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What Sets Uveal Melanoma Apart, and How Can We Address It? A Comprehensive Review of Pathophysiology, Diagnosis and Treatment

Karina Lissak, Zuzanna Szczepaniak, Agata Konopka, Natalia Wdowiak, Martyna Choinka, Małgorzata Komarów, Dominika Karasińska, Jakub Kalisiak, Mateusz Koralewicz, Milena Orzeł, Bartłomiej Orzeł
Karina Lissak, MD
Lower Silesian Oncology Center in Wrocław,
Hirszfelda Square 12, 53-413 Wrocław, Poland
ORCID: 0009-0000-9084-4060
karina.lis2323@gmail.com

Zuzanna Szczepaniak, MD
Provincial Specialist Hospital in Wrocław,
H. Kamieńskiego Str. 73a, 51-124 Wrocław, Poland
ORCID: 0009-0004-8025-6037
zuzanna.a.szczepaniak@gmail.com

Agata Konopka, MD
A. Falkiewicz Specialist Hospital,
Warszawska Str. 2, 52-114 Wrocław, Poland
ORCID: 0009-0000-1004-0629
agatakonopka21@gmail.com

Natalia Wdowiak, MD
Provincial Specialist Hospital in Wrocław,
H. Kamieńskiego Str. 73a, 51-124 Wrocław, Poland
ORCID: 0009-0004-3894-9921
natalia.wdowiak5@gmail.com

Martyna Choinka, MD
University Clinical Hospital in Poznań,
Przybyszewskiego Str. 49, 60-355 Poznań, Poland
ORCID: 0009-0005-0951-3368
m.choinka@op.pl

Małgorzata Komarów, MD
Lower Silesian Oncology Center in Wrocław,
Hirszfelda Square 12, 53-413 Wrocław, Poland
ORCID: 0009-0005-8293-5030
gosiakomarow7@gmail.com

Dominika Karasińska, MD
Wrocław Medical University,
wyb. Ludwika Pasteura 1, 50-367 Wrocław, Poland
ORCID: 0009-0003-1215-5165
dakarasinska@gmail.com

Jakub Kalisiak, MD
Independent Public Complex of Health Care Facilities of the
Ministry of Interior and Administration on Poznań,
Dojazd Str. 34, 60-631 Poznań, Poland
ORCID: 0009-0000-2472-3148
kubakalisiak@gmail.com

Mateusz Koralewicz, MD,
107 Military Hospital in Wałcz
Kołobrzeska Str. 44, 78-600 Wałcz, Poland
ORCID: 0009-0002-3970-5190
mateuszkoralewicz98@gmail.com

Milena Orzeł, MD
Wrocław Medical University,
wyb. Ludwika Pasteura 1, 50-367 Wrocław, Poland
ORCID: 0009-0005-1303-2778
milenadudek@op.pl

Bartłomiej Orzeł, MD
Wrocław Medical University
wyb. Ludwika Pasteura 1, 50-367 Wrocław, Poland
ORCID: 0009-0003-1442-6790
bartekorzel@wp.pl

Corresponding author: Karina Lissak, karina.lis2323@gmail.com

Abstract: Uveal melanoma (UM) is a serious condition that requires prompt medical attention. It represents the most primary intraocular cancer in adults, with an incidence of approximately 5.2 individuals per million annually. Almost 50% of patients with UM progress to metastatic disease, predominantly to the liver. UM encompasses any malignant

tumor originating from melanocytes within the uveal tract, which includes the iris, ciliary body, and choroid. Treatment strategies for UM are influenced by several key factors, such as tumor size, anatomical location, and the patient's overall health condition. These strategies may involve radiation therapy, surgical intervention, laser therapy, targeted therapy and immunotherapy. UM is often considered an immune-privileged tumor, with a distinct immune profile compared to CM.

Objectives: This article aims to identify the unique challenges in managing uveal melanoma and provide insights to enhance the understanding and treatment of this rare malignancy. The goal is to improve clinical outcomes for patients and gain a deeper understanding of the complexity and distinctive nature of uveal melanoma.

Methods: A literature review was conducted based on the PubMed database, using the following words: "intraocular cancer", "non-cutaneous melanoma," "ocular melanoma", "uveal melanoma", "GNAQ", "GNA11", "transpupillary thermotherapy", "targeted therapy". Only articles published between 2010 and 2024 were included to endure the inclusion of recent advancements and findings.

This article aims to highlight the unique characteristics and challenges associated with this rare form of melanoma. By providing detailed information, the article seeks to enhance understanding and management of UM.

Conclusions:

・UM is the most common form of NCM and predominantly affects older Caucasians, with a much higher incidence rate compared to other racial and ethnic groups.

・UM is significantly influenced by specific genetic mutations, particularly in the GNAQ and GNA11 genes, which are present in approximately 80-90 % of cases and are critical in tumorigenesis due to their role in activating cell signal pathways.

