Pharmacology I: What HemOnc Clinicians Must Know in Immunotherapy

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Overview

Review drug names and classes

Mechanism of Action

Adverse effect and management case series

Immunotherapy Agents

Immune Checkpoint Inhibitors

PD-1	PD-L1	CTLA-4
• Cemiplimab • Dostarlimab • Nivolumab • Pembrolizumab • Retifanlimab • Tislelizumab • Toripalimab	• Atezolizumab • Avelumab • Durvalumab	• Durvalumab • Tremelimumab

Mechanism of Action

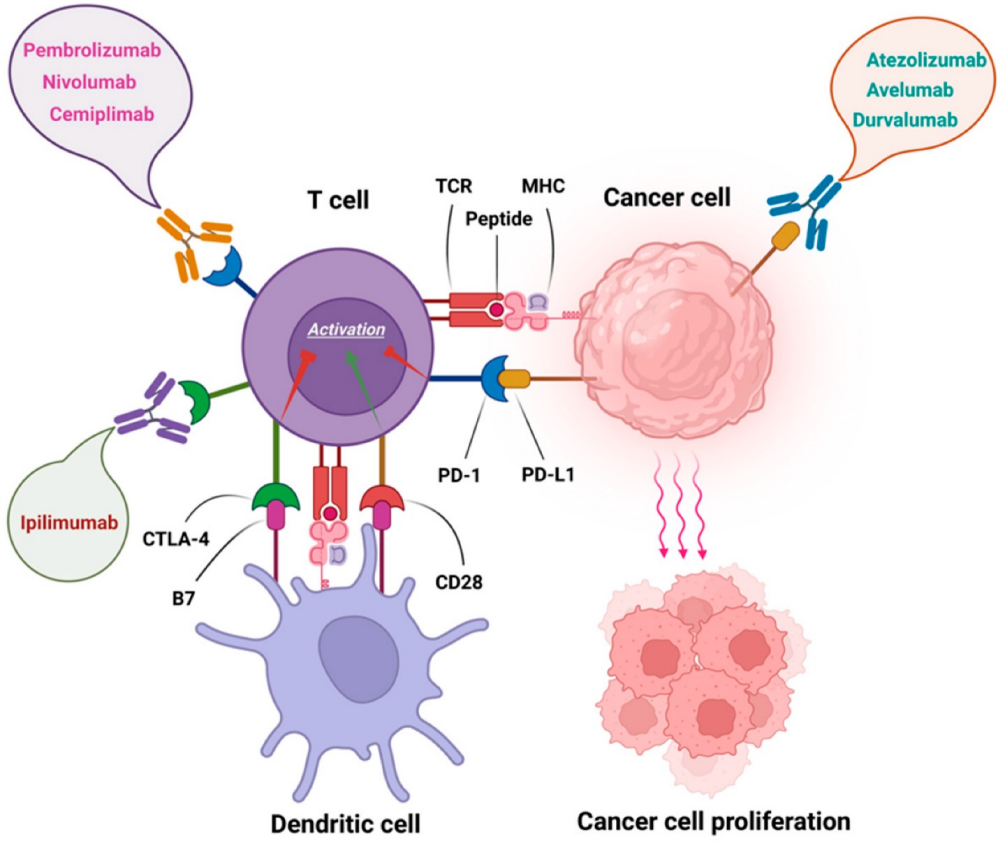
<u>Rationale for Use:</u>

CTLA-4 inhibition supports T-cell expansion

PD-L1 inhibition overcomes T-cell suppression at tumor site

Combining with chemotherapy:

