WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 2, 693-706. Research Article ISSN 2277– 7105

UVEAL MELONOMA: CURRENT AND EMERGING TREATMENT OPTIONS

S. D. Rihana*, G. Sandhya Rani, G. Sumanjali, G. Jyothi, G. Chaitanya and D. Rama Brahma Reddy

Nalanda Institute of Pharmaceutical Sciences.

Article Received on
25 Nov. 2018,

Revised on 15 Dec. 2018,
Accepted on 05 Jan. 2019

DOI: 10.20959/wjpr20192-13943

***Corresponding Author**
S. D. Rihana
Nalanda Institute of Pharmaceutical Sciences.

ABSTRACT

Uveal melanoma (UM) is the most probable intraocular malignancy and arises from melanocytes in the iris, ciliary body, or choroid. primary diagnosis and local treatment is crucial, as survival corresponds with primary tumor size. However, approximately 50% of patients will develop metastatic pathological condition with 6–12 months' survival from metastatic diagnosis. Genomic analyses have led to the advancement of gene-expression profiles that effectively forecast metastatic progression; unfortunately, no adjuvant therapy has been shown to prolong survival to date. New insights into the molecular biology of UM have discovered recurrent activating mutations in genes encoding for the G-protein α-subunit, GNAQ and GNA11, and improved understanding of the downstream signaling pathways MAPK, PI3K/Akt, and Hippo have managed an array of new targets for treatment of this disease. Studies are under way with rationally developed regimens targeting these pathways, and innovative agents are under development. We inspect the diagnosis, management, and surveillance of primary UM and the adjuvant therapy trials under way.

KEYWORDS: uveal melanoma, ocular melanoma, GNAQ, GNA11, MAP kinase, MEK, metastasis.

INTRODUCTION

Uveal melanoma (UM) is a unusual malignancy that arises from melanocytes within the uveal tract of the eye. Although UM is often diagnosed at an primary stage, local treatment methods come with significant visual morbidity and metastatic progression is not uncommon, portending an extremely under privileged prognosis. Much has been learned about the pathophysiology of UM, but despite these advances improvements in complete survival have

not been achieved. Only recently have unique therapeutics appeared that rationally target the known mechanisms of this disease, and a number of trials are under way attempting to change the disease course. In this analysis, we focus on the diagnosis of UM, therapeutic options for local control, and the pursuit of effective adjuvant therapy.

Pathophysiology

Dissimilar cutaneous melanoma, UM is genetically described by a small number of alterations; however, several of these changes have been well characterized and been found to change intracellular signaling, surface-receptor expression, and ligand production. Although cutaneous melanomas are driven by MAPK activation through mutations in BRAF (~50% of cases), NRAS (10%–25% of cases), or loss of function in NF1 (14% of cases), UM infrequently docks such changes and rather is characterized by point mutations in the G-protein α-subunit. GNAQ and GNA11 are genes that code for the α-subunit of G proteins that performs in conjunction with G-protein-coupled receptors. G protein and G-protein-coupled receptor-signal transduction come to pass through the conversion of GDP to GTP, which activates the G protein and signals via downstream effector proteins. for the G protein to return to its inactive state, GTP mandatorily be hydrolyzed to GDP. It has been exhibited that glutamine at the 209 position is mandatory for GTPase activity, and mutations that rattle this activity cause a constitutively active GTP-bound state. This is analogous in mechanism to the better-known RAS oncogenes that code for monomeric G proteins, which are frequently constitutively or inappropriately activated in many malignancies.

Enucleation: In the olden days, enucleation was the essential treatment for the primary intraocular tumor. Still today, it is the treatment of preferred when there is small chance to save vision, which is usually the case for large, advanced UM, tumors located around the optic disc, tumors presenting with extensive bleeding or retinal detachment, or vitreous hemorrhage. Another way, the UM can be managed conservatively in an attempt to save vision and the globe.

In terms of survival, many studies depicted no differences in the mortality rates comparing surgical treatments and conservative treatments. in a multicenter prospective randomized trial, COMS correlated enucleation and radiotherapy among comparable patients with medium-sized choroidal melanomas that would be suitable for either form of treatment. With long-term follow-up, the course demonstrated no differences in survival outcomes and little

difference in quality-of-life consequences between both methods of treatment. As a result, there has been a extensive shift towards eye- and vision-conserving treatments.

