Ophthalmological Monitoring in Patients Undergoing BRAF and MEK Inhibitors in *BRAF*-Mutated Cutaneous Malignant Melanoma: A Retrospective Study

Monitorização Oftalmológica em Doentes com Melanoma Maligno Cutâneo *BRAF*-Mutado Submetidos a Inibidores do BRAF e MEK: Um Estudo Retrospetivo

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ABSTRACT

INTRODUCTION: The combination of BRAF and MEK inhibitors (BRAFi and MEKi) is a key treatment for stage III and IV *BRAF*-mutated cutaneous malignant melanomas. While ocular adverse effects are common, few studies are using real-world data to characterize these complications.

METHODS: This retrospective observational study at Hospital de Santa Maria, Lisbon, aimed to conduct a comprehensive analysis of all patients with *BRAF*-mutated cutaneous stage III and IV malignant melanoma who were by protocol referred for ophthalmic screening before, during and after undergoing therapy with BRAFi and MEKi between 2016 and 2023. Demographic and clinical data were collected, with statistical analysis using chi-square, Fisher's exact tests, and t-tests.

RESULTS: Thirty-two patients were included, 17 (53.1%) of whom are female. The average age of the sample is 60.8±12.3 years. Twenty-one (65.6%) patients underwent treatment with dabrafenib+trametinib (D+T), seven with vemurafenib+cobimetinib (V+C) and four with encorafenib+binimetinib (E+B). The median time between melanoma diagnosis and treatment onset was 9.3 months (IQR 3.6-17.3). The median ophthalmological follow-up was 6.8 months (IQR 3.3-13.5). Nine patients (28.1%) presented ophthalmological adverse effects: serous retinal detachment in seven (21.9%), five of which presented serous detachment of the fovea; anterior uveitis in two (6.3%); and panuveitis with papillitis in one (3.1%). The majority (88.9%) of patients with complications presented bilateral involvement and in 2/3 of cases, patients were asymptomatic. There was a suspension of the therapeutic regimen only in one patient (11.1%). The median interval between the start of therapy and the emergence of complications was 57.8 days (IQR 25.9-241.8). There was a difference (p=0.010) in the proportion of adverse effects between the three regimens (D+T:14.3%; E+B:25.0%; V+C:71.4%), particularly between D+T and V+C (p=0.009). The incidence of adverse effects did not appear to depend on gender (p=1.000), age (p=0.367) or melanoma stage (p=0.303). There is no statistically significant association between the occurrence of complications and mortality (p=0.694).

CONCLUSION: Despite a high incidence of ocular complications with BRAFi and MEKi, most patients remain asymptomatic, highlighting the need for regular ophthalmological monitoring, especially in the first 3 months, to detect and manage complications early.

KEYWORDS: Melanoma, Cutaneous Malignant; Protein Kinase Inhibitors/therapeutic use; Proto-Oncogene Proteins B-raf/antagonists & inhibitors; Proto-Oncogene Proteins B-raf/genetics; Skin Neoplasms/drug therapy.

RESUMO

INTRODUÇÃO: A combinação de inibidores BRAF e MEK (BRAFi+MEKi) é um tratamento-chave para os melanomas malignos cutâneos *BRAF*-mutados em estádio III e IV. Embora os efeitos adversos oculares sejam comuns, existem poucos estudos que utilizam dados do mundo real para caracterizar estas complicações.

MÉTODOS: Este estudo observacional retrospetivo no Hospital de Santa Maria, Lisboa, teve como objetivo realizar uma análise de todos os doentes com melanoma maligno cutâneo de estádio III e IV *BRAF*-mutado que foram, por protocolo, encaminhados para monitorização oftalmológica antes, durante e após terapêutica com BRAFi+MEKi entre 2016 e 2023. Foram recolhidos dados demográficos e clínicos, com análise estatística através de testes de qui-quadrado, exato de Fisher e testes-t.

