Ocular Adverse Events (OAEs) in Newer Chemotherapeutic Agents: An Overview of Clinical Presentation and Management Strategies

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Introduction

- Development of molecularly targeted anticancer therapies and immunotherapy continues to revolutionize treatment of cancer.
- U.S. Food and Drug Administration (FDA) accelerated approvals of novel targeted therapies allowed for introduction of these agents into the clinic at a rapid rate.
- On-and off-target ocular toxicities are prevalent treatment-related adverse events of newer therapies including antibody drug conjugates (ADCs) and Immune Checkpoint Inhibitors (ICIs).
- Ocular toxicities associated with ADCs and immunotherapy have heterogeneous presentations and pathogenesis requiring unique and often complex monitoring, and management.

Purpose

- To provide an updated review of treatment-emergent ocular toxicity associated with new and novel oncologic therapies and summarize guidelines and best practice strategies for prevention, monitoring and management.
- Inadequate amount of literature surrounding the topic in newer anticancer agents (ADCs and ICIs).
- Published Literature Review in *Expert Opinion on Drug Safety* in August, 2023.

NCODA

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Results

Incidence

- Newer **ADCs** such as **enfortumab vedotin, mirvetuximab soravtansine,** and **tisotumab vedotin** have been implicated with OAEs in clinical trials. These agents have now been updated to carry box warnings for associated Ocular Toxicities.
- Incidence of OAEs in **enfortumab, mirvetuximab,** and **tisotumab** have been found to be as high as 46%, 52%, and 53% respectively wiith toxicities ranging in severity from Grade 1 to 4.
- OAEs in **ICIs** pose less of a threat to patients than their ADC counterparts and are considered a rare complication but remain important to recognize.
- Incidence of OAEs across all ICIs have been stated to be ~1% with the majority of toxicities being mild. However, growing popularity of combination therapies of ADCs and ICIs.

Management Strategies

- **Scan QR Code for Helpful Tables and Figures surrounding in-depth management strategies for all treatments discussed below.**
- Both mirvetuximab and tisotumab have recommendations for prophylactic care in addition to considerations during treatment.
  - Corticosteroid eye drops (e.g. dexamethasone or prednisolone) in both ADCs but also additional vasoconstrictor eye drops in tisotumab patients.
  - Eye drops are required to be brought to the infusion room for tisotumab in addition to recommended application of cold-pack therapy during/post infusion.
- Multidisciplinary approach - Visual acuity & slit lamp eye exam by eye care provider (ophthalmologist or optometrist) at baseline and as indicated for ADC treatments.
  - Avoid eye irritants and contact lenses.
- Management of ICI driven immune-related AEs should be based on grading of OAEs
  - Frequency and severity of different graded toxicities should guide treatment decisions i.e. holding treatment, dose modifications, and discontinuation of treatment.

Results

Clinical Presentation

- **Enfortumab**
  - Off-target or non-antigen mediated toxicity
  - Dry eye symptoms most common
  - Other toxicities with corneal involvement may occur such as keratitis, blurred, vision, amd limbal stem cell deficiency.
- **Mirvetuximab**
  - Off-target or non-antigen mediated toxicity
  - Blurred vision and keratopathy (29% all grades; 8% grade 3; 1% grade 4) being the most common symptoms.
  - Other reported ocular toxicities were dry eye. photophobia, cataracts, and eye pain.
- **Tisotumab**
  - On-target or antigen-dependent toxicity
    - May explain why ocular toxicity with tisotumab is confined to the ocular surface.
  - The most common ocular event was grade 1/2 conjunctivitis and dry eye, which occurred in 26% and 23% of patients respectively.
  - Keratitis, retinal hemorrhage, and ulcerative keratitis were rare and occurred in 11%, 1%, and 2% of patients, respectively.
- **Immune Checkpoint Inhibitors**
  - Immune dysregulation resulting in an increase in inflammatory pathways.
  - Immune related adverse events including uveitis, retinal vasculitis leading to optic neuropathies as well as dry eyes.
- **Time to onset**
  - OAEs across all ADCs have a median time of onset of ~1-2 months across therapies.
  - Onset of OAEs in ICIs range from 2 to 65 weeks with a mean time of 17 weeks.

Conclusion

- Despite causing fewer off-target toxicities relative to traditional chemotherapies, adverse events associated with targeted treatments can still affect healthy tissues including the eye.
- Ocular toxicities are prevalent treatment-related AEs of newer therapies including ADCs and immunotherapy.
- Implementation of successful eye care plans, as well as monitoring and mitigation strategies requires a multidisciplinary team of oncology providers, eye care providers, clinical oncology pharmacists, and nursing staff.