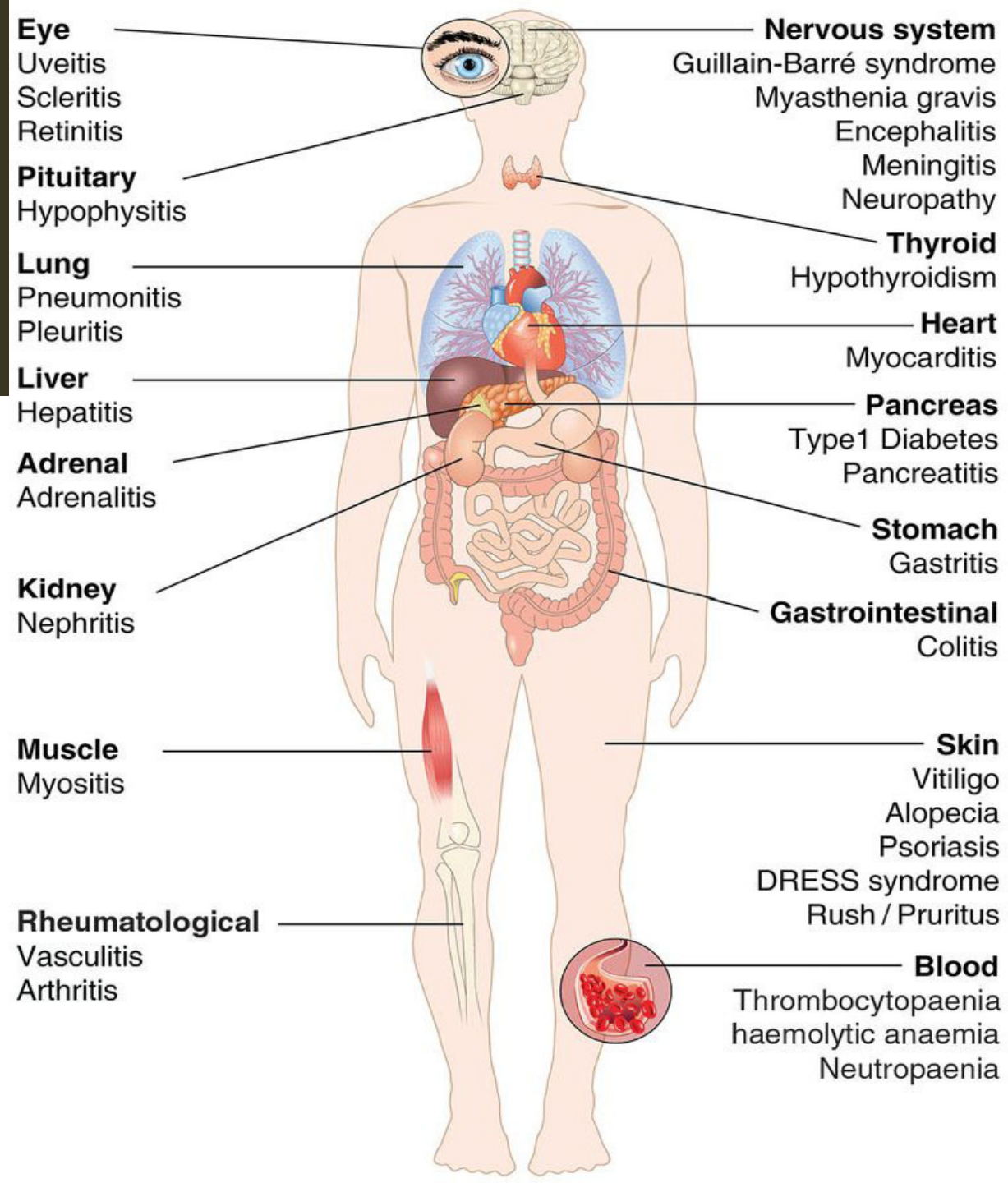
Chemotherapy induces tumor cell death and antigen release, which primes immune system



Curr. Oncol. 2022, 29(5), 3044-3060

Spectrum of irAEs

- ICIs associated with a variety of immune-mediated toxicities
- irAEs tend to be delayed in onset and inflammatory or autoimmune in nature
- Toxicities affect almost any organ



Choi J, et al. Immune Netw. 2020;20(1):e9.
Weinmann SC, et al. Rheumatology (oxford). 2019;58(Suppl 7):vii59-vii67.
Varricchi G, et al. ESMO Open. 2017;2(4):e000247. Figure 3; p. 6.

