

ADVANCES IN
Cancer
IMMUNOTHERAPY™



Identification and Management of Immune-Related Adverse Events in the Emergency Setting

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Society for Immunotherapy of Cancer

Disclosures

- Eisai Co., Ltd., Genentech, Inc., Novartis AG, Pfizer, Consulting Fees (example of financial relationship listing from COI form)
- If no conflicts state: No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

CTLA-4 and PD-1/PD-L1

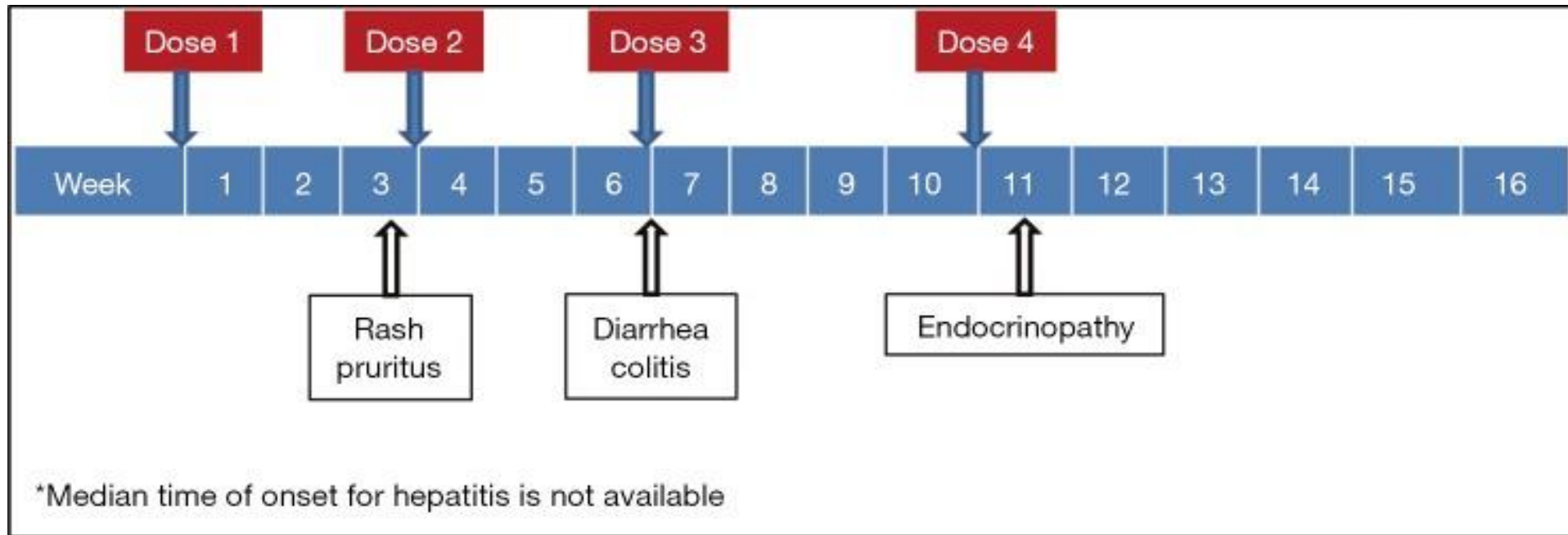
Immune checkpoint mechanisms

- Involved in maintaining appropriate immune response
- Downregulates & prevents inappropriate activity
- Autoimmune type response
- Thinking “Chemo” will lead to incorrect AE strategy
- Immunotherapy AEs similar to Graft versus Host disease

