeloid cells, and enhances the cytotoxicity of monocytes in relation to the tumor cell line [28].

Radioembolization with microspheres containing a radioactive isotope, such as yttrium-90, involves their introduction into the hepatic artery through catheters. After the radioactive particles reach the tumor site, a high dose of radiation is delivered directly to the cancer cells. The microspheres continue to emit radiation for several weeks, destroying the tumor, including in patients with uveal melanoma metastases to the liver, but sparing surrounding healthy tissue [29].

Conclusion

Thus, over the past decades, various methods of locoregional treatment of uveal melanoma liver metastases have been tested and implemented into practice. These include surgical interventions (surgeries and ablative procedures), hepatic arterial drug infusions, immunoembolization, transarterial chemoembolization, radioembolization, and isolated liver perfusion. All have demonstrated varying degrees of effectiveness and occupy an important place in the combined treatment of this patient population. The search for new systemic therapy regimens and research into modern drugs, including immunotargeted ones, continues. The combination of regional techniques with systemic treatment appears very promising.

In our study, transarterial chemoembolization and isolated liver perfusion proved to be effective and well-tolerated methods of locoregional treatment in patients with uveal melanoma liver metastases. They allow for optimal delivery of drug combinations, in varying combinations, to the affected organ, in this case, the liver.

Prolonged exposure to high concentrations of chemotherapy drugs is possible, as is the use of additional organ ischemic techniques, achieved by ligating several feeding vessels and introducing embolic particles into the vascular bed, without significant systemic toxic effects. Regional techniques can be used in patients with extensive liver damage and comorbidities. However, the extent of damage should not exceed 75% of the liver, and liver function should not be significantly impaired.

Despite the ongoing relevance of treating patients with metastatic uveal melanoma, and the literature offers many years of international clinical experience, there are currently no randomized clinical trials demonstrating the superiority of one method or drug over another. The approach of specialists is based on empirical data and the individual clinician's preferences in technique and drug combinations and is not statistically significant. There is a clear need for randomized multicenter trials to standardize treatment for this complex group of patients.

In Russia, these patients are concentrated in large oncology centers that offer a full range of both systemic and locoregional treatments, and have the necessary equipment and specialist pool.

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