Toxicity Management Guidelines/Resources

National Comprehensive Cancer Network (NCCN)

- Management of Immunotherapy-Related Toxicities

Society for Immunotherapy of Cancer (SITC)

- Immune Checkpoint Inhibitor-Related Adverse Events

American Society of Clinical Oncology (ASCO)

- Management of Immune-Related Adverse Effects in Patients Treated with Immune Checkpoint Inhibitor Therapy

European Society for Medical Oncology (ESMO)

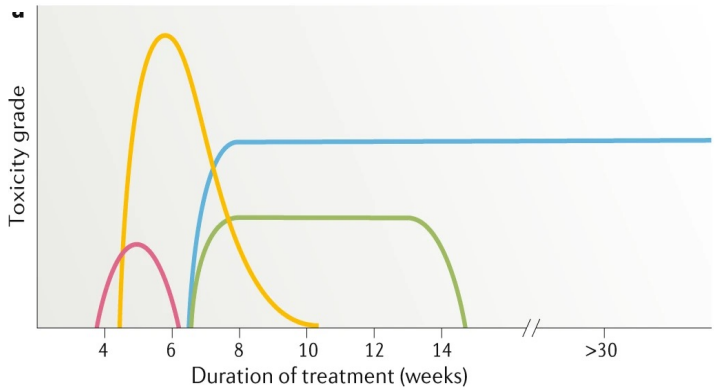
- Management of Toxicities from Immunotherapy

Toxicity Management Pearls: ICI Toxicity Kinetics

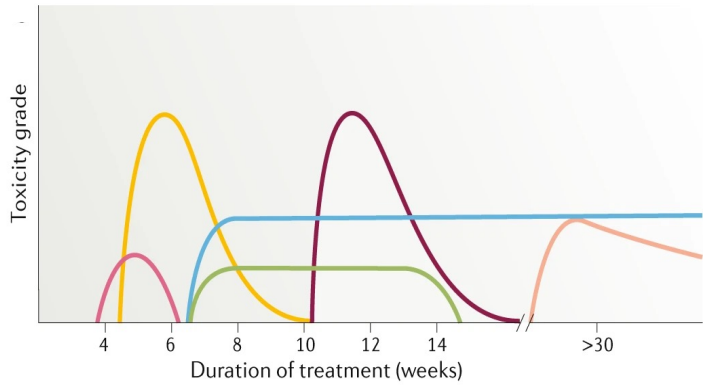
Onset of irAEs generally occurs between 2 and 16 weeks after ICI initiation

- Early occurrence within days to delayed onset up to 26 weeks, with a median onset of approximately 40 days
- Some reports have noted onset within a few days of starting therapy and > 1 year after completion

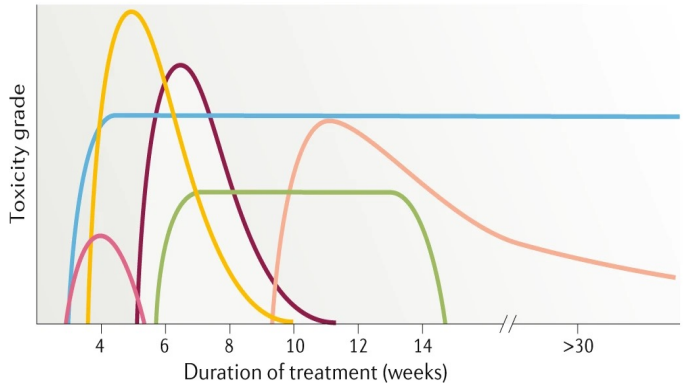
CTLA-4 Inhibitor

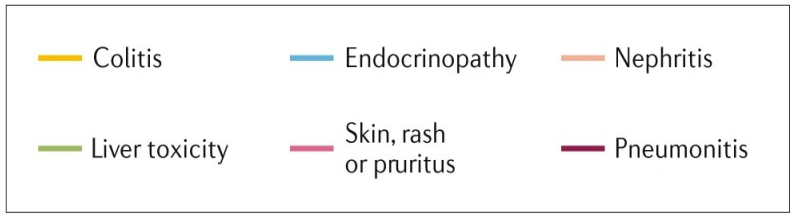


PD-1 or PD-L1 Inhibitor



CTLA-4 + PD-1





Schneider BJ, et al. J Clin Oncol. 2021;39(36):4073-4126.
Martins F, et al. Nat Rev Clin Oncol. 2019;16(9). Figure. 1; p. 567.