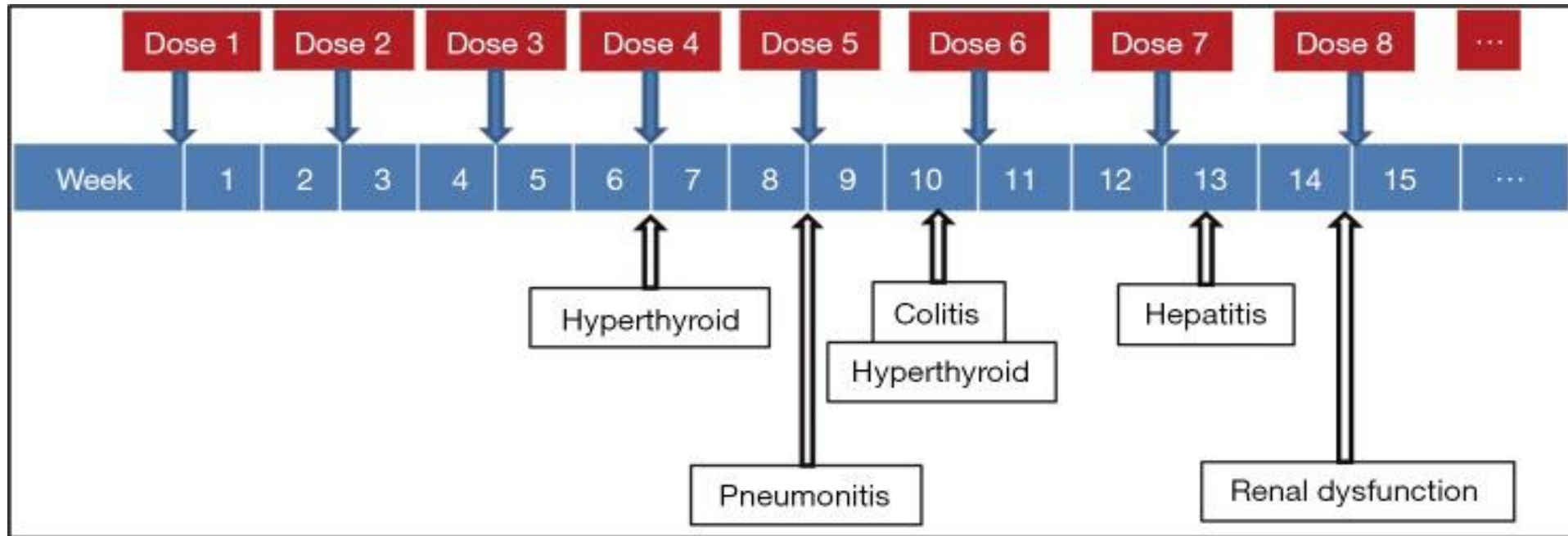
Timing of irAE incidence

- Most irAEs occur within three months of treatment initiation
- irAEs can occur past treatment completion
- Some irAEs are dose-dependent
- ~10% of overall irAEs grade 3/4

Timing of irAE incidence



Timing of irAE incidence



irAE Grades

- 1 Asymptomatic
- 2 Symptomatic
- 3 Severe symptoms
- 4 Life-threatening

• Treatment depends on grade

- 1 • Corticosteroids not usually indicated
 - • Continue immunotherapy
- 2 • If indicated, start oral prednisone 0.5-1 mg/kg/day if patients can take oral medication. •
 - Hold immunotherapy during corticosteroid use
- 3 • Start prednisone 1-2 mg/kg/day.
 - Hold immunotherapy;
- 4 • Start prednisone 1-2 mg/kg/day).
 - Discontinue immunotherapy

irAE Treatment

- Corticosteroids
 - Prednisone
 - Dexamethasone
 - Methylprednisolone
 - Hydrocortisone
 - Cortisone
- Mycophenolate mofetil (CellCept)
 - Standard BID
- TNF inhibitors
 - Infliximab
 - Adalimumab
 - Others

Dermatologic Toxicity
Diarrhea/ Colitis
Hepatitis
Endocrinopathies
Pneumonitis
Pancreatic irAEs
Renal insufficiency
Ophthalmologic irAEs
Rare irAEs

