ADVANCES IN Cancer IMMUNOTHERAPY™

irAEs: Immune Related Adverse Events Management and Mitigation

Mary Nakamura MD
Professor of Medicine
Division of Rheumatology
UCSF

AMERICAN ACADEMY OF EMERGENCY MEDICINE

ACCC
Association of Community Cancer Centers

sitc
Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Disclosures

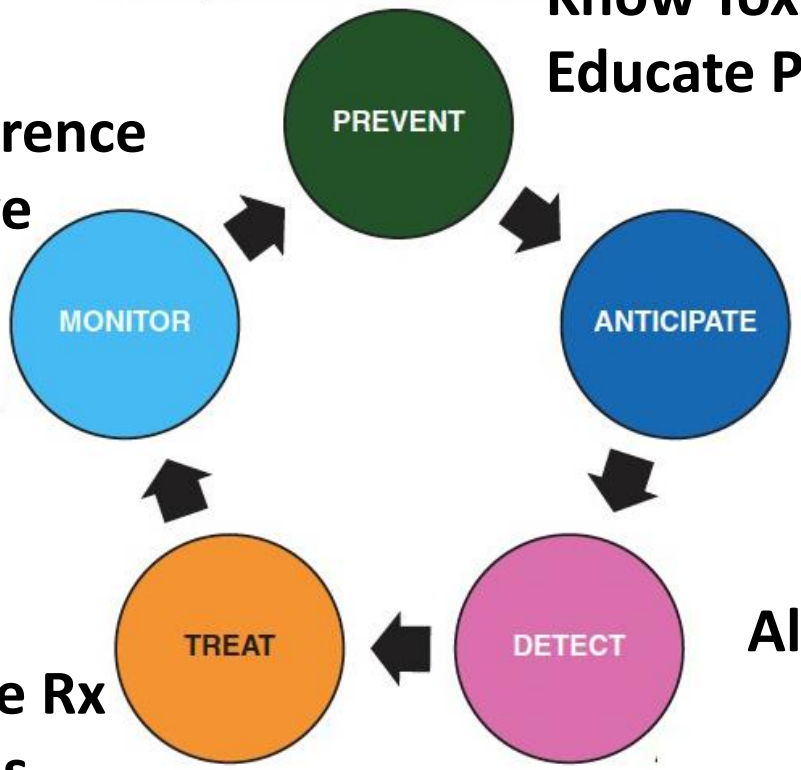
- No disclosures
- I will be discussing non-FDA approved treatments during my talk today
- No treatments are currently FDA approved for treatment of irAEs (immune-related adverse events)

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

The Five Pillars of Immunotherapy Toxicity Management



Know Toxicity Spectrum
Educate Patients

Baseline studies
Monitoring
on and off rx

Always consider irAEs!

Immunosuppressive Rx
Consultant Referrals
Immunotherapy Suspension

Possibility of Recurrence
Immunosuppressive Complications

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Champiat Ann Oncol 2016;27:559-574

ADVANCES IN Cancer IMMUNOTHERAPY™

Case 1

Mr. S is a 65 yo male with a history of rheumatoid arthritis and a recent diagnoses of stage IV melanoma with lung involvement

He plans to start Pembrolizumab

at 2mg/kg every 3 wks.

He asks what are the most common adverse events with this immunotherapy?

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

What are Common irAEs? (Immune related adverse events)

• Dermatologic	47-65%	rash
• Colitis	30-48%	diarrhea
• Hepatitis	5-30%	elevated LFT's
• Endocrine	5-10%	hypothyroid hypophysitis

