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ADVANCES IN Cancer IMMUNOTHERAPY™

Practical Barriers in Cancer Immunotherapy Treatment

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Consultancy - Amgen
- I will not be discussing non-FDA approved indications during my presentation.

Outline

1. Developing expertise within the healthcare team
2. Patient education
3. Immune-related adverse event (IRAE) management
4. Other practical issues

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Developing expertise within the healthcare team

Strategies for team organization

- Immuno-Oncology (IO) Champion
  - Responsible for leading the relevant programs and staff education
- Patient education group
  - Core group to manage patient education, including the review of existing patient materials and/or the development of new materials specific to IO agents and management of their adverse effects
- Try to standardize care pathways whenever possible
  - Protocols, Checklists, IO toxicity clinic

Staff education

- Proactively update oncology staff on new information
- Use of resources including on-site training/education, conferences, web-based modules, toolkits, guideline review
  - SITC
  - Canadian Association of Nurses in Oncology
  - Cancer Care Ontario
  - Canadian Association of Pharmacy in Oncology
  - American Society of Clinical Oncology
- Subspecialty consultant education
  - Identify subspecialty leads and ensure they provide training and resources to their team

Question 1

Have you participated in an immunotherapy staff education session at your centre?

- 1. Yes
- 2. No

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Patient Education

Patient education

- Education session prior to starting immunotherapy
  - Physician, nurse, pharmacist
  - Consider video, online materials
- Take-home materials
  - Side effects, wallet card, symptom diary, contact information
- Topics to address:
  - What is immunotherapy and indication
  - Side effects and management
  - Plan for monitoring and reporting

Sources of patient information

- Provincial Cancer Agency
  - Cancer Care Ontario
- Canadian Cancer Society
- William Osler Health System
- SITC
- Locally developed materials

Cancer Care Ontario Patient Information

- Toolkits → Immune checkpoint inhibitor toxicity management toolkit
  - Immunotherapy – what you need to know (English/French)
  - Side effects and how to manage (very broad and brief)

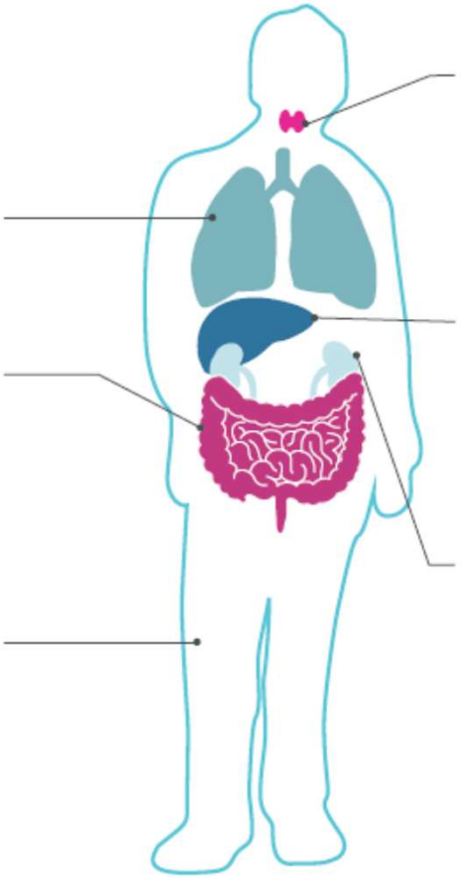
- Drug Formulary
  - Specific immunotherapy drug patient information sheets
  - Provides more details of side effects and management
    - Requires supplemental teaching

William Osler HS Patient Booklet

TOPICS

Cheema, Nematollahi. 2020.
www.williamoslerhs.ca/immunotherapy

William Osler HS Patient Booklet



Inflammation of hormone glands (thyroid):

Some treatments may affect your hormones, which may cause tiredness, dizziness or fainting, unexpected changes in behaviour, irritability, feelings of hot and cold, confusion, heart palpitations, changes in vision, sudden weight changes, constipation, or unusual headaches.