Dermatologic toxicity presentations

- Often presents ~ three weeks post-therapy initiation
- Mild – maculopapular rash with or without symptoms
 - Pruritis, burning, tightness
 - 10% - 30% TBSA
 - Limiting ADL's
 - Topical steroids, hydroxyzine, diphenhydramine
 - Cort
- Moderate – diffuse, nonlocalizing rash
 - 30% - 50% TBSA
 - Topical corticosteroids, hydroxyzine, diphenhydramine
 - Consider systemic corticosteroids if no improvement within one week (0.5 – 1mg/kg/day)

Dermatologic toxicity presentation

- Severe
 - Blisters, dermal ulceration, necrotic, bullous or hemorrhagic
 - Systemic corticosteroids 1 – 2mg/kg/day prednisone equivalent
 - Taper over one month following improvement
- Vitiligo
 - Most cases permanent
 - No treatment
 - Intra oral lesions – consider candidiasis

Stevens Johnsons Syndrome (SJS)/ TEN (Toxic Epidermal Necrolysis)



Vitiligo



Diarrhea/ colitis presentation

- Mild - <4 stools above baseline/day
- Treatment
 - Symptomatic: oral hydration & bland diet
 - No corticosteroids
 - Avoid medications
 - Budesonide – no significant difference

Diarrhea/ colitis presentation

- Moderate – 4-6 stools above daily baseline
 - Abdominal pain, blood or mucus in stool
 - Testing – *C. diff*, lactoferrin, O & P, stool Cx
 - Systemic corticosteroids 0.5mg/kg/day prednisone equivalent if symptoms persist > one week

Diarrhea/ colitis presentation

- Severe – >6 stools above daily baseline
 - Peritoneal signs, ileus or fever
 - Admission
 - IV hydration
 - Rule out perforation
 - Stool studies

Diarrhea/ colitis presentation

- Severe – >6 stools above daily baseline
 - Systemic corticosteroids 1-2mg/kg/day equivalent, if no perforation
 - Hold if clinically stable until stool studies available (24hrs)
 - Unstable – High dose corticosteroids: methylprednisolone 125 mg IV daily x 3 days to evaluate responsiveness
 - Consider empiric antibiotics for fever or leukocytosis
 - Infliximab 5 mg/kg if non responsive to corticosteroids
 - Consider mycophenolate mofetil for select patients

Hepatotoxicity presentation

- 8 -12 weeks after therapy initiation
- Grade 2 toxicity
 - $2.5 < \text{AST/ALT} < 5$ times ULN
 - $1.5 < \text{Bilirubin} < 3$ times ULN
 - Corticosteroids 0.5-1 mg/kg/day & 1 mo. taper
- Grade ≥ 3 toxicity
 - Admission
 - Methylprednisolone IV 125mg/day
 - Consider mycophenolate mofetil 500mg PO Q12hrs
- Avoid alcohol & acetaminophen

Endocrinopathy presentations

- >10% all reported irAE cases
- Can arise while receiving checkpoint inhibitors
- Hypophysitis
 - 1-2 months after initiation of therapy
 - Fatigue, headaches, visual field defects
 - ACTH, TSH, FSH, LH, GH, prolactin
 - Imaging – enlarged pituitary gland
 - Corticosteroids 1 mg/kg/day, or IV dexamethasone 6 mg Q6hr x 3 days, or methylprednisolone 125 mg daily

