Targeted Therapy and Their Ocular Complications

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13.1 Introduction

The rapid advancements in the field of oncology have resulted in the transition from cytotoxic chemotherapeutic agents to molecularly targeted therapies that interfere with cellular signaling pathways important for the survival and propagation of neoplastic cells. Some of these agents have changed the landscape in the management of several hematologic and solid malignancies. Molecularly targeted agents are selected and designed to provide the maximal antitumor affect with the minimal functional alteration of the normal healthy cells [1]. However, the complexity of cellular pathways proves very difficult to design therapeutic agents that do not overlap with the physiologic activities of the normal human tissues. The recognition of a myriad of distinct adverse effects related to the molecularly targeted therapies has emerged over the last decade with their increased clinical usage [2, 3].

Molecularly targeted agents act through the variety of specific mechanisms, which results in the unique side effects related to a specific agent. Clinically recognized side effects depend on the cellular pathways which are inhibited and their expression in the different ocular and adnexal tissues. Most ocular tissues have been found susceptible to the development of side effects secondary to these drugs, from the periocular skin to the central nervous system visual pathways. Familiarity of the ophthalmologists with the potential ocular side effects is important for the early recognition of ocular toxicities.

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13.2 Specific Agents

13.2.1 Tyrosine Kinase Inhibitors

Tyrosine kinases are enzymes involved in signal transduction pathways regulating cell growth and response to the extracellular stimuli. Human malignant cells develop mutations that can lead to constantly activated tyrosine kinase enzymes resulting in uncontrolled cellular growth and proliferation. Inhibition of aberrantly activated tyrosine kinase enzymes was the first success story of molecularly targeted therapy [4].

Imatinib (Gleevec™), also known as signal transduction inhibitor (STI)-571, was the first FDA-approved molecularly targeted agent in May 2001, which inhibits abnormally fused break point cluster-Abelson (BCR-ABL) tyrosine kinase in chronic myelogenous leukemia (CML) caused by the 9:22 translocation. Subsequently, it was discovered that imatinib also blocks the activity of tyrosine kinases associated with platelet-derived growth factor receptor (PDGFR) and c-Kit (CD117), the receptor for stem-cell factor (SCF). Blockade of mutated c-Kit results in apoptosis of gastrointestinal stromal tumor (GIST) cells and dramatic regression of neoplastic lesions [5, 6].

PDGFR and c-Kit tyrosine kinases are prevalent in dermal dendrocytes that reside in normal human skin including periorbital area. There is some evidence that PDGRF signaling pathway plays a role in the regulation of interstitial fluid pressure and its inhibition in dermal dendrocytes may lead to the extravasation of plasma into the extracellular space. Anatomical structure of the periorbital skin makes it very susceptible to the interstitial fluid changes. It is not surprising that the most common ophthalmic side effect of imatinib therapy is the development of periorbital swelling affecting around 70 % of treated patients. Peripheral edema occurs less frequently affecting about 29 % of patients. The severity of periorbital edema may range from mild to moderate, which is the most common presentation, to severe swelling resulting in the obstruction of visual axis. Edema usually develops 2–3 months after the initiation of therapy, but it can be seen as soon as 1 day or up to a year after the beginning of medication. The increased dose may be associated with the higher rates of periorbital edema. The management of periorbital edema in cancer patients treated with imatinib depends on the severity of symptoms and may include observation for mild edema, low-dose diuretics such as furosemide for moderate edema, and surgical debulking of the excessive edematous tissue in very severe cases. Periorbital edema almost never requires the cessation of cancer therapy because it can be successfully managed by medical or surgical approaches [7–9].

Epiphora is also a common complaint in patients treated with imatinib. It occurs in about 18 % of treated patients occurring almost exclusively in patients who also had concomitant periorbital edema. Clinical evaluation of these patients showed no evidence of punctual, canalicular, or nasolacrimal duct obstruction as probing or irrigation revealed patent tear outflow system. Half of the patients were noted to have conjunctival chemosis related to the fluid collection underneath the conjunctiva or conjunctivochalasis partially blocking the opening of inferior puncta. Concomitant periorbital edema may disrupt the functional force of pretarsal orbicularis oculi muscle and result in lacrimal pump dysfunction. Imatinib metabolism may also lead to by-product secretion and its accumulation in tear film, which could act as an irritant causing overproduction of tears. Most patients with mild epiphora can be observed. If symptoms are severe enough to interfere with quality of life, 40 mg of furosemide daily and prednisolone acetate (1 %) four times a day were found to be effective in alleviating symptoms [9, 10].

