Ocular Toxicity
and
Biological care

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Introduction

- During the last 20 years, biological care has become more and more relevant in oncologic therapy.
- The field of oncology has entered the era of molecularly targeted therapy.
- The development of targeted agents inhibits multiple pathways responsible for growth and survival of cancer cells.

- These drugs are called:
  1. targeted therapy
  2. biological response modifiers
  3. immunotherapy.
There are various hypotheses regarding targeted agents’ interaction with cancer cells:

★ They act on intracellular signaling of cancer cells through the direct link to transmembrane receptors.

★ They inhibit intracellular tumor-specific proteins and they influence the growth of the tumor’s own vessels.

★ They stimulate the immune system so that it is susceptible to antigens of the tumor cells.

This approach has fewer side effects than traditionaly to toxic drugs that act non specifically on all dividing cells of the body.
The eye

- The eye is a downstream portion of the brain and cerebral side effects of drugs may affect the visual pathways and the visual cortex.

- It is an organ that combines in complex ways the neural network system with blood vessels, muscles and skin.

- The eye consists of three layers:
  1. fibrous: sclera, cornea
  2. vascular: iris, choroid
  3. nervous: retina
Ocular tissue have different receptor-specific patterns that do not occur in this form elsewhere in the body.

Daniel J. Et al., Journal of Clinical Oncology, 2012
In literature there are few reports of side effects of targeted therapy on the eye.

If they exist, there is often only a small number of patients included.

I review the studies on side effects of biological agents on the eye in oncology.

Processing from the surface of the eye to the retina, we can observe:

- Blurred vision
- Photophobia
- Accelerated growth of eyelashes
- Limitation of ocular motility
- Conjunctivitis
- Cataract
- Abnormal lacrimation
- Dry eye
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The eye

Ocular side effects of biological care:

1. Orbital myositis
2. Edema periorbital
3. Eyelid edema
4. Blepharitis
5. Trichomegaly, poliosis
6. Ectropion, entropion
7. Conjunctivitis
8. Dry eye
9. Keratopathy
10. Uveitis: episcleritis, scleritis, iridocyclitis
11. Ocular hypertension
12. Cataract
13. Optic disc edema
14. Papillitis
15. Multifocal bilateral choroidal neovascularization
16. Polypoidal choroidal vasculopathy
17. Cystoid macular edema
18. Diplopia
19. Mydriasis
20. Deficiency of accommodation
**Orbital myositis**

**Cause: Ipilimumab**

Human monoclonal antibody which is used for the treatment of metastatic malignant melanoma.

The ipilimumab causes changes in the pituitary gland and consequently symptoms similar to Graves disease: dry eye, proptosis, swelling of the extraocular muscles, iridocyclitis.

The orbital myositis is autoimmune and can cause painful diplopia.

It can be demonstrated histologically in the deltoid muscle.

**Pathogenesis:**

- a cross-reaction of the antibody with the iris pigment epithelium
- a cross-reaction because of reinforced T-cell response

Leucouflet M et Al., *Ann Dermatol Venereol*, 2013

Min et Al., *Eur J Endocrinol.*, 2011


Orbital myositis

**Cause: Imatinib**

Is a selective inhibitor of several tyrosine kinases that is used for the treatment of chronic myeloid leukemia (c-kit proto-oncogene, PDGF receptor kinase).

**Pathogenesis:** Inhibition of c-kit and platelet-derivated growth factor receptor tyrosine kinases present in dermal dendrocytes leads to increase capillary permeability and fluid extravasion and accumulation.

The orbit may be particularly susceptible to fluid accumulated because fluid can be trapped in the space formed by septal attachment between the inferior orbit wall and the lower eyelid skin.

The edema occurs between 5 weeks and 8 weeks after starting the treatment.

The periorbital edema is often mild and does not require therapy.

DeLuca C. et Al., *Optom Vis Sci.*, 2012
Mc Clelland CM et Al., *Clin Ophthalmol.*, 2010
Cause: Bisphosphonates

Inhibit the differentiation of osteoclast precursors and are used prevent skeletal related events in patients with multiple myeloma, breast cancer, and prostate cancer.

The symptoms occur within 48 hours of initial infusion and are accompanied by acute phase systemic symptoms, such as fever, myalgia, and flu-like symptoms.

Pathogenesis: Several ophthalmologic toxicities have been reported:

- conjunctivitis, uveitis, scleritis, episcleritis, optic neuritis.

Suggests a possible immune-mediated mechanism.


Colucci A et al., *Ocul Immunol Inflamm*, 2009
**Conjunctivitis**

**Cause:** AZD6244

is a potent mitogen-activated protein kinase inhibitor.