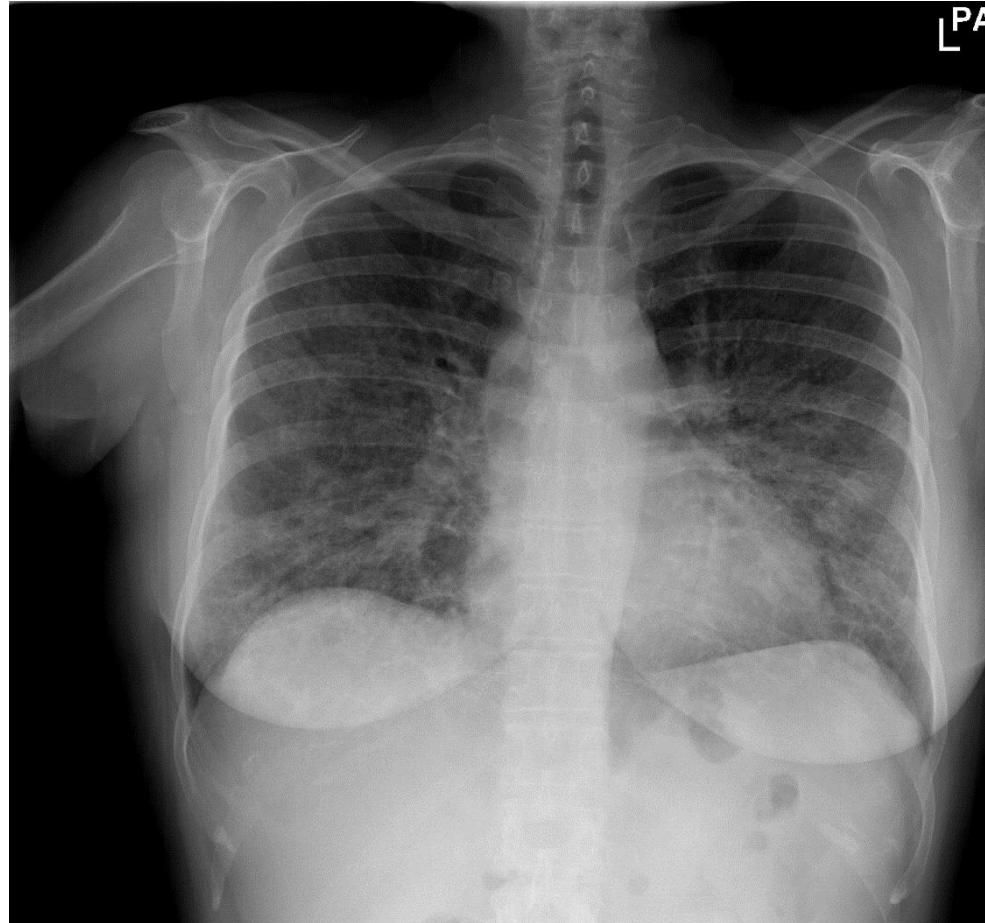
Endocrinopathy presentation

- Hypothyroidism
 - 1 wk-19 months onset after therapy initiation
 - Appropriate levothyroxine replacement
- Hyperthyroidism
 - Check TSH level
 - Acute thyroiditis secondary to immune activation
 - Corticosteroids 1 mg/kg for symptomatic patients
- Adrenal Insufficiency
 - Admission
 - Corticosteroids 60-80 mg prednisone or equivalent

Pneumonitis presentation

- Can arise during treatment with checkpoint inhibitors
- Symptomatic ~ 5 months after treatment initiation
- New cough or dyspnea
- Multiple grades
 - Grade 2
 - Admission
 - Prednisone/prednisolone
 - Taper over one month after improvement seen
 - Grade 3-4
 - Admission
 - Prednisone/prednisolone
 - Taper over six weeks

Pneumonitis presentation



Pancreatic irAE presentations

- Elevated amylase and/or lipase
 - Can arise during treatment with checkpoint inhibitors
 - Without overt pancreatitis – monitor patient
 - Symptomatic Grade 3/4 incidences – hold therapy
- New onset diabetes with diabetic ketoacidosis
 - Normal ED treatment
 - Aggressive treatment of DKA