Champiat Ann Oncol 2016;27:559-574

ADVANCES IN Cancer IMMUNOTHERAPY™

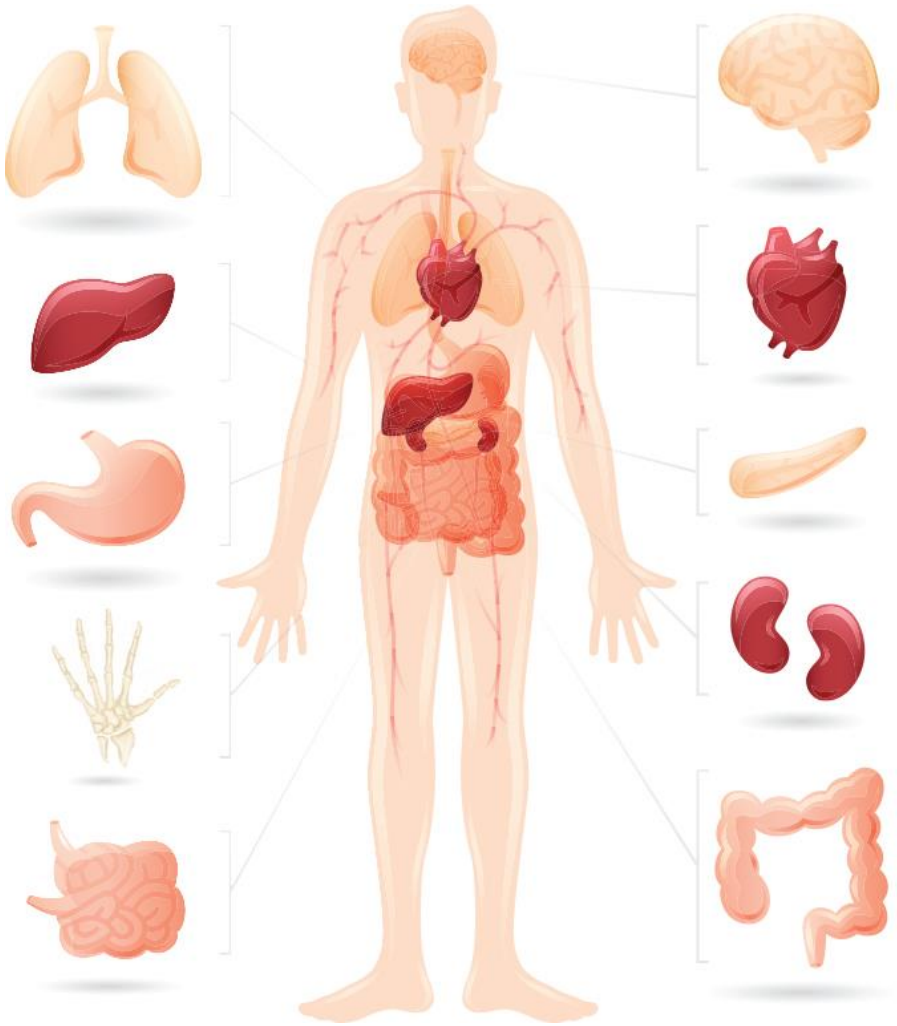
Pneumonitis

Hepatitis

Gastritis

Arthritis

Ileo-enteritis



Cerebritis

Hypophysitis

Thyroiditis

Myocarditis

Pancreatitis

Type 1 Diabetes

Nephritis

Colitis

Dermatitis

Champiat Ann Oncol 2016;27:559-574

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Does autoimmune disease increase irAE risk?

- Very Limited data on this topic
- Not an absolute contraindication
- Must be decided on case to case basis
- Flares of preexisting disease occur
- irAE not necessarily same as pre-existing disease
- Tumor Response rates similar to general population

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Immunotherapy in autoimmune disease patients

- Retrospective study -advanced melanoma (PD-1 agents)
  - 52 patients - pre-existing autoimmune disorder
    - 33 % response rate
    - 38 % flare of the autoimmune disorder
    - flares were relatively mild

