

NAVIGATING THE ROLLERCOASTER OF IMMUNOTHERAPY SIDE EFFECTS



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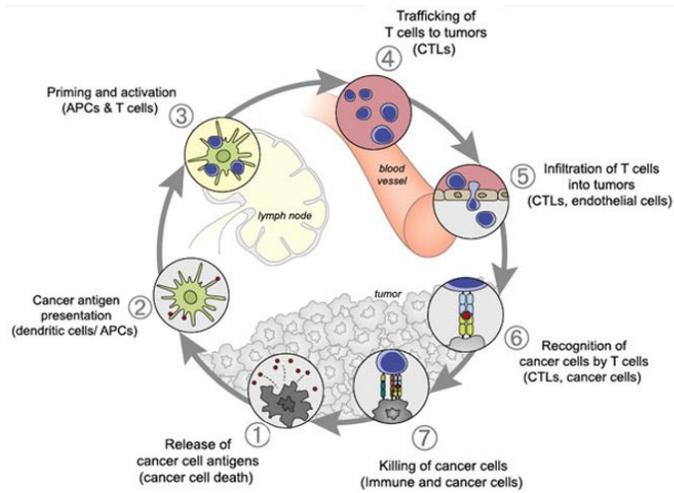
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OBJECTIVES

- Review the spectrum of IO toxicities
- Discuss the duration of toxicities
- Basic strategies of side effect management

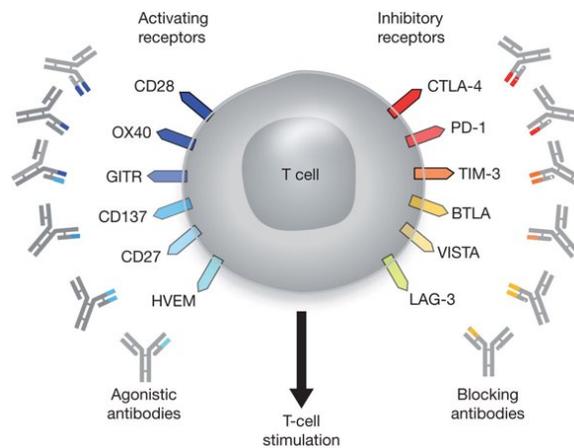
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How is the immune system involved in cancer cell surveillance?



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T-cell Targets/Regulators



Mellman I et al. Nature: 480: 480-9, 2011

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WHAT IS IMMUNOTHERAPY?

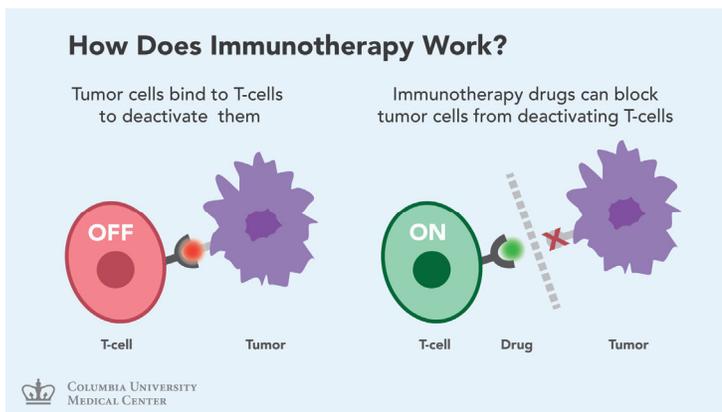
- ICI (Immune Checkpoint Inhibitors) or IO
- Immune Checkpoints
 - Exist to protect against inflammation and autoimmunity
 - Help to dampen the immune response
 - In the setting of cancer, these checkpoints can lead to immune tolerance of tumors.
 - “Hide” from our immune system



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Immune Checkpoint Inhibitors

- Drugs that block the signal that dampens/slows the immune response
- Allows for an enhanced T-cell anticancer response



<https://alternativehealthscience.com/how-immunotherapy-has-helped-get-closer-to-curing-cancer/>

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IMMUNOTHERAPY HAS REVOLUTIONIZED CANCER TREATMENT

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."



