Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Possible Side Effects of Chemotherapy on Eyesight

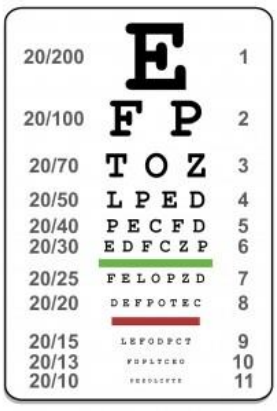
Introduction

Visual perception is the ability to interpret one's surrounding environment by processing information that is contained in visible light. The resulting perception is also known as eyesight, sight, or vision.

[Picture Credit: Eyesight]

The visual system allows individuals to assimilate information from their surroundings. The act of seeing starts when the cornea and then the lens of the eye focuses an image of its surroundings onto a light-sensitive membrane in the back of the eye, called the retina. The lens of the eye focuses light on the photoreceptive cells of the retina, also known as the rods and cones, which detect the photons of light and respond by producing neural impulses. These signals are processed by different parts of the brain, from the retina upstream to central ganglia in the brain.

Normal Vision



Studies have found that 'normal' vision is being able to see a certain size line on the eye chart (the Snellen Chart) from 20 feet away. If one has 20/20 vision, one can see clearly at 20 feet what should normally be seen at that distance. If one has 20/40 vision, it means that one must be as close as 20 feet to see what a person with 'normal' vision can see at 40 feet. So, the first number refers to the distance one stands from the chart, and the second number is the distance a person with 'normal' vision could read the same line one correctly reads – the larger the second number, the worse one's vision.

[Picture Credit: Snellen Chart]

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Chemotherapy and Eyesight

Almost all cancer chemotherapy drugs have side effects, including effects on the visual system. Some drugs can cause tear deficiency in the eyes which leads to discomfort and some blurring of vision. Other chemotherapy drugs can promote the formation of cataracts which reduce the clarity of vision. Still other cancer-treating drugs can cause optic neuropathy, a deterioration of the optic nerve which carries vision information from the eye to the brain.

[Picture Credit: Left-sided Ptosis]

It is important to mention any vision changes one is experiencing with one's oncologist so that a referral can be made to an ophthalmologist.

Though not a common side effect, it is said that breast cancer treatment may affect one's eyes, including one's vision.

- Eye problems may include:
- red, itchy, or dry eyes
- watery eyes
- conjunctivitis (pink eye)
- blurry or double vision
- seeing dark spots
- dulled vision where colours are not as bright as usual
- seeing halos or rainbow like rings around lights
- misty vision
- vision less clear than usual
- loss of areas of vision
- headaches

Breast cancer treatments that may cause eye problems include:

- certain chemotherapy drugs
- Certain Hormonal therapy drugs

One should speak to one's oncologist regarding possible eye problems that may arise from chemotherapy treatment.

Ocular Adverse Effects of Anti-Cancer Chemotherapy

An ophthalmologist should be part of the team caring for patients undergoing systemic chemotherapy for baseline examination and ongoing assessment. Baseline examination will help to diagnose adverse effects caused later due to chemotherapeutic agents and diagnose any pre-existing conditions, especially in elderly patients. It is easy to miss association between chemotherapy and visual changes.

The following is a list of commonly used cancer chemotherapeutic agents along with their ocular side effects.

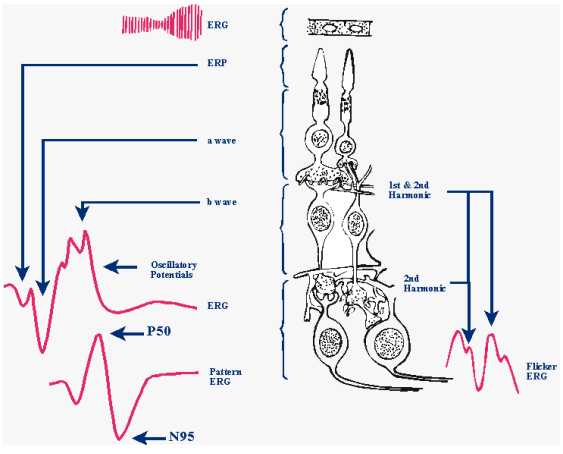
Alkylating agents - Alkylating agents have the cytotoxic ability to substitute hydrogen atoms in certain organic compounds by alkyl groups. They include platinum complexes, nitrogen mustard derivatives, alkyl sulphonates and nitrosoureas.

