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 newer anticancer agents (ADCs and ICIs).
- To summarize guidelines and best practice strategies for prevention, monitoring and management.
- To provide an updated review of treatment-emergent ocular toxicities associated with ADCs and ICIs.

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 with 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.

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.

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, and 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 1%, 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.