

Do You Immuno? Supporting Patients with Advanced Malignancy Receiving Immunotherapy – From Symptom Management to Effective Communication and Beyond!

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Disclosure

- All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Learning Objectives

- List current indications for immunotherapy in oncology.
- Summarize potential adverse effects of immunotherapies.
- Review new ASCO and ESMO Guidelines on supportive care management.
- Develop a supportive care plan for a patient experiencing adverse effects from immunotherapy, including agent selection and monitoring parameters.
- Describe the ethical considerations around utilization of immunotherapies in advanced illness.
- Given a patient case, describe the elements of a short, effective counseling session pertaining to initiation and monitoring for patients starting immunotherapy treatments.

Immunotherapy

- “A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection or other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way.”

Immunotherapy and Advanced Malignancy

- Blockbuster treatments that can extend lives
- Hope that this will be a miracle treatment
- Worry is that crucial end of life conversations about palliative care and hospice are not happening
- Is knowledge about these medication enough to drive decision-making about their use in advanced malignancy?

Approved indications for immune checkpoint inhibitors include:

- A** Prostate Cancer
- B** Breast cancer
- C** Lymphoma
- D** Leukemia

Targets of Immunotherapy/Checkpoint Inhibitors (ICPIs)

- PD-L1 (Programmed death-1 receptor ligand)
- PD-1 (Programmed death-1 receptor)
- CTLA-4 (Cytotoxic T lymphocyte-associated antigen 4)

PD-L1 Agents

- Atezolizumab (Tecentriq[®])
 - Metastatic urothelial carcinoma, metastatic non-small cell lung cancer
- Avelumab (Bavencio[®])
 - Metastatic Merkel cell carcinoma, metastatic urothelial carcinoma
- Durvalumab (Imfinzi[®])
 - Metastatic urothelial carcinoma, unresectable Stage III non-small cell lung cancer

PD-1 Agents

- Nivolumab (Opdivo[®])
 - Hodgkin’s lymphoma, liver carcinoma, melanoma, colorectal cancer, urothelial carcinoma, NSCLC, renal cell carcinoma, squamous cell carcinoma of head and neck
- Pembrolizumab (Keytruda[®])
 - Cervical cancer, colorectal cancer, gastric cancer, head and neck cancer, Hodgkin’s lymphoma, melanoma, urothelial carcinoma, NSCLC, microsatellite instability-high solid tumors, primary mediastinal large B-cell lymphoma

CTLA-4 Agent

- Ipilimumab (Yervoy[®])
 - Adjuvant, unresectable or metastatic melanoma, renal cell carcinoma, metastatic colorectal cancer

Clinical trials show the time to response for ICPI's in advanced malignancy is:

- A 6 months
- B 6 weeks
- C 2 months
- D 2 weeks

Efficacy in Advanced Lung Cancer

- Nivolumab in previously treated Squamous Cell NSCLC – CheckMate 017
 - OS 9.2 months vs 6.0 months with docetaxel
 - RR 20% vs 9%
 - Time to response 2.2 months
- Nivolumab in previously treated Nonsquamous NSCLC – CheckMate 057
 - OS 12.2 months vs 9.4 months with docetaxel
 - RR 19% vs 12%
 - Time to response 2.1 months

Efficacy in Advanced Lung Cancer

- Pembrolizumab in previously treated advanced NSCLC – KEYNOTE-010
 - OS 10.4 months (2mg/kg) vs 12.7 months (10mg/kg) vs 8.5 months (docetaxel)
 - PFS 3.9 months vs 4.0 months vs 4.0 months
 - Patients with >50% expression PD-L1 OS significantly longer compared to docetaxel (14.9 months/17.3 months vs 8.2 months)
 - Median time to response was 9 weeks
 - RR 18% vs 18% vs 9%

Efficacy in Advanced Lung Cancer

- Pembrolizumab in previously untreated advanced NSCLC – KEYNOTE-024
 - Had to have PD-L1 of at least 50% to be included in trial
 - PFS 10.3 months vs 6.0 months (investigator choice platinum-based chemotherapy)
 - RR 44.8% vs 27.8%
 - Time to response 2.2 months

Which of the following statements are true of PD-1 inhibitors?