RESULTADOS: Foram incluídos 32 doentes, 17 (53,1%) do sexo feminino. A idade média da amostra é de 60,8±12,3 anos. Vinte e um (65,6%) doentes foram tratados com dabrafenib+trametinib (D+T), sete com vemurafenib+cobimetinib (V+C) e quatro com encorafenib+binimetinib (E+B). O tempo mediano entre o diagnóstico do melanoma e o início do tratamento foi de 9,3 meses (IQR 3,6-17,3). A mediana do seguimento oftalmológico foi de 6,8 meses (IQR 3,3-13,5). Nove doentes (28,1%) apresentaram efeitos adversos oftalmológicos: descolamento seroso da retina em sete (21,9%), dos quais cinco com envolvimento foveal; uveíte anterior em dois (6,3%); e panuveíte com papilite em um (3,1%). A maioria (88,9%) apresentava complicações bilaterais e em 2/3 dos casos os doentes eram assintomáticos. Houve suspensão do esquema terapêutico apenas em um doente (11.1%). O intervalo mediano entre o início da terapêutica e o aparecimento de complicações foi de 57,8 dias (IQR 25,9-241,8). Verificou-se uma diferença (p=0,010) na proporção de efeitos adversos entre os três regimes (D+T:14,3%; E+B:25,0%; V+C:71,4%), particularmente entre D+T e V+C (p=0,009). A incidência de efeitos adversos não pareceu depender do género (p=1,000), idade (p=0,367) ou estádio do melanoma (p=0,303). Não existe associação entre a ocorrência de complicações e a mortalidade (p=0,694).

CONCLUSÃO: Apesar da elevada incidência de complicações oculares com BRAFi+MEKi, a maioria dos doentes permanece assintomática, realçando a necessidade de um acompanhamento oftalmológico regular, especialmente nos primeiros 3 meses, para detetar e tratar precocemente complicações.

PALAVRAS-CHAVE: Inibidores de Proteínas Quinases/uso terapêutico; Melanoma Maligno Cutâneo; Proteínas Proto-Oncogénicas B-raf/antagonistas e inibidores; Proteínas Proto-Oncogénicas B-raf/genética.

INTRODUCTION

Cutaneous malignant melanoma is an aggressive form of skin cancer that is often diagnosed at an advanced stage.[1] The advent of targeted therapies, particularly BRAF and MEK inhibitors (BRAFi and MEKi), has revolutionized the treatment of advanced stage *BRAF*-mutant cutaneous melanoma, significantly improving patient disease free survival and overall survival outcomes.[2] *BRAF* mutations, most notably the *BRAF V600E* mutation, which is present in half of all subtypes of cutaneous melanoma, drive uncontrolled cell proliferation via the mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK) pathway, making the development of BRAFi and MEKi critical for halting disease progression.[3] Currently, combination therapies are preferred over monotherapy due to their superior efficacy, as BRAFi monotherapy often leads to resistance through MAPK pathway reactivation caused by *MEK1* mutations.[4] There are three approved combinations by the European Medicines Agency (EMA) and Food

and Drug Administration (FDA): dabrafenib + trametinib (D+T), vemurafenib + cobimetinib (V+C), and encorafenib + binimetinib (E+B). However, despite their remarkable effectiveness, emerging evidence points to significant toxicities associated with these treatments.[2]

Ocular complications are increasingly recognized as a significant adverse effect of BRAFi and MEKi therapies.[4] Despite the growing body of literature on this topic, real-world data on the incidence and management of ocular toxicities in patients undergoing BRAFi and MEKi therapy remain limited. Most existing studies have either examined these complications within the controlled settings of clinical trials, where strict inclusion criteria and more frequent, detailed ophthalmologic monitoring are applied than in real-world practice, or relied on data from adverse event reporting systems, which are inherently limited by biases and reporting inconsistencies.[5] Given the growing use of BRAFi and MEKi in clinical practice, there is a critical need for real-world data to better understand the incidence and management of ocular adverse events. Real-world studies offer the advantage of reflecting routine clinical settings, where patients and health system factors may alter the prevalence and severity of complications.

This study aims to fill this gap by providing information on the types and frequency of ocular adverse events in a clinical setting. Specifically, we will examine the incidence, distribution and management of ocular complications in a cohort of patients receiving these treatments in routine clinical practice.

MATERIAL AND METHODS

This retrospective, observational, and descriptive single-center study was conducted at the Hospital de Santa Maria in Lisbon, Portugal. All patients with *BRAF*-mutated cutaneous stage III and IV malignant melanoma who were proposed to BRAFi + MEKi combination treatment were referred for ophthalmological monitoring as part of their treatment protocol, which was established through collaboration between the Medical Oncology and Ophthalmology services. As part of the protocol, all patients underwent a baseline Ophthalmology consultation before initiating BRAFi + MEKi therapy, followed by routine follow-up visits at 1 month (±1 week), 2 months (±1 week), 3 months (±2 weeks), 6 months (±4 weeks) and 12 months (±4 weeks) after treatment initiation. Additional consultations were conducted as clinically indicated. At each visit, patients underwent a comprehensive ophthalmological examination, including best corrected visual acuity, intraocular pressure measurement, anterior segment assessment through biomicroscopy and posterior segment evaluation via fundoscopy and optical coherence tomography spectral domain (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany).

Patients were eligible for inclusion in this study if they met the following criteria: diagnosed with *BRAF*-mutated cutaneous stage III or IV malignant melanoma; follow-up in the Medical Oncology department at Hospital de Santa Maria; underwent treatment with a combined regimen of BRAFi + MEKi, with therapy initiation between January 1, 2016, and December 31, 2023; attended at least two Ophthalmology consultations during the study period, with a minimum follow-up of one month.

The following situations marked the end of a patient's follow-up: death; missing the initial ophthalmology appointment; missing two consecutive follow-up ophthalmology appointments; discontinuation or alteration of the BRAFi+MEKi regimen; initiation of immunotherapy.

For data collection, the following variables were recorded from clinical reports: gender, age at the first ophthalmologic evaluation, survival status, stage of malignant melanoma, BRAFi+MEKi treatment regimen, presence of complications, presence of symptoms, laterality of the complications, date of diagnosis, date of treatment initiation, date of symptom/complication onset, date of ophthalmologic follow-up initiation, date of ophthalmologic follow-up termination, duration of ophthalmologic follow-up, time from drug initiation to complication onset, treatment regimen decision, complication progression, date of complication resolution, time between symptom onset and resolution, and date of drug discontinuation. The complications were classified and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[6] Mortality was assessed as a binary outcome (alive/dead) at the end of the available observation period.

Statistical analysis was performed using SPSS Statistics (version 27). Descriptive statistics were generated to summarize the demographic and clinical characteristics of the sample. Categorical variables, such as gender, melanoma stage, and treatment regimen, were analyzed using chi-square or Fisher's exact tests, depending on the expected frequencies. Subgroup analyses were conducted based on the specific BRAFi + MEKi regimen used. The association between ocular complications and mortality was analyzed using Fisher's exact test. A significance level of $p<0.05$ was considered statistically significant for all tests.

RESULTS

The patient demographic data are presented in Table 1. A total of sixty-four eyes from thirty-two patients were included in the analysis. Most patients were female (53.1%), and the average age was 60.8 ± 12.3 years. The majority of patients were in stage IV malignant melanoma (87.5%), with the remaining patients in stage III. Regarding treatment, twenty-one (65.6%) patients underwent treatment with D+T, seven with V+C and four with E+B.

Regarding systemic medical history, half of the patients (n=16) had arterial hypertension, four had type 2 diabetes *mellitus*, eight had dyslipidemia, and four had benign prostatic hyperplasia. In terms of ocular history, none of the patients had a history of prior ocular inflammation or retinal detachment. Isolated findings included one patient with myopic chorioretinopathy, one with a choroidal nevus, one with a choroidal hemangioma, and one with age-related macular degeneration (AMD), none of whom experienced ocular complications related to treatment.

The median time between melanoma diagnosis and treatment onset was 9.3 months (IQR 3.6 - 17.3) and the median

Table 1. Patient demographics.

	Total (n=32)	D+T (n=21)	V+C (n=7)	E+B (n=4)
Age - mean ± SD	60.8 ± 12.3 years	61.4 ± 12.7 years	65.5 ± 7.6 years	56.1 ± 13.4 years
Gender - n (%)				
Feminine	17 (53.1)	12 (57.1)	2 (50.0)	3 (42.9)
Masculine	15 (46.9)	9 (42.9)	2 (50.0)	4 (57.1)
Melanoma stage - n (%)				
III	4 (12.5)	4 (19.0)	0 (0.0)	0 (0.0)
IV	28 (87.5)	17 (81.0)	4 (100.0)	7 (100.0)
Comorbilities - n (%)				
Arterial hypertension	16 (50.0)			
Type 2 diabetes *mellitus*	4 (12.5)			
Dyslipidemia	8 (25.0)			
Prostate benign hyperplasia	4 (12.5)			
Time from diagnosis to treatment onset - median (IQR)	9.3 (3.6 - 17.3) months			
Ophthalmologic follow-up - median (IQR)	6.8 (3.3 - 13.5) months			

D+T - dabrafenib + trametinib. V+C - vemurafenib + cobimetinib. E+B - encorafenib and binimetinib. IQR - interquartile range.

ophthalmological follow-up was 6.8 months (IQR 3.3 - 13.5).

The description of patients who developed ocular adverse effects is presented in Table 2. Nine patients (28.1%) experienced ocular adverse effects during their treatment. The majority were female (55.6%), and the average age was 57.7 ± 11.2 years. All patients were in stage IV malignant melanoma. Five (55.6%) patients underwent treatment with V+C, three with D+T and one with encorafenib and binimetinib (E+B).

Two thirds of these patients were asymptomatic, while the remaining third reported decreased visual acuity. The most common complication was serous retinal detachment, observed in seven patients (21.9%), five of whom had involvement of the fovea. Other complications included anterior uveitis in two patients (6.3%) and panuveitis with papillitis in one patient (3.1%). One patient presented with both retinal detachment and panuveitis.

Among the serous retinal detachments, five out of seven (71.4%) were asymptomatic. In contrast, two out of three patients with uveitis reported blurred vision. According to the CTCAE classification, six of the seven serous retinal detachments were grade II, while two of the three uveitis

Table 2. Characterization of registered adverse effects.

Patient ID	Sex	Age	Alive	Melanoma stage	BRAFi + MEKi	Symtom	Side	Complication	CTCAE grade	Ophthalmologic follow-up (mo)	Time to adverse event (mo)	Therapeutic decision	Complication resolution	Time of resolution since complication onset (d)
1	Male	74	Yes	IV	E+B	Blurred vision	OU	Serous retinal detachment of retina (involving macula)	II	95.3	1	Mantain	Complete	84
2	Female	49	Yes	IV	D+T	Blurred vision	OS	Uveitis	II	85.1	10.8	Mantain	Complete	17
3	Female	69	Yes	IV	D+T	None	OU	Serous retinal detachment of retina	II	4.1	3.3	Mantain	Complete	23
4	Female	55	No	IV	D+T	None	OU	Uveitis	II	3.2	5.1	Mantain	Unknown	
5	Male	67	No	IV	V+C	None	OU	Serous retinal detachment of retina (involving macula)	II	12	0.5	Mantain	Partial	
6	Male	60	No	IV	V+C	Blurred vision	OU	Retinal detachment; Uveitis; Papilledema	III; III; III	12.7	0.7	Suspend	Complete	243
7	Female	44	No	IV	V+C	None	OU	Serous retinal detachment of retina (involving macula)	II	2.3	1.9	Mantain	Complete	30
8	Female	59	No	IV	V+C	None	OU	Serous retinal detachment of retina (involving macula)	II	14.4	15.9	Mantain	Complete	15
9	Male	42	No	IV	V+C	None	OU	Serous retinal detachment of retina (involving macula)	II	3.4	1.4	Mantain	Partial	

SD - standard deviation. OU - both eyes. OS - left eye. D+T - dabrafenib + trametinib. V+C - vemurafenib + cobimetinib. E+B - encorafenib and binimetinib.

cases were grade II. The majority (88.9%) of patients with complications exhibited bilateral involvement.