**Pathogenesis:**

the mechanism of MEK inhibitor induced visual toxicity is unclear.

Banerji U et al., *Clin Cancer Res*, 2010

Tolcher AW et al., *J Clin Oncol*, 2011
Uveitis

**Cause: Bisphosphonates**

Causes conjunctivitis, uveitis, scleritis, episcleritis, eyelid edema, optic neuritis and periorbital edema.

**Pathogenesis:** it is possible an immune mediated mechanism for these toxicities.

**Cause: Ipilimumab**

Is a humanized monoclonal antibody against cytotoxic T-cell lymphocyte antigen-4 and enhance the immune response against tumors. Ocular side effects are uveitis, iritis, papillitis and blepharitis.


Colucci A et al., *Ocul Immunol Inflamm*, 2009

Leucouflet M et Al., *Ann Dermatol Venerol*, 2013

Min et Al., *Eur J Endocrinol*, 2011
Keratopathy, Dry eye

**Cause: Inhibitors of Epidermal Growth Factor Receptor:**

Gefitinib and Erlotinib inhibit the tyrosine kinase of EGFR, Cetuximab and Panitumumab are monoclonal antibodies that bind to EGFR directly.

Are used for the treatment of many solid tumors, including non small cell bronchial carcinoma, pancreatic carcinoma, colorectal carcinoma and basal cell carcinoma.
Pathogenesis: EGFR is one of the key receptors in wound healing of the cornea.

After setting a corneal epithelial wound, EGFR is increasing expressed and epithelial cells migrate in the wound area.

Next, there is a shift: the immigrating epithelial cells express EGFR and increase their proliferation rate by binding EGF.

If the tyrosine kinase of EGFR is inhibited, corneal wound healing is delayed.

Xu KP rt al., Invest Ophthalmol Vis Sci, 2004
Nakamura Y et al., Exp Eye Res, 2001
**Keratopaty**

*Cause: Vandetanib:*

Inhibits the tyrosine kinases of both EGFR and VEGF receptors.

It is used for treatment of non-small cells lung cancer.

There are several reports of the development of a cornea verticillata during vandetanib therapy.

It appears as a vortex-like brownish lines within the corneal epithelium. These lines develop because of the interference of vandetanib with EGFR. The reason for the vortex shape is attributable to the migration behavior of the corneal epithelial cells. The deposits lead to blurred vision.

There is a complete regression of the lesion after cessation of therapy.


Yet S. et al., *Cornea*, 2009
**Keratopathy**

**Cause: Tamoxifen**

Is an oral selective estrogen receptor modulator used to treat hormone receptor-positive early and advanced breast cancer.

A variety of corneal deposits have been described in patients receiving long-term tamoxifen, including subepithelial deposits, whorls and band-line opacities.

**Cause: Imatinib**

Can cause ulcerative keratitis with perilimbal infiltrates similar to in rheumatoid arthritis.


Pavlidis et al., *Cancer*, 69

Ashford et al., *Cancer*, 61
Pathogenesis: EGF stimulates proliferation of the epithelial cells of the meibomian glands in the eyelid.

If the effect of EGF is inhibited, meibomian glands become inflamed.
Dry eye

The patient complains of red eye and eyelid, foreign body sensation. In addition, reduced visual acuity may be reported and due to an alteration in the quantity and quality of tears.

The worst case scenario is the progression of corneal erosion to corneal perforation.

In case of trichomegaly contributing to corneal erosion, a simple epilation of the eyelashes can be performed.

Artificial tears use for the duration of therapy at 6 times per day should be recommended to patients receiving EGFR inhibitors.

Liu S et al., Invest Ophthalmol Vis Sci, 2013
Fraunfelder FT et al., Cutan Ocul Toxicol, 2012
Alexandrescu DT et al., Dermatol Online J, 2009
Xu KP rt al., Invest Ophthalmol Vis Sci, 2004
Nakamura Y et al., Exp Eye Res, 2001
Vascular endothelial growth factor receptor inhibitors (VEGF).

Are used for treatment of renal cell carcinoma and gastrointestinal stromal tumors.

**Sunitinib**: can lead to reversible posterior leukencephalopathy syndrome (RPLS).

This disease is due to a disturbance of cerebral vascular autoregulation, which leads to hypertension with dilation of cerebral arterioles. The endothelium cannot withstand this pressure, so a breakdown of the blood-brain results. This goes with visual disturbances and neurological symptoms (vigilance, headache, generalized seizure). It causes edema in the area of the visual cortex which leads to a central visual field defect.