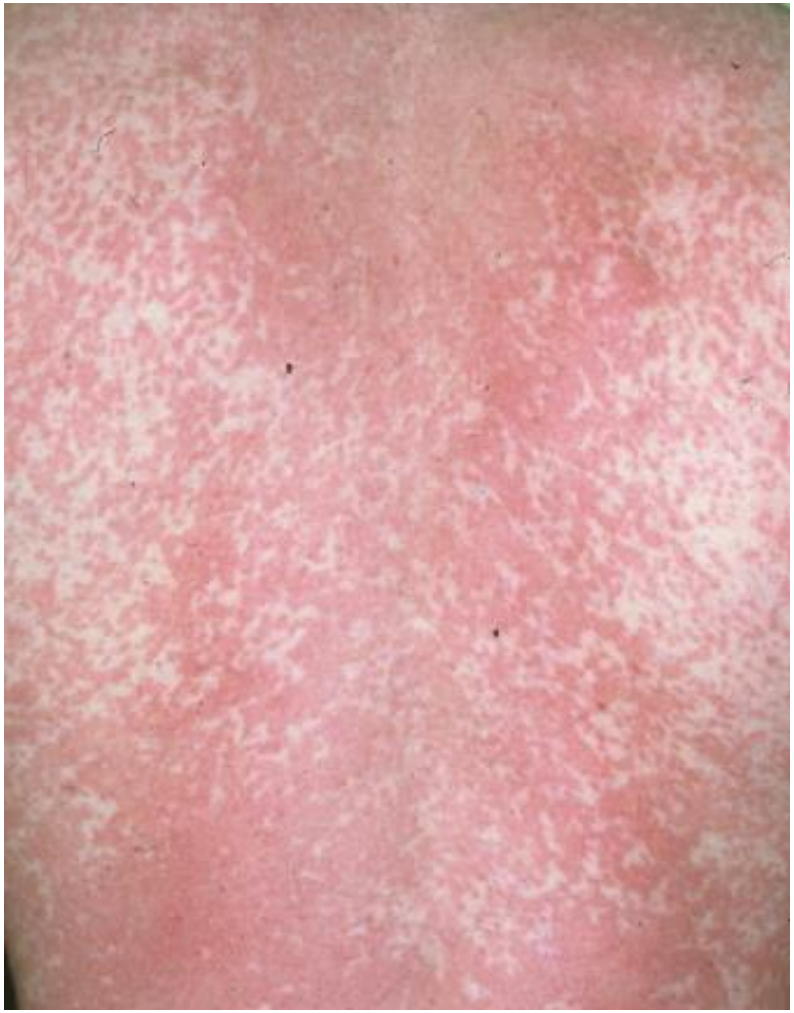
- Retrospective study -advanced melanoma (CTLA-4 agent)
  - 30 patients - pre-existing autoimmune disorder
    - 20 % response rate
    - 27 % flare of the autoimmune disorder

Johnson *JAMA Oncol* JAMA Oncol. 2016;2(2):234-240.
Bertrand *BMC Med*. 2015;13(1):211.

ADVANCES IN Cancer IMMUNOTHERAPY™

Mr. S returns to clinic for evaluation prior to dose #4 of Pembrolizumab

- for the past week he has had a pruritic rash on his back, chest and arms



How will you treat him now?

He now wants to review the rare side effects again

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Common Terminology Criteria for Adverse Events

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Covering <10% body surface area (BSA)	Covering 10-30% BSA	Covering >30% BSA	More severe IV antibiotics, burn unit admission
Diarrhea	Increase of <4 stools over baseline	Increase of 4-6 stools over baseline	Increase of ≥7 stools hospitalization indicated, incontinence	Life-threatening consequences, urgent intervention
Hepatotoxicity	AST or ALT >ULN- 3 x ULN or T. bili >ULN–1.5xULN	AST or ALT > 3-5 x ULN or T. bili >1.5–3xULN	AST or ALT >5-20 x ULN or T. bili >3–10xULN	AST or ALT >20 x ULN or T. bili >10xULN
Endocrine, pneumonitis	Asymptomatic	Symptomatic	Severe symptoms, hospitalization indicated	Life-threatening

CTCAE inadequate to describe severity of many irAEs

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Dermatologic irAEs

- Common
  - diffuse, maculopapular rash
  - and/or pruritis
  - vitiligo
- Usually manageable with topical glucocorticosteroids
- If persistent Grade 2 and Gr 3
  - HOLD Immunotherapy
  - Prednisone 1mg/kg of prednisone
  - Restart when Grade 1 or less
- Permanently discontinue for Grade 4 or persistent grade 3

- Rare
  - Bullous pemphigoid
  - Steven's Johnson/TEN
  - Neutrophilic dermatoses

Spain, Cancer Treatment Reviews 44 (2016) 51–60

Mr. S returns with new complaint of diarrhea

Treated with topical steroids with resolution of rash, immunotherapy continued, now has a week of diarrhea up to 8x/day

Should You

A. Hold PD-1 antibody
B. Check stool cultures, ova & parasites, c. difficile
C. Start systemic corticosteroids (1-2 mg/kg/day of prednisone + IV fluids)
D. GI consult for scope with colon biopsies with rapid pathologic review – due to suspicion for immune-related colitis
E. CT abd; check Quantiferon

All of the above

A. Hold PD-1 antibody
B. Check stool cultures, ova & parasites, c. difficile
C. Start systemic corticosteroids (1-2 mg/kg/day of prednisone IV + IV fluids)
D. GI consult for scope with colon biopsies with rapid pathologic review – due to suspicion for immune-related colitis
E. CT abd; check Quantiferon

- Concern with grade 3 colitis
  - rapid progression to intestinal perforation
  - If no improvement in 2-3 days of IV steroids
  - advance to anti-TNF (infliximab therapy, 5mg/kg IV)

