Adverse events in immunotherapy

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Unique features of immune-related Adverse Events “irAEs”

- Safety profile is based on the mechanism of action:
  - **Most commonly affected organs** with “higher antigen load”:
    - Gastrointestinal: Diarrhea, colitis
    - Skin: Rash, Erythema (several patterns)
    - Liver: Asymptomatic Laboratory transaminases elevation, pancreatic enzymes elevation
    - Endocrine systems: thyroiditis, hypophisitis
  - **Can occur in any organ system**
Different patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab

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http://onlinelibrary.wiley.com/doi/10.1002/cncr.27969/full#fig2
Immunotherapies AEs & Management Overview

• Inflammatory nature of AEs
  • Due to Mechanism of Action
• Mostly low grade AEs and manageable
• Education is key for a successful control of those events
• management is to suppress the inflammation and in most cases it is reversible
• If not properly managed, can lead to serious outcomes
  • Symptoms worsening
  • Onset of complications
    • e.g., perforation
• AEs treatment guidelines established
  • Early recognition of signs and symptoms
  • Subject education
  • Low grade AEs: symptomatic and topical therapies
  • Persistent low-grade or severe events: Systemic corticosteroids

Lin, JCO 2008
Kahler, JDDG 2011
General Summary for AE treatment

1. Identify Event
2. Hold Study Therapy
3. Reference Toxicity guidelines
4. Possible continuation of study therapy
5. Early Intervention with steroids
6. Look for alternative etiology
Challenges around irAEs

I. Identifying irAEs

1. No standard approach to identifying irAEs
   - Any inflammatory event without an alternative etiology
   - Any inflammatory event without an alternative etiology and managed with steroids
   - Any event that was managed with steroids

2. No standard approach to terminology used to describe irAEs
   - Immune related Adverse Events
   - Immune Mediated Adverse events
   - Events of Special Interest

3. Investigator based assessment vs an independent assessment of causality
Challenges around irAEs (cont.)

I. Identifying irAEs

4. Patient education is key to ensure proper early detection
   - Most events can’t be identified in a physical exam:
     - Fatigue or headache: underlying endocrinopathy
     - Abdominal pain: colitis
     - Itchiness
   - Patients might be reluctant to report low grade events (to stay on treatment)
   - Patients often self medicate (OTC) and only seeks medical advice with worsening of symptoms
   - Patients often go to a specialist and not their oncologist for acute adverse events
Challenges around irAEs (cont.)

2. Characterizing irAEs

1. Phase 1 studies
   - Most PD1/PDL1 Mab didn’t achieve an MTD and doses were selected based on totality of data (safety, efficacy, PK and PD)
   - Time to onset of irAEs varies based on molecule and organ affected: limitations of 3+3 study
   - DLT period might not be appropriate approach to capture some of the delayed effect
   - It’s important to evaluate the entirety of the safety data & experience generated in Phase 1, including safety data outside of the traditional DLT window, when making dose-selection decisions
   - Participation is commonly limited to Immuno-oncology highly experienced investigators
   - Strict management guidelines are implemented in the clinical trials
   - Very close monitoring
Challenges around irAEs (cont.)

2. Characterizing irAEs

2. Real world evidence

➢ Safety could be different from that reported in clinical trials

➢ irAEs are not managed by the medical oncology team but rather:
  ➢ Emergency room physician
  ➢ Specialists such as pulmonologists, gasteroenterologists or internists

➢ Lack of awareness of toxicity management guidelines and events are commonly managed by non-steroid containing regimen for the fear of antagonizing anti-tumor effect

➢ Toxicities are managed like small molecule or chemotherapy induced adverse events e.g potent anti-diarrheals to control a resistant diarrhea
Framework for detecting and managing irAEs

1. Need for standardization of definition of irAEs
   1. Input from regulators, academic and industry representatives
   2. Considering including “immune-related” as separate preferred terms in CTCAE criteria

2. Clinical trials conduct
   1. Need for novel phase 1 study designs that can capture delayed adverse events
   2. Continuing to closely monitor & evaluate AE data from the ongoing development program as well as exposure to the drug during the peri-approval period (through expanded access) and subsequently in the post-marketing setting
   3. Including community hospitals and oncology units in clinical trials to gain clinical experience
   4. Investigators assessment vs independent assessment

3. Patient education:
   1. Patients commonly research “efficacy” of novel agents and might miss safety piece
   2. Ensure increasing patient’s awareness to the importance of reporting low grade or new onset of any side effect
   3. Utility of (PRO)
   4. Investigator’s causality assessment vs Patient Reported Outcome (PRO) and Health Related Quality of Life

4. Expanding the awareness outside of medical oncology field
   1. Material geared towards research nurses, study coordinators
   2. Involving emergency room physicians, specialists and internists
Thank You