Radiation Therapy

Radiation therapy methods include brachytherapy, photon-based external-beam radiation, and charged-particle radiation. These procedures have exhibited excellent local control and globe preservation; however, long-term vision loss is common. Brachytherapy associated in securing a radioactive plaque to the episclera to distribute a fixed dose of focal radiation to a tumor. The usual radioisotopes used are ^{125}I and ^{106}Ru. ^{125}I emits γ-radiation, which penetrates more profoundly into tissues than the β-emitting ^{106}Ru (<6 mm tumor thickness). The American Brachytherapy Society advocates against brachytherapy in patients with tumors with extra ocular extension, large basal diameters, blind painful eyes, and those with no light-perception vision. Regional recurrence rates are 7%–10% for ^{125}I, 14.7% for ^{106}Ru, and 3.3% with ^{103}Pd.Although helped with good local control, brachytherapy is associated with complications, including radiation-induced retinopathy (45%–67%), cataracts (44%), neovascular glaucoma (28.3%), and macular edema (24.5%).these complexity lead to moderate vision loss in 58% of patients and less visual acuity (best corrected worse than 5/200) in 28% within 2 years. Outcomes may be enhanced with the use of intravitreal bevacizumab, with 33% distinguishing moderate vision loss and 15% developing poor visual acuity. Traditional ophthalmologic exams for years are required to monitor complications.

Studies of proton-beam therapy have also demonstrated optimistic results. A latest retrospective cohort study of patients with T3–T4 choroidal melanomas conduct with proton-beam therapy demonstrated a 5-year local control rate of 94%, enucleation rate of 19.5%, and preservation of visual acuity ≥20/200 of 20%.A case course of tumors of all stages create primary proton-beam therapy to achieve a 96.4% local control rate and 95% eye-retention rate with median follow-up of 5 years.

Conservative therapy

Photocoagulation, Photodynamic Therapy

Photodynamic therapy (PDT) subsists of the excitation of an intravenously conduct photosensitizer by a specific wavelength enforced to the target region. Its tissue effects are nonthermal; generated free radicals and highly reactive singlet oxygen species inducing.

Cell and tissue destruction through complex mechanisms that remain incompletely understood. These include cellular, vascular, and immunogenic pathways. The relative contribution of each pathway is thought to be dependent upon the characteristics of the photosensitizer, the treated tissue, and treatment parameters (time and dose).Verteporfin, a second-generation photosensitizer, has been shown to work primarily by persuading vascular occlusion. It is FDA-approved for the treatment of age-related macular degeneration, and has been used in large clinical trials with few adverse effects. In tumors, its effects are thought to be attributed to a combination of vascular occlusion, direct cytotoxicity, and activation of the immune system. There is some proof however, that PDT is more effective in lightly pigmented melanomas compared more densely pigmented tumors. A small number of in vivo choroidal melanoma animal models have achieved partial tumor remission with treatment; photosensitizing effects, including initial tumor-growth arrest and tumor necrosis, were demonstrated. In human studies, there is limited clinical experience. Small series using PDT with verteporfin as primary therapy have shown it to be effective in achieving complete regression. One further study used PDT with verteporfin as second-line therapy, demonstrating partial effect, with growth arrest achieved in two of four patients, who were subsequently able to avoid enucleation. However, histopathologic studies of three UM cases 1 week after treatment with PDT (with verteporfin) and bevacizumab showed viable melanoma cells with no necrosis. The logical conclusion is that PDT is ineffective in the treatment of these UMs, with viable UM cells seen at both short- and long-term histopathological review. This same study also found that use of PDT as a preoperative adjuvant therapy prior to biopsy eliminated bleeding at the biopsy site, an indication that may be promising in the future with further investigation. Thus, comprehensive clinical studies are still required to determine optimal case-selection criteria, treatment parameters, and the efficacy of PDT with verteporfin as a primary or adjuvant treatment.

Surgery

Enucleation is the most common surgery performed for UM, and is appropriate for patients with vision loss, extensive extra ocular growth, circumferential tumor invasion, and large tumor diameter. Preenucleation external-beam radiation therapy has been studied, without additional benefit observed, and thus is not recommended. Interestingly, the COMS quality-of-life report depicted that patients undergoing enucleation were less likely to have anxiety than patients treated with brachytherapy.