The Nobel Prize in Physiology or Medicine 2018. NobelPrize.org.
Nobel Media AB 2018. Mon. 22 Oct 2018.
<<https://www.nobelprize.org/prizes/medicine/2018/summary/>>

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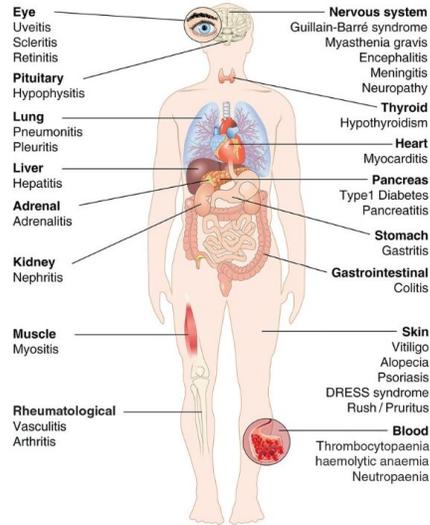
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FDA-
Approved
ICIs

- PD1
- PDL1
- CTLA4
- LAG3
- Combinations

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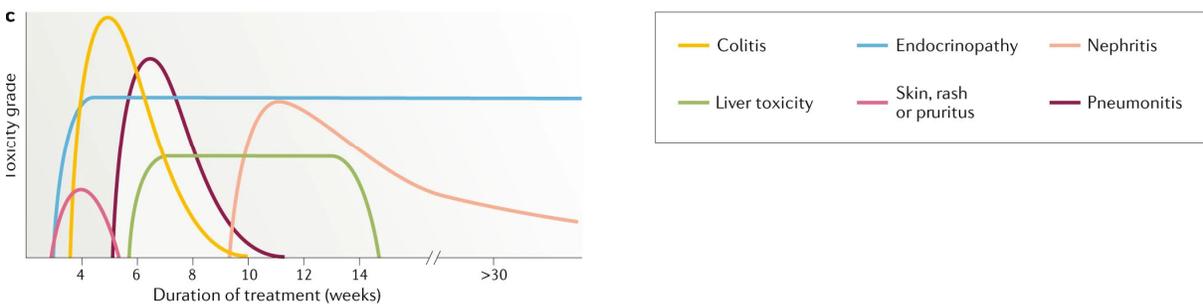
Potential IO Toxicities – EVERY system!



Front Immunol, 29 March 2022

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Timing varies...



Martins, F., Sofiya, L., Sykietis, G.P. *et al.* Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 16, 563–580 (2019).

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MOST FREQUENT IRAEs

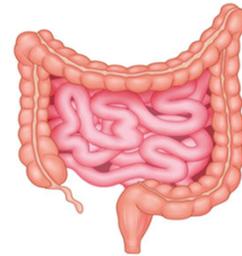
SKIN



THYROID



GI TRACT



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Most Common IRAEs

Endocrine

- Thyroid dysfunction
- Hypophysitis

Cutaneous

- Rash
- Dermatitis
- Pruritis

Musculoskeletal

- Arthralgia
- Myalgias

Lung

- Pneumonitis

Gastrointestinal

- Colitis
- Diarrhea
- Hepatitis

Schneider et al, 2021; Puzanov et al, 2017; Trinh et al, 2019.

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Uncommon IRAEs

Cardiac

- Myocarditis
- Pericarditis
- Arrhythmias

Hematologic

- Hemolytic anemia
- Red cell aplasia
- Thrombocytopenia
- Myelodysplasia
- Hemophilia

Endocrine

- Pancreatitis
- Type 1 diabetes mellitus
- Adrenal insufficiency

Renal

- Interstitial nephritis
- Granulomatous nephritis

Neurologic

- Encephalitis
- Meningitis
- Myasthenia gravis
- Guillain-Barré syndrome
- Peripheral neuropathies

Ophthalmologic

- Uveitis
- Episcleritis
- Blepharitis
- Optic nerve swelling
- Ulcerative keratitis
- Vogt-Koyanagi-Harada

Schneider et al, 2021; Puzanov et al, 2017; Trinh et al, 2019.



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Basics of side effect management:

- Minimal prospective data
- Guidelines from clinical experience/reporting
- Initial strategies stem from melanoma trials & reports
- irAEs are believed to arise from general immunologic enhancement – we tipped the balance "too far"
- Temporary immunosuppression can be an effective treatment in most cases



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General toxicity

- Fatigue
 - Common: 16-24%
 - Variable impact
 - Be sure to exclude other causes

- Infusion reactions
 - Rare
 - Fevers/Chills
 - During infusion or up to 48 hours after
 - ?tumor flare

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Dermatologic toxicity

- Most common: 30-40%
- Earliest to appear (avg ~3-4 weeks)

- Pruritis
- Maculopapular, faint, red rash
 - Trunk or extremities
 - Often migrates

- Biopsy not always necessary



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Skin toxicity

- Vitiligo
- Alopecia
- Rarely SJS or TEN
 - Blisters/peeling
- Mucositis or dry mouth
- Treatment is often topical
 - Emollients
 - Steroid creams
 - Anti-itch medications



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Enterocolitis

- Diarrhea is common
- Colitis symptoms:
 - Cramping
 - Abdominal pain
 - Mucus
 - Blood in stool
- Average onset ~6 weeks
- Can involve the upper GI tract as well



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Colitis management

- Call when 3-4 loose stools MORE than your normal
 - Grade 1
 - Anti-diarrheal
 - Good hydration
- Once more significant:
 - Steroids (budesonide, prednisone, methylprednisone)
 - Often need a colonoscopy and biopsy

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Endocrinopathies



- Later onset (~11-12 weeks)
 - Has been reported >6 month later
- Very non-specific symptoms
 - Can creep up on you
- Most common: **Hypothyroidism**
- Typically not reversible

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How do we manage irAEs?

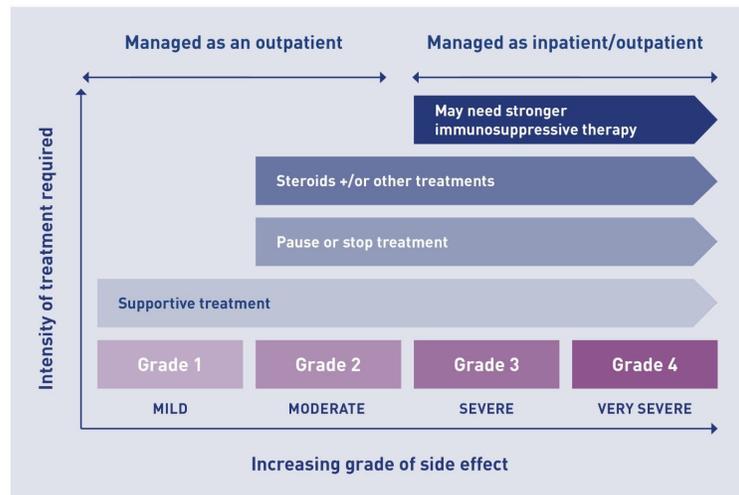
- First we grade them (assess severity)
- CTCAE

0	No adverse events or within normal limits
1	Mild
2	Moderate
3	Severe, not life threatening
4	Life threatening, urgent intervention required
5	Death

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Early detection is key!

- MULTIDISCIPLINARY TEAM
OFTEN NECESSARY



Grade 2

- Hold therapy until \leq grade 1
- Corticosteroids if no resolution within 1 week

Grade 3 or 4

- Discontinue therapy (? permanently)
- High dose steroids; gradually taper over at least one month when grade 1
- If no improvement in \sim 3 days of IV steroids, then add infliximab or other agent (may repeat)

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Corticosteroids are cornerstone



- Dose depends on grade of toxicity
 - 0.5 - 1 mg/kg/day
- Continue until down to grade 1
- Taper duration depends on organ involved

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Challenges of steroids



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What if steroids aren't enough?

MMF
Infliximab
Azathioprine
Trial of IV
IVIG
Tocilizumab

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IrAEs can mean response!!

a **b**
c **d**

Nicolas PY - 2022/06/01 - European Journal of Nuclear Medicine and Molecular Imaging ER -

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Limited long-term data on toxicities

- MOST are entirely reversible!
- More prevalent than initially thought
- Most common chronic irAEs:
 - Endocrinopathies
 - Hypothyroidism
 - Diabetes
 - Rheumatologic
 - Arthritis
 - Dry mouth
- ? Cardiovascular effects?

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Highs and Lows of the Ride



- Occasionally feels like riding a roller coaster in the dark.
- You never know when the next twist or turn is coming
- Both physical and emotional effects

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CHALLENGES OF IO

- SIDE EFFECTS
- PHYSICAL EFFECTS
 - A delicate balance
- EMOTIONAL EFFECTS
 - Lots of unknowns:
 - Timing of side effects
 - Pseudoprogression
 - Duration of treatment
- LONG-TERM MANAGEMENT
 - Cancer surveillance
 - Delayed toxicity
 - Stopping therapy



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But also, SO much hope!

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WHAT CAN YOU DO?



Early reporting of symptoms



Keep a diary to track symptoms and alert your medical team every couple of days of changes.



Make sure all providers know you are on or have received IO

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Omaha, Nebraska

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