・Other mutations, such as those in BAP1, SF3B1, and EIF1AX, are less common but have a strong correlation with metastasis risk and patient prognosis. Specifically, BAP1 mutations are linked to more aggressive disease and higher metastatic rates.

・Despite extensive research, metastatic UM remains an incurable disease, largely due to the limited effectiveness of current treatments in significantly improving patient survival.

・Efforts are intensifying to find new and effective treatments for this challenging disease, with a particular focus on immunotherapeutic methods. Growing understand of UM biology and the development of new biomarkers will guide future drug development and the design of clinical trials.

Keywords: intraocular cancer, non-cutaneous melanoma, ocular melanoma, uveal melanoma, GNAQ, GNA11, transpupillary thermotherapy, targeted therapy

Introduction

Melanoma is the most lethal form of skin cancer originating from the malignant transformation of melanocytes. These pigment-producing cells, derived from the neural crest during embryonic development, impart color to the skin, hair and eyes [1, 2]. The term

"melanocytes" is derived from the Greek words "melas", meaning "black", and "kytos", meaning "cell", highlighting their role in melanin production.

Due to the widespread presence of melanocytes, melanocarcinoma can manifest anywhere in the body, regardless of the specific anatomical location or tissues type [2]. Based on its location, melanoma is classified into cutaneous (skin) and non-cutaneous (non-skin) types. Non-cutaneous melanomas (NCM) are further categorized by their origin into ocular, mucosal, and indeterminate primary melanomas. These types are relatively uncommon, with ocular and mucosal melanomas representing 5.5% and 1.3% of all melanomas in North America, respectively [3, 4].

Intraocular melanoma of the ciliary body and choroid is the most frequent NCM and the most prevalent primary ocular tumor in adults [5]. NCMs are a diverse group of cancers with distinctive biological characteristics compared to cutaneous melanomas (CM), each representing unique diagnostic and treatment challenges based on its anatomical origin [6].

Ocular melanoma is the most common form of NCM, encompassing any melanoma occurring in the eye, though it is often used synonymous with uveal melanoma (UM) due to its predominance. UM arises in the pigmented region of the eye known as the uvea (or uveal tract), which is the middle layer of the eye and consists of three main parts: the iris, ciliary body, and choroid. The uvea plays a crucial role in supplying blood to the eye, regulating light entry, and assisting accommodation [5, 7]. Other ocular melanomas, such as conjunctival melanoma, are significantly rarer [5].

For purpose of the paper, we divided the article in following sections:

1. Epidemiology, Risk Factors, and Clinical Characteristics.
2. Pathophysiology - General Overview.
3. Clinical Manifestations.
4. Diagnosis.
5. Treatment.

1. Epidemiology, Risk Factors, and Clinical Characteristics

In the United States, UM affects approximately 5.2 patients per million annually, predominantly individuals aged 60 years and older. Although UM constitutes only 3% of all melanoma cases, it represents around 80% of all NCM. This neoplasm predominantly affects Caucasians, with an incidence rate 8-10 times higher compared to individuals of other races or ethnicities. The ratio of UM in Black: White patients is estimated at 1:15 to 1:50 [8]. Documented inherent risk factors include light-colored eyes (blue or grey) and skin color, as

well as a lack of tanning ability. The role of sun exposure as a risk factor remains debated [5, 8, 9, 10]. Between 30% and 50% of those affected by UM die due to metastases, which develop in up to 50% of patients and typically involve the liver [10, 11].

In 2024, the American Cancer Society estimated approximately 3.320 new cancers (mainly melanomas) of the eye and orbit in the United States, with 1.780 cases in men and 1.540 in women. Additionally, about 560 deaths from these cancers were anticipated, including 260 in men and 300 in women. Primary eye cancers can occur at any age, but the risk increases with age. While the rate of UMs has remained stable over the past few decades, the incidence of conjunctival melanomas has risen. Notably, secondary eye cancers, which spread to the eye from other body parts, are more common than primary eye [12]. UM is the most common primary intraocular tumor found in adults [8, 9]. This malignancy is linked to a high mortality rate, with the liver being the most frequent site for metastatic spread. Metastases occur in up to 50% of patients, and the average survival period following the detection of liver metastases is approximately 8 months [11].

The disease originates from melanocytes within the uveal tract, which encompasses the iris, choroid, and ciliary body. Based on their anatomical location, UMs are classified into two primary categories: anterior and posterior UMs. Anterior UMs, which arise within the iris, constitute up to 10% of all UM cases. These tumors are generally less aggressive in nature and have a lower tendency to metastasize. On the other hand, posterior UMs, which occur within the choroid or ciliary body, account for 90% of cases and are often highly aggressive [9]. Posterior UM is the most common primary malignant intraocular tumor in adults, with more than 25% of patients developing fatal metastatic disease within 10 years of treatment for the primary tumor [13].

2. General Overview of Pathophysiology

UMs arise from the aberrant clonal expansion of uveal melanocytes. The pathophysiology of UM involves a multifactorial process that includes: genetic mutations, chromosomal aberrations, inflammation, immune responses, inflammatory pathways, and prognostic factors [14, 15].