Following the diagnosis of ocular complications, eight out of nine patients continued their treatment without dose adjustment. One patient, who presented with bilateral foveal retinal detachment and panuveitis with papillitis, discontinued V+C therapy and experienced complete resolution of symptoms within 17 days. Among the nine patients with ocular complications, six achieved complete resolution, two showed partial improvement before being lost to follow-up, and one patient was lost to follow-up immediately after the diagnosis.

The median time from treatment initiation to the onset of ocular complications was 57.8 days (IQR 25.9–241.8), while the median time to complete resolution following diagnosis was 26 days (IQR 16.5–123.8). When considering only patients who continued treatment without interruption, the median resolution time was slightly shorter, at 23 days (IQR 16.0–57.0). The median ophthalmological follow-up among patients who experienced ocular complications was 12.0 months (IQR 3.3–49.8).

Statistical analysis revealed a significant difference in the proportion of ocular adverse effects between treatment regimens (p=0.010), with 14.3% in the D+T group, 25.0% in the E+B group, and 71.4% in the V+C group, as illustrated in Fig. 1. Pairwise comparisons showed a significant difference between D+T and V+C (p=0.009), but no significant difference between E+B and V+C (p=0.242), nor between D+T and E+B (p=0.527). There was no statistically significant association between the occurrence of ocular adverse effects and gender (p=1.000), age (p=0.367), or melanoma stage (p=0.303). Similarly, systemic comorbidities such as arterial hypertension (p=1.000), type 2 diabetes *mellitus* (p=0.303), dyslipidemia (p=0.654), and benign prostatic hyperplasia (p=1.000) were not identified as risk factors for the development of ocular complications.

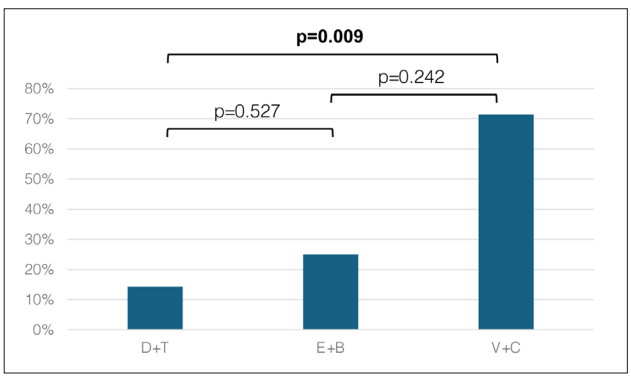

Figure 1. Incidence of adverse effects by therapeutic combination.
D+T - dabrafenib + trametinib. V+C - vemurafenib + cobimetinib. E+B - encorafenib and binimetinib.

The mortality rate in our sample was 56.3%, with 52.2% in patients without ocular complications and 66.7% in those with ocular complications, showing no statistically significant difference (p=0.694).

DISCUSSION

This study is one of the few to specifically assess ocular complications in patients undergoing BRAFi and MEKi therapy in real-world clinical settings, within an adverse effect monitoring framework. Our findings are significant, as most existing safety data stem from clinical trials and adverse event reporting systems, which are often limited by their controlled environments and inherent methodological constraints, respectively.

We found that 28.1% of our patients experienced ocular adverse events, with a significant variability between different therapeutic combinations, with V+C showing a higher rate of ocular toxicities compared to D+T and E+B (71.4% *vs* 14.3% *vs* 25.0%, respectively). The incidence of ocular complications in phase III clinical trials was 21% in COLUMBUS (E+B) and 17% in coBRIM (V+C), while ocular adverse events were not routinely monitored in the COMBI-v (D+T) trial.[7] However, these numbers from clinical trials may be underestimated. A retrospective study reported a 35% incidence in the D+T group,[8] and two small prospective studies found that all (100%) patients on V+C and E+B combination therapy had ocular adverse effects.[9,10] A study based on the FDA adverse event reporting system indicated D+T as the group with the most adverse effects notifications, but this result might be explained by the earlier FDA approval and more approved indications of this combination compared to the other combinations, resulting in a possible over-reporting bias.[4] Overall, the literature presents a wide range of incidence, due to the lack of uniformity in the description, diagnosis and reporting of the adverse effects.