Toxicity Management Pearls: General Recommendations for ICIs

Grade 1	Therapy should be continued with close monitoring, except for some neurologic, hematologic, and cardiac toxicities
Grade 2	Consider holding and resume when symptoms and/or laboratory values revert ≤ grade 1 Corticosteroids may be administered—particularly for pneumonitis, neurology, or hepatitis
Grade 3	Hold and initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent) **Corticosteroids should be tapered over the course of at least 4-6 weeks <u>after resolution to Grade 1</u>** If symptoms do not improve with 48-72 hours of high-dose steroid, biologics may be offered for some toxicities
Grade 4	Permanent discontinuation, except for endocrinopathies that have been controlled by hormone replacement
Supportive care considerations	Infection prophylaxis (PJP, fluconazole, zoster), PPI/H2RA for gastritis, calcium + vitamin D for osteoporosis
Hypophysitis consideration	Initiate thyroid replacement only after adrenal replacement to prevent precipitating adrenal crisis

Schneider BJ, et al. J Clin Oncol. 2021;39(36):4073-4126.

Case Series

Case 1: MJ

WBC 5.4	Na 129	SCr 0.75	T bili 0.9
Hgb 12.8	K 5.4	Glucose 105	ALT 30
Plt 134k	Cl 98	CO_2 24	AST 29

Vital signs: Temp: 36.6C, BP: 95/68, Pulse: 62

What additional workup is needed?

KW is a 68-year-old male with newly diagnosed squamous cell carcinoma of the lung with metastases to contralateral lung, liver and bones. Molecular testing revealed mutations in KRAS and STK11, and PD-L1 is 17%

He achieves PR after 4 cycles of carboplatin+ paclitaxel+ durvalumab+ tremelimumab and presents to clinic today for initiation of maintenance durvalumab

He reports new onset mild headache, dizziness, nausea, severe fatigue and appears mildly confused in clinic

Case 1: MJ

Panhormone panel:

Cortisol mcg/dL	1.6 (4.3-22.4)
ACTH pg/mL	<5 (0-46)
FSH mIU/mL	0.8 (1.5-12.4)
LH mIU/mL	<0.7 (1.7-8.6)
Prolactin ng/mL	3 (4-15.2)
TSH mcg/dL	1.7 (4.5-11.7)
Free T4 ng/dL	0.3 (0.93-1.7)
Testosterone ng/dL	150 (300-1000)

MRI brain with pituitary cuts reveals diffusely enlarged pituitary gland and infundibulum and no lesions suspicious for metastases
or leptomeningeal enhancement

Based on imaging and laboratory results, MJ is diagnosed with hypophysitis

Case 1: MJ

In addition to an urgent endocrinology consult, which of the following interventions should be made for MJ today?

A. Continue immunotherapy; initiate levothyroxine and hydrocortisone supplementation
B. Hold immunotherapy; initiate 1 mg/kg prednisone, levothyroxine and hydrocortisone
C. Hold immunotherapy; initiate hydrocortisone today and initiate levothyroxine in 5 days
D. Continue immunotherapy and initiate 20 mg prednisone

Case 2: KW

KW is an 88-year-old female never smoker who presented with a large left pleural effusion with history of catheter placement and VATS procedures for pleural-based nodules which were positive for epitheliod mesothelioma

PMH: HTN, dyslipidemia, psoriasis limited to skin and no history of immunosuppressive medication, cSCC, superficial spreading melanoma

Completes 12 weeks of ipilimumab + nivolumab treatment and progresses in June 2023. She undergoes pleurodesis and has her catheter removed while undergoing screening for a clinical trial.