2.1 Genetic Mutations

The development of UM is strongly influenced by specific genetic mutations. Five genes are predominantly associated with the oncogenesis of UM: GNAQ, GNA11, BAP1, SF3B1, and EIF1AX [15].

Mutations in the GNAQ (Guanine nucleotide-binding protein q) and the GNA11 (Guanine nucleotide-binding protein subunit alpha-11) genes are particularly significant, occurring in approximately 80-90% of all UM cases. These genes encode oncogenic G-protein alpha subunits q and 11, respectively, which play crucial roles in cells signaling pathways, regulating growth and differentiation. GNAQ and GNA11 mutations are mutually exclusive, are not associated with patient outcomes, and lead to the constitutive activation of these downstream signaling pathways, contributing to tumorigenesis. Given their high mutations frequency and impact on signaling, GNAQ and GNA11 are considered potential therapeutic targets. In contrast, CMs typically harbor mutations in the BRAF (B-Raf Proto-Oncogene, Serine/Threonine Kinase) or NRAS genes [10, 16, 17, 18, 19].

Less frequently, other notable gene mutations in UM include mutations in BAP1 (BRCA1-associated protein 1), SF3B1 (Splicing Factor 3b Subunit 1) and EIF1AX (Eukaryotic Initiation Factor 1A, X-linked). These mutations are each significantly linked to the risk of metastasis. BAP1 mutations, which include missense and nonsense mutations, frame-shift deletions, and splice site mutations, are associated with more aggressive forms of UM and higher rates of metastasis , whereas mutations in EIF1AX and SF3B1 correlate with more favorable prognoses and a younger patient demographic [19, 20]. The SF3B1 mutation, found in approximately 25% of UM cases are associated with an intermediate risk of metastasis [21].

2.2 Chromosomal Aberrations

Chromosomal aberrations in Uveal Melanoma (UM) are closely linked to the genetic and epigenetic landscape of the tumor. UM typically exhibits simpler chromosomal anomalies compared to other cancers, with significant differences based on specific secondary driver mutations. For instance, BAP1-mutated UM is strongly associated with monosomy 3, whereas SF3B1-mutated UM shows complex karyotypes characterized by CSVs (multiple chromosomal structural variants), including loss of chromosome 6q, gain of 6p, and 8q. SF3B1 mutations are associated with a high number of chromosomal alterations, particularly at the distal ends of chromosomes, and are frequently observed alongside other aberrations like those in chromosome 11, which can impact prognosis. This complex chromosomal instability in SF3B1-mutated UM reflects its distinct molecular subtype and contributes to its unique tumorigenic and metastatic behavior [10, 22].

2.3 Immune Landscape

The immune landscape in UM includes an increased presence of lymphocytes, macrophages, and the expression of HLA (Human Leukocyte Antigen) class I and II molecules, which is associated with a worse prognosis and poorer outcomes. UM tumors are characterized by the presence of tumor-specific antigens and tumor-infiltrating immune cells, such as CD4 and CD8 (Cluster of Differentiation 4 Positive and 8 Positive) cells. These immune cells are typically involved in the anti-tumor immune response. However, UM also shows a significant presence of regulatory T cells [11]. Regulatory T-cells, also known as Tregs, are a specialized subset of T cells whose function is to suppress a variety of immune responses to self-antigens, playing a critical role in maintaining peripheral tolerance and preventing autoimmune disorders. Furthermore, Tregs reduce immune reactivity to antigens encoded by oncoproteins, thereby managing pathological immune responses that might facilitate cancer progression [23, 24, 25].

2.4 Inflammatory Pathways

In UM, various inflammatory signaling pathways - such as IL6-JAK-STAT3 (Interleukin 6, Janus Kinase, Signal Transducer and Activator of Transcription 3), IL2-STAT5 (Interleukin 2, Signal Transducer and Activator of Transcription 5), INF-α/γ (Interferon Alpha/Gamma), and TNF-α (Tumor Necrosis Factor Alpha), exhibit notably elevated hazard ratios, reflecting their connection with increased risk and poorer prognosis in UM.

Inflammatory molecules, including NF-κB (Nuclear Factor kappa B), COX-2 (Cyclooxygenase-2, also known as Prostaglandin-Endoperoxide Synthase 2), and CXCL10 (C-X-C motif chemokine ligand 10), which are mainly expressed in macrophages, are associated with a deteriorated prognosis. These elements contribute to a less favorable clinical outcome [14].

2.5 Prognostic Factors

The prognosis for UM contingent upon a multitude of risk factors, including the dimensions and anatomical location of the neoplasm, the extent of its metastatic dissemination, and the patient's overall physiological status [26].

Although the development of UM is predominantly regarded as an idiosyncratic occurrence, several predisposing factors have been identified, including light iris and skin pigmentation, reduced tanning ability, northern European ancestry, and albeit infrequently, a familial history of UM. Furthermore, individuals with pre-existing choroidal nevi are at heightened risk, with

the incidence of malignant transformation of such lesions ranging from 1 in 5.0000 to 1 in 8.845 cases.