Friedman JAMA Oncol. 2016;2(10):1346-1353

irAEs by organ system (immune-related adverse events)

- GI
  - Colitis
    - Intestinal perforation
  - Hepatitis
  - Ileitis/enterocolitis
  - Gastritis
  - Biliary Tract
- Endocrine
  - Hypothyroid
  - Hyperthyroid
  - Hypophysitis
  - Adrenal Insufficiency
  - Type 1 Diabetes/DKA
  - Type 2 Diabetes

Spain, Cancer Treatment Reviews 44 (2016) 51–60

Less Common irAEs by organs (immune-related adverse events)

- Pulmonary
  - Pneumonitis
    - Cryptogenic Organizing Pneumonia
    - UIP, DIP, NSIP
  - Sarcoid
    - need to rule out new tumor

Hypoxia can be out of proportion to evidence inflammatory disease can can progress rapidly

- Neurologic
  - Cerebritis
  - Peripheral Neuropathy
  - Myasthenia Gravis
    - Often occurs with myositis
    - Bulbar sx, diplopia
  - Optic Neuritis
  - Guillain-Barre

Spain, Cancer Treatment Reviews 44 (2016) 51–60

Less Common irAEs by organs (immune-related adverse events)

- Eye
  - Uveitis
  - Scleritis
  - Orbital Inflammation
  - Dry eyes
- Renal
  - Interstitial Nephritis
  - Glomerulonephritis
- Rheumatologic
  - Inflammatory arthritis (seronegative)
  - Myositis
  - Sjogren's syndrome
  - Reactive arthritis
  - Vasculitis/SLE
  - PMR/GCA
- Heme
  - Hemolytic Anemia
  - ITP , neutropenia

Spain, Cancer Treatment Reviews 44 (2016) 51–60

ADVANCES IN Cancer IMMUNOTHERAPY™

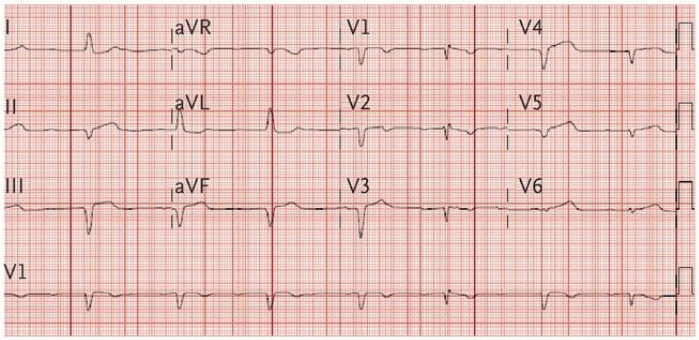
The NEW ENGLAND JOURNAL of MEDICINE

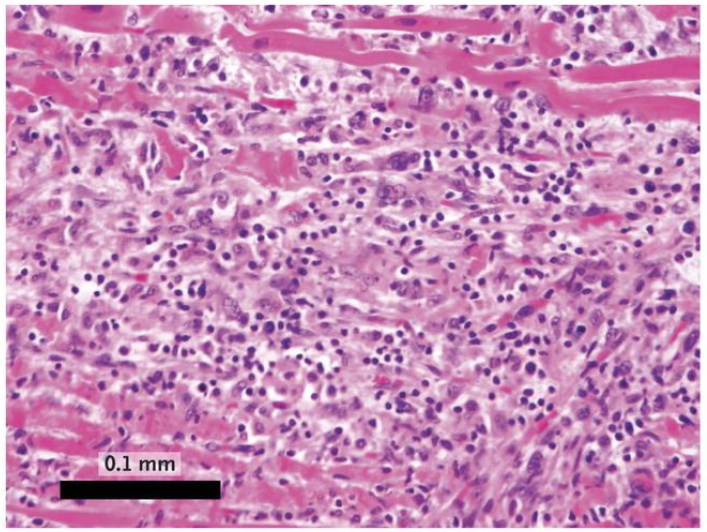
HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade





Often occurs with myositis

Can be fatal

Can present with CHF, arrythmias, chest pain

Johnson, N Engl J Med 2016; 375:1749-1755

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Principles of Management of irAEs

- Hold immunotherapy for grade > 2
- Initiate corticosteroids (1–2 mg/kg of prednisone)
  - IV for grade 3 or above or failure to respond
- Consider infliximab (5mg/kg, particularly for colitis)
- Consider advancing therapy if no improvement with corticosteroids