Platinum complexes

(i) Cisplatin: Cisplatin, a heavy metal compound, is an established drug for treatment of head and neck, lung, cervical, ovarian and testicular cancer, upper gastrointestinal malignancies, osteogenic sarcoma, neuroblastoma, recurrent brain tumours in children, and urinary bladder cancer. Cisplatin is known to produce non-specific blurred vision, papilloedema. Papilloedema is a condition in which increased pressure in or around the brain causes the part of the optic nerve inside the eye to swell.

- Unilateral as well as bilateral retrobulbar neuritis and optic neuritis have been reported for high doses as well as cumulative dose regimens.
- Transient cortical blindness, temporary homonymous hemianopia (visual field loss on the left or right side of the vertical midline. It can affect one eye but usually affects both eyes) and macular pigmentary changes more likely to occur at high-dose intravenous regimens.
- Several cases of women who were treated with high cumulative doses of cisplatin for ovarian tumours have been reported with blurred vision, decreased colour vision, irregular pigmentation in the macula, and cone dysfunction on electro-retinogram (ERG). Electroretinography (ERG) is an eye test used to detect abnormal function of the retina (the light-detecting portion of the eye). Specifically, in this test, the light-sensitive cells of the eye, the rods and cones, and their connecting ganglion cells in the retina are examined.

[Picture Credit: Electroretinography]



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[Picture Credit: Electroretinogram (ERG)]

- A case of a 55 year old man, who received cisplatin as salvage regimen for non-Hodgkin's Lymphoma was reported who developed bilateral irreversible visual loss with visual field showing central scotoma (an area of partial alteration in the field of vision consisting of a partially diminished or entirely degenerated visual acuity that is surrounded by a field of normal – or relatively well-preserved – vision) bilaterally.
- Intra-carotid administration of cisplatin has led to severe ocular and orbital toxicity like ipsilateral retrobulbar neuritis. Cases of central retinal artery occlusion, leading to ipsilateral visual loss from severe retinal or optic nerve ischaemia were also reported.
- After supra-ophthalmic infusion of cisplatin, a case of uveal effusion with exudative retinal detachment, enlarged recti muscles and inflammation of surrounding soft tissue has been reported.

(ii) Carboplatin: Carboplatin is used as treatment primarily for lung cancer, head and neck cancer, ovarian cancer, breast cancer, gastro-intestinal cancers and osteogenic sarcoma.

- Carboplatin may cause maculopathy (pathological condition of the macula, an area at the centre of the retina that is associated with highly sensitive, accurate vision) and optic neuropathy, weeks after intravenous administration.
- Intra-carotid therapy can cause severe ocular and orbital toxicity.
- Sub-tenon injection of carboplatin has been associated with limitation of ocular motility.

(iii) Oxaliplatin: Oxaliplatin is third generation 1,2 diaminocyclohexane platinum derivative, used mainly for colon, recurrent or metastatic oesophageal cancer, locally advanced or metastatic pancreatic cancer, recurrent epithelial ovarian, relapsed or refractory non-Hodgkin's lymphoma and palliative treatment of testicular cancer.

- Several patients with metastatic colorectal cancer reported blurred vision, eye pain, and visual field cuts.
- Besides this, low rate of visual disturbances, including tearing, conjunctivitis and abnormal lacrimation (tear formation) was also reported in trials.