BRAFi + MEKi combination therapies can cause adverse effects from both drug classes, potentially with a synergistic or additive effect.[4] The exact mechanism underlying these complications is still not fully understood.[11]

BRAFi therapy is primarily associated with anterior segment effects, including anterior uveitis and abnormalities involving the iris and ciliary body.[4,12] In our study, we observed a uveitis incidence of 9.4%. This rate falls within the range reported by other studies, where two cohort studies have documented uveitis incidences of 3.8% and 18.5%, respectively.[8,13] In our cohort, we observed a case of bilateral panuveitis with papillitis in a patient undergoing treatment with vemurafenib. This finding aligns with several case reports describing similar ocular manifestations, including Vogt-Koyanagi-Harada (VKH)-like syndrome, in patients receiving BRAFi, particularly vemurafenib.[14,15]

MEKi therapy, on the other hand, has been linked to retinal and choroidal abnormalities.[16] The term MEKAR (MEK inhibitor-associated retinopathy) was proposed to describe the class effect of retinal damages observed with the use of MEK inhibitors.[17] MEKAR is characterized by the accumulation of subretinal fluid, leading to serous detachment of the neurosensory retina.[18,19] This condition is typically bilateral, multifocal, relatively symmetrical, and often involves the fovea.[17] In our study, MEKAR was the most common finding, affecting 21.9% of the patients, a very similar incidence observed in COLUMBUS (E+B) and coBRIM (V+C) trials.[5] The majority (about 70%) of patients with MEKAR

in our cohort were asymptomatic. The reported rate of asymptomatic MEKAR varied across studies, with 57% in the coBRIM (V+C) trial and 31% in the COLUMBUS (E+B) trial,[5] but a post-hoc analysis of clinical trials and a prospective study revealed an incidence up to 90% and 100% of the patients, respectively.[9,20] These results highlight the underreporting of MEKAR ocular adverse events in the absence of routine monitoring, emphasizing the importance of proactive monitoring for early detection of the most common complication of the MEKi therapy.

The median time to onset of ocular complications in our study was 57.8 days. Although adverse effects typically emerge on the first days to weeks of treatment with MEKi[10] and on the first weeks to months of treatment with BRAFi,[21] some retrospective studies present cases of late toxicity, with average times that can go up to 87 days.[8]

In our study, the vast majority (89%) of patients who developed ocular toxicities, including those with MEKAR, were able to continue their BRAFi + MEKi treatment without requiring dose modifications. The self-limiting nature of these complications is highlighted by the median resolution time of 26 days. Only one patient required treatment discontinuation due to serous retinal detachment combined with panuveitis and papillitis. Despite the initial severity of symptoms, full resolution was achieved within 17 days following therapy cessation. Our relatively low rate of treatment discontinuation aligns with previous studies that highlight the generally manageable course of ocular toxicities with appropriate supportive care.[19]

In terms of uveitis management, most cases reported in the literature are mild and responsive to topical corticosteroids, allowing patients to continue BRAFi + MEKi therapy without interruptions.[19]

Likewise, MEKAR cases are generally mild and self-limited. Regular controls with OCT-SD without any treatment are usually sufficient; however, in severe cases, dose reduction or interruption of the MEKi might be necessary.[19] Although retinal thinning, potentially an early indicator of retinal atrophy, has been observed with long-term treatment MEKi, these changes have not been associated with any functional impairment.[10]

While decision-making algorithms have been proposed for managing ocular adverse events associated with BRAFi and MEKi therapies, no consensus has been reached.[4] Studies emphasize the importance of individualized clinical judgment when addressing these ocular side effects, as permanent or temporary discontinuation of BRAFi + MEKi therapy is typically required in only a minority of cases. Additionally, the simultaneous presence of other systemic adverse effects, such as cardiotoxicity, hepatotoxicity, or cutaneous reactions, can also impact treatment decisions.[19] These systemic effects must be carefully considered alongside ocular complications when determining the need for treatment modifications or discontinuation. Therefore, an effective multidisciplinary communication between the ophthalmologist, the oncologist and other specialists is essential.