Increased intraocular pressure (IOP) is a possible complication from imatinib therapy in patients with CML, and the literature reports supporting it are very scarce. A report from Italy showed that 1.6 % of 250 patients treated with imatinib developed increased IOP, which required either discontinuation of therapy or reduction in dose. One patient required glaucoma surgery. The same group also reported several patients developing recurrent conjunctival hemorrhages in spite of no evidence of thrombocytopenia or coagulation

abnormalities. It is postulated that the inhibition of c-kit enzyme found on mast cells that populate the conjunctival substantia propria make the mucosa more vulnerable to mild trauma [11].

Imatinib can very rarely lead to vision-threatening complications compromising the function of retina or optic nerve. Experimental models demonstrated widespread apoptosis of retinal ganglion cells (RGCs) in the cell culture treated with imatinib for up to 48 h due to downstream disruption of PDGF receptor signaling mediators that promoted the survival of RGCs. Animal experiments indicated that high-dose (1.65 mg) intravitreal injection of imatinib resulted in extensive retinal necrosis in contrast to low-dose (165 or 825 μg) injection that showed no ocular toxicity [12]. These experimental models only underline possible retinal toxicities and in no way simulate in vivo imatinib effect from the current oral dosing of the medication. Nevertheless, there are very sparse reports of imatinib causing optic disc edema, retinal hemorrhages, retinal neovascularization, and cystoid macular edema. There was a resolution of side effects and improvement in visual acuity after the dose reduction or cessation of imatinib therapy in these reports [11, 13–16].

It is of paramount importance to rule out neoplastic infiltration of the optic nerve prior to suspecting imatinib toxicity as a culprit for the optic nerve disease.

Dasatinib and *nilotinib* are newer inhibitors of tyrosine kinases, including the BCR-ABL tyrosine kinase, that are used for the treatment of Philadelphia chromosome-positive CML that is resistant to imatinib. Their safety profile may be distinct from imatinib, but given the similar mechanism of action between these agents, the potential for development of ocular side effects will remain present [17].

13.2.2 Epidermal Growth Factor Receptor Inhibitors

The epidermal growth factor receptor family (also known as ErbB) consists of four receptors: the epidermal growth factor receptor (EGFR/ErbB1/HER1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4). Their function is essential for the normal growth and differentiation of epithelial cells. It is highly expressed in the various ocular tissues including the periocular skin, hair follicles, meibomian and lacrimal gland, conjunctiva, and cornea. It is not surprising that the most side effects of EGFR inhibitors are related to the ocular surface [18].

Erlotinib (TarcevaTM) is a potent inhibitor of EGFR tyrosine kinase competitively blocking ATP binding site at the active tyrosine kinase region and disrupting downstream cellular signaling cascade, used for the treatment of locally advanced or metastatic non-small cell lung cancer and pancreatic cancer. Ocular side effects were reported in up to 12 % of treated patients during the clinical trial mostly consisting of the ocular surface disease. Inhibition of EGFR may disrupt keratin gene expression within the eyelash follicles leading to the abnormal growth cycle and trichomegaly affecting 29 % of patients [18, 19]. The aberrant eyelashes can rub against the ocular surface resulting in corneal abrasion and ulceration. The mechanical trauma caused by trichomegaly is accentuated by the EGFR inhibition causing meibomian gland secretion abnormalities, the abnormal quality and quantity of the tear film and delayed corneal epithelial healing. The prompt recognition of these side effects is important to prevent vision-threatening corneal infections. Eyelash trimming, aggressive lubrication, and topical antibiotic instillation with careful monitoring are common therapeutic approaches. The tear film abnormality can be treated with oral doxycycline and artificial tears. Erlotinib was also reported to cause periorbital rash, blepharitis, hyperemia, and telangiectasia that can be treated with topical Maxitrol eye ointment and fluorometholone (0.1 %) ointment (Fig. 13.1) [18–20]. Cessation of therapy can lead to the healing of persistent epithelial defect, but it is rarely necessary to discontinue therapy unless severe corneal disease develops. Corneal perforation was reported in a patient treated with erlotinib for stage IV lung squamous cell carcinoma that required surgical intervention and discontinuation of therapy due to severe vision-threatening side effects [21].