Nitrogen mustard derivatives

(i) Chlorambucil: Chlorambucil is indicated in adult Hodgkin's Lymphoma, adult follicular non-Hodgkin's Lymphoma and adult Chronic Lymphocytic Leukaemia.

- Keratitis was the most common side effect observed.
- A case treated for nephrotic syndrome has been reported to develop diplopia (double vision), bilateral papilledema and retinal haemorrhages.

[Picture Credit: Double Vision]

(ii) Cyclophosphamide: Cyclophosphamide is used in treatment of many malignancies including breast cancer, lymphomas and leukaemias, retinoblastoma, small cell lung cancer, ovarian cancer, sarcomas and multiple myeloma.

- Blurred vision, kerato-conjunctivitis sicca, blepharo-conjunctivitis and pin point haemorrhages have been reported as its ocular adverse effects.
- A case of irreversible lacrimal duct stenosis in a women receiving adjuvant chemotherapy for early stage breast cancer was reported.
- It was also reported that patients developed reversible epiphora (excessive watering of the eye).

(iii) Ifosphamide: This drug is used in the treatment of soft tissue sarcoma, osteosarcoma, non-Hodgkin's Lymphoma, small cell lung cancer, ovarian, testicular and cervical cancer.

- Blurred vision and florid conjunctivitis has been reported.

Alkyl sulphonates

(i) Busulphan: Busulphan is used for chronic myeloid leukaemia and other myeloproliferative disorders.

- The most common ocular side effect is posterior sub-capsular cataract.
- Non-specific blurred vision and kerato-conjunctivitis sicca may also occur after busulphan infusion.

Nitrosoureas

(i) Carmustine: It is mainly used as treatment for brain neoplasms, palliative treatment of multiple myeloma, refractory or relapsed Hodgkin's and non-Hodgkin's Lymphoma, cutaneous T-cell Lymphoma and metastatic malignant melanoma.

- There have been several reports of ocular toxicities associated with its use.
- A patient with myeloma on carmustine therapy developed bilateral acute optic neuro-retinitis. Loss of depth perception and blurring of vision was reported in two patients (out of 31 patients) with breast cancer treated with carmustine with adriamycin.
- Several other cases of retinopathy, progressive blindness with diplopia (double vision), blurred vision, retrobulbar pain, optic neuritis and optic atrophy has also been reported.
- A case of decreased visual acuity due to marked retinopathy with haemorrhages, exudates and retinal infarcts has been reported.
- A patient developed 'counting fingers vision' (vision worse than 20/400) with a fundus picture, consistent with central retinal artery occlusion.

[Picture Credit: Blurred Vision]

Antimetabolites

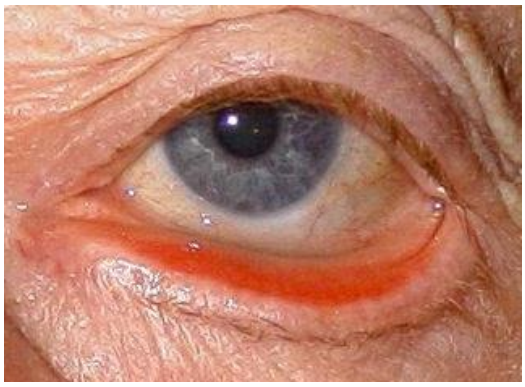
Pyrimidine analogs

(i) Cytosine arabinoside: Cytosine arabinoside interferes with DNA synthesis by inhibiting DNA Polymerase enzyme. It is used for treatment of acute myeloid leukaemia, acute lymphocytic leukaemia, lymphomatous meningitis and during blast crisis of chronic myeloid leukaemia.

- Numerous ocular side-effects such as ocular pain, tearing, foreign body sensation, photophobia (sensitivity to light), blurred vision with evidence of bilateral conjunctival hyperaemia and fine corneal punctate opacities have been reported.
- After intrathecal (into the spinal column) injection of cytosine arabinoside, severe visual loss due to optic neuropathy has been reported.

(ii) 5-Fluorouracil (5-FU): 5-FU is an established anti-cancer agent used in skin, head and neck, breast, gastro-intestinal and cervical cancer.

- The ocular adverse effects reported include blurred vision, ocular pain, photophobia, excessive lacrimation, eye irritation, conjunctivitis, circumferential oedema, ectropion (outward turning of eyelid) and keratitis.



[Picture Credit: Ectropion]

- The topical use also impairs corneal and conjunctival re-epitheliasation.
- A case of irreversible lacrimal duct stenosis was reported in a women receiving adjuvant chemotherapy for early stage breast cancer.
- Patients who received prolonged high doses of 5-FU, developed canalicular fibrosis leading to permanent intractable epiphora (watering of the eyes).

(iii) Capecitabine: Capecitabine is a prodrug of 5-fluorouracil and shares its toxicities with it. It is used for treatment of metastatic breast cancer, colon cancer, and advanced gastric carcinoma.

- Cases of ocular irritation, decreased vision and corneal deposits were reported.

Folic acid analogues

(i) Methotrexate: Methotrexate is a folic acid antagonist used in breast cancer, choriocarcinoma, osteogenic sarcoma, acute leukaemia, advanced mycosis fungoides (cutaneous lymphoma) and head and neck cancer.

- The ocular toxicities caused by methotrexate consists of peri-orbital (around the eye) oedema, ocular pain, blurred vision, photophobia (sensitivity to light), conjunctivitis, blepharitis (inflammation of the eyelid) and decreased reflex tear secretions. When methotrexate is administered by intra-thecal (into spinal column) route as in acute leukaemias, optic neuropathy and inter-nuclear ophthalmoplegia (paralysis or weakness of one or more of the muscles that control eye movement) can develop and, this can be potentiated by concurrent cranial irradiation usually used in such cases.

[Picture Credit: Periorbital Oedema]

- Intra-carotid administration of methotrexate in combination with intravenous cyclophosphamide, resulted in macular oedema and retinal pigment epithelial changes in all patients, despite intra-carotid injection of mannitol.

    - A case was reported in which a reduced full field ERG in B-wave amplitude was reported.

(ii) Pemetrexed: It is indicated for use in malignant pleural mesothelioma and locally advanced or metastatic non–small cell lung cancer. Increased lacrimation (tear formation), ocular surface disease including conjunctivitis has been reported in 1% to 5% patients.

Purines analogues

(i) Fludarabine: It is used for treatment of refractory B-cell chronic lymphocytic leukaemia, advanced low grade non-Hodgkin's Lymphoma, refractory or relapsed acute leukaemias and mycosis fungoides.

- The ocular toxicities caused include diplopia (double vision), photophobia (light sensitivity) and, decreased visual acuity secondary to optic neuritis with or without disc oedema or cortical blindness.

(ii) Pentostatin: Pentostatin is used for treatment of hairy cell leukaemia, cutaneous T-cell lymphoma and chronic lymphocytic leukaemia.

- It has been found to be associated with abnormal vision, amblyopia (dimness of sight), conjunctivitis, dry eye, problems with lacrimation (tear formation), photophobia (sensitivity to light), retinopathy and watery eyes.

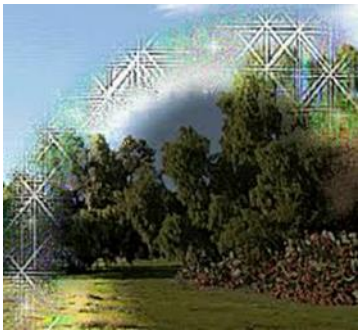
[Picture Credit: Photophobia]

Mitotic Inhibitors

Taxanes

(i) Paclitaxel: Paclitaxel is known to produce neurotoxocity when used for its indications in metastatic or relapsed breast cancer and advanced ovarian cancer.

Both transient scintillating scotoma (a blind spot in the visual field that is bordered by shimmering or flashing light) and visual impairment have been reported after its use. Other ocular side-effects induced by paclitaxel include photopsia (the perception of light as luminous rays or flashes) and possible ischaemic optic neuropathy.



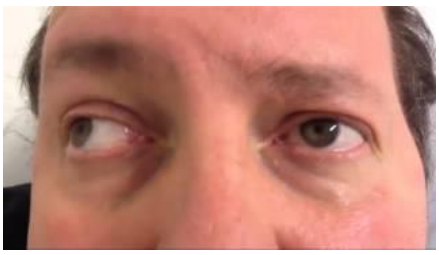
[Picture Credit: Scotoma]

(ii) Docetaxel: It is indicated in locally advanced, metastatic and refractory breast cancer, advanced gastric and gastro-oesophageal adenocarcinoma, locally advanced head and neck cancer, metastatic prostate cancer and locally advanced or metastatic non-small cell lung carcinoma.

- A case of erosive conjunctivitis and punctual stenosis secondary to docetaxel administration was reported.
- Canalicular narrowing and naso-lacrimal duct obstruction in three patients were also reported.

Plant alkaloids

Vincristine, vinblastine, vindesine, vinorelbine: They are used for acute lymphoblastic leukaemia, Ewing's sarcoma, Hodgkin's Lymphoma, non-Hodgkin's Lymphoma, lung cancer, breast cancer and soft tissue sarcomas.



[Picture Credit: Ophthalmoplegia]

- Cranial nerve palsies (paralysis), optic neuropathy, optic atrophy, cortical blindness and night blindness are the ocular side-effects of these plant alkaloids.

- The cranial nerve palsies include ptosis (drooping upper eyelid), internal ophthalmoplegia (paralysis or weakness of one or more of the muscles that control eye movement), corneal hyperesthesia (abnormal increase in sensitivity to stimuli) and lagophthalmos (inability to close the eyelids fully).

[Picture Credit: Lagophthalmos]

Topoisomerase Inhibitors

(i) Topoisomerase inhibitor II: Etoposide is a topoisomerase-II inhibitor.

- Intra-arterially administered etoposide results in arterial thrombosis which can affect the eye by occluding central retinal artery.
- Etoposide is used for the treatment of retinoblastoma in combination with cisplatin or carboplatin. Due to synergistic effects with cisplatin two cases of retinal toxicities have been reported.

(ii) Topoisomerase inhibitor I: Irinotecan and topotecan are topoisomerase-I inhibitors used for cytotoxic treatment of carcinoma.

- They do not have any significant ocular adverse effects reported yet.

Antibiotics

Anthracyclines

(i) Doxorubicin: It is used in combination regimens in the treatment of breast cancer, ovarian cancer, non-Hodgkin's Lymphoma, sarcoma and acute leukaemia.

- Excessive lacrimation (tear formation) and conjunctivitis have been reported as its ocular adverse effects.

(ii) Mitomycin-C: Mitomycin-C is used in combination chemotherapy regimens in gastric, pancreatic, colon, lung, urinary bladder, breast and cervical cancer. It is also used as hypoxic cell selective cytotoxic agent in combination with radiation therapy in anal and head and neck cancers.

- The only known ocular toxicity after systemic use of Mitomycin-C is blurred vision.
- All other severe ocular toxicities were reported after topical use in ophthalmologic surgeries.

(iii) Mithramycin (Plicamycin): Mithramycin is used in treatment of hypercalcaemia of malignancies and for testicular cancer.

- There was a single case reported of peri-orbital pallor in absence of anaemia as ocular adverse effect.