In our sample, the risk of developing ocular adverse effects during BRAFi + MEKi therapy did not appear to be influenced by demographic or clinical factors such as gender, age, melanoma stage, or comorbidities including arterial hypertension, type 2 diabetes, dyslipidemia, and benign prostatic hyperplasia. These findings are consistent with a post-hoc analysis of the coBRIM trial, which identified increasing age as a significant risk factor for MEKAR, while gender, hypertension, diabetes, and dyslipidemia were not significantly associated with ocular toxicity.[22] One notable difference, however, is that the analysis of the coBRIM sample found individuals with a history of ocular inflammation or infection to be at highest risk, an association we could not assess, as none of the patients in our cohort presented such a history. The absence of a relationship between melanoma stage and ocular toxicity is particularly relevant, suggesting that disease severity does not appear to increase the risk of these adverse events.

Regarding mortality, Kaplan-Meier survival curves were initially considered; however, due to the limited follow-up time and the high degree of censoring, survival analysis was deemed unfeasible for this sample. Instead, mortality was assessed as a binary outcome (alive or deceased) within the available observation period, and the association between treatment regimen and mortality was analyzed using Fisher's exact test. The lack of a significant association between ocular complications and mortality in our study suggests that these toxicities, though potentially impactful on quality of life, do not appear to influence overall survival outcomes. Notably, to our knowledge, no studies have directly investigated the relationship between ocular toxicities and survival rates in melanoma patients undergoing targeted therapy. Our findings support the prevailing understanding that, while ocular complications warrant careful monitoring and management, they do not contribute to worsened survival outcomes in this patient population.

While our study offers valuable insights, it is important to acknowledge its limitations. The most significant is the relatively small sample size, particularly within the subgroups of different treatment regimens, which substantially reduces the statistical power of our analyses. Additionally, the mean ophthalmological follow-up time of 6.8 months is relatively short and may not be sufficient to detect late-onset or long-term ocular adverse events. A critical limitation is the excess of flexibility of the follow-up intervals. Although ophthalmological assessments were scheduled at standardized intervals (baseline, 1 month, 2 months, 3 months, 6 months and 12 months), follow-up became less frequent after 6 months, with appointments after 12 months conducted only when clinically necessary. This is particularly relevant, as two patients were diagnosed with ocular complications after more than 12 months, and the lack of standardization in this timeframe could have impacted the timely detection of these complications. The retrospective, single-center design may also limit the generalizability of our findings. Furthermore, a significant proportion of patients undergoing systemic therapy missed their scheduled ophthalmological monitoring visits, potentially introducing selection bias and underestimating the true incidence

of ocular toxicities in this population. Future multicenter, prospective studies with larger cohorts and longer follow-up periods are needed to better understand the spectrum, timing, and management of ocular adverse effects associated with BRAFi and MEKi therapies.

CONCLUSION

This study is one of the few to assess ocular complications in real-world clinical practice in patients undergoing BRAFi and MEKi therapy. Our findings highlight that, while ocular complications are common, particularly in patients receiving the V+C combination, most patients remain asymptomatic. Importantly, the majority of these complications are manageable with supportive care or temporary treatment adjustments. These results emphasize the need for regular ophthalmologic monitoring of all patients undergoing BRAFi + MEKi combination therapies, especially within the first three months of treatment, when complications are most likely to develop.

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AWARDS AND PREVIOUS PRESENTATIONS

This study was submitted to presentation at the 67º National Congress of Ophthalmology, Portugal.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

All authors contributed to the study conception and design. The data collection and analysis were performed by Vasco Lobo. Vasco Lobo wrote the first draft of the manuscript, and all authors participated in the revision of the manuscript. All authors read and approved the final version.

Todos os autores contribuíram para a concepção e o desenho do estudo. A recolha e a análise dos dados foram realizadas por Vasco Lobo. Vasco Lobo redigiu a primeira versão do manuscrito, e todos os autores participaram na revisão do manuscrito. Todos os autores leram e aprovaram a versão final.

RESPONSABILIDADES ÉTICAS

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

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