Recent research has elucidated several critical prognostic determinants integral to the assessment of primary UM cases. Age at diagnosis is a principal prognostic factor, with individuals over 60 years of age exhibiting a significantly higher propensity for metastatic progression compared to younger and middle-age cohorts [7, 15, 26]. Pediatric cases of UM are infrequent, and the prognosis for affected children is markedly more favorable, with 5-year and 10-year survival rates of 97% and 92%, respectively [27]. Additionally, gender has been found to influence UM prognosis, with male patients generally presenting with a more adverse outcome, characterized by a higher incidence of metastasis and reduced survival rates, particularly within the initial decade following diagnosis. Histologically, UM is categorized as spindle, epithelioid, or mixed. Notably, epithelioid cell morphology is correlated with a poorer prognosis [7, 15].

Other factors that worsen the prognosis and are linked to an increased risk of metastasis include: deep scleral infiltration, presence of extraocular infiltration, high mitotic index, infiltration of the optic nerve, intrinsic vascularization of the tumor and inflammatory infiltration within the tumor mass, particularly involving T lymphocytes and macrophages [27].

GEP (Gene Expression Profiling) is a valuable technique used to simultaneously measure the expression of thousands of genes, offering a comprehensive overview of cellular function. GEP classification has demonstrated superior prognostic accuracy compared to other variable assessed. It differentiates between primary UMs with low metastatic risk (class 1 tumors) and those with a high metastatic risk (class 2 tumors). When considering GEP classification, BAP1 mutations have emerged as the most precise predictor of metastasis-free survival and melanoma-specific mortality. Conversely, mutations in SF3B1 and EIF1AX may serve as useful indicators of favorable prognosis [19, 28].

2.6 Environmental Factors

Unlike cutaneous melanomas, UV (ultraviolet) light has not been implicated in the pathogenesis of UM, except in cases of occupational exposure, such as in arc welders. Moreover, current evidence does not support any significant influence of dietary habits, smoking, or alcohol consumption on the incidence of UM [29].

3. Clinical Manifestations

UM often manifests with a range of clinical symptoms which vary based on the tumor's size and location [13]. About 30% of patients report no symptoms [27]. The most frequent symptom is painless loss or distortion of vision, referred to as metamorphopsia. In cases involving larger tumors, patients may experience photopsia. Photopsia occurs due to associated serous retinal detachment and refers to the perception characterized by flashing or flickering of light in the visual field, often described by patients by seeing sparks, lightning, or streaks of light. In its early stages, UM can be asymptomatic. Consequently, it may be incidentally discovered during routine eye examination, particularly when the clinician performs pupillary dilation to conduct a comprehensive fundoscopic evaluation. The clinical presentation varies depending on whether the tumor is located in the anterior or posterior segment of the eye [13].

When UM involves the anterior segment of the eye, clinical may include discoloration of the iris or persistent redness of the episclera [30]. In exceedingly rare instances, advanced iris melanoma may manifest with secondary glaucoma as a consequence of tumor invasion into the anterior chamber angle. This can lead to obstruction of the trabecular meshwork by pigment-laden macrophages or the development of neovascularization [13]. Tumors located in the ciliary body can lead to increased and asymmetric astigmatism because of the displacement of the intraocular lens. The anterior anatomical position of the iris, coupled with the potential for visible changes - particularly in individuals with lighter irides - facilitates earlier detection, diagnosis and, intervention of melanomas originating in this site. Furthermore, in exceptional instances, an eye rendered functionally blind or obscured by a dense cataract may conceal an occult melanoma [30].

4. Diagnosis

Iris melanoma is often detected incidentally during slit-lamp examinations, usually 10 to 20 years earlier than other types of uveal melanoma. Patients might notice changes in iris color, known as heterochromia, or experience pupillary distortion, or corectopia. The tumor is typically circumscribed and located inferiorly, with common complications including ectropion iridis, hyphema, secondary glaucoma, cataract, and extraocular extension. Secondary glaucoma arises from trabecular meshwork invasion or direct compression of the angle. Diagnosing diffuse iris melanoma can be challenging due to its infiltrative nature, while ring iris melanoma, a rare form, can mimic unilateral pigmentary glaucoma.

For posterior uveal melanoma, diagnosis is generally made through slit-lamp biomicroscopy and indirect ophthalmoscopy under dilated pupils, as many tumors, especially those in the ciliary body, can grow asymptomatically for years. Fundoscopic examination often reveals a pigmented, dome-shaped nodular mass located beneath the retinal pigment epithelium, though the appearance may vary, with some tumors exhibiting a mushroom shape or causing retinal detachment. Imaging techniques such as B-scan ultrasonography are essential for evaluating tumor dimensions and extent, particularly in opaque intraocular media, while enhanced depth imaging spectral-domain OCT (Optical Coherence Tomography) provides detailed views of deeper choroidal structures.