Hormonal agents

Tamoxifen

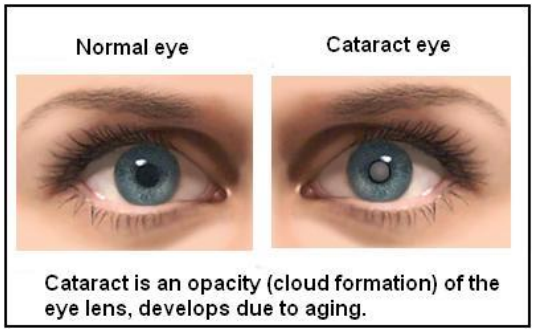
It is used as adjuvant therapy of oestrogen dependent breast carcinoma.

- Patients were reported who developed keratopathy and retinopathy after tamoxifen use.
- Decreased visual acuity, bilateral macular oedema, retinal yellow-white dots and corneal opacities, bilateral optic neuritis and retinal haemorrhages has also been reported.
- On the whole, the most common tamoxifen induced ocular toxicities remain to be the retinopathy and cataract, lesions of cornea and optic nerve.

Anastrazole

The incidence of cataract with anastrazole usage was found to be lesser than with tamoxifen. The ATAC (Armidex, Tamoxifen, alone or in combination) trial randomised patients with hormone receptor positive localised breast cancer to five years of anastrazole or tamoxifen use.

- Cataracts were described in 6% patients receiving anastrazole versus 7% receiving tamoxifen.



Cataract is an opacity (cloud formation) of the eye lens, develops due to aging.

[Picture Credit: Cataract]

Monoclonal antibodies

(i) Rituximab: Rituximab was approved by US-FD

(ii) A (Food and Drug Administration, U.S.A.) in 1997 and is used to treat B-cell non-Hodgkin Lymphoma. It is a monoclonal antibody against the CD20 antigen, found on B cells. It works, in part, by labelling cells so that the immune system can attack them.

- Ocular side-effects described with rituximab usage are conjunctivitis, transient ocular oedema, burning sensation, transient visual changes or permanent and severe loss of visual acuity.

(iii) Alemtuzumab: Alemtuzumab is an antibody against the CD52 antigen, which is found on both B cells and T cells. It was FDA approved in 2001 to treat some patients with B-cell chronic lymphocytic leukaemia.

- Adverse reactions identified during post-approval use of alemtuzumab are optic neuropathy and endophthalmitis (inflammation of the interior of the eye).

(iv) Cetuximab: Cetuximab is an antibody against the EGFR (epidermal growth factor receptor) protein, which is present in large amounts on some tumor cells and helps them grow and divide. Cetuximab blocks the activation of EGFR. It was FDA approved in 2004 to treat some advanced colorectal cancers as well as some head and neck cancers.

- One case report described a patient with squamous blepharitis.

[Picture Credit: Blepharitis]

- A case treated with combined chemotherapy including cetuximab for colorectal carcinoma showed accelerated growth of eyelashes with persistent bilateral corneal erosions.

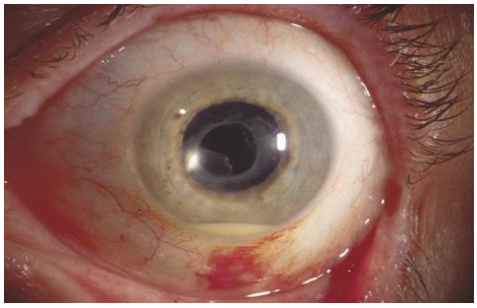
(v) Panitumumab: It targets epidermal growth factor receptor (EGFR) antigen. It is used to treat EGFR-expressing, metastatic colo-rectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin and irinotecan containing chemotherapy regimens.

Ocular toxicities included but are not limited to growth of eyelashes; conjunctivitis; ocular hyperaemia (blood congestion); increased lacrimation; eye/eyelid irritation.

(vi) Bevacizumab: Bevacizumab targets the VEGF (vascular endothelial growth factor) protein, which is normally made by tumour cells to attract new blood vessels to feed their growth. Bevacizumab attaches to VEGF and blocks it from signalling for new blood vessels formation. It was approved by FDA in 2004 and is used to treat metastatic colorectal cancer, with intravenous 5-florouracil–based chemotherapy for first- or second-line treatment, non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease, metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer, glioblastoma, as a

single agent for adult patients with progressive disease following prior therapy and, metastatic renal cell carcinoma with interferon alfa.