- A** High grade toxicities are more common with PD-1 inhibitors
- B** The most common ADE reported is nausea
- C** Rates of toxicity are dose-related
- D** Fatigue is linked to hypothyroidism

Potential Adverse Events

- Rash/inflammatory dermatitis
- Colitis
- Hepatitis
- Pneumonitis
- Primary hypothyroidism
- Hyperthyroidism
- Primary adrenal insufficiency
- Hypophysitis
- Diabetes
- Inflammatory arthritis
- Myositis
- Polymyalgia-like syndrome
- Nephritis
- Myasthenia Gravis
- Guillain-Barre Syndrome
- Peripheral neuropathy
- Autonomic neuropathy

Potential Adverse Effects (cont'd)

- Aseptic meningitis
- Encephalitis
- Transverse myelitis
- Autoimmune hemolytic anemia
- Acquired thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Aplastic anemia
- Lymphopenia
- Immune thrombocytopenia
- Acquired hemophilia
- Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis
- Venous thromboembolism
- Uveitis/iritis
- Episcleritis
- Blepharitis

Rates of ADE

- The most common ADE reported is fatigue with PD-1 and PD-L1 inhibitors (16-37%, 12-24%)
 - Mechanism is poorly understood as a minority of patients have hypothyroidism
- High grade toxicities are less common in PD-1 inhibitors compared to CTLA-4 drugs
 - 10-27% of patients on ipilimumab develop grade 3 to 4 toxicities at the 3mg/kg dose; 41.6% in 10mg/kg dose; 55% in combination therapy with PD-1/PD-L1

Management

- With everything that potentially could go wrong, where do you turn to?
- New guidelines!
 - ESMO 2017
 - Haanen JBAG, Carbonnel F, Robert C et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. *Ann Oncol* 28 (Suppl 4):2017;iv119-iv142.
 - ASCO 2018
 - Brahmer JR, Lacchetti C, Schneider BL et al. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 36 (17):2018;1714-68.
 - NCCN 2018 – ‘in partnership with ASCO’

Guideline Methodology

- ESMO
 - Literature was selected by authors
 - 9 organ systems reviewed with recommendations
- ASCO
 - Included 38 systematic reviews and 166 primary studies
 - Much of evidence consisted of systematic reviews of observational data, consensus guidelines, case series and case reports
 - Relied on informal consensus for the recommendations
 - 10 organ systems reviewed with recommendations

Clinical Practice Case Study

- Geisinger Health
- Medication Therapy Disease Management Clinic (MTDM)
 - Hematology/Oncology pharmacist run clinic
 - Main focus is on oral chemotherapy, however with potential side effects from immunotherapy, MTDM also monitors some of these patients
 - Pharmacists work under collaborative practice
 - Monitor patients for ADEs, focus on thyroid abnormalities

How would you manage Grade 2 skin toxicity?

- A** Immediately initiate systemic steroids
- B** Continue immunotherapy and initiate topical steroids
- C** Discontinue immunotherapy and refer to dermatology
- D** Continue immunotherapy and monitor as it should be self-limiting

ESMO Skin Toxicities

Symptom grade	Management	Assessment/investigations
Grade (G) 1: skin rash with or without symptoms, <10% BSA	Avoid skin irritants, avoid sun exposure, topical emollients recommended; topical steroids (mild) cream daily +/- oral or topical antihistamines for itch; proceed with treatment	Physical exam; exclude other causes (viral illness, infection, other drug rash)
Grade 2: rash covers 10-30% BSA	Supportive management; topical steroids (mod strength) daily or (potent) twice daily +/- oral or topical antihistamines for itch; proceed with treatment	Consider dermatology referral and skin biopsy
Grade 3: rash covers > 30% BSA or grade 2 with substantial symptoms	Hold treatment; topical treatments; initiate oral steroids; restart therapy at grade 1/mild grade 2 after discussion with patient and consultant	Dermatology review, consider punch biopsy and clinical photography
Grade 4: skin sloughing > 30% BSA with associated symptoms	IV steroids; emergent dermatology review; discontinue treatment	Punch biopsy, clinical photography

ASCO Skin Toxicities

Grading	Management
G1: symptoms do not affect QOL or controlled with topical regimen and/or oral antipruritic	Continue treatment; treat with topical emollients and/or mild-moderate potency topical corticosteroids; counsel patients to avoid skin irritants and sun exposure
G2: inflammatory reaction that affects QOL and requires intervention based on diagnosis	Consider holding treatment and monitor weekly for improvement – if not resolved hold until G1; consider initiating prednisone; treat with topical emollients, oral antihistamines and medium to high potency topical steroids
G3: as G2 with failure to respond to indicated interventions for a G2 dermatitis	Hold therapy and consult dermatology; treat with emollients, oral antihistamines and high-potency topical steroids; initiate prednisone
G4: all severe rashes unmanageable with prior interventions and intolerable	Hold therapy and consult dermatology; IV steroids; admit patient; consider change in treatment

Patient Case

- JL is a 29 yo female on pembrolizumab phase 1 clinical trial for metastatic cervical cancer, s/p one dose
- 1 week after treatment, she begins having 10 loose stools a day, has progressive nausea and vomiting (onset pre-dated pembrolizumab treatment), and presents to the hospital. Stool studies are all negative.