FNAB (Fine-needle aspiration biopsy) is increasingly used for genetic analysis, which helps in assessing prognosis and metastatic risk. Gene expression profiling (GEP) classifies uveal melanomas into Class 1 tumors, which have a lower to intermediate metastatic risk, and Class 2 tumors, which present a significantly higher risk. The AJCC (American Joint Committee on Cancer) classification system for choroidal melanoma includes tumor size and extent, with categories ranging from small to large tumors based on basal diameter and apical height [26, 31].

5. Treatment

The therapeutic approach to UM is determined by several key factors, including the tumor's size, anatomical location, involvement of the surrounding structures, tumor activity, status of the fellow eye, as well as the patient's general health status and encompasses radiation therapy, surgery, laser therapy, chemotherapy and immunotherapy [26].

5.1 Radiation Therapy

Radiotherapy is a cancer treatment approach in oncology that utilizes ionizing radiation to selectively target and destroy malignant cells by inducing DNA damage and can be administered through various techniques [32]. Each radiotherapy modality has its own advantages and potential complications, with the choice between these eye-preserving methods primarily depending on the treatment center's resources as well as tumor and patient characteristics. Brachytherapy involves attaching a plaque containing a radioisotope, such as iodine-125, ruthenium-106, or palladium-103 to the sclera, which is later removed after several days. External beam radiation therapy, which includes proton beam therapy and stereotactic radiosurgery using gamma knife or cyber knife, delivers a focused radiation beam

to the tumor; in the case of proton beam therapy, this often requires the prior attachment of tantalum clips to the sclera before irradiation [33].

5.2 Surgery

The UM tumor can be excised using either exoresection or endoresection techniques. Exoresection involves en bloc removal via a scleral incision, while endoresection entails fragmenting and extracting the tumor through a vitreous cutter passed through the retina. The use of endoresection for choroidal melanoma is debated due to concerns about potential iatrogenic tumor cell dissemination [8, 34]. Enucleation is the second most frequently used treatment for UM, indicated in up to 40% of cases. It is typically reserved for large tumors or those involving the optic disc, exceeding 18 mm in basal diameter or 12 mm in thickness, as well as tumors with poor visual prognosis or moderate extraocular extension. Enucleation has largely been supplanted by various forms of radiotherapy and laser therapy [8]. The procedure involves the insertion of an orbital implant, with similar outcomes observed for both nonporous and porous implants. Evisceration is contraindicated, and exenteration is only required in rare cases of extensive orbital invasion [8, 35].

5.3 Laser Therapy

Laser photocoagulation, employing brief high-energy light pulses, is linked to a high rate of tumor recurrence, prompting its replacement by transpupillary thermotherapy (TTT). TTT uses a 3-mm beam of infrared laser to elevate tumor's temperature slightly for about one minute, aiming to induce localized thermal effects. Due to TTT's potential limitation in completely eradicating scleral tumor cells, it is often combined with radioactive plaque to enhance treatment efficacy. Furthermore, the combination of proton beam therapy and TTT has been effective in reducing the need for enucleation in cases of large tumors. Nonetheless, recent retrospective analysis from Leiden, where TTT was developed, found no significant outcome differences between plaque therapy with or without TTT. Additionally, certain tumors may respond positively to photodynamic therapy using agents such as verteporfin [35, 36].

5.4 Targeted Therapy and Immunotherapy

Targeted therapy is a type of cancer treatment designed to specifically target and interfere with molecular mechanisms or pathways that are crucial for the growth and survival of cancer

cells. In the other hand, immunotherapy leverages the body's own immune system to recognize, target, and eradicate cancer cells.

Trametinib and selumetinib are both inhibitors of MEK (Mitogen-Activated Protein Kinase/extracellular Signal-Regulated Kinase), which is an integral enzyme in the MAPK/ERK (Mitogen-activated Protein Kinase/ Extracellular Signal-Regulated Kinase) signaling pathway. This pathway is critical for regulating various cellular processes, including growth, proliferation, and survival. MEK plays a crucial role in the MAPK/ERK pathway by mediating the phosphorylation and activation of ERK (Extracellular Signal-Regulated Kinase), which subsequently affects cellular functions. The pathway is often dysregulated in cancer due to mutations in upstream components such as the KRAS (Kirsten Rat Sarcoma Viral Oncogene Homolog) and BRAF genes. A MEK is a key effector in these signaling pathways, it represents a significant target for cancer therapy, including UM.

Trametinib is administered orally once daily and has shown benefits in progression-free survival and overall survival compared to traditional chemotherapy in various cancers [37]. However, Amaro et. al (2023) indicated that trametinib alone may reduce tumor size in animal models, through there is a potential for tumor regrowth after discontinuation [38]. Common side effects include rash, diarrhea, peripheral edema, and fatigue, which are typically manageable through dose adjustments and supportive care [37].