- Rechallenge – possible if resolve to < grade 1
- Likely permanent discontinuation with severe irAEs > grade 3

ADVANCES IN Cancer IMMUNOTHERAPY™

Case 2

Mr T. 75 year old male with melanoma currently on Nivolumab/Ipilimumab combination therapy

He reports 5 days of

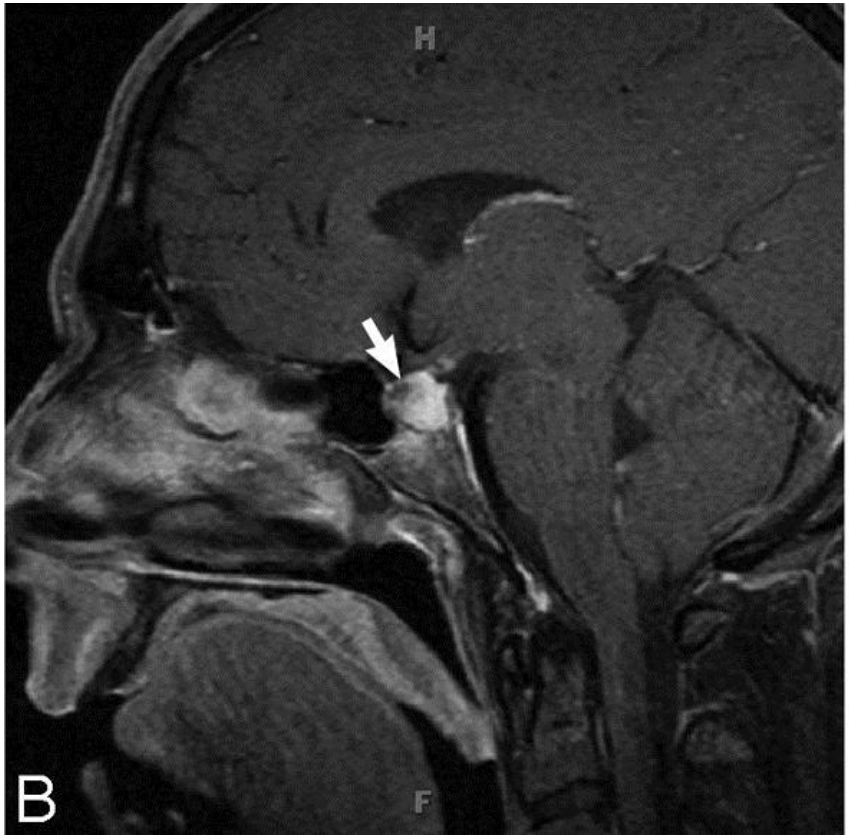
- Moderate Headaches
- Severe fatigue
- Weakness
- Nausea
- Diplopia

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Evaluation

- low cortisol, ACTH
- Low testosterone levels
- Free T4 and TSH were normal
- Normal extraocular movements
  - Negative anti–acetylcholine receptor tests
- MRI: no evidence brain metastases
  - Presence of inflammation of the pituitary
- Improvement in symptoms with IV steroids
- Hypophysitis is often permanent-requiring replacement rx



Amer Jour of Neuroradiology October 2009, 30 (9) 1751-1753

ADVANCES IN Cancer IMMUNOTHERAPY™

Principles of Management of irAEs

- Grade 2 and above usually require hold of immunotherapy
- Grade 3 and above usually requires discontinuation
- irAEs can accelerate quickly-and can be fatal
- Combination anti-PD-1/CTLA-4 immunotherapy significantly increases the grade 3-4 AE rate
- Most irAEs occur in first few months of therapy, they can present late and potentially after discontinuation of drug
- irAEs may persist after discontinuation of immunotherapy

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Principles of Management of irAEs

- Early consultation with organ specific consultants
- Treatment of irAEs requires multidisciplinary team
  - Many patients have more than one organ system

- When initiating immunosuppression
  - remember special risk groups – hx +PPD, HBcAb positive or HBsAg positive
  - PCP prophylaxis
- Infection and recurrent autoimmunity can look the same
- New tumor or tumor recurrence needs to be considered

ADVANCES IN Cancer IMMUNOTHERAPY™

- Autoimmunity is frequent in patients treated with checkpoint inhibitors
- Always consider irAEs which can present with vague symptoms
- Form a multidisciplinary team of specialists to assist in diagnosis and management of difficult cases

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer