ADVANCES IN Cancer IMMUNOTHERAPY™

Nursing Perspective on irAEs: Patient Education, Monitoring and Management

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- Speaker's Bureau Genentech
- I *will not* be discussing non-FDA approved indications during my presentation.

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Objectives

- Improve the early recognition, education and management of immune-related side effects in cancer immunotherapy patients
- Identify strategies for the management of toxicities
- Determine key points for patient education on the management of side effects

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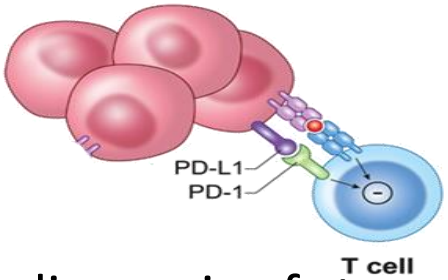

Case Study

- Mr. M.C. is a 65-year-old male with a recent diagnosis of stage IV melanoma to the lungs. Patient has consented to start pembrolizumab (checkpoint inhibitor) at 200mg every 3 wks.

- Mr. M.C and family would like to know what are the most common adverse events with this immunotherapy?

- What is the nurse's role in managing these toxicities?

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U.S. FDA Approved Immune-Checkpoint Inhibitors

Squamous Cell Head & Neck Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy

Malignant Melanoma
Adj./1L ipilimumab
1L nivolumab ± ipilimumab
Adj. nivolumab
1L pembrolizumab

Merkel Cell Carcinoma
2L avelumab

Hepatocellular Carcinoma
2L nivolumab after sorafenib

Adv. Renal Cell Carcinoma
2L nivolumab after anti-angiogenic therapy

Locally Adv. or Met. Urothelial Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy
or in platinum-ineligible patients
1/L atezolizumab after platinum chemotherapy
1L avelumab after platinum chemotherapy
1L durvalumab after platinum chemotherapy

Immune-related Adverse Events (irAEs)

Non-Small Cell Lung Cancer
1L pembrolizumab TPS≧50%
1L pembrolizumab +pemetrexed/carboplatin
in non-squamous NSCLC
2L pembrolizumab TPS≧1%
2L nivolumab
2L atezolizumab NSCLC
Maintenance durvalumab after chemoradiation

Gastric & GEJ Carcinoma
3L pembrolizumab after fluoropyrimidine- and
platinum-CTx +/- HER2 therapy & CPS≧1

Classical Hodkin Lymphoma
4L pembrolizumab
3L nivolumab after auto-HSCT and BV
4L nivolumab and after auto-HSCT

MSI-H or dMMR Cancers
2L nivolumab in CRC after FOLFOXIRI
2L pembrolizumab in CRC after FOLFOXIRI
2L pembrolizumab in any MSI-H/dMMR cancer

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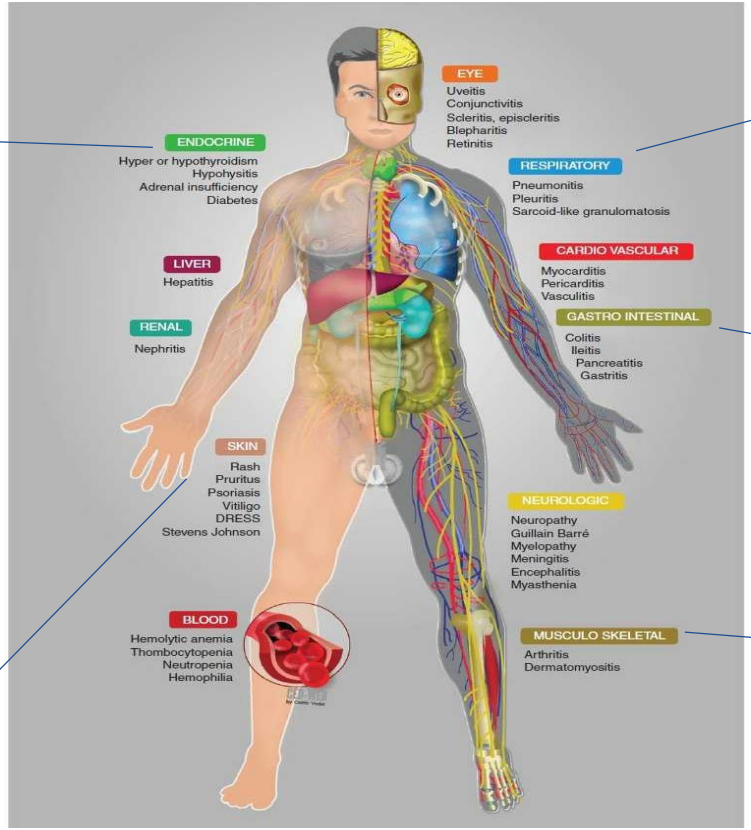
Toxicity Spectrum: Immune Related Adverse Events