Selumetinib is a highly-selective, ATP (Adenosine Triphosphate)-uncompetitive allosteric inhibitor of MEK1 and MEK2. As a monotherapy, selumetinib has been largely ineffective agains UM cell lines due to the activation of alternative signaling pathways, such as c-JUN (cellular JUN) or PI3K/AKT (Phosphoinositide 3-Kinase/Protein Kinase B), which are associated with drug resistance. Combinations of selumetinib with c-JUN inhibitors or PI3K/AKT inhibitors have shown promising results in inducing apoptosis in UM cell lines [39].

UM is considered an immune-privileged tumor, differing from CM in its immune profile. UM tumors generally exhibit lower levels of CD8+ lymphocytes and PD-L1 (Programmed Death-Ligand 1) expression compared to CM, indicating a more immunosuppressed microenvironment.

Targeting angiogenesis in UM has had limited success in clinical trials. While some drugs have shown disease stabilization in over 50% of patients, the overall responses rates remain low. For instance, sorafenib achieved a best observed response rate of only 1.7% in UM patients, although cabozantinib showed better PFS (progression-free survival) compared to CM. Combining antiangiogenic drugs with other treatments might improve efficacy, as

evidenced by the improved results seen with the combination of bevacizumab and radiotherapy in UM mouse models [40, 41].

There is a growing focus on developing new and effective therapies for UM, with particular attention to immunotherapeutic approaches. Advances in understanding UM biology and the development of new biomarkers are expected to guide future drug development and clinical trial design [41].

6. Discussion

Uveal melanoma represents the most prevalent subtype of NCM and disproportionately affects older Caucasian individuals. Its incidence rate is notably higher in this population compared to other racial and ethnic groups. The development of UM is closely tied to specific genetic mutations, particularly those occurring in the GNAQ and GNA11 genes, which are found in approximately 80-90% of cases. These mutations play a critical role in tumorigenesis by activating key cell signaling pathways. In addition to GNAQ and GNA11 mutations, other genetic alterations, such as those in BAP1, SF3B1, and EIF1AX, also contribute to the pathogenesis of UM, albeit with varying frequencies. Among these, BAP1 mutations are of particular concern due to their strong association with a more aggressive disease phenotype and increased metastatic potential. SF3B1 and EIF1AX mutations, while less common, are also significant as they correlate with different prognostic outcomes, including metastasis risk.

Despite the substantial progress made in understanding the molecular mechanisms underlying UM, the prognosis for metastatic UM remains bleak. Current therapeutic options have shown limited success in prolonging patient survival, highlighting the urgent need for more effective treatment strategies. Metastatic UM continues to be an incurable disease, in large part due to the lack of therapies that can significantly alter its clinical course. Given these challenges, research efforts are increasingly focused on exploring novel therapeutic approaches, with immunotherapy emerging as a particularly promising avenue. Advances in the understanding of UM's biological underpinnings, coupled with the identification of new biomarkers, are expected to guide the development of more targeted therapies and improve the design of future clinical trials. Such efforts are crucial in the quest to improve outcomes for patients suffering from this difficult-to-treat malignancy. This ongoing research holds the potential to transform the current therapeutic landscape for UM, providing hope for more effective treatments in the future.

Authors' contribution:

Conceptualization: Karina Lissak

Methodology: Zuzanna Szczepaniak, Natalia Wdowiak

Software: Martyna Choinka, Małgorzata Komarów

Check: Karina Lissak, Agata Konopka, Milena Orzeł

Formal analysis: Dominika Karasińska, Jakub Kalisiak

Investigation: Dominika Karasińska, Jakub Kalisiak, Mateusz Koralewicz

Resources: Zuzanna Szczepaniak, Natalia Wdowiak, Bartłomiej Orzeł

Data curation: Martyna Choinka, Małgorzata Komarów

Writing - rough preparation: Karina Lissak, Agata Konopka, Martyna Choinka, Małgorzata Komarów

Writing - review and editing: Karina Lissak

Visualization: Karina Lissak, Mateusz Koralewicz

Supervision: Karina Lissak, Milena Orzeł, Bartłomiej Orzeł

Project administration: Karina Lissak

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References:

1. Heistein JB, Acharya U, Mukkamalla SKR. Malignant Melanoma. [Updated 2024 Feb 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470409/

2. Guo, W., Wang, H., & Li, C. (2021). Signal pathways of melanoma and targeted therapy. Signal transduction and targeted therapy, 6(1), 424. https://doi.org/10.1038/s41392-021-00827-6

3.Leonardi, G. C., Falzone, L., Salemi, R., Zanghì, A., Spandidos, D. A., Mccubrey, J. A., Candido, S., & Libra, M. (2018). Cutaneous melanoma: From pathogenesis to therapy (Review). International journal of oncology, 52(4), 1071–1080. https://doi.org/10.3892/ijo.2018.4287

4. Murphy, G., Hussey, D., & Metser, U. (2014). Non-cutaneous melanoma: is there a role for (18)F-FDG PET-CT?. The British journal of radiology, 87(1040), 20140324. https://doi.org/10.1259/bjr.20140324