Alternative surgical modalities include transretinal endoresection and transscleral resection. These methods are site- and surgeon-dependent, with the majority of data coming from single-institution case series. Transscleral resection may be attempted in patients with large tumors who are not candidates for radiation therapy who seek eye-retaining treatment. The betterment of transscleral resection is enhanced vision preservation; however, this is a complex procedure with associated complications. Complications include retinal detachment (21%), ocular hypertension (21%), sub macular hemorrhage (16%) and high rates of repeat vitreoretinal surgery (44%–70%). Hypotensive anesthesia may be used to reduce bleeding, but acts as a additional risks.

Frequency rates are higher with transscleral resection when compared to either enucleation or brachytherapy. In a retrospective review comparing transscleral resection to ^{125}I brachytherapy for patients with tumor height >7.5 mm, 61.1% versus 5.6% maintained visual acuity >20/200, without significant difference in rates of metastasis. In this study, the more number of patients in the transscleral resection group received adjuvant ^{106}Ru plaque therapy. A matched case-control study evaluating transscleral resection versus iodine brachytherapy found similar results, with improved vision conservation after transscleral resection but above local recurrence in the transscleral group. Significantly, no difference in 8-year all-cause mortality, melanoma specific mortality, or quality of life was observed. The series of transscleral resections of large UM with longest follow-up comes from Innsbruck Medical University, where 5- and 10-year local tumor repetition was 24% and 32%, respectively. Five- and 10-year metastatic rates of 28% and 44% were detected. In this study, lack of ruthenium adjuvant therapy brought a 4.4-fold greater risk of recurrence. The concern for local recurrence in transscleral resection was again seen when studying ciliochoroidal melanomas with considerable height, where the frequency rate was 41% at 5 years with resection compared to 7% with brachytherapy. Neoadjuvant therapies have been used initially to transscleral resection in an struggle to enhance local control. Although mean follow-up was only 3.2 years, a case squeal of neoadjuvant proton-beam irradiation followed by resection exhibited, enhanced local recurrence rates, with no effect upon metastasis, when compared to historical controls. Of note, 70% undergone vitreoretinal surgery secondary to complications of tumor resection. Estimated risk of local recurrence was 4.2% and 10.4% at 3 and 5 years, respectively, with risk of metastasis 28.4% and 40.3%, respectively.

Laser therapy

Photodynamic laser photocoagulation and transpupillary thermal therapy (TTT) are modalities that direct focused energy to destroy tumor vascular supplies and reduce local recurrences by injecting and activating light-sensitive compounds and free radicals. TTT has shown some efficacy in treatment of residual choroidal melanomas and as adjuvant therapy after brachytherapy, when plaque tilt may have limited radiation delivery. TTT has been effective as fundamental therapy in up to 80% of cases of small or indeterminate lesions with few risk factors. A study of ruthenium brachytherapy with or without TTT exhibited higher rates of tumor regression, globe preservation, and recurrence-free survival with adjuvant TTT. In contrast, Tarmann et al found that brachytherapy with TTT did not improve tumor control, but contributed to worse visual outcomes.

Novel therapies for Primary disease

Despite present treatment methods for primary disease achieve frequent local control, complications, including vision loss, are common, and novel approaches are much needed. Several novel approaches are currently in development.

ICON-1 is a structural variant of human factor VII being advanced by Iconic Therapeutics. Factor VII is the natural ligand of tissue factor, which is commonly overexpressed and upregulated in UM and contributes to tumor growth, thrombosis, angiogenesis, and metastasis. ICON-1 binds to cells over expressing tissue factor, initiating a signal cascade targeting immune cells to pathological tissue while leaving normal tissue intact. A Phase I study is continuing to test safety and allow ability of intravitreal ICON-1 at three dosing regimens in patients with primary UM planning to endure enucleation.

One more tumor-targeted approach to treating UM is being developed by Aura Biosciences. Their lead drug, AU-011, consists of virus-like fragments that selectively bind cancer cells, conjugated to infrared-activated molecules that destroy tumor membranes upon activation with an ophthalmic laser. Preclinical studies exhibited human papillomavirus-modeled virus-like particles bind to heparin sulfate proteoglycans on disrupted epithelium, but do not bind to intact epithelium. Papillomavirus capsids bind various tumor-derived cell lines in vitro and in vivo in orthotopic models for ovarian and lung cancers, and complete tumor eradication was found histopathologically. AU-011 has been admitted an “orphan” drug designation by the US Food and Drug Administration, and clinical trials are to start in 2016.