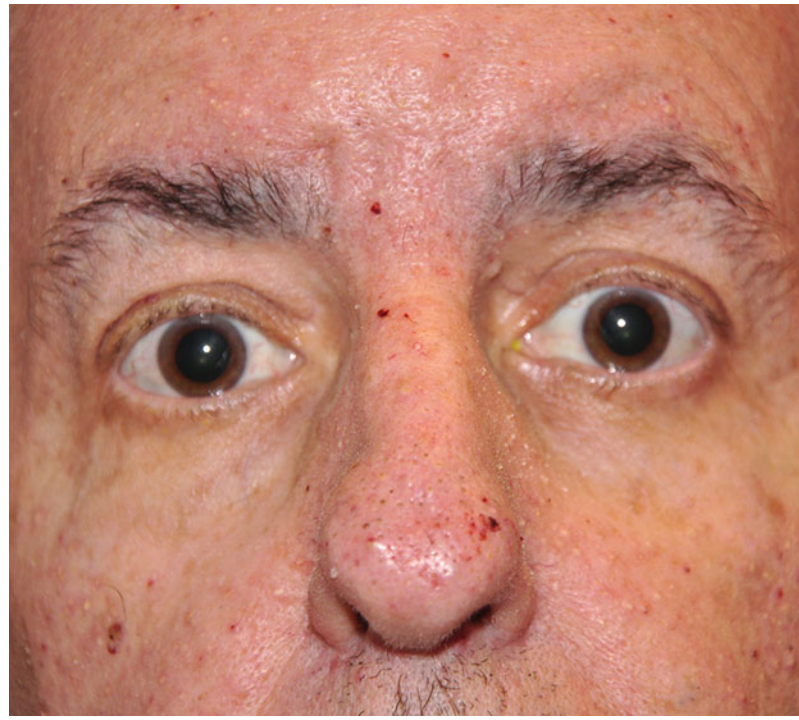

Fig. 13.1 Periorbital rash, hyperemia, and telangiectasia induced by *erlotinib (Tarceva™)*

Gefitinib (Iressa™) inhibits the EGFR tyrosine kinase activity by competitive blockade of ATP binding site, used for the treatment of non-small cell lung cancer in patients who have activating mutations in EGFR gene caused by in-frame deletions within exon 19 and the L858R point mutation, which are more prevalent in non-smokers, Asians and women [22]. The ocular side effects of gefitinib overlap with the side effects of erlotinib given its similar mechanism of action. During the clinical trial, gefitinib therapy was found to cause trichomegaly, meibomitis, tear film abnormalities, and reversible recurrent corneal erosions in 8 % of patients. The side effects can be managed by eyelash epilation, systemic doxycycline, topical corticosteroids, and antibiotic ointments [20, 23].

Cetuximab (Erbitux™) is a chimeric antibody targeting the extracellular domain of EGFR that prevents ligand-dependent signaling and receptor dimerization. Its antitumor activity differs from erlotinib and gefitinib, even though these medications target the same enzyme. It is used in conjunction with radiation therapy for regionally advanced squamous cell carcinoma of the head and neck and as a single agent for EGFR-positive metastatic colorectal cancer [24]. Ocular side effects of cetuximab are similar to the side effects noted in the patients treated with erlotinib or gefitinib. In one report, tear film abnormalities and dry eye symptoms were noted in 67 %, blepharitis (63 %), trichomegaly or trichiasis (38 %), and eyelid rash or hyperemia (38 %) of treated patients [18]. Most commonly, side effects of cetuximab are mild and can be easily managed; however, if not addressed promptly, recurrent corneal irritation may cause scarring and permanent blindness.

Panitumumab (Vectibix™) is a fully humanized, recombinant IgG2k antibody against the extracellular domain of EGFR. The binding of EGFR on cell surface by panitumumab does not mediate antibody-dependent cell-mediated cytotoxicity that is a characteristic of cetuximab. It is used for the treatment of metastatic colorectal carcinoma [25]. Ocular side effects from panitumumab are rarely reported, but they are expected to be similar to the side effects caused by other EGFR inhibitors such as cetuximab, erlotinib, and gefitinib. There is a single case report of

severe bilateral multiple epithelial defects resulting in corneal melting and perforation in one of the eyes after the infusion of panitumumab in a patient with metastatic colorectal cancer. The perforation was sealed with a conjunctival flap, and aggressive bilateral lubrication was initiated to prevent further progression of corneal disease, which resulted in significant clinical improvement. Symptoms recurred after the second panitumumab infusion, which prompted the cessation of therapy secondary to the blinding ocular side effects [21]. Evaluation of patients with ocular complaints is important to recognize early toxicity and prevent rare devastating corneal decompensation.

Trastuzumab (Herceptin™) is a humanized IgG1 kappa monoclonal antibody against the external domain of HER2 (ErbB2). It is used for the treatment of HER2-positive breast cancer and HER2-positive metastatic gastric or gastroesophageal junctional adenocarcinoma. It was the first monoclonal antibody approved for the treatment of a solid malignancy [26]. Experimental animal models showed that trastuzumab was effective in preventing corneal neovascularization by blocking EGFR upregulation of angiogenic factors, which could potentially be beneficial in patients with corneal neovascularization [27]. Ocular side effects of trastuzumab therapy are usually mild and rarely reported. In a study of 112 patients treated with trastuzumab combined with antimicrotubule agent DM1, 31.3 % of patients reported ocular problems most commonly consisting of dry eyes, increased lacrimation, conjunctivitis, and blurred vision [28]. Bilateral ischemic maculopathy was reported in a single case manifesting as the enlargement of foveal avascular zone and cystoid macular edema after trastuzumab infusion for the treatment of metastatic breast cancer. Discontinuation of therapy resulted in stabilization of the disease, and reintroduction of trastuzumab treatment caused the progression of capillary dropout and vision loss. It is postulated that trastuzumab blockade of pro-angiogenic factors by inhibition of HER2 receptors might have resulted in damage of susceptible retinal capillary network [29].

13.2.3 Inhibitors of Angiogenesis

Bevacizumab (Avastin™) is a humanized monoclonal IgG1 antibody against vascular endothelial growth factor (VEGF-A) with molecular weight of 149 kD. It binds VEGF and prevents its activation of surface receptors VEGFR-1 and VEGFR-2 found on the surface of endothelial cells. This disrupts the receptors activation and downstream molecular cascade, which is a critical step in angiogenesis. Bevacizumab has received the FDA approval as a combination therapy for metastatic colon cancer, non-small cell lung cancer, renal cell cancer, and glioblastoma multiforme [30]. It has been used as an off-label treatment of age-related macular degeneration (AMD) since 2005. Multiple studies have demonstrated the safety of intraocular bevacizumab, and the reported side effects are mostly related to the injection procedure rather than the medication [31, 32]. Ocular side effects from systemic bevacizumab therapy are rarely reported in the literature. Severe optic neuropathy has occurred in 1.2 % of 503 glioblastoma patients treated with bevacizumab and 0.2 % of 567 glioblastoma patients treated without bevacizumab suggesting its possible role in development of optic nerve disease [33]. Bevacizumab has also been implicated in the development of posterior reversible encephalopathy syndrome (PRES), which causes reversible cortical blindness by disruption of CNS visual pathways. Patients with PRES are found to have vasogenic edema primarily involving parietal and occipital lobes [34, 35]. It is hypothesized that PRES develops due to combination of increased arterial blood pressure and changes in endothelial function from bevacizumab leading to dysfunction of blood–brain barrier and resulting in posterior cerebral edema. Withdrawal of bevacizumab and blood pressure control lead to resolution of symptoms and visual recovery [36].

Sunitinib (Sutent™) is a VEGFR, EGFR, and PDGFR inhibitor used to treat kidney and liver cancers. Several cases of posterior reversible encephalopathy syndrome have been reported following sunitinib therapy. It is thought that mechanism of PRES development related to sunitinib is similar

to that of bevacizumab and includes increased systemic blood pressure and changes in endothelial cells function of cerebral vasculature [36, 37]. A single case report described development of bilateral optic disc edema in a patient treated with sunitinib for advanced renal cell carcinoma (RCC). The resolution of edema was noted 2 months after stopping sunitinib [38]. Neurosensory retinal detachment is also a potential side effect of sunitinib therapy. Bilateral serous retinal detachments developed in a patient treated for metastatic RCC. Two weeks after discontinuation of therapy, subretinal fluid was reabsorbed and the normal retinal contour was reestablished. The same clinical picture developed following re-initiation of sunitinib. Since anti-VEGF agents such as bevacizumab can be used to treat neurosensory detachment, it is thought that sunitinib inhibition of target enzymes other than VEGF is likely responsible for this side effect [39].

13.2.4 mTOR Pathway Inhibitors

Perifosine is an inhibitor of phosphoinositide-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway specifically blocking Akt activity at low micromolar concentrations. It also affects other signal transduction pathways, including the c-Jun N-terminal kinase pathway, all of which are associated with programmed cell death, cell growth, cell differentiation, and cell survival. Perifosine is used to treat myeloma and neuroblastoma. It is being investigated for the treatment of metastatic colorectal carcinoma [40]. Cases of ulcerative keratitis presenting with perilimbal ring-shaped infiltrates resembling autoimmune keratitis have been reported in patients treated with combination therapy of imatinib and perifosine for gastrointestinal stromal tumors resistant to imatinib monotherapy. Withdrawal of perifosine resulted in improvement of keratitis in several patients. It has been speculated that combination therapy might have provoked this reaction; however, no similar cases of ulcerative keratitis have been reported following imatinib therapy. The exact mechanism of corneal toxicity remains poorly understood, but it is postulated that perifosine might have triggered sensitization to corneal self-antigens resulting in autoimmune-like keratitis. A combination of oral and topical corticosteroids, topical antibiotics, and lubricating agents was used to successfully treat peripheral ulcerative keratitis in the effected patients [41]. Rapidly progressive corneal ring infiltrates leading to complete corneal opacification, and peripheral corneal thinning occurred in a patient treated with perifosine monotherapy for Waldenstrom's macroglobulinemia. Aggressive systemic immunosuppressive therapy halted the progression of disease and resulted in resolution of autoimmune reaction; however, the patient ultimately required penetrating keratoplasty to clear visual axis [42]. Ocular complaints should be promptly investigated in patients treated with this agent, since early therapy might prevent serious ocular sequelae.

13.2.5 Anaplastic Lymphoma Kinase (ALK) Inhibitor

Crizotinib (Xalkori™) is a first-in-class inhibitor of the anaplastic lymphoma kinase (ALK), a protein kinase involved in carcinogenesis. It is approved for the treatment non-small cell lung cancer positive for ALK gene rearrangements. Visual complaints including blurred vision, photopsia, photophobia, floaters, and diplopia were reported in 62 % of treated patients in the phase I and phase II clinical trials. The visual disturbances (unknown mechanism) usually commenced within 2 weeks of the initiation of therapy and were transient in nature minimally impacting, the patients' quality of life. No vision-threatening or permanent ocular side effects have been reported in the studies [43].

13.2.6 Mitogen-Activated Protein Kinase RAS-RAF Signaling Pathway

Mitogen-activated protein kinase pathway is a complex cellular signaling pathway that regulates multiple essential cell functions including growth, survival, differentiation, and inflammation. Deregulation of this critical cellular

transduction cascade may lead to abnormal cell proliferation and tumorigenesis, which is found to be present in multiple human cancers. Numerous molecularly targeted agents inhabiting the RAS-RAF-MEK-ERK/MAPK signaling pathway are currently being investigated for the treatment of multiple different malignancies [44]. Ocular toxicities related to these medications have emerged. Transient blurring of vision, photopsias, and colored spots have been reported with several agents. A phase I trial of MEK inhibitor *trametinib* for the treatment of multiple different advanced solid malignancies demonstrated ocular toxicity in 31 (15 %) out of 206 patients involved in the trial, mostly including blurred vision and photophobia. Four patients developed serious ocular events with three cases of central serous retinopathy (CSR) and one case of central retinal vein obstruction (CRVO). CSR resolved upon withdrawal of trametinib [45]. Another MEK Inhibitor *RO4987655 (CH4987655)* also demonstrated ocular toxicities in 13 (27 %) of treated patients including a case each of CRVO and CSR [46]. Mitogen-activated protein kinase inhibitors are promising targets of abnormally activated transduction molecules in this critical regulatory pathway of cellular metabolism. Most of these agents are currently being investigated in phase I or phase II clinical trials, but the increased rate of ocular toxicities has been recognized necessitating careful monitoring of vision complaints in treated patients (Fig. 13.2).

Vemurafenib (Zelboraf™) received FDA approval in August 2011 for the treatment of melanoma harboring V600E mutations in the BRAF gene. The protein kinase BRAF is one of the critical enzymes in RAS-RAF cellular signaling pathway, and its deregulation leads to abnormal cellular proliferation and survival independent of extracellular growth factors. One of the most common side effects of vemurafenib therapy occurring in 26 % of treated patients was development of cutaneous neoplasms including basal-cell carcinoma, keratoacanthoma, and squamous cell carcinoma, which may potentially arise from the periocular area. Several ocular complications were reported in clinical trials. Most common ophthalmic side effect in phase III clinical trial was development of iritis which was reported in ten patients, who were managed with topical corticosteroids and mydriatic ophthalmic drops (Fig. 13.3). One case of CRVO was reported in phase II clinical trial requiring discontinuation of therapy [47, 48].