Hypothyroid
Hypophysitis
Adrenal insufficiency
Diabetes



Shortness of breath
Dyspnea on exertion
Cough

Colitis
Pancreatitis

Arthritis

Maculopapular rash
Pruritus
DRESS
Vitiligo (positive factor)

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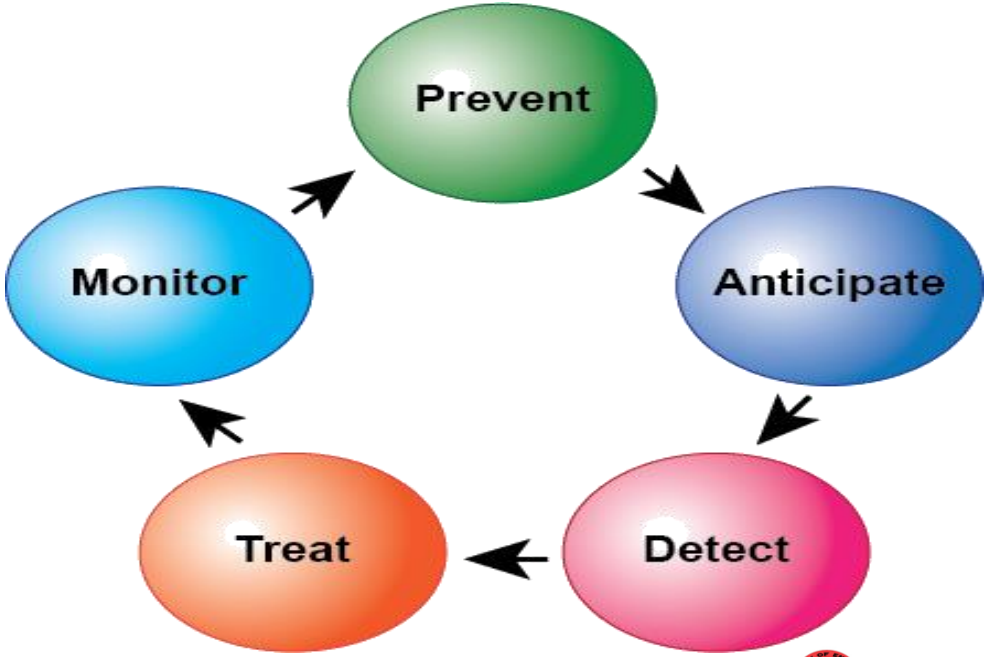
The Five Pillars of Toxicity Management



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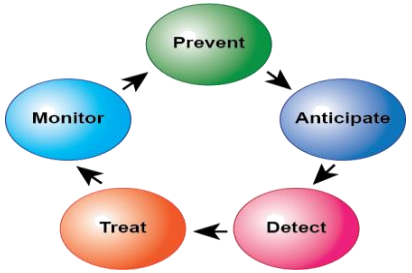
Nurse's Role in Management of Patient's Receiving Immunotherapy

- Review & assess
  - Co-morbidities (dermatologic, endocrinopathies, gastrointestinal)
  - Medications
- Patient & family education
  - Most common side effects, including variability in the timing of onset
  - Importance of early & ongoing communication regarding side effects
  - Most common treatment of these toxicities



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Treatment-related Adverse Events

Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	23 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

* Shown are treatment-related adverse events of any grade that occurred in more than 5% of the patients in any treatment group who had one or more treatment-related adverse events of grade 3 or 4. The relatedness of the adverse event to treatment was determined by the investigators. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Two deaths that were considered by the investigators to be related to a study drug occurred in the nivolumab group (neutropenia) and in the ipilimumab group (colonic perforation) within 100 days after the last dose of study drug; two additional deaths in the nivolumab-plus-ipilimumab group (one due to cardiac insufficiency and autoimmune myocarditis, and one due to liver necrosis) that were considered by the investigator to be related to a study drug were reported more than 100 days after the last dose of study drug.

Wolchok JD et al. N Engl J Med 2017;377:1345-1356

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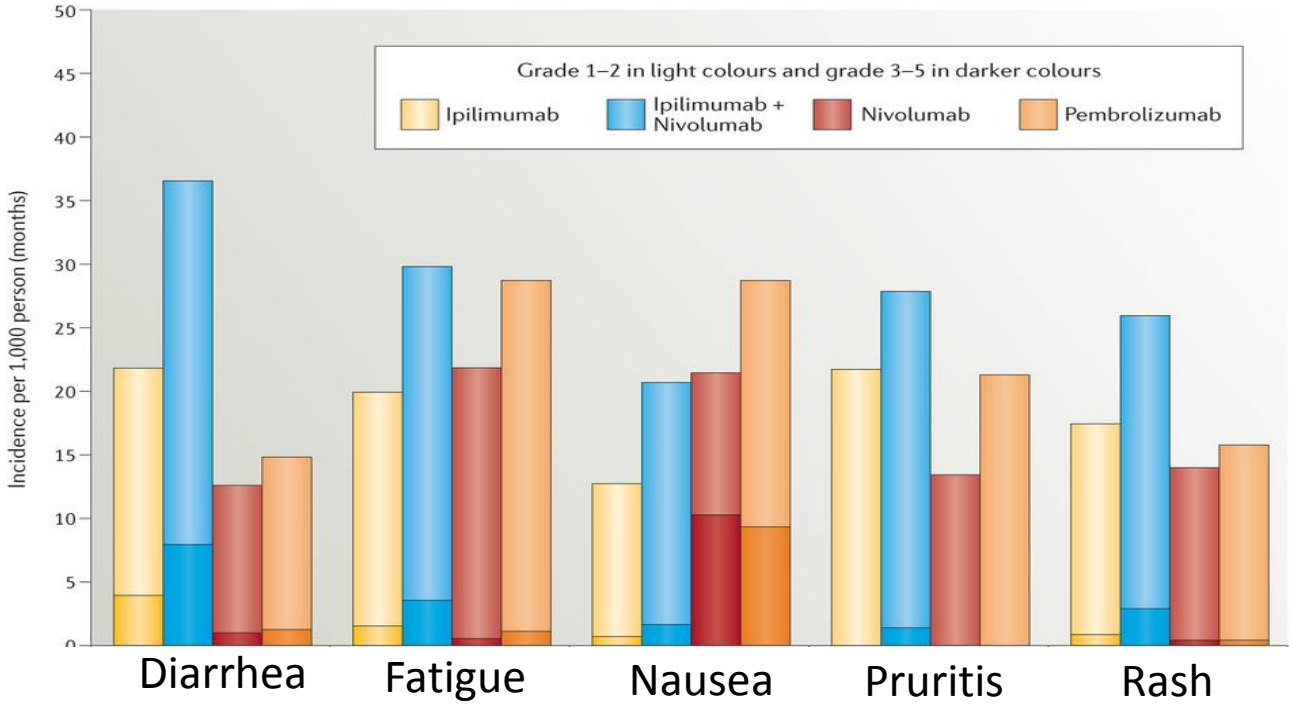
Symptoms to look for with immune check-point inhibitors