5. Nora V. Laver, Margaret E. McLaughlin, Jay S. Duker; Ocular Melanoma. Arch Pathol Lab Med 1 December 2010; 134 (12): 1778–1784. doi: https://doi.org/10.5858/2009-0441-RAR.1

6. Wong, V. K., Lubner, M. G., Menias, C. O., Mellnick, V. M., Kennedy, T. A., Bhalla, S., & Pickhardt, P. J. (2017). Clinical and Imaging Features of Noncutaneous Melanoma. AJR. American journal of roentgenology, 208(5), 942–959. https://doi.org/10.2214/AJR.16.16800

7. Eye Cancer. (Ocular Melanoma). American Cancer Society. https://www.cancer.org/cancer/types/eye-cancer/about.html (accessed on 23.07.2024)

8. Kaliki, S., & Shields, C. L. (2017). Uveal melanoma: relatively rare but deadly cancer. Eye (London, England), 31(2), 241–257. https://doi.org/10.1038/eye.2016.275

9. Doherty RE, Alfawaz M, Francis J, et al. Genetics of Uveal Melanoma. In: Scott JF, Gerstenblith MR, editors. Noncutaneous Melanoma [Internet]. Brisbane (AU): Codon Publications; 2018 Mar. Chapter 2. Available from: https://www.ncbi.nlm.nih.gov/books/NBK506982/ doi: 10.15586/codon.noncutaneousmelanoma.2018.ch2

10. van Weeghel C, Wierenga APA, Versluis M, van Hall T, van der Velden PA, Kroes WGM, Pfeffer U, Luyten GPM, Jager MJ. Do GNAQ and GNA11 Differentially Affect

Inflammation and HLA Expression in Uveal Melanoma? Cancers. 2019; 11(8):1127. https://doi.org/10.3390/cancers11081127

11. Bronkhorst, I. H., & Jager, M. J. (2013). Inflammation in uveal melanoma. Eye (London, England), 27(2), 217–223. https://doi.org/10.1038/eye.2012.253

12. Key Statistics for Eye Cancer. https://www.cancer.org/cancer/types/eye-cancer/about/key-statistics.html (accessed on 29.07.2024)

13. Intraocular (Uveal) Melanoma Treatment (PDQ) - Patient Version. https://www.cancer.gov/types/eye/patient/intraocular-melanoma-treatment-pdq (accessed on 12.08.2024)

14. Fuentes-Rodriguez, A.; Mitchell, A.; Guérin, S.L.; Landreville, S. Recent Advances in Molecular and Genetic Research on Uveal Melanoma. Cells 2024, 13, 1023. https://doi.org/10.3390/cells13121023

15. Choroidal and Ciliary Body Melanoma. https://eyewiki.org/Choroidal_and_Ciliary_Body_Melanoma#Symptoms (accessed on 13.08.2024)

16. Koopmans, A., Vaarwater, J., Paridaens, D. et al. Patient survival in uveal melanoma is not affected by oncogenic mutations in GNAQ and GNA11. Br J Cancer 109, 493–496 (2013). https://doi.org/10.1038/bjc.2013.299

17. Jager, M.J., Shields, C.L., Cebulla, C.M. et al. Uveal melanoma. Nat Rev Dis Primers 6, 24 (2020). https://doi.org/10.1038/s41572-020-0158-0

18. Silva-Rodríguez, P., Fernández-Díaz, D., Bande, M., Pardo, M., Loidi, L., & Blanco-Teijeiro, M. J. (2022). GNAQ and GNA11 Genes: A Comprehensive Review on Oncogenesis, Prognosis and Therapeutic Opportunities in Uveal Melanoma. Cancers, 14(13), 3066. https://doi.org/10.3390/cancers14133066

19. Decatur, C. L., Ong, E., Garg, N., Anbunathan, H., Bowcock, A. M., Field, M. G., & Harbour, J. W. (2016). Driver Mutations in Uveal Melanoma: Associations With Gene Expression Profile and Patient Outcomes. JAMA ophthalmology, 134(7), 728–733. https://doi.org/10.1001/jamaophthalmol.2016.0903

20. Uner, O.E., See, T.R.O., Szalai, E. et al. Estimation of the timing of BAP1 mutation in uveal melanoma progression. Sci Rep 11, 8923 (2021). https://doi.org/10.1038/s41598-021-88390-6

21. Drabarek W, van Riet J, Nguyen JQN, Smit KN, van Poppelen NM, Jansen R, Medico-Salsench E, Vaarwater J, Magielsen FJ, Brands T, et al. Identification of Early-Onset

Metastasis in SF3B1 Mutated Uveal Melanoma. Cancers. 2022; 14(3):846. https://doi.org/10.3390/cancers14030846

22. Nguyen JQN, Drabarek W, Yavuzyigitoglu S, Medico Salsench E, Verdijk RM, Naus NC, de Klein A, Kiliç E, Brosens E. Spliceosome Mutations in Uveal Melanoma. International Journal of Molecular Sciences. 2020; 21(24):9546. https://doi.org/10.3390/ijms21249546