Inflammation of the liver (hepatitis):

Feeling like throwing up, pain in the right side of your stomach, fever, yellowing of the eyes, easy bleeding/bruising, change in colour of poo, or dark, tea-coloured urine may be a sign that your treatment is affecting your liver. Your doctor will test your blood regularly to check your liver function.

Inflammation of kidney (nephritis):

If your treatment affects your kidneys, you may experience back pain and swelling of your face or legs. You may also notice that your pee is much darker than usual, or that you are peeing less or more frequently, including in the middle of the night.

Cheema, Nematollahi. 2020.
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CIOSK PATIENT SYMPTOM DIARY

COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

Use this symptom diary to help you manage side effects related to your immunotherapy. Please take a few minutes each day to complete this diary.

Keeping track of your symptoms is important and will help your healthcare team provide the best care for you.

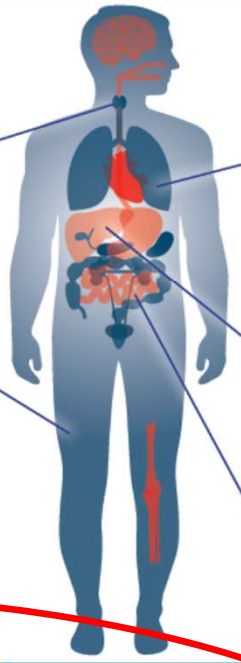
Use the picture and chart below as a guide to track symptoms when you complete your diary.

If your symptoms are in the yellow or red rating, please contact your healthcare team (yellow rating) or go to the nearest emergency room (red rating).

HORMONES
- Headache/Dizziness
- Fatigue
- Weight loss/gain
- Sensitive to hot/cold
- Heart palpitations

SKIN
- Rash
- Itching
- Mouth sores
- Blistered/peeling skin

OTHER
- Swelling
- Muscle or joint pain
- Muscle weakness



LUNGS
- Shortness of breath
- Chest pain
- New or worsening cough (with or without fever)

LIVER
- Dark, tea-coloured urine
- Yellowing of the whites of eyes
- Right-sided abdominal pain
- Easy bleeding/bruising

DIGESTION
- Frequent, watery stools
- Dark, tarry, or sticky stools
- Nausea/Vomiting
- Pain/Tenderness in abdomen

	RECORD & DISCUSS AT NEXT APPOINTMENT	CONTACT NURSE/HCP/ CANCER CENTRE	GO TO EMERGENCY ROOM
Skin	Redness; Flushing	No improvement with cream (24 hrs); itchy	
Digestion	2-3 bowel movements above normal	More than 2-3 bowel movements above normal	Blood (dark, tarry); mucus; abdominal pain
Liver		Right-sided abdominal pain	Yellowing in whites of eyes; dark or tea-coloured urine
Lungs		New cough	Sudden shortness of breath
Hormones		Increased fatigue	Chest pain; heart irregularities

Cheema, Nematollahi. 2020.
www.williamoslerhs.ca/immunotherapy

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Question 2

Who provides patient education for immunotherapy at your centre?

- 1. Physician
- 2. Nurse
- 3. Pharmacist
- 4. Physician assistant
- 5. More than one of the above
- 6. Other

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Toxicity management

Identify high-risk patients at baseline

- Ensure thorough history to rule out autoimmune disease
- Establish a baseline
  - Screening laboratory investigations
  - Bowel habits
- Combination therapies
- Complex medical or social history

- Consider developing a checklist

Communication with other providers

- Family doctor and other specialists for comorbidities
  - Consider a letter such as that provided on William Osler to list the possible organ systems involved and treatment may require corticosteroids
- Subspecialists to manage IRAEs
- Strategy for nursing and pharmacy phone lines

Proactive monitoring and self-management

- Starts with patient education
- Depends on an open and clear plan for communication

- Consider a weekly monitoring program for high–risk patients
  - Nursing phone calls using checklist
  - Consider other providers: pharmacist, physician assistant
- Consider patient symptom diary
  - With understanding of when to contact healthcare team

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CIOSK COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

PATIENT SYMPTOM DIARY

Your daily side effect tracker – keep track of your symptoms throughout the week here. To help you notice any changes, write down what is normal for you before starting treatment.