Adjuvant treatments

Adjuvant therapy (AT) may consist of radiotherapy or systemic therapy, such as chemotherapy, immunotherapy, hormone therapy, biological therapy, or target therapy. Although this treatment modality is well established in some tumors, there are few studies of AT in UM.

Lane et al 61 treated 121 high-risk UM patients with adjuvant interferon alfa-2a after radiation or enucleation from 1995 to 1999. They defined high-risk patients as: age ≥ 56 years, largest tumor dimension ≥ 15 mm, ciliary body involvement, or extrascleral tumor extension. The treatment was practiced as 3 million International Units subcutaneously three times per week over a 2-year course. This AT, however, had no significant influence on melanoma-related mortality (rate ratio 1.02, 95% CI 0.68–1.5; P = 0.91).

Gomer 17 treated 22 high-risk UM patients with AT intra-arterial hepatic fotemustine. Planned treatment duration was 6 months, starting with 4-weekly doses of 100 mg/m, and after a 5-week rest this was repeated every 3 weeks. The 5-year survival rate of the experimental group was 75%, correlated to 56% of a matched-control group. Their data suggested a survival benefit, although it was not statistically significant.

Few studies have been done applying AT in local eye treatment. De Potter and Jamart 62 applied indocyanine green in 30 patients with choroidal melanoma before treatment with TTT. They found no difference in the regression pattern compared to 30 patients treated only with TTT. Nonetheless, in vitro studies showed that UM cells treated with amfenac, a cyclooxygenase-2 inhibitor, become more radiosensitive and may decrease tumor recurrence and radiation-induced complications while broadening the indications for radiotherapy in UM tumors.

Immunotherapy

As UM arises in an immune-privileged site, the eye, it could be responsive to T-cell-based immunotherapy. Most of the immunotherapy treatments tested in UM are extensions from previous experiences with cutaneous melanoma, but the genetic differences between these two tumors indicate that an immunotherapy specifically for UM should be developed. Ipilimumab is a fully human anticytotoxic T-lymphocyte antigen-4 monoclonal antibody that seems to improve overall survival in patients with advanced cutaneous melanoma. Danielli et al a 107 performed a multicenter study with ipilimumab of 13 pretreated patients with

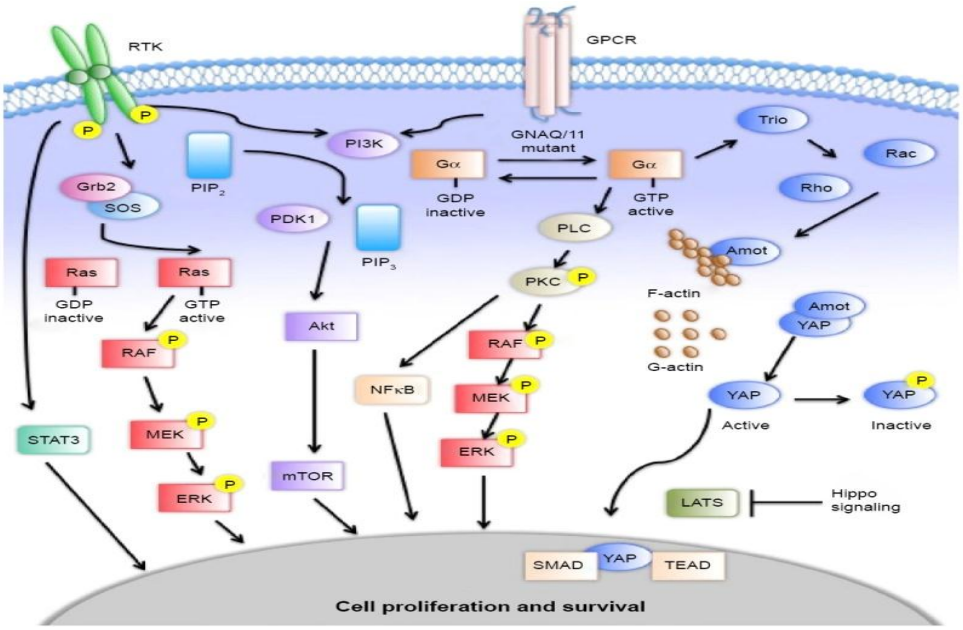
metastatic UM in six different European institutions. No objective responses were observed, but two patients achieved stable disease, a third achieving stable disease after initial disease progression.