Ipilumamab:
CTLA-4

Nivolumab:
PD-1

Pembrolizumab:
PD-1



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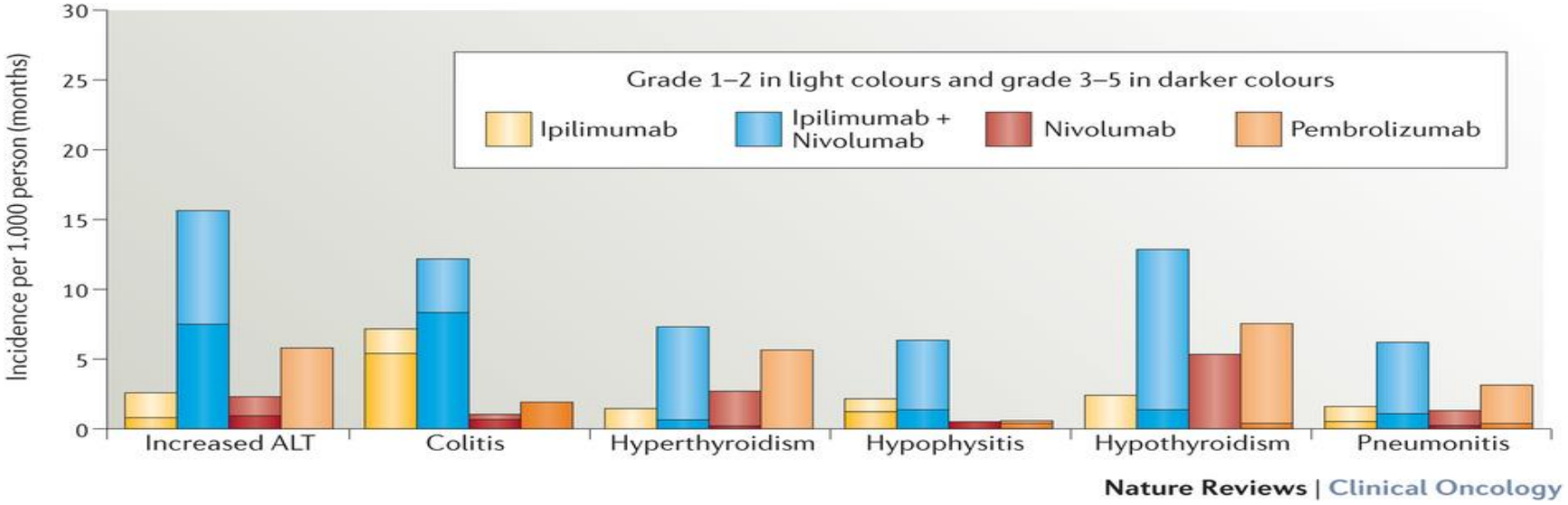
Clinical features for adverse events with immune check-point inhibitors



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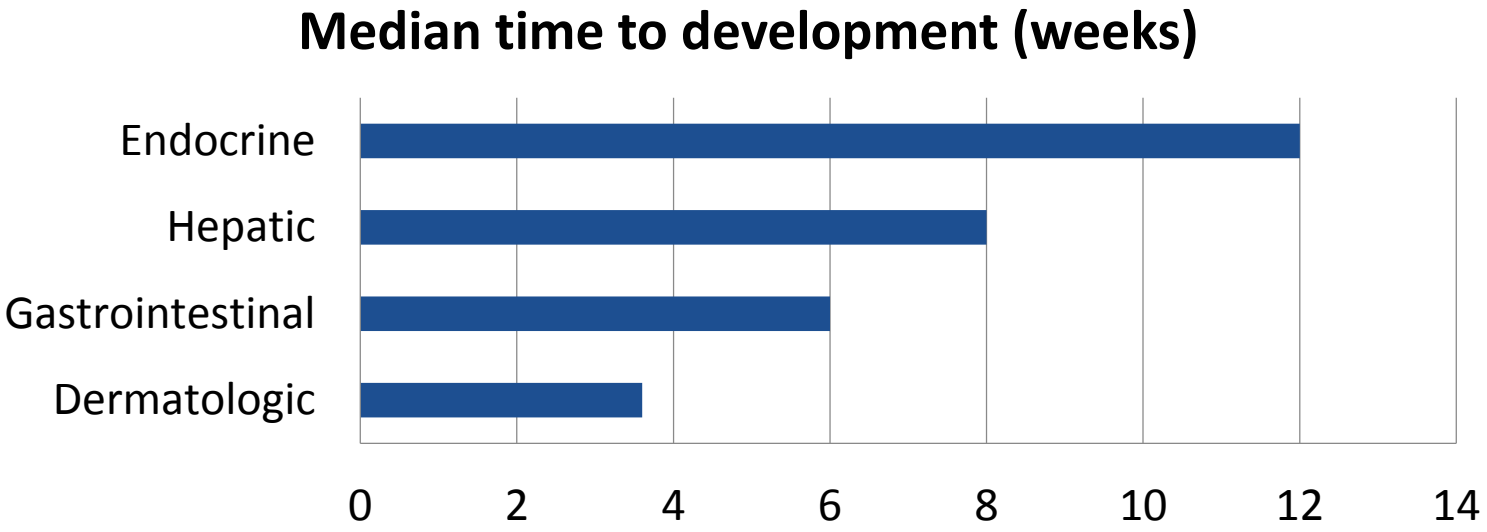
Immune checkpoint inhibitors-irAEs



Weber J et al, J clin Oncol 2012

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General Principles of Toxicity Management

- Reversible toxicities when recognized quickly and treated appropriately
- Treatment may include:
    - Corticosteroids (initiate at 1 -2 mg/kg/day of prednisone or equivalent)
    - Consider other therapies if no improvement with corticosteroids; such as tumor necrosis alfa (TNF-α) antagonists (infliximab) for GI toxicities and mycophenolate mofetil in hepatotoxicity.
    - Dose delay, omission or discontinuation of the immunotherapy; should hold immunotherapy for grade ≥2
- Corticosteroids may require a long tapering duration to prevent recurrence of symptoms
- Re-challenge with checkpoint inhibitor may only be done, if clinically appropriate, once a patient is receiving 10 mg of oral prednisone or equivalent or less.

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Villadolid J and Amin A. *Transl Lung Cancer Res* 2015; 4 (5): 560-575

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Educate patients: constant communication of symptoms is essential sooner rather than later

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related death*	0		0.3		0.3	

Grade 3/4 is life-threatening

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

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Managing irAEs

Table 4. Typical management of irAEs

Severity—CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily[a]
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

CTCAE = Common Terminology Criteria for Adverse Events

Champiat S, et al, Ann Oncol, 2016

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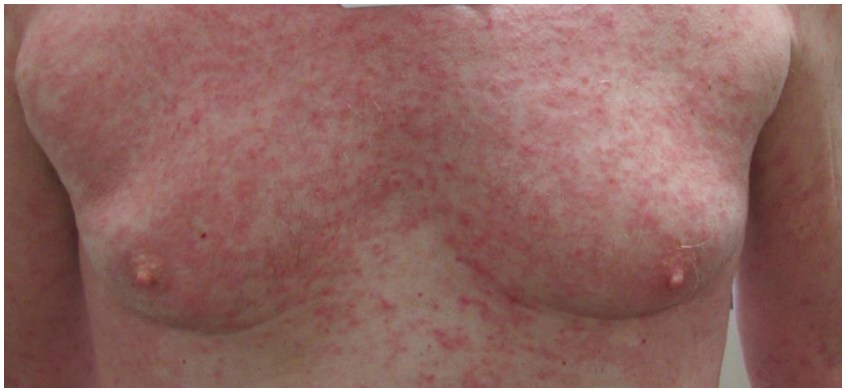
Case Study - rash

Mr. M.C. returns to clinic for evaluation prior to dose #4 of pembrolizumab.



He reports that for the past week he has had a pruritic rash on his chest, abdomen and arms. What next?

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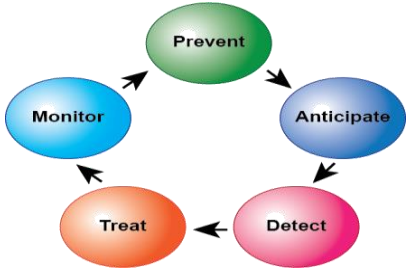
Nurse's role: rash



Anticipate/Prevent

- Skin toxicities can be seen in up to 58% of cases
- Autoimmune conditions can worsen
- Occupational/recreational activities (exposure to outdoors/high temps can worsen skin AEs)
- Possibility of developing hypopigmentation (vitiligo correlated to positive outcome)

Monitor

- New onset of rash
- New lesions
- Itching
- Sunburn
- Photosensitivity

Manage

- Educate patient about potential side effects
- Grade 1: topical OTC hydrocortisone / oral diphenhydramine
- Grade 1/2: triamcinolone or clobetasol cream, diphenhydramine or hydroxyzine (if and when)
- Grade 2: hold treatment, oral corticosteroids
- Grade 3/4: discontinue agent

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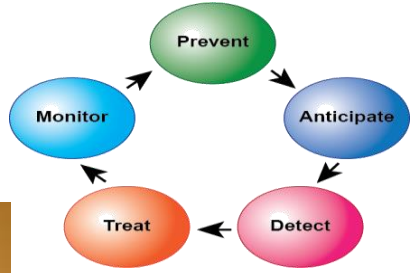
Nurse's role: rash



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Case study

- B.C. is 56-year-old female with a diagnosis of Stage IV melanoma. She is now on nivolumab 240 mg every two weeks infused over 60 minutes. Today she reports that for the past five days she has had SOB, cough and DOE.
- O^2 saturations at RA 95% and 89% during ambulation
- As the primary nurse, what would be your best course of action?

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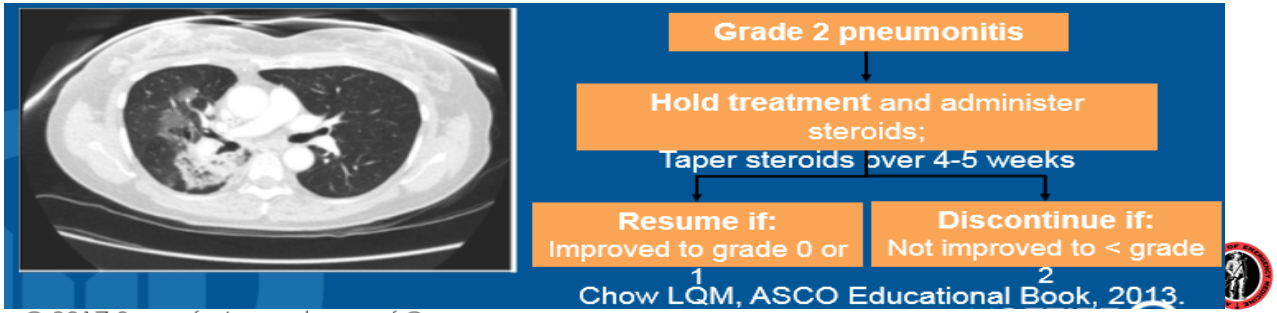
Pneumonitis is more common with anti-PD1/CTLA-4 combination therapy

- Important to address respiratory symptoms and check oxygen saturations at each visit
- On any patients where pneumonitis is suspected based on H&P or clinical exam, provider will hold treatment and order a CT scan of the chest.
- Specific management is necessary for grade 2 or greater pneumonitis.



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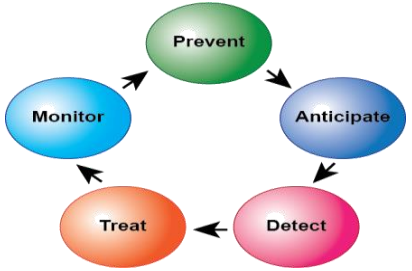

Nurse's role: pneumonitis

Anticipate/Prevent

- Pneumonitis on single vs combination immunotherapy
- Exposure to heavy smoke areas / smoking cessation
- Vaccinations (flu + pneumonia
- Pneumonia vs PE vs CHF

Monitor

- SOB, DOE, CP, persistent cough, fevers, worsening fatigue
- Pulse-ox at rest and ambulation

Manage

- Educate patient about potential side effects
- Grade 1: asymptomatic
- Grade 2: chest x-ray or CT, anticipate steroid taper
- Grade 3/4: discontinue agent, IV steroids and fluids (if not effective, infliximab), oxygen therapy

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Immune-mediated endocrinopathies

- More common with anti-PD-1 than anti CTLA-4. All grades 9%
- Hypophysitis - with nivo/ipi median time to onset was about 2.7 months.
  Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
  - Rule out brain metastasis
  - Hold for symptoms and/or any Grade 3/4
  - Give steroids (IV followed by PO 1-2mg/kg) tapered over four weeks and replace appropriate hormones
    - Hormone replacement may be required for life in ~50% of patients

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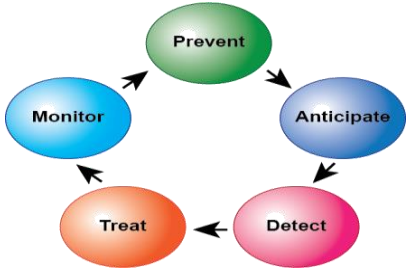

Nurse's role: endocrinopathies

Anticipate/Prevent

- Hypothyroidism
- Hyperthyroidism
- Hypophysitis
- Adrenal insufficiency
- Especially in combination ipi/nivo

Monitor

- Labs: Free T4, TSH, ACTH, cortisol and testosterone (in males)
- Worsening fatigue
- Constipation
- Headaches
- Dizzy episode(s)
- Muscle weakness

Manage

- Hormonal replacement therapy or steroid taper accordingly

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Immune checkpoint inhibitors irAEs

- Rare toxicities
  - Type I and II diabetes mellitus
  - Pancreatitis-usually asymptomatic amylase/lipase elevations (hold for grade 3/4)
  - Myositis
  - Renal toxicity (acute interstitial nephritis)
  - Autoimmune myocarditis
  - Neurologic toxicities

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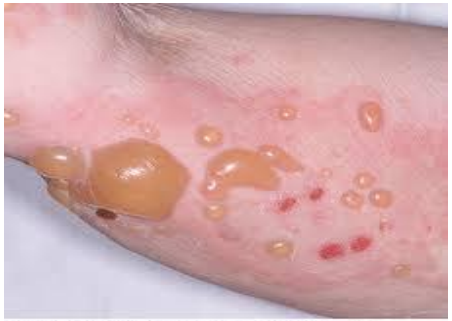
Immune checkpoint inhibitors irAEs

Rare toxicities

Bullous pemphigoid



- Bullous pemphigoid
- Myasthenia-like syndrome-motor paralysis, intravenous immune globulins
- Optic neuritis-photophobia, pain, blurred vision, may correlate with colitis
- Sarcoidosis-lymphadenopathy
- Hematologic toxicities

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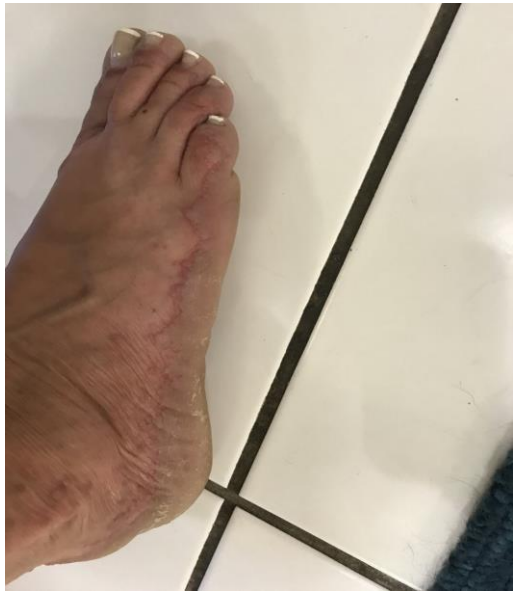
Immune checkpoint inhibitors irAEs

Rare toxicities

Hand Foot Syndrome



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Case Study

MS is a 37 y/o male with Stage IV M1c metastatic melanoma with metastases to multiple lymph nodes and left femoral head.

- He was seen as a new patient for treatment options; he was treatment naïve.
- He began treatment on ipilimumab (3 mg/kg) + nivolumab (240 mg).

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Case Study

- 3/5, he received dose #1 of both drugs
- 3/12, seen in clinic for weekly FU. He had no complaints except mild fatigue. No lab abnormalities.
- 3/26, the patient received dose # 2 of both drugs
- 4/9, patient called office complaining of fatigue, nausea, and diarrhea with minimal response to loperamide. Urged to come to clinic

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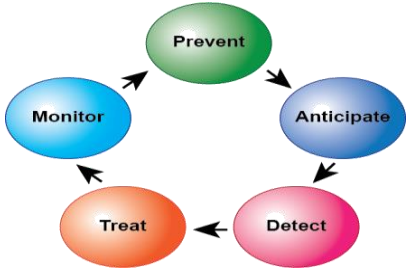

Nurse's role: GI toxicities

Anticipate/Prevent

- Diarrhea can be seen in up to 48% of cases
- Autoimmune conditions can worsen
- Avoid foods that cause loose stools
- Rule out infections (c-diff)
- Remain well-hydrated

Monitor

- Worsening loose stools
- Dehydration
- Abdominal pain/cramping
- Bloody stools

Manage

- Educate patient about potential side effects
- Grade 1: hydration, loperamide, bland diet
- Grade 2: diphenoxylate/atropine QID, budesonide, stool studies, possible sigmoidoscopy/colonoscopy & steroid taper
- Grade 3/4: discontinue agent, IV steroids and fluids (if not effective, infliximab)

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Case Study

On 4/9 in clinic:

- BP-107/64 Pulse-88 RR-16 T-99.2F
- Patient admits to 9-12 episodes of diarrhea with cramps over the weekend.
- Labs demonstrate: AST 499U/L (range: 21-72U/L), ALT 251 (range: 17-59U/L), Bilirubin WNL

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Liver Toxicity

- Workup
  - Blood work (CMP)
  - Rule out viral etiology
  - Rule out drug-induced causes
  - In anticipation of potential infliximab therapy, check PPD or QuantiFERON testing to rule out TB.

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Case Study

- He was initiated on methylprednisolone 200 mg IV in clinic and admitted for management with high dose corticosteroids
- On 4/10, patient reported now 4 episodes overnight
- On 4/12 LFTS decreased to AST 252U/L (previously 499 U/L) and ALT 179 (previously 251 U/L)
- The patient was discharged from the hospital when diarrhea resolved and continued an oral steroid taper
- Ipi/nivo was discontinued and the patient was subsequently enrolled in a clinical trial.

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Conclusions

- Nurses have an ESSENTIAL role in monitoring and managing patients undergoing treatment with immunotherapy.
- Potential irAEs grade 2 and above require frequent visits, drug hold/discontinuation and corticosteroids.
- Combination anti-PD-1/CTLA-4 immunotherapy significantly increases the grade 3-4 AE rate.
- Close monitoring for irAEs is mandatory for prevention of serious adverse events, decreased ER visits and improved patient outcomes.
- As immunotherapies indications broaden, our understanding of toxicity identification and management is essential to make the risk-benefit ratio favorable.

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Questionnaire for nurses to guide discussions with patients on CPI therapy

Ask patients about their signs and symptoms	Yes answers may indicate the patient is experiencing an irAE
Are you experiencing any diarrhea, increased bowel movements, watery stools, or any cramping or pain in your belly?	Gastrointestinal irAEs
Have you been having a hard time sleeping or feeling sleepier than usual? Are you experiencing headaches, light-headedness, or changes in mood?	Endocrine irAEs
Does your skin feel itchy anywhere, or have you noticed any new rashes, or any changes in pigmentation?	Dermatologic irAEs
Have you noticed any weakness or trouble gripping or dropping things? Do you have tingling in your fingers or toes?	Neurologic irAEs
Have you noticed any changes in vision or problems with your eyes?	Ocular irAEs

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