YOUR NAME: _____ TREATMENT: _____ INFUSION DATE: _____ WEEK #: _____

What's normal for me	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Skin My skin is _____in colour/appearance	Write down any differences in the appearance of your skin:						
Bowel movements I usually have __ bowel movements a day that are _____ consistency	Write down any changes in number or consistency of your bowel movements:						
Urine Colour of urine is normally _____	Write down any changes in urine colour:						
Breathing My breathing bothers me during activities _____	Write down any changes to your breathing. Any cough?						
Pain On a scale of 1-10 (10=severe), my pain is usually ____ and located _____; it lasts for _____	How painful? Where? How long? Describe the pain?						
Tiredness I usually sleep __ a day	How many hours did you sleep today?						
Other I usually experience: _____	Write down anything else that is different from normal:						
New Medications Record your medications on the sheet provided.	Write down any new medications you took today:						

Cheema, Nematollahi. 2020.
www.williamoslerhs.ca/immunotherapy

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Question 3

Does your centre use a proactive monitoring strategy?

- 1. Yes
- 2. No

Pathways and guidelines for toxicity management

- ASCO Practice Guideline- management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy
- Cancer Care Ontario Toolkits

Brahmer, 2018, JCO

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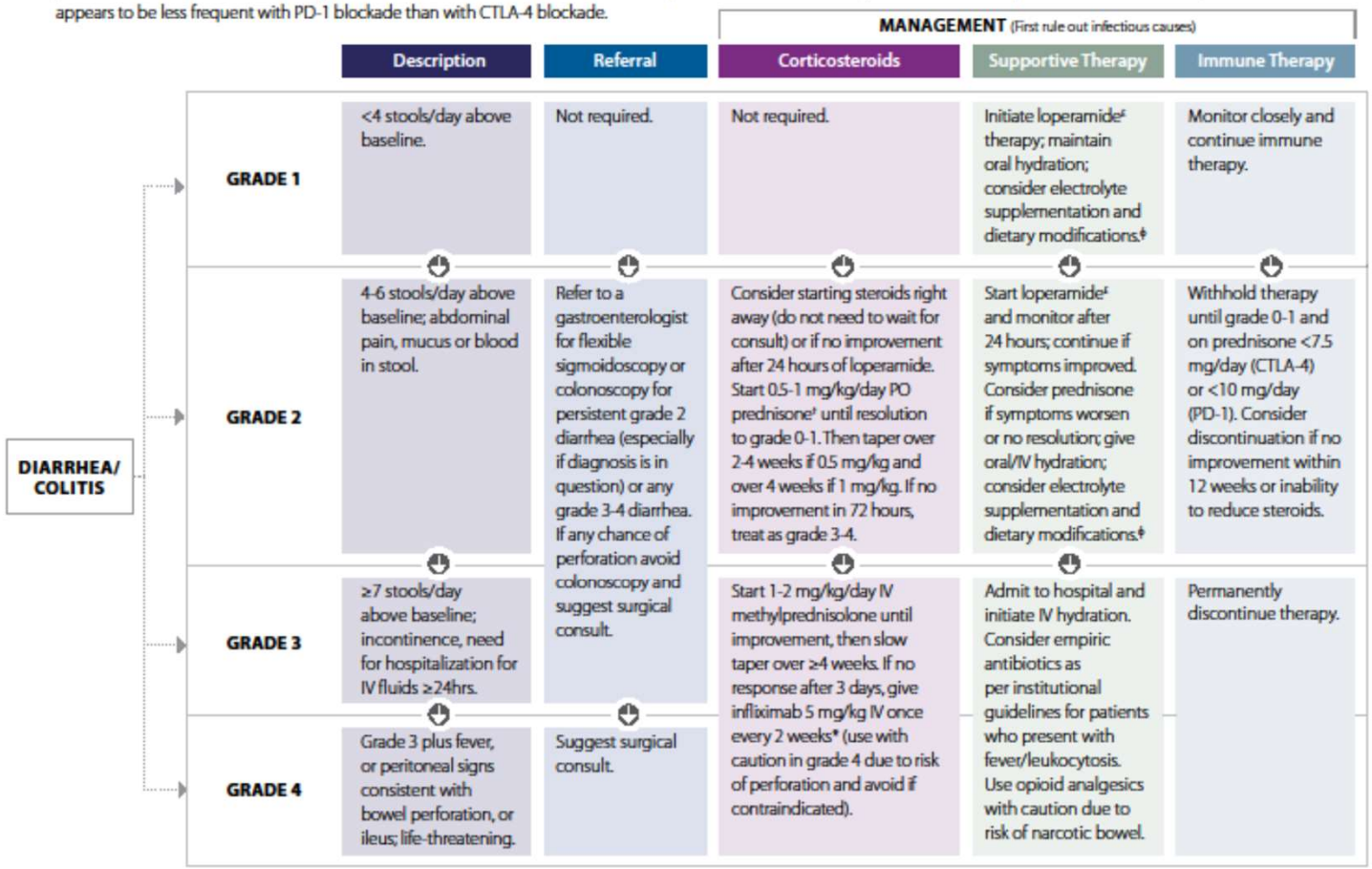
FIGURE 2
Management of Immune-Related Diarrhea/Colitis[1,4,5,10,13,14,17-19]