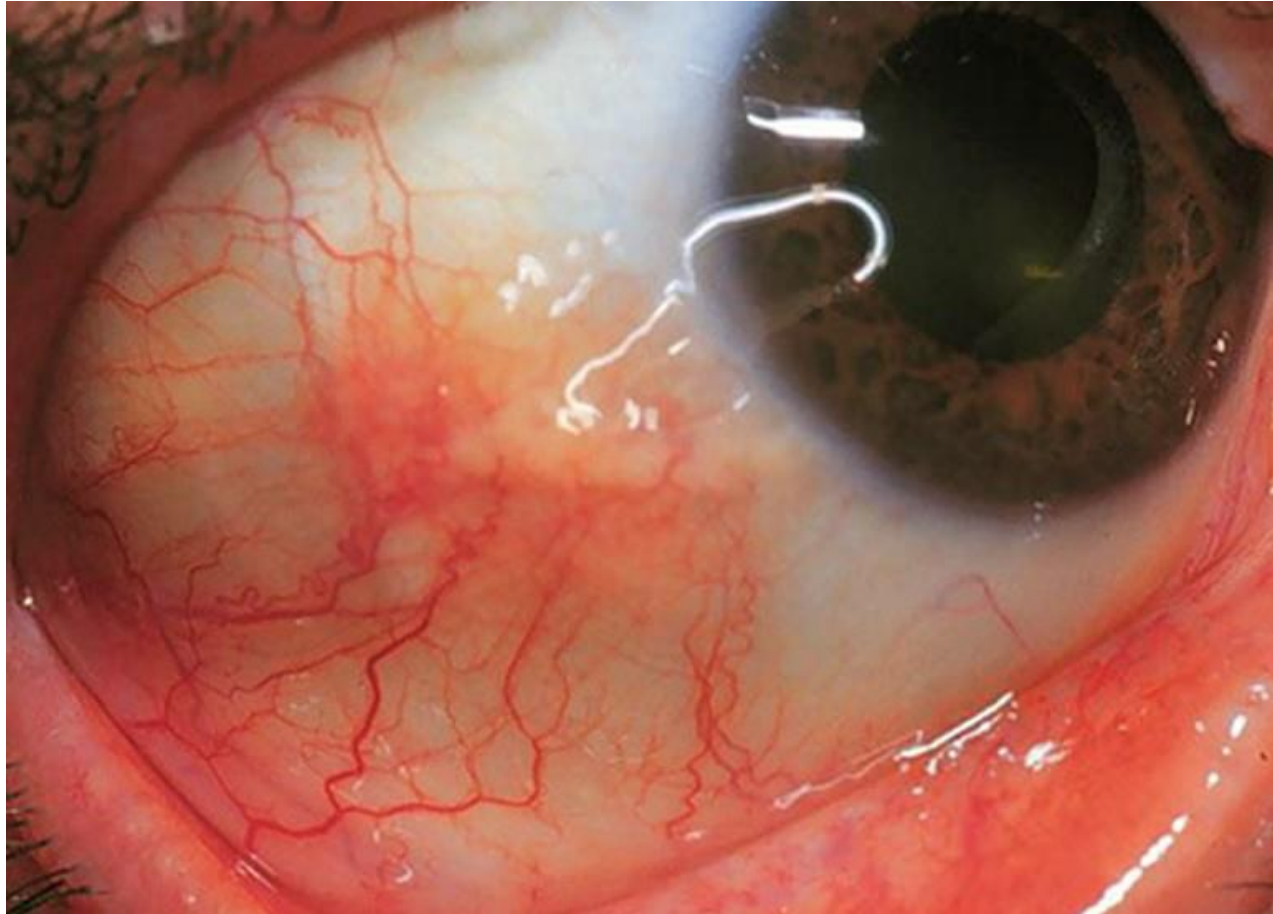
Renal insufficiency presentation

- <1% of overall irAE cases
- 10-12 months after initiation of treatment
- Grade 1: up to 1.5x baseline
- Grade 2/3: 1.5 - 6x baseline
- Full recovery with high dose corticosteroids.
 - (>40 mg/day)

Opthalmologic irAE presentations

- <1% of overall irAE cases
- Episcleritis
- Uveitis
- Conjunctivitis
- Topical corticosteroids – prednisolone acetate 1%

Opthalmologic irAE presentation



Opthalmologic irAE presentation



Opthalmologic irAE presentation



Rare irAE presentations

- <1% of overall irAE cases
 - Red cell aplasia
 - Thrombocytopenia
 - Hemophilia A
 - Gullian-Barre syndrome
 - Myasthenia gravis
 - Posterior reversible encephalopathy syndrome
 - Aseptic meningitis
 - Transverse myelitis
 - ??

Questions

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