**Crizotinib** is an inhibitor of anaplastic lymphoma kinase, a tyrosine kinase.

It is used for the treatment of non-small cell lung cancer. Ocular problems are described as light trails, flashes or brief image persistences.
Bevacizumab is a monoclonal antibody that is used for the treatment of colorectal carcinoma. It induced vasospasm triggers the syndrome. This can cause cortical blindness, which is not fully reversible.

Ipilimumab is a human monoclonal antibody that is used for the treatment of metastatic malignant melanoma. In literature are reported one case of multifocal bilateral choroidal neovascularization during therapy with ipilimumab.

Optic disc edema, papillitis, cystoid macular edema

Demir M et al., Clin Ophthalmol, 2011
Fielden M et al., Acta Ophthalmol, 2011
Penha FM et al., Ophthalmic Res, 2010
Georgopoulos M et al., Br J Ophthalmol, 2009
Although the systemic use of these agents in oncology is increasing common, direct **ocular administration** (intravitreal injections) is used for the treatment of a variety of ocular conditions.

**Intravitreal injections of VEGF pathway inhibitors are effective in the treatment of several ocular disorders including diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal vein occlusion complications.**
Cystoid macular edema

**Cause:** Tamoxifen:

Is a selective estrogen receptor modulator that is used as an adjuvant therapy for breast cancer.

Side effects of the eye include crystalline retinopathies. The crystalline deposits focus in the macular area and in the peripheral retina. They can cause structural changes in the macula. The most common is a cystoid structure without evidence of macular edema. This changes leads to a pronounced loss of vision.

Macular edema has been described in patients with a high total cumulative dose.


Gianni L et al., *Cancer*, 2006
Cystoid macular edema

**Cause: Tamoxifen:**

An Australian research group reported the occurrence of a macular hole.

Tamoxifen crosses the blood-aqueous barrier and can be detected both in the aqueous humor and in the vitreous. There are case reports on the occurrence of optic neuritis on tamoxifen therapy with centrocecal scotoma and visual loss which resolved after interruption of treatment.

Tamoxifen penetrate the choricapillary barrier, triggering glycosaminoglycan deposition between the nerve fiber and inner plexiform layers of the retina, causing axonal degeneration with prolonged exposure. Also may inhibit lysosomal proteases required for phagocytosis by the retinal pigment epithelium.
Interferons:

Cause alterations in the retina: ischemic change of the ocular fundus, retinal hemorrhages, cotton-wool spots as a sign of swelling of nerve fibers. These changes are similar to the clinical findings in diabetic retinopathy and arterial hypertension.

There are two theories for this pathology:

1. interferons stimulate the formation of immune complexes and these are deposited in the blood vessels and lead to vascular occlusion and ischemia.

2. interferons lead to vasospasms that cause occlusion of the retinal vessels.
Interferons:

There are several reports of combined vascular occlusion (artery and vein) during interferon therapy.

Also anterior ischemic optic neuropathy (AION) has been reported in 36 patients. It is a closure of small capillaries that supply the optic nerve head, which is associated with partial amputation of the visual field and often a dramatic loss of visual acuity. Sometimes the patients may develop double vision related to the complex immunological effects of interferons.

Jenisch T et al., Ophthalmologe, 2012
Fraunfelder FW et al., Ophthalmology, 2011
Wei YH et al., Ocul Immunol Inflamm, 2009
Mydriasis, deficiency of accommodation

Cause: Ganglioside GD2 antibodies

Is an glycosphingolipid which is highly expressed on neuroblastoma cells.

GD2 is also expressed in the ciliary body and the iris, so a cross-reaction with antibody is possible.

Ten children showed mydriasis and deficiency of accommodation as parasympathetic lesions.

Castel V et al, Clin Transl Oncol., 2010

Kremens B et al., Cancer Immunol Immunother., 2002
Our experience

In our study enrolled 430 patients (oncologic and survivors), of whom 40 underwent eye examination.

- Ophthalmologic examination revealed the following data:
  - 1. dry eye: 80% of cases
  - 2. blepharitis: 40% of cases
  - 3. keratitis: 2% of cases

Patients with recurrent episodes of keratitis were treated with Sunitinib
Our experience

before ... during ... after ... Sunitinib
Take home message
Take home message

- The new targeted therapies are not free of side effects on different organs also affecting the eye.
- Therefore in the management of cancer patients is very important close cooperation between oncologist and ophthalmologist to diagnose and treat any complications of ocular targeted drugs.
- Everything to improve the quality of life of cancer patients.
Take home message

Our goal is:

Transform healthcare in take care of patient
Ocular Toxicity and Biological care

Thank you