Background: It is important to rule out other etiologies that may be responsible for diarrhea, such as *C difficile* infections. Severe diarrhea has been observed in patients treated with immune therapy. The median time to onset is 6 to 8 weeks for ipilimumab and nivolumab, and 3.4 months for pembrolizumab. Diarrhea/colitis appears to be less frequent with PD-1 blockade than with CTLA-4 blockade.



‡ loperamide 4 mg followed by 2 mg q4h or after every loose BM until diarrhea-free for 12hrs (max 16 mg/day)
† or equivalent
¶Refer to CCO Diarrhea Guidelines: https://www.cancercareontario.ca/en/symptom-management/3151
* if infliximab is contraindicated (possibility of perforation, sepsis, TB, NYHA 3/4 CHF), consider mycophenolate mofetil or other immunosuppressive agents

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FIGURE 1
Management of Immune-Related Dermatologic Toxicities[1,2,4,10,13,14]

Background: Skin toxicities related to immune therapy typically presents as erythematous, reticular, and maculopapular rash and are often located across the trunk and extremities. The median time to onset is 3 to 6 weeks (ranges up to 17 weeks for ipilimumab and nivolumab). Pruritus, sometimes severe, may occur in the absence of a frank rash. Rashes are usually mild (grade 1-2) and can be managed symptomatically. Severe rashes (grade 4), such as bullous pemphigoid, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN), are reported in <5% of patients. Any signs of desquamation at any grade should be considered a medical emergency and treated as grade 4.

			MANAGEMENT		
	Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
DERMATITIS					
GRADE 1	Macules/papules covering <10% BSA with or without associated symptoms[¶].	Not required.	Not required; can consider topical steroids (e.g. mild symptoms: hydrocortisone 1% or moderate symptoms: betamethasone 0.1% cream).	Apply thick emollients (e.g., urea based cream) or oatmeal baths; avoid sun; cool compress for itching; consider PO anti-histamines or anti-pruritic (e.g. diphenhydramine or hydroxyzine).	Monitor closely and continue immune therapy unless symptoms are intolerable. If symptoms are intolerable, hold therapy until resolution to grade 0-1.
GRADE 2	Macules/papules covering 10-30% BSA with or without associated symptoms[¶]; limiting ADL.	Consider dermatology consult if persistent grade 2 symptoms lasting >1-2 weeks.	Topical steroids; consider PO prednisone 0.5-1 mg/kg/day if symptoms persists >7 days, then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg once resolved to grade 0-1.		
GRADE 3	Macules/papules covering >30% BSA with or without associated symptoms[¶]; limiting self care ADL; local superinfection.	Refer to dermatology if grade 3-4 for consult ± biopsy.	Start 0.5-1 mg/kg/day PO prednisone then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg once resolved to grade 0-1. If severe consider IV steroids (as below).	Above plus consider oral antibiotics if needed.	Withhold therapy until resolution to grade 0-1; consider discontinuation if no improvement within 12 weeks.
GRADE 4	SJS[¥] or widespread mucosal ulcerations: complicated rash with full-thickness dermal ulceration or necrosis; life-threatening.		Start 1-2 mg/kg/day IV methylprednisolone, then taper over ≥4 weeks once resolved to grade 0-1.	Admit to hospital for supportive management - fluids and electrolytes; consider empiric antibiotics as per institutional guidelines if needed.	Discontinue therapy.