IL-2 is an FDA-approved immunostimulatory cytokine for stage 4 cutaneous melanoma, with an overall response rate of 20% and complete response rate of 5%–10%. However, no clinical trials of IL-2 in metastatic UM have been performed. Soni et al 108 reported an 8-year-old girl with UM metastatic to liver and pancreas who was treated with high dose bolus IL-2 and thalidomide. The patient experienced minimal toxicity and had stable disease for 23 months. From a series of nine cases of long-surviving metastatic UM patients, two received IL-2 and one received IL-2 plus programmed death (PD)-1 monoclonal antibody vaccine.

The combination of BOLD with interferon-α showed objective response rates of approximately 20%; however, further studies did not confirm this result. Nonetheless, Al-Jamal et al 108 reported one case of a long-surviving metastatic UM that was treated with BOLD and recombinant interferon. The patient had several small metastatic nodules in the liver and was not eligible for surgical resection. Following treatment, the patient was still alive after 72 months, when the report was made.

Huppert et al 74 treated 48 liver metastatic UM patients with fotemustine (via the hepatic artery or via peripheral vein) and interferon-α2 and IL-2. Just 2% (one patient) achieved complete response, and 12.5% (six patients) achieved a partial response, with an overall response rate of 14.5%.

PD-1 protein, a T-cell co inhibitory receptor, and one of its ligands, PD-L1, play a role in the capability of tumor cells to escape the host's immune system. Their blockage enhances immune function and serves as antitumor activity. Clinical trial NCT00729664 with an antibody-mediated blockade of PD-L1 induced durable tumor regression and prolonged stabilization of disease in advanced cutaneous melanoma and other types of cancer. Its efficacy in UM is yet to be obstinate.



RESULTS

UM is the most probably intraocular malignancy, and despite admirable local control with available therapies, little progress has been made to alter the disease course. Radiation therapy and enucleation have been the backbone of therapy for decades, with little to no efficacy demonstrated from traditional chemotherapy in the primary, adjuvant, or metastatic setting. The future of UM treatment is evolving rapidly. unique therapeutic strategies are emerging for the executing of primary UM, such as the targeting of tissue factor and heparin sulfate proteoglycans, which have led to the initiation of early phase trials. In the adjuvant and metastatic settings, an enhanced grasping of UM pathophysiology has led to the study of newer therapies that target the dysregulated pathways, as well as the immunological response to this disease, and will hopefully lead to enhanced outcomes; however, further work is needed. As our understanding of oncogene addiction emerges, combination regimens that stop feedback escape will be supplementary investigated and advanced therapeutics that target driving genetic events developed. Agents that change gene expression and epigenetics, like HDAC and DNA methyltransferase inhibitors, will be further studied and next-generation immunotherapies that not only release inhibition of existing immune responses but actively guide our immune system to malignant cells, like IMCgp100, will move through development. In order for this to appear, extensive study must take place, and prolonged funding of clinical trials and development of newer therapies will be critical to improving outcomes for patients with this challenging disease.

DISCUSSION

UM is a frightening tumor, and despite the accuracy in the clinical diagnosis and new therapeutic modalities for treatment of the intraocular tumor, a significant proportion of the patients will develop metastasis and die of the disease. There is no difference in survival between surgical and conservative treatments of the intraocular tumor. Therefore, conservative treatments are selected if there is a chance to save vision. Enucleation is reserved for patients with larger tumors or with blind painful eyes, and exenteration is indicated only when there is extra ocular extension and orbital invasion. Metastasis of UM can occur late in the course of the disease, and the liver is the main site of metastasis. Once patients develop metastases, the prognosis is generally poor; however, treatment of the metastatic disease does seem to improve the overall survival time. There are different modalities for the management of the metastatic nodules, including resection when possible, HIA chemotherapy, chemoembolization, immunoembolization, and isolated hepatic perfusion. Conventional systemic adjuvant chemotherapy does not seem to improve the overall survival of these patients, although new promising systemic therapies including TTh are gaining credibility, with several clinical trials currently in progress. Despite the different mutations found in UM and cutaneous melanoma, these tumors have been largely studied together regarding treatment options. Several studies have demonstrated that they are distinct tumors, and in our opinion they should be regarded as different entities.

CONCLUSION

In conclusion, there are very few studies of AT for UM. More studies with different promising systemic therapies and combination treatments are needed. The low prevalence rate of this tumor may contribute to the difficulty in initializing clinical trials.

ACKNOWLEDGEMENT

RDC serves a mentor and/or advisory board member for AstraZeneca, Aura Biosciences, Iconic Therapeutics, Janssen, Merck, Novartis, Rgenix, and Thomson Reuters. BPM serves as a consultant for Aura Biosciences. The other authors report no competition of interest in this work.

REFERENCES

1. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. Cancer, 2005; 103(5): 1000–1007. [PubMed]

2. Singh AD, Topham A. Incidence of uveal melanoma in the United States: 1973–1997. Ophthalmology, 2003; 110(5): 956–961. [PubMed]
3. Damato B. Progress in the management of patients with uveal melanoma: the 2012 Ashton Lecture. Eye (Lond), 2012; 26(9): 1157–1172. [PMC free article] [PubMed]
4. Damato EM, Damato BE. Detection and time to treatment of uveal melanoma in the United Kingdom: an evaluation of 2,384 patients. Ophthalmology, 2012; 119(8): 1582–1589. [PubMed]
5. Andreoli MT, Mieler WF, Leiderman YI. Epidemiological trends in uveal melanoma. Br J Ophthalmol, 2015; 99(11): 1550–1553. [PubMed]
6. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology, 2011; 118(9): 1881–1885. [PubMed]
7. Hu DN, Yu GP, McCormick SA, Schneider S, Finger PT. Population-based incidence of uveal melanoma in various races and ethnic groups. Am J Ophthalmol, 2005; 140(4): 612–617. [PubMed]
8. Virgili G, Gatta G, Ciccolallo L, et al. Incidence of uveal melanoma in Europe. Ophthalmology, 2007; 114(12): 2309–2315. [PubMed]
9. Park SJ, Oh CM, Kim BW, Woo SJ, Cho H, Park KH. Nationwide incidence of ocular melanoma in South Korea by using the National Cancer Registry Database (1999–2011) Invest Ophthalmol Vis Sci, 2015; 56(8): 4719–4724. [PubMed]
10. Shields CL, Kaliki S, Livesey M, et al. Association of ocular and oculodermal melanocytosis with the rate of uveal melanoma metastasis: analysis of 7872 consecutive eyes. JAMA Ophthalmol, 2013; 131(8): 993–1003. [PubMed]
11. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association of cutaneous and iris nevi with uveal melanoma: a meta-analysis. Ophthalmology, 2009; 116(3): 536–543. e2. [PubMed]
12. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science, 2010; 330(6009): 1410–1413. [PMC free article] [PubMed]
13. Gallagher RP, Elwood JM, Rootman J, et al. Risk factors for ocular melanoma: Western Canada Melanoma Study. J Natl Cancer Inst, 1985; 74(4): 775–778. [PubMed]
14. Lains I, Bartosch C, Mondim V, et al. Second primary neoplasms in patients with uveal melanoma: a SEER database analysis. Am J Ophthalmol, 2016; 165: 54–64. [PubMed]

15. Tucker MA, Shields JA, Hartge P, Augsburger J, Hoover RN, Fraumeni JF., Jr Sunlight exposure as risk factor for intraocular malignant melanoma. N Engl J Med, 1985; 313(13): 789–792. [PubMed]
16. Shah CP, Weis E, Lajous M, Shields JA, Shields CL. Intermittent and chronic ultraviolet light exposure and uveal melanoma: a meta-analysis. Ophthalmology, 2005; 112(9): 1599–1607. [PubMed]
17. de Lange MJ, Razzaq L, Versluis M, et al. Distribution of GNAQ and GNA11 mutation signatures in uveal melanoma points to a light dependent mutation mechanism. PLoS One, 2015; 10(9): e0138002.[PMC free article] [PubMed]
18. Shields CL, Furuta M, Berman EL, et al. Choroidal nevus transformation into melanoma: analysis of 2514 consecutive cases. Arch Ophthalmol, 2009; 127(8): 981–987. [PubMed]
19. Shields JA, Sanborn GE, Augsburger JJ. The differential diagnosis of malignant melanoma of the iris: a clinical study of 200 patients. Ophthalmology, 1983; 90(6): 716–720. [PubMed]
20. Shields JA, Augsburger JJ, Brown GC, Stephens RF. The differential diagnosis of posterior uveal melanoma. Ophthalmology, 1980; 87(6): 518–522. [PubMed]
21. Heng DY, Kollmannsberger C. Sunitinib. Recent Results Cancer Res, 2010; 184: 71–82. [PubMed]
22. Crosby MB, Yang H, Gao W, Zhang L, Grossniklaus HE. Serum vascular endothelial growth factor (VEGF) levels correlate with number and location of micrometastases in a murine model of uveal melanoma. Br J Ophthalmol, 2011; 95(1): 112–117. [PMC free article] [PubMed]
23. Barak V, Pe'er J, Kalickman I, Frenkel S. VEGF as a biomarker for metastatic uveal melanoma in humans. Curr Eye Res, 2011; 36(4): 386–390. [PubMed]
24. Chana JS, Wilson GD, Cree IA, et al. c-myc, p53, and Bcl-2 expression and clinical outcome in uveal melanoma. Br J Ophthalmol, 1999; 83(1): 110–114. [PMC free article] [PubMed]
25. Augsburger JJ, Corrêa ZM, Shaikh AH. Quality of evidence about effectiveness of treatments for metastatic uveal melanoma. Trans Am Ophthalmol Soc, 2008; 106: 128–135. discussion 135–137. [PMC free article] [PubMed]
26. Kermer V, Baum V, Hornig N, Kontermann RE, Müller D. An antibody fusion protein for cancer immunotherapy mimicking IL-15 trans-presentation at the tumor site. Mol Cancer Ther, 2012; 11(6): 1279–1288. [PubMed]

27. Bosch JJ. Immunotherapy of uveal melanoma. Dev Ophthalmol, 2012; 49: 137–149. [PubMed]
28. Danielli R, Ridolfi R, Chiarion-Sileni V, et al. Ipilimumab in pretreated patients with metastatic uveal melanoma: safety and clinical efficacy. Cancer Immunol Immunother, 2012; 61(1): 41–48. [PubMed]
29. Soni S, Lee DS, DiVito J, Jr, et al. Treatment of pediatric ocular melanoma with high-dose interleukin-2 and thalidomide. J Pediatr Hematol Oncol, 2002; 24(6): 488–491. [PubMed]
30. Al-Jamal RT, Eskelin S, Pyrhonen S, Kivela T. Long-term progression-free survival in metastatic uveal melanoma after chemoimmunotherapy and consolidation thermoablation. Acta Oncol, 2009; 48(3): 476–479. [PubMed]
31. Rajpal S, Moore R, Karakousis CP. Survival in metastatic ocular melanoma. Cancer, 1983; 52(2): 334–336. [PubMed]
32. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med, 2012; 366(26): 2455–2465. [PMC free article] [PubMed]
33. Einhorn LH, Burgess MA, Gottilieb JA. Metastatic patterns of choroidal melanoma. Cancer, 1974; 34: 1001–1004. [PubMed]
34. Gragoudas ES, Egan KM, Seddon JM, et al. Survival of patients with metastases from uveal melanoma. Ophthalmology, 1991; 98(3): 383–389. [PubMed]
35. Pyrhönen S, Hahka-Kemppinen M, Muhonen T. A promising interferon plus four-drug chemotherapy regimen for metastatic melanoma. J Clin Oncol, 1992; 10(12): 1919–1926. [PubMed]
36. Kath R, Hayungs J, Bornfeld N, et al. Prognosis and treatment of disseminated uveal melanoma. Cancer, 1993; 72: 2219–2223. [PubMed]
37. Nathan F, Sato T, Hart E. Response to combination chemotherapy of liver metastasis from choroidal melanoma compared with cutaneous melanoma; Presented at: Annual meeting of the American Society of Clinical Oncology; April 10–13, 1994; San Francisco, CA, USA.
38. Atzpodien J, Lopez Hänninen E, Kirchner H, et al. Chemoimmunotheraphy of advanced malignant melanoma: sequential administration of subcutaneous interleukin-2 and interferon-alpha after intravenous dacarbazine and carboplatin or intravenous dacarbazine, cisplatin, carmustine and tamoxifen. Eur J Cancer, 1995; 31A(6): 876–881. [PubMed]

39. Proebstle TM, Scheibenbogen C, Sterry W, Keilholz U. A phase II study of dacarbazine, cisplatin, interferon-alpha and high-dose interleukin-2 in “poor-risk” metastatic melanoma. Eur J Cancer, 1996; 32A(9): 1530–1533. [PubMed]
40. Nathan FE, Berd D, Sato T, et al. BOLD+interferon in the treatment of metastatic uveal melanoma: first report of active systemic therapy. J Exp Clin Cancer Res, 1997; 16(2): 201–208. [PubMed]