- Ocular adverse reactions that have been reported from unapproved use for treatment of various ocular disorders during post-approval use of bevacizumab are endophthalmitis; intraocular inflammation such as iritis and vitritis; retinal detachment; other retinal disorders; increased intraocular pressure; haemorrhage following intraocular injection including conjunctival, vitreous haemorrhage or retinal haemorrhage; vitreous floaters; visual disturbances; ocular hyperaemia (blood congestion); ocular pain and/or discomfort.



[Picture Credit: Endophthalmitis]

The FDA revoked (on 18-11-2011), the agency's accelerated approval of the breast cancer indication for bevacizumab.

Drugs Targeting Signal Transduction

(i) Imatinib: It is indicated in treatment of adults with newly diagnosed Philadelphia chromosome positive (Ph+) CML in chronic phase; treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy.

- Peri-orbital oedema due to fluid retention is reported in 47.2% of patients.
- Dry eyes, visual disorders including blurred vision, reduced visual acuity, and visual disturbance (1% to less than 10%) were reported.

(ii) Nilotinib: Clinical trials data show that ocular adverse effects caused by nilotinib are uncommon (less than 1%).

- Eye disorders reported are haemorrhage, reduced visual acuity, peri-orbital oedema, conjunctivitis, eye irritation and dry eye.

[Picture Credit: Conjuctivitis]

(iii) Vemurafenib: It is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF mutation.

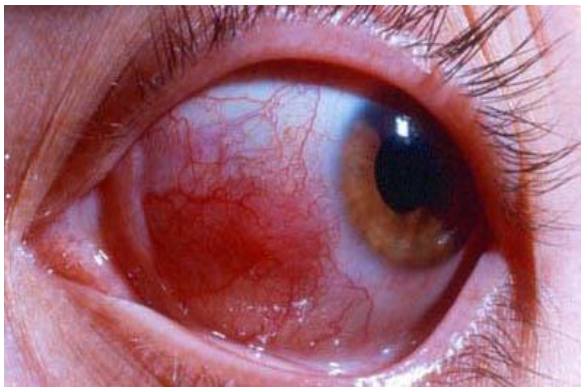
- Serious ophthalmologic reactions including uveitis, iritis and retinal vein occlusion, have been reported. Routine monitoring of patients on vemurafenib for ophthalmologic reactions is recommended.

(iv) Erlotinib: Corneal ulcerations and perforations, excessive eyelash growth including in-growing eyelashes, and thickening of the eyelashes have been reported.

- Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving erlotinib therapy in non-small cell cancer and pancreatic cancer clinical trials.

[Picture Credit: Ocular Hyperaemia]

(v) Everolimus: Inhibitor of mammalian target of rapamycin (mTOR), which is a serine-threonine kinase. It is indicated in advanced pancreatic neuroendocrine tumours and advanced renal cell carcinoma.



- The ocular toxicities reported are eyelid oedema, ocular hyperaemia, conjunctivitis.

(vi) Temsirolimus: Temsirolimus is also inhibitor of mTOR and is indicated in treatment of advanced renal cell carcinoma.

- No ocular adverse effect associated with temsirolimus use has been reported so far.

(Journal of Cancer Therapeutics & Research - ISSN 2049-7962; Drugs.com; WebMD; Mayo Clinic; Chemocare; Physiopedia; RxList; Cancer Treatment Centers of America; MyVCM; Cancer Research UK; Continuing Medical Education; MacMillan.org.uk; Perry's Chemotherapy Book; American Brain Tumour Association; General Aspects of Chemotherapy; University of Rochester Medical Center; Hindawi; Patient.info; Navigating Care; OncoLink).

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Ocular Hyperaemia
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