¶ as per CTCAE version 4.0 = pruritus, burning, tightness or equivalent
¥ Symptoms indicative of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): macules rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing.

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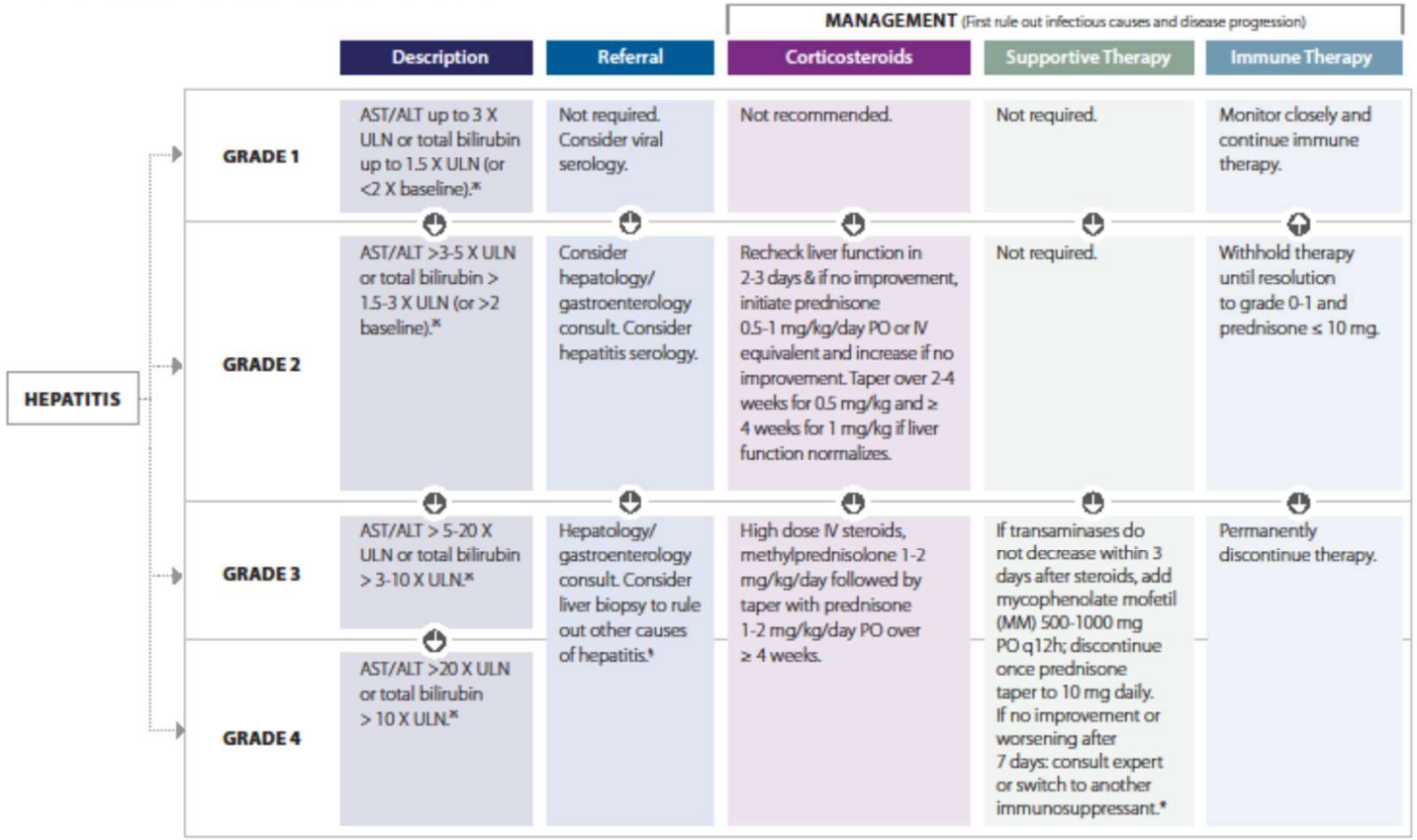
FIGURE 7

Management of Immune-Related Hepatic Toxicities[1,4,5,7,8,11,13,14,23,31]

Background: Hepatotoxicity related to immune-therapy typically presents as elevated LFTs mainly AST, ALT, GGT and rarely bilirubin. The patient is usually asymptomatic and onset is variable with average 8-12 weeks after start of therapy. Rarely, patients present with fever, fatigue, nausea and abdominal pain. Monitoring LFTs are recommended at baseline and prior to each dose. Hepatic adverse events are usually grade 1-2 and occur in approximately 1-6% of patients on PD-1 inhibitors and more frequently in patients on CTLA-4 inhibitors but still <10%.



§ Hepatitis A, C, CMV
* Tacrolimus 0.10-0.15 mg/kg/day; In the case of severe hepatotoxicity, the decision to use infliximab should be made after careful consideration of risk and benefit, and discussion with the patient.
※ For patients being treated with ICIs for hepatocellular carcinoma, these values may differ. Refer to the ICI product monograph.

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FIGURE 9

Management of Immune-Related Pneumonitis[1,7,9,14,23,31,34]

Background: Pneumonitis is a non-infectious lung inflammation with interstitial and alveolar infiltrates. Although pneumonitis is rare (<5%) it can be life threatening; fortunately, the incidence of grade 3 or 4 toxicity is low (<1%) for both CTLA-4 and PD-1 blocking antibodies. Clinical presentation includes dry, unproductive cough, tachypnea, dyspnea, tachycardia, cyanosis, and fatigue. Oxygen saturation may fall with progression, especially after exercise. Chest imaging typically shows ground glass opacities or patchy nodular infiltrates, particularly in lower lobes. The median time of onset of pneumonitis is 19 weeks (range 0.3-84 weeks) for pembrolizumab, 9 weeks (range 4-26 weeks) for nivolumab and 11 weeks when on combination therapy.

		MANAGEMENT (First rule out infectious causes)			
		Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
PNEUMONITIS	GRADE 1	Asymptomatic; diagnostic radiological observations only; no intervention needed.	Monitor oxygen saturation and chest x-ray or CT every cycle and consider pulmonary and infectious disease consults.	Consider 1 mg/kg/day PO prednisone or 1 mg/kg/day IV methylprednisolone.	Not required.	If patient is on steroids, consider withholding treatment until resolution.
	GRADE 2	Symptomatic; medical intervention indicated; limiting instrumental ADL.	Pulmonary and infectious disease consults.	Start 1-2 mg/kg/day PO prednisone or IV equivalent, taper over ≥4 weeks. If no improvement after 48 to 72 hours or worsening, treat as grade 3-4.	Consider hospitalization for daily monitoring of symptoms and re-imaging every 1-3 days. Start empiric antibiotics if suspicious for infection.	Withhold therapy until resolution to grade 0-1 without complications & prednisone dose tapered to <10 mg/day. Discontinue immune therapy if toxicity recurs.
	GRADE 3	Severe symptoms; limiting self care ADL; oxygen indicated.	Pulmonary and infectious disease consults. Consider bronchoscopy & lung biopsy to investigate for pulmonary infection.	Start 2-4 mg/kg/day methylprednisolone IV then taper over ≥6 weeks; if no improvement after 48 hours or worsening, additional immunosuppression such infliximab 5 mg/kg IV once q2weeks can be administered (avoid if contraindicated*).	Admit to hospital and start prophylactic antibiotics for opportunistic infections. Oxygen and ventilation support if necessary.	Permanently discontinue therapy.
	GRADE 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intubation and ventilation).				

* If infliximab is contraindicated (possibility of perforation, sepsis, TB, NYHA 3/4 CHF), consider mycophenolate mofetil (500-1000 mg BID) or other immunosuppressive agents

Cancer Care Ontario, 2020.

Question 4

Do staff at your centre who receive calls from patients use an established guideline or framework for immune-related toxicity management?

- 1. Yes
- 2. No

Reimbursement and lag in approvals

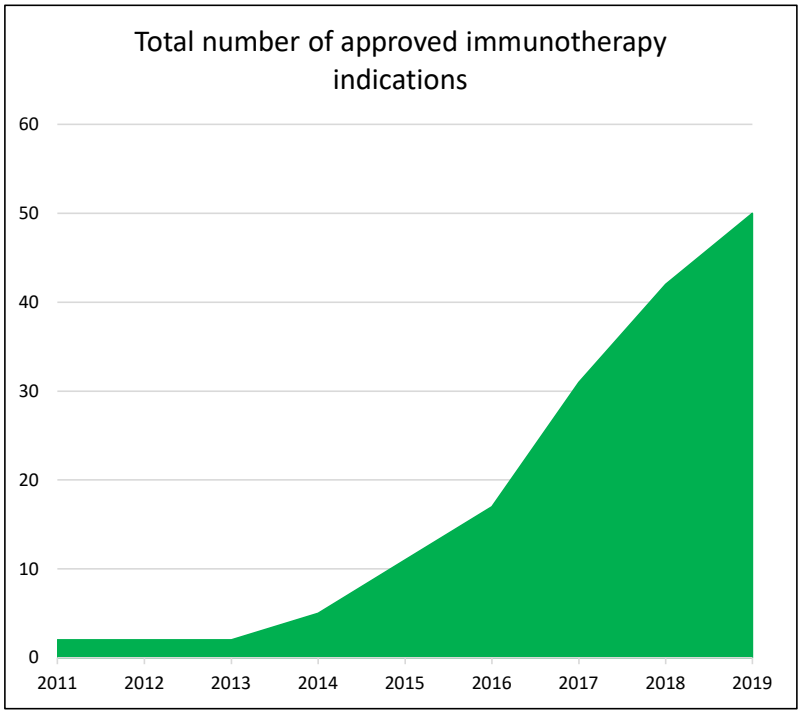
- Compassionate Access Programs
  - Using private infusion clinics
    - Understand the care model, who is providing monitoring and oversight
  - Drug reimbursement navigators

Sunnybrook Local Practices

- Variable
- Nurse education led by local medical oncologists
- Melanoma group
  - Weekly nursing calls for high-risk patients, combination therapy nivolumab + ipilimumab, or ipilimumab
- Endocrinology clinic for IO toxicity
- Immunotherapy toxicity service being planned

IO Pipeline and Research

- Current treatments are the “tip of the iceberg” when looking at manufacturers’ Immuno-Oncology (I-O) pipelines
- Not only new products, but a myriad of new combinations and regimens



Future Considerations

- Expansion to new tumour types and new lines of therapy
- Increasing utilization of checkpoint inhibitors in combination with other agents (e.g., chemo, targeted, immunotherapeutic)
- Emergence of biosimilars
- CAR T treatments
  - Few specialized centres, potential for high toxicity, require local expertise and systematic approach

Summary

- Immunotherapy care delivery requires a multidisciplinary approach and includes subspecialists
- Patient education and empowerment is essential
- Involvement of nursing and other practitioners for proactive toxicity follow up for high risk patients is valuable
- Develop local champions and build an organized and consistent approach to care delivery