Updates in Immunotherapy Toxicity Management

Sarah Norskog, PharmD, BCOP
UCHealth
GI Oncology/Phase I Clinical Trials/
Surgical Oncology/Head and Neck Oncology/Sarcoma

Disclosures

I have no relevant financial relationships with commercial interests pertaining to the content of this presentation.

Learning Objectives

- Compare and contrast toxicities associated with immune checkpoint inhibitors, adoptive cell therapies and bispecific T-cell engagers.
- Identify common immune checkpoint inhibitor toxicities and develop management plans.
- Describe grading and management of cytokine release syndrome related to adoptive cell therapies and bispecific T-cell engagers.

Cancer Immunotherapy

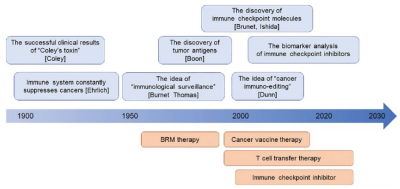


Image Hiromichi, 2020

Types of Cancer Immunotherapy

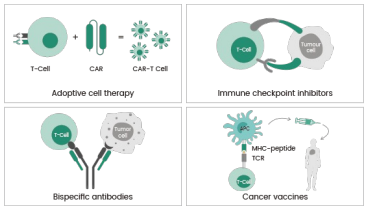


Image SinoBiological, 2023

Immune Checkpoint Inhibitors (ICIs)

- ICIs block inhibitory signaling of T cells, allowing T cells to remain active, recognize and kill cancer cells
  - "Release the brakes of the immune system"
- Role in therapy
  - FDA approved for over 20 cancer types
    - Site agnostic approval
    - 43 distinct indications
  - Monotherapy or combination ICI therapy
  - Combined with chemotherapy or targeted therapy

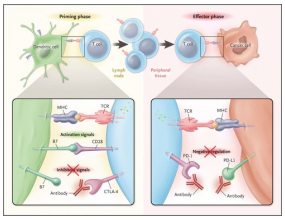
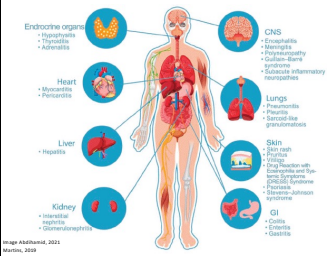


Image Rebas, 2012
Weideo, 2024
NCCN Management of Immunotherapy-Related Toxicities 2024

ICI Toxicities



- Toxicities are autoimmune in nature
- Incidence and severity is variable
  - CTLA-4 inhibitors
    - Any grade 72%, severe grade 24%
    - Higher rates of colitis compared to PD-L/PD-L1
  - PD-1/PD-L1inhibitors
    - Any grade 26.8%, severe grade 6.1%
    - Higher rates of pneumonitis compared to CTLA-4
  - Combination therapy associated with higher rates and severity over all
    - Severe grade 55-60%
  - Dose dependent
    - CTLA-4 > PD-1/PD-L1
  - Indication

Image Abdihamid, 2021
Martins, 2019

ICI Toxicity Kinetics

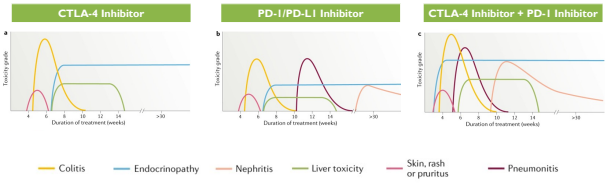


Image Martins, 2019

Management of ICI Toxicities

- Early recognition and intervention is key
- Immunosuppression
  - Steroids
    - First line for most ICI toxicities
    - Prednisone 1-2 mg/kg/day for 4-8 weeks
    - Prolonged tapers - increase dose if any sign of recurrence during taper
  - Immunomodulators
    - Secondary agents used for refractory or recurrent toxicity
    - Toxicity dependent
      - Infliximab, vedolizumab, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, tocilizumab, methotrexate, etc
- Endocrinopathies are generally managed through hormone replacement

Prophylaxis
- Pneumocystis jiroveci pneumonia
  - Bactrim or dapsone
- Steroid induced gastritis
  - Proton pump inhibitor or H2-antagonist

NCCN Management of Immunotherapy-Related Toxicities 2024

ICI Colitis

- Presentation - watery diarrhea, cramping, and urgency
- Work up
  - Rule out infectious etiology
  - Consider CT with contrast for moderate or severe
  - Consider GI consultation for scope +/- biopsy for moderate or severe

Mild < 4 BMs above baseline	**Moderate** 4-6 BM above baseline per day, colitis symptoms	**Severe** >6 BM above baseline per day, colitis symptoms, interference with ADLS, hospitalization
• Loperamide and/or Lomotil for 2-3 days • If persistent or progressive symptoms treat as grade 2	• Prednisone or methylprednisolone 1-2 mg/kg/day • If no response in **3 days** consider adding infliximab or vedolizumab	• Consider inpatient care • IV methylprednisolone 1-2 mg/kg/day • If no response in **1-2 days** consider infliximab or vedolizumab

Infliximab vs Vedolizumab

- Retrospective review of patients with ICI Colitis (n=156)
  - Equivalent clinical remission rates
  - Infliximab associated with a quicker time clinical response
  - Vedolizumab associated with shorter duration of steroid therapy and lower rate of recurrence
- NCCN does not signify for preference
- Single vs multiple dose strategy?
  - >/= 3 doses of either agent were associated with improved overall survival
  - Dosed a week 0, 2 and 6
- Cost
  - Infliximab ~$3,500/dose
  - Vedolizumab ~$10,400/dose

Table 2 IMDC-related characteristics in patients treated with vedolizumab and infliximab alone (N=156)

Characteristic	Vedolizumab n=62	Infliximab n=94	P value
Doses of SIT, mean (SD)	3 (2)	2 (1)	<0.001
Median duration from first dose of SIT to symptom remission or improvement to grade 1, days (IQR), n=138	18 (10–40)	13 (8–29)	0.012
Hospitalization, no (%)	40 (65)	67 (71)	0.367
Median duration of hospitalization, days (IQR), n=107	10 (5–15)	14 (8–19.8)	0.043
Multiple hospitalizations, no (%)	10 (16)	26 (28)	0.005
Clinical remission, no (%)	55 (89)	83 (88)	0.785
Recurrent IMDC, no. (%)	8 (14)	27 (29)	0.007
Immunosuppressant-associated infection, no (%)	12 (19)	23 (25)	0.184

ICI, immune checkpoint inhibitor; IMDC, immune-mediated diarrhea and colitis; IV, intravenous; SIT, selective immunosuppressive therapy.

Zou, 2021

ICI Myocarditis

- Low incidence (1.14%) but highest rate of mortality (39.7%)
- Presentation: Chest pain, shortness of breath, fatigue, palpitations arrhythmia, syncope, generalized weakness
- Work-up and evaluation:
  - Early cardiology consult
  - ECG, telemetry monitoring
  - Troponin, CPK, BNP
  - Echocardiogram
  - Chest radiograph
  - Consider stress test and cardiac MRI
- Treatment
  - Inpatient admission for cardiac monitoring
  - Methylprednisolone 1 g/day for 3-5 days
  - If no improvement in 24 hours add on immunomodulator
    - Abatacept, IVIG, Mycophenolate, Antithymocyte Globulin, Alemtuzumab
    - Infliximab – use with extreme caution in LVEF
- Triple M syndrome occurs in 42% of patients – Myocarditis, Myositis and Myasthenia Gravis

ICI Adrenal insufficiency

- Incidence 0.7-4.2%
- Etiology can be primary (5.3%), secondary (92.7%), or mixed (1.9%)
- Presentation
  - Fatigue, anorexia/loss of appetite, headache, and nausea/vomiting
  - Dehydration, hypotension, and electrolyte imbalances
  - Adrenal crisis
- Treatment
  - Steroid replacement with hydrocortisone or prednisone +/- fludrocortisone
  - Education on stress dose steroids in cases of infection or trauma
- Hormone replacement is life-long
- ICI may be resumed once endocrine replacement has been established

Weber, 2017
Rahman, 2023
NCCN Management of Immunotherapy-Related Toxicities 2024

ICI Rechallenge

- Patient specific risk vs. benefit consideration
- Hold therapy until toxicity resolves to ≤ grade 1
- Generally safe to rechallenge after mild ICI toxicities
- Permanent discontinuation generally warranted for severe ICI toxicities or moderate toxicity of high risk

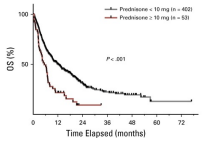
- ICI toxicity recurrence rate 28.8% with rechallenge
  - ICI colitis recurrence 37%
  - ICI pneumonitis recurrence 34%

Dolladille, 2020
NCCN Management of Immunotherapy-Related Toxicities 2024

Impact of Immunosuppression on ICIs

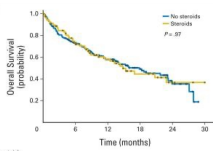
- Immunosuppression at initiation of ICI likely reduces ICI efficacy

Retrospective review of 640 patients with NSCLC receiving PD-1/PD-L1. Ninety patients using steroids for dyspnea, fatigue, and brain metastases



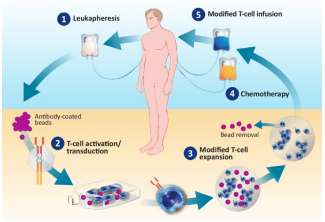
- Immunosuppression initiated after ICI toxicity occurs does not appear to diminish ICI efficacy

Retrospective review of 245 patients with melanoma who developed an ipilimumab ICI toxicity



Horvat, 2015
Arbour, 2018
NCCN Management of Immunotherapy-Related Toxicities 2024

Adoptive Cell Therapy



Chimeric Antigen Receptor T-Cell (CAR T)

Tisagenlecleuce (Kymriah)
- Acute Lymphoblastic Leukemia, Diffuse Large B-cell Lymphoma, Follicular Lymphoma

Axicabtagene Ciloleucel (Yescarta)
- Large B-Cell Lymphomas, Diffuse Large B-cell Lymphoma, Follicular Lymphoma

Brexucabtagene Autoleucel (Tecartus)
- Mantle Cell Lymphoma, Acute Lymphoblastic Leukemia

Ciltacabtagene Autoleucel (Carvykti)
- Multiple Myeloma

Idecabtagene Vicleucel (Abecma)
- Multiple Myeloma

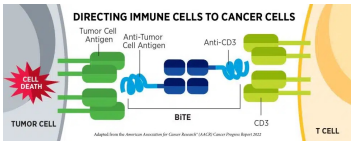
Lisocabtagene Maraleucel (Breyanzi)
- Large B-Cell Lymphomas

T-cell receptor (TCR) therapy

Afamitresgene Autoleucel (Tecelra)
- Synovial Sarcoma

Image M Glunk, 2017
Table, 2021

Bispecific T-Cell Engagers



- **Teclistamab (Tecvayli)** - Multiple Myeloma
- **Elranatamab (Elrexfio)** - Multiple Myeloma
- **Talquetamab (Talvey)** - Multiple Myeloma
- **Blinatumomab (Blincyto)** – B-cell ALL
- **Glofitamab (Columvi)** – DLBCL, LBCL
- **Epcoritamab (Epkinly)** – DLBCL, LBCL
- **Mosunetuzumab (Lunsumio)** - Follicular Lymphoma
- **Tebentafusp (Kimmtrak)** - Melanoma
- **Tarlatamab (Imdelltra)** - Small Cell Lung Cancer

Image AACR, 2023

Cytokine Release Syndrome (CRS)

Presentation
- Fever
- Hypotension
- Hypoxia
- Cardiac arrhythmia, cardiac failure, renal insufficiency and capillary leak syndrome

Timing

CAR T-Cell: Average onset 2-3 day, duration 7-8 days

Treatment
- Dexamethasone
- Tocilizumab
- Refractory: Siltuximab or Anakinra

NCCN Management of Immunotherapy-Related Toxicities 2024

Immune Effector Cell-Associated Encephalopathy (ICE)

Presentation

- Encephalopathy, Delerium, Aphasia, Lethargy, Headache, Motor dysfunction, Agitation
- Seizure, Increased intracranial pressure

Onset

- CAR T-Cell: Average onset 4-10 days, Average duration 14-17 days

Treatment

- Dexamethasone or methylprednisone
- Antiepileptics
- Anakinra
- **Tocilizumab does not cross the blood brain barrier **

NCCN Management of Immunotherapy-Related Toxicities 2024

TILs

- Tumor-infiltrating Lymphocytes
- Lifileucel (Amtagvi) was FDA approved February 2024
- Unresectible or metastatic melanoma previously treated with PD-1 inhibitor and BRAF inhibitor if indicated.
- Aldesleukine (IL-2) is administered post cell infusion to promote T-cell activity
  - Hypotension, fever, chills, dyspnea, somnolence, capillary leak syndrome, hallucination

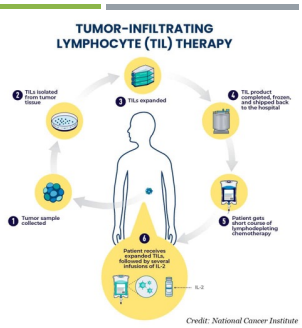


Image Phillips, 2024

Resources

National Comprehensive Cancer Network

- Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Management of Immunotherapy-Related Toxicities

American Society of Clinical Oncology

- Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

European Society of Medical Oncology

- Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

JL is a 53 year old male with recently diagnosed unresectable hepatocellular carcinoma. He is schedule to start systemic therapy with dual immunotherapy, tremelimumab plus durvalumab. What potential side effects should JL be counseled on?

A. Immune Effector Cell-Associated Encephalopathy

B. Cytokine release syndrome

C. Neutropenia

D. Pneumonitis

KD is a 37F with metastatic melanoma being admitted from oncology clinic for ICI colitis. She is currently cycle 2 day 12 of ipilumumab/nivolumab. She was started on prednisone 1 mg/kg/day 2 days prior with no improvement of her diarrhea. She endorses 8 bowel movements per day along with abdominal cramping.

What is the most appropriate treatment option for KD?

A. Add on oral budesonide 9 mg daily.

B. Add on loperamide and diphenoxylate/atropine as supportive care.

C. Give infliximab 5 mg/kg IV once and discontinue prednisone.

D. Give vedolizumab 300 mg IV once and continue prednisone.

References

- American Association for Cancer Research. (2023, November 14). BiTEs help the immune system destroy cancer cells. American Association for Cancer Research. https://www.aacr.org/blog/2023/11/14/bites-help-immune-system-destroy-cancer-cells
- Arbour, K. C., Mezquita, L., Long, N., et al. (2018). Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. Journal of Clinical Oncology, 36(28), 2872–2878.
- Brahmer, J. R., Lacchetti, C., Schneider, B. J, et al. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *Journal of Clinical Oncology*, 36(17), 1714-1768.
- Dolladille, C., et al. (2020). IAMA Oncology, 6, 865–871.
- Gough, P., Zenk, L., Thomas-Schoemann, A., et al. (2023). Clinical spectrum and evolution of immune-checkpoint inhibitors toxicities over a decade—a worldwide perspective. eClinicalMedicine, 70, 102536.
- Haanen, J. B. A. G., Carbonnel, F., Robert, et al. (2022). Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*, 33(12), 1217-1238.
- Horvat, T., Adel, N. G., Dang, T. et al. (2015). Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. Journal of Clinical Oncology, 33(28), 3193–3198.
- Jeddeo Paul et al. Overlapping and non-overlapping indications for checkpoint inhibitors in the US. *JCO* 42, 11057-11057(2024).
- Martins, F., Sofiya, L., Sykiotis, G. P., et al. (2019). Adverse effects of immune-checkpoint inhibitors: Epidemiology, management, and surveillance. Nature Reviews Clinical Oncology, 16(9), 563–580.
- McGuirk, J., Waller, E., et al. (2017). Building blocks for institutional preparation of CT1019 delivery. Cytotherapy, 19
- National Comprehensive Cancer Network. (2024). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Management of Immunotherapy-Related Toxicities*. Version 2.2024. Retrieved from NCC
- Olivas, D., et al. (2023). A phase 3 study (TILVANCE-301) to assess the efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated unresectable or metastatic melanoma. Journal of Clinical Oncology, 41(16_suppl). TPS9607.
- Olivaji, R. A., et al. (2023). Adrenal insufficiency in patients on immune checkpoint inhibitors: An AA of Lo Data study. Journal of Clinical Oncology, 41(16_suppl), e14675.
- Omar, A., Abeid, O., & Tibera, R. (2025). Defining the correlation between immune-checkpoint inhibitors-related adverse events and clinical outcomes: A narrative review. ecancermedicalscience, 15, 1316.
- **Rebas, A. (2012). Tumor immunotherapy directed at PD-1. *New England Journal of Medicine*, 366(26), 2517.**
- Phillips, C. National Cancer Institute. (2024, August 15). *FDA approves first TIL therapy for advanced melanoma*. https://www.cancer.gov/news-events/cancer-currents-blog/2024/fda-approves-til-therapy-melanoma
- Rolla, R., Vellyar, C., Sideris, M., & Davies, J. (2021). T-cell-based immunotherapies for haematological cancers, Part A: A SWOT analysis of immune checkpoint inhibitors (ICIs) and bispecific T-cell engagers (BiTEs). Anticancer Research, 41, 1123–1141.
- Schneider, B. J., et al. (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. Journal of Clinical Oncology, 39, 4073–4126.
- Weber, J. S., et al. (2017). Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. Journal of Clinical Oncology, 35, 785–792.
- Zou, F., Faleck, D., Thomas, A., Harris, J., et al. (2021). Efficacy and safety of vedolizumab and infliximab treatment for immune-mediated diarrhea and colitis in patients with cancer: A two-center observational study. Journal for ImmunoTherapy of Cancer, 9(11), e003277.

QUESTIONS

Sarah.Norskog@UCHealth.org