23. Grover, P., Goel, P. N., & Greene, M. I. (2021). Regulatory T Cells: Regulation of Identity and Function. Frontiers in immunology, 12, 750542. https://doi.org/10.3389/fimmu.2021.750542

24. Kaliki, S., Shields, C. L., & Shields, J. A. (2015). Uveal melanoma: estimating prognosis. Indian journal of ophthalmology, 63(2), 93–102. https://doi.org/10.4103/0301-4738.154367

25. Lamas, N. J., Martel, A., Nahon-Estève, S., Goffinet, S., Macocco, A., Bertolotto, C., Lassalle, S., & Hofman, P. (2021). Prognostic Biomarkers in Uveal Melanoma: The Status Quo, Recent Advances and Future Directions. Cancers, 14(1), 96. https://doi.org/10.3390/cancers14010096

26. Uveal Melanoma. Melanoma Research Alliance. https://www.curemelanoma.org/about-melanoma/types/uveal-melanoma (accessed on 14.08.2024)

27. Rutkowski P., Romanowska-Dixon B., Markiewicz A., Zieniewicz K., Kozak K., Rogala P., Świtaj T. (2022). Diagnostic and therapeutic management of patients with ocular melanomas - recommendations of the Polish Society of Oncology. http://doi.org/10.5603/NJO.2022.0054

28. Harbour J. W. (2014). A prognostic test to predict the risk of metastasis in uveal melanoma based on a 15-gene expression profile. Methods in molecular biology (Clifton, N.J.), 1102, 427–440. https://doi.org/10.1007/978-1-62703-727-3_22

29. Tarlan, B., & Kıratlı, H. (2016). Uveal Melanoma: Current Trends in Diagnosis and Management. Turkish journal of ophthalmology, 46(3), 123–137. https://doi.org/10.4274/tjo.37431

30. Chattopadhyay C, Kim DW, Gombos DS, Oba J, Qin Y, Williams MD, Esmaeli B, Grimm EA, Wargo JA, Woodman SE, Patel SP. Uveal melanoma: From diagnosis to treatment and the science in between. Cancer. 2016 Aug 1;122(15):2299-312. https://doi.org/10.1002/cncr.29727

31. Branisteanu, D. C., Bogdanici, C. M., Branisteanu, D. E., Maranduca, M. A., Zemba, M., Balta, F., Branisteanu, C. I., & Moraru, A. D. (2021). Uveal melanoma diagnosis and current

treatment options (Review). Experimental and therapeutic medicine, 22(6), 1428. https://doi.org/10.3892/etm.2021.10863

32. Gong, L., Zhang, Y., Liu, C., Zhang, M., & Han, S. (2021). Application of Radiosensitizers in Cancer Radiotherapy. International journal of nanomedicine, 16, 1083–1102. https://doi.org/10.2147/IJN.S290438

33.Gelmi, M. C., & Jager, M. J. (2024). Uveal melanoma: Current evidence on prognosis, treatment and potential developments. Asia-Pacific journal of ophthalmology (Philadelphia, Pa.), 13(2), 100060. https://doi.org/10.1016/j.apjo.2024.100060

34. Hamza, H. S., & Elhusseiny, A. M. (2018). Choroidal Melanoma Resection. Middle East African journal of ophthalmology, 25(2), 65–70. https://doi.org/10.4103/meajo.MEAJO_73_18

35. Dogrusöz, M., Jager, M. J., & Damato, B. (2017). Uveal Melanoma Treatment and Prognostication. Asia-Pacific journal of ophthalmology (Philadelphia, Pa.), 6(2), 186–196. https://doi.org/10.22608/APO.201734

36. Maheshwari, A., & Finger, P. T. (2023). Laser treatment for choroidal melanoma: Current concepts. Survey of ophthalmology, 68(2), 211–224. https://doi.org/10.1016/j.survophthal.2022.05.002

37. Hoffner, B., & Benchich, K. (2018). Trametinib: A Targeted Therapy in Metastatic Melanoma. Journal of the advanced practitioner in oncology, 9(7), 741–745.

38. Amaro, A. A., Gangemi, R., Emionite, L., Castagnola, P., Filaci, G., Jager, M. J., Tanda, E. T., Spagnolo, F., Mascherini, M., Pfeffer, U., & Croce, M. (2023). Cerivastatin Synergizes with Trametinib and Enhances Its Efficacy in the Therapy of Uveal Melanoma. Cancers, 15(3), 886. https://doi.org/10.3390/cancers15030886

39. Kim, D. W., & Patel, S. P. (2014). Profile of selumetinib and its potential in the treatment of melanoma. OncoTargets and therapy, 7, 1631–1639. https://doi.org/10.2147/OTT.S51596

40. Castet, F., Garcia-Mulero, S., Sanz-Pamplona, R., Cuellar, A., Casanovas, O., Caminal, J. M., & Piulats, J. M. (2019). Uveal Melanoma, Angiogenesis and Immunotherapy, Is There Any Hope?. Cancers, 11(6), 834. https://doi.org/10.3390/cancers11060834