Case 2: KW

She starts treatment in September with a bispecific CTLA-4 and PD-1 antibody and after 6 weeks a restaging CT shows findings concerning for infection, drug toxicity/inflammation, or disease progression

Patient also complains of R wrist pain thought not to be inflammatory and Grade 1 diffuse pruritic maculopapular rash, and is asymptomatic from a respiratory standpoint

C3D1 the decision is made to hold drug and refer to pulmonary for bronch with biopsies and BAL, which shows evidence of organizing pneumonia

Case 2: KW

KW is placed on observation and returns to clinic 6 weeks later for restaging CT scan
which demonstrates persistent left lower lung consolidation and new right lung opacifications, from which she remains asymptomatic

KW is diagnosed with grade 1 pneumonitis and will follow up in 6-8 weeks

Approximately 4 weeks later KW comes into the ER with acute hypoxic respiratory failure requiring supplemental O2 and a CT demonstrating worsening lung infiltrates

She is started on methylprednisolone 1 mg/kg for grade 3 pneumonitis + broad spectrum antibiotics to cover for possible superimposed pneumonia

Case 2: KW

KW experiences worsening oxygen desaturation on admission day 2 and is started on high flow oxygen at 40L/min, given a dose of furosemide IV and started on nebulizers ATC.

Which of the following is the next best step to manage KW's pneumonitis?

A. Maintain--it has only been 48 hours and too early to expect improvement

B. Increase methylprednisolone to 2 mg/kg

C. Add infliximab 5 mg/kg

D. DC steroids and start infliximab 5 mg/kg

Case 2: KW

KW's respiratory status slowly improved and she was able to be discharged with a 6 week steroid taper on admission day 7—no repeat dosing of infliximab

Repeat CT chest 4 weeks later shows near complete resolution of opacities and stable mesothelioma disease

Patient remains on observation ~5 months after admission with mostly stable imaging findings

Case 3: JV

JV is a 77-year-old male who presented in 10/2021 with sarcomatoid malignant pleural mesothelioma (MPM). Follow-up molecular testing was negative for BRAF, KRAS, EGFR, and ALK D5F3

Patient was initiated on ipilimumab + nivolumab with stable disease. After 4 months of therapy, patient complains of mild itching and arthropathy and grade 2 colitis

Immunotherapy was held and patient was started on a steroids x 1 week with minimal improvement

Case 3: JV

Infliximab 5 mg/kg was initiated with slight improvement and a dose was repeated at 3 weeks

Restaging CT 1 month later shows: decreased right pleural thickening with unchanged enhancing nodularity and no evidence of new disease

What to do next?

Case 3: JV

Decision was made to resume nivolumab but diarrhea recurred 1 week later

Patient was given vedolizumab x 3 doses (0, 2, 6 weeks) which resolved diarrhea completely

Disease remained stable until ~7 months later when restaging CT showed enlarging multifocal pleura-based tumor of the right hemithorax and patient was offered RT vs home hospice

Patient presented to our clinic for second opinion in 2/2023 (~14 months post diagnosis) and received palliative radiation to the chest 45 Gy

Immunotherapy and irAEs

irAEs may not be a bad thing:

- Development of irAEs may confer a survival benefit
- More irAEs = better OS?
- OS benefit regardless of immunosuppressive treatment (ie: don't be afraid to use steroids)
- Use of immunosuppressive agents does not truncate response to therapy

With few exceptions can resume ICIs after grade 1-2 toxicity if patient's disease is not stable and they were having a response

- Can consider concurrent vedolizumab if resumption after colitis

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doi: 10.1186/s40425-018-0346-6
doi: 10.1200/JCO.2015.66.1389

Colitis: Vedolizumab vs Infliximab

	Infliximab	Vedolizumab	p
Remission (%)	88	89	0.79
Steroid exposure (days)	50	35	<0.001
Hospitalization (%)	28	16	0.005
Hospital stay (days)	13.5	10.5	0.043
Time to clinical response (days)	13	17.5	0.012

Zou F, et al. J Immunother Cancer. 2021;9(11):e003277.

Summary

- Immune checkpoint inhibitors are ever-expanding in indication and in approved agents so it is imperative to have a working understanding of managing toxicities
- Remind patients to communicate early and frequently to providers for any perceived changes in symptoms and that they are never "off" of immunotherapy
- There are many guidelines to help manage patients experiencing irAEs
- The mainstay of treatment for irAEs remains corticosteroids and taper over 4-6 weeks once symptoms resolve to Grade 1 or less
  - Many additional immunomodulators can be utilized in combination with steroids for refractory patients depending on which organ system is effected
- Consider active surveillance vs resumption of immunotherapy once irAEs resolved depending on patient response and which specific irAEs were experienced