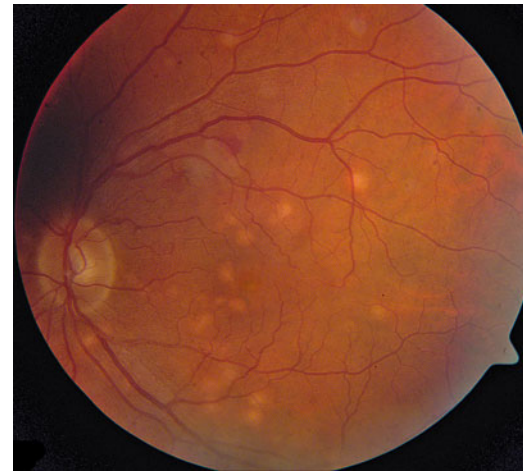

Fig. 13.2 This 50-year-old woman underwent enucleation for a large choroidal melanoma in January 2008. She was started on experimental MEKI for breast metastasis 6 months ago. Visual acuity 20/20 in the left eye. Fundus examination revealed multiple sub-RPE deposits of yellow/vitelliform material (Courtesy: Dr. Louise Mawn and Dr. Anita Agarwal, Nashville, TN)

13.2.7 Immunotherapy

Ipilimumab (Yervoy™) is a fully humanized monoclonal antibody against the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) preventing its interaction with the co-stimulatory molecules CD80 and CD86 (B7-1 and B7-2) on antigen-presenting cells. CTLA-4 acts as a regulatory molecule suppressing T-cells and its inhibition results in activation of T-cell lymphocytes enhancing immune response directed toward immunogenic tumor cells. It was FDA approved for the treatment of metastatic melanoma. Development of episcleritis and uveitis were reported in 1 % of patients in clinical trials usually occurring 2 months after initiation of therapy. Mild intraocular inflammation responded well to topical corticosteroids therapy. However, severe cases of ocular inflammation required cessation

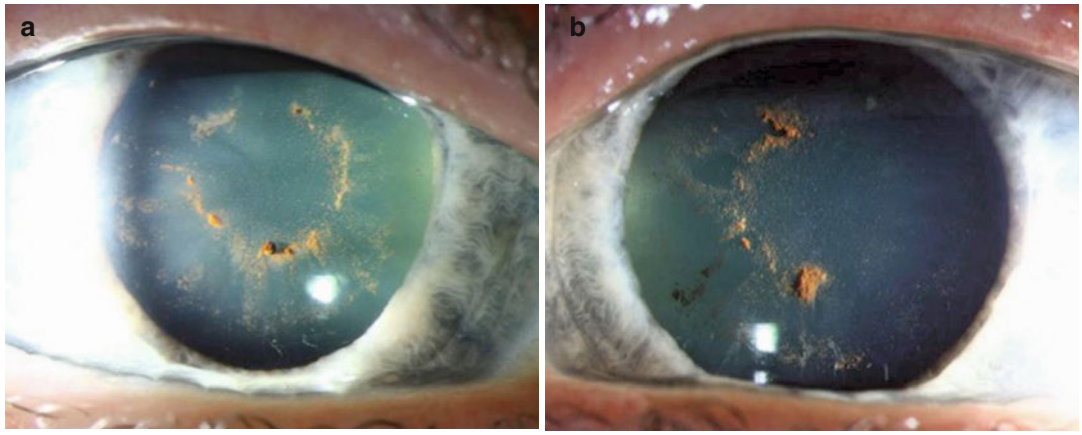

Fig. 13.3 Iritis is the most common ophthalmic side effect of *vemurafenib (Zelboraf™)*. Right eye (**a**) and left eye (**b**)

of ipilimumab therapy and initiation of systemic corticosteroids to prevent severe ocular damage [49, 50]. Abrupt development of drug-induced Graves disease was reported in a single case after a second infusion of ipilimumab presenting as severe proptosis, diplopia, and exposure keratitis. MRI demonstrated fusiform extraocular-muscle enlargement characteristic of Graves disease. The patient required cantholysis and responded well to systemic corticosteroids [51].

Conclusions

With increased clinical usage of molecularly targeted agents, distinct adverse effects have emerged. As molecularly targeted agents act through specific mechanisms, they result in unique side effects. Most ocular tissues are susceptible to the development of side effects from the periocular skin to intraocular structures (iritis) and central visual pathways. Familiarity of ophthalmologists with the potential ocular side effects is important for the early recognition of ocular toxicities.

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