What do you think is happening?

- A** Disease progression leading to increased nausea and vomiting
- B** Sounds like standard side effects from treatment – should get better with time
- C** Pembrolizumab-induced colitis
- D** A and C

Background on Colitis

- GI toxicity is well described for anti-CTLA4, less so for anti-PD-1/PDL1
- Occurs in 27-54% of patients on anti-CTL4
 - Frequency of colitis ranges from 8-22%
 - Colon perforation in 1-1.5% of melanoma patients on ipilimumab; up to 6.6% in RCC
 - 1.1% of patients die of complications of ipilimumab-induced colitis
 - NSAID use may increase risk; limited data on risks in ulcerative colitis of Crohn's disease

Colitis with Anti-CTL-4

- Onset any time during treatment course – up to several months after last dose
- Most commonly presents as diarrhea
- Can present with abdominal pain, hematochezia, weight loss, fever, vomiting
- May also be associated with mouth ulcers, anal lesions, extra-intestinal manifestations
- Associated with anemia, increased CRP, low serum albumin
- Rule out GI infections and tumor-related symptoms

Colitis with Anti-PD1

- 1-2% of cases of grade 3-4 with pembrolizumab
- Median time to onset 3 months
- Most common symptoms: diarrhea, followed by nausea/vomiting and abdominal pain
- Four patterns:
 - Acute colitis similar to CTLA-4 agents
 - Microscopic colitis
 - Upper GI involvement
 - Pseudo-obstruction
- 87.5 % responded to steroids

What is the recommended treatment for Grade 3-4 colitis?

- A** Hold treatment and start prednisone 3 mg/kg/day
- B** Continue treatment, admit to hospital and provide supportive care
- C** Stop treatment and start prednisone 1 mg/kg/day
- D** Hold treatment, admit to hospital, and provide supportive care

Colitis Management G1-2

Grade	ESMO Management	ASCO Management
G1: ESMO (< liquid 3 stools/day over baseline (BL)); ASCO (< 4 loose stools/day over BL)	<ul style="list-style-type: none"> Continue therapy. Oral fluids, loperamide, diet modification If >14 days or worsens – prednisolone 0.5-1 mg/kg/day or oral budesonide 9 mg daily Baseline liver function/CBC/stool studies 	<ul style="list-style-type: none"> Continue therapy; alternatively may hold temporarily and resume if G1 Monitor for dehydration; recommend dietary changes Expedited phone contact with patient/caregiver Gastroenterology consult for prolonged cases
G2: >4-6 stools/day over BL, abdominal pain, blood in stool or nausea, nocturnal episodes ASCO	<ul style="list-style-type: none"> Hold treatment Steroids (as with G1) if persist > 3 days or worsens Outpatient tests as with G1 Abdominal xray for signs of colitis; schedule colonoscopy/ sigmoidoscopy Contact patient every 72 hours 	<ul style="list-style-type: none"> Hold treatment until recover to G1 Consider permanently discontinue CTLA-4; may restart PD-1/L1 if recover to G1 Loperamide if no infection Consult gastroenterology Steroids, 1 mg/kg/day prednisone/equivalent, taper over at least 4-6 weeks (once G1) EGD/colonoscopy, endoscopy recommended Consider monitoring of lactoferrin/calprotectin

Colitis Management G3

Grade	ESMO Management	ASCO Management
G3: >6 stools per day over BL or within 1h hour of eating	<ul style="list-style-type: none"> • Hospitalization and isolation • Hold treatment • Labs as above. Consider imaging • Methylprednisolone 1-2 mg/kg • Gastroenterology; colon/sigmoidoscopy • If no improvement in 72h, scope & infliximab 5 mg/kg, repeat in 2 weeks • Alternative: MMF 500-1000 mg BID or tacrolimus • Loperamide 4 mg, then 2 mg q 30 min before meals and with each loose stool 	<ul style="list-style-type: none"> • Consider permanently discontinuing CTLA-4; may restart PD-1/L1 when G1 • Steroids (initial dose 1-2 mg/kg/d prednisone/equivalent) • Hospitalization if dehydration or electrolyte imbalance • Persist > 3-5 days or recur, consider IV steroid/infliximab • Colonoscopy if immunosuppression/risk for opportunistic infections & if anti-TNF/steroid refractory

Colitis Management G4

Grade	ESMO Management	ASCO Management
G4: Life-threatening consequences (ASCO)	Same as G3.	<ul style="list-style-type: none"> • Permanently discontinue treatment • Hospitalize or closely monitor as outpatient • 1-2 mg/kg/d methylprednisolone/equivalent until G1, then taper over 4-6 weeks. • Early infliximab 5-10 mg/kg if refractory w/in 2-3 days • Lower GI endoscopy if refractory symptoms or concern of new infection.

What is the recommendation for monitoring for thyroid toxicity?

- A** At initiation and at completion of therapy
- B** Every cycle and 4 to 6 weeks after completion
- C** Every 2 weeks for the duration of treatment
- D** Monthly if there are abnormalities present at baseline

Thyroid ADE

- Baseline endocrine panel: TSH, free T4, T3
 - Baseline abnormal values do not preclude treatment, discuss with endocrinologist if uncertain
- ESMO suggests monitoring every cycle with CTLA-4 inhibitor then 4-6 weeks after last cycle
 - Every cycle for first 3 months with PD1/PD-L1 drugs, then every 2nd cycle thereafter
- Fall of TSH across 2 measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed

Primary Hypothyroidism

Grading	ESMO Management	ASCO Management
G1: TSH < 10mIU/L and asymptomatic	Repeat next cycle	Continue treatment, close monitoring of TSH, FT4
G2: moderate symptoms; able to perform ADL; TSH > 10 mIU/L	Normal FT4: consider thyroxine Low FT4: initiate thyroxine	May hold treatment until symptoms resolve to baseline; consider endocrine consult; initiate hormone supplementation; monitor TSH every 6-8 weeks titrate to normal TSH; can use FT4 testing every 2 weeks to monitor adequacy of replacement if initially low; once treated, monitor every 6 weeks while on active treatment
G3-4: severe symptoms, medically significant or life threatening consequences, unable to perform ADL		Hold treatment until symptoms resolve; endocrine consult; may admit for IV therapy if signs of myxedema; thyroid supplementation as above

Hypothyroidism Treatment

- Without risk factors, full replacement can be estimated with ideal body weight to 1.6 mcg/kg/day
- For elderly or fragile patients with multiple comorbidities, start at levothyroxine 25-50 mcg and titrate up

Hyperthyroidism

Grading	ESMO Management	ASCO Management
G1: asymptomatic or mild symptoms	Elevated FT4: repeat next cycle	Continue treatment with close follow up and monitoring of TSH, FT4 every 2-3 weeks
G2: moderate symptoms, able to perform ADL	Low FT4: check 9am cortisol	Consider holding treatment until symptoms return to baseline; beta-blocker for symptomatic relief; hydration and supportive care; for persistent hyperthyroidism (>6 weeks) or clinical suspicion, work up for Graves disease and consider thionamide; refer to endocrine for Graves disease
G3-4: severe symptoms, medically significant or life threatening consequences, unable to perform ADLs		Hold treatment; endocrine consult; beta blocker; if concerned about thyroid storm, admit and start on steroids

Hyperthyroidism Treatment/Considerations

- Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal
- Graves disease is generally persistent and is due to increased thyroid hormone production that can be treated by antithyroid medical therapy
- Physical exam findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral

Steroid Pearls

- 1/3 - 2/3 of patients receiving IV steroids either do not respond or have a relapse during tapering
 - Require infliximab unless contraindicated
- Dosing: Grade 2-4
 - 1 mg/kg/day prednisone or equivalent
 - Taper over at least 4-6 weeks
- Preferred agent?
- Supportive care for adverse effects
 - Insomnia
 - Psychosis/agitation
 - GI symptoms
 - Metabolic changes

To Steroid...

- Garant A, et al. 2017
 - Clinical trials exclude patients on corticosteroids
 - Systematic review of 27 articles
 - Data suggests concomitant administration may not lead to poorer clinical outcomes
 - No objective data on the types or dose threshold for clinical interaction
 - Consideration of stratified randomization and treatment sequence evaluations in prospective trials

To Steroid...

- Retrospective review of 290 patients, single center
 - 34% (n=98) experienced Grade 1 or 2 immunotherapy-related adverse effects (irAEs)
 - Dermatitis (n=57), hypophysitis (n=18), elevated LFTs (n = 17), diarrhea (n = 15)
- 5.2% (n = 15) reported grade 3 or 4 irAes
 - Dermatitis, enterocolitis, autoimmune hepatitis, myositis, myasthenia gravis, pneumonitis, pleuritis, pancreatitis
 - 8% on ICPI, 4% on cytokine therapy, 2% on vaccine trial
 - Had significantly improved ORR (25% vs 6%, p = 0.039), disease control rate (67% vs. 21%, p<0.001), TTP (30 weeks vs. 10 weeks, p=0.0040)
 - All evaluable patients (n = 4) had continued response
 - OS 15 months vs. 8 months (p=0.10)

To Steroid...

- Fuji, et al. – 80% of patients with \geq grade 3 irAEs received steroids, all continued to respond when re-challenged with ICPI
- Horvat, et al. Retrospective review of 298 melanoma patients on ipilimumab
 - 85% experienced irAE of any grade – 30% received steroids, 10% required anti-TNF α
 - No difference in OS or time-to treatment failure vs. steroid/TNF naïve

Or Not to Steroid...?

- Animal study – blunted anti-CTLA4 effect and reversal of tumor growth inhibition after 7 days
- Downey et al – no statistically significant effect on PS
 - Median duration of response with steroids – 19.3 months vs. 30.6 months for all responders
- Margolin, et al. Phase 2, open-label trial of ipilimumab in melanoma with brain metastases
 - Patients receiving steroids had decreased OS
 - Dose and duration of dexamethasone were not reported

Bingliang Chen JP, et al. 98th AACR Annual Meeting. 2007.

Downey SG et al. *Clin Cancer Res.* 2007;13:6681-6688.

Margolin K, et al. *Lancet Oncol.* 2012; 13:459-465.

Or Not to Steroid...?

- Arbour KC, et al. 2018
- PD-(L)1-naïve patients with advanced NSCLC to assess for corticosteroid use at initiation of PD(L)-1 therapy in two treatment centers
- 14% (n=90) of 640 patients received corticosteroids \geq 10 mg prednisone equivalent
- Indications dyspnea (33%), fatigue (21%), brain metastases (19%)
- Baseline corticosteroids associated with decreased ORR, PFS, OS with PD(L)-1 blockade (ORR 0.42, P=0.053, PFS HR 1.31; P=0.03; OS HR 1.66, P<0.001).
 - Despite adjusting for smoking history, performance status, history of brain metastases (PFS HR 1.3; P = 0.03; OS HR 1.7; P<0.001)

Patient Case

- JL is a 61 yo male on ipilimumab for metastatic melanoma (metastases to lung), he finished the course of 4 doses
- 3 weeks later, the oncology clinic received a call from the patient's frantic daughter. He was acting very odd and unlike himself – she reported that he was standing on his front porch in an open bathrobe (and nothing else) with a shotgun and rambling to himself. She asked for advice from the clinic. The research nurse also reported to the MD that the patient had been leaving long rambling voicemails on her work phone at all hours.

What would you advise the daughter?

- A** Call the police, that man has a gun!
- B** Bring the patient in for evaluation
- C** Give it some time, the side effects will wear off eventually
- D** A and B

Patient Case

- The daughter was advised to bring the patient in to the hospital for evaluation. If he would not come willingly, she was advised to call the police to bring him in for a psych hold
- He was admitted to the hospital with sodium of 120 (135-146). AM cortisol level 0.5 ug/dL (4-22 ug/dL) and ACTH <5 pg/mL (6-50 pg/mL)

What is the likely side effect this patient is experiencing?

- A** Infection
- B** Hypophysitis
- C** Adrenal insufficiency
- D** Hyperthyroidism

Symptoms of Adrenal Insufficiency

- Symptoms depend on the rate and extent of loss of adrenal function, whether mineralocorticoid production is preserved and degree of stress
- Main manifestation is shock
 - However can also have nonspecific symptoms of anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion or coma
 - Abdominal tenderness, which may be elicited on deep palpation and is usually generalized
- Diagnostic work up should include adrenocorticotrophic hormone (ACTH), AM cortisol, and basic metabolic panel
 - High ACTH, low cortisol in line with diagnosis
 - If results are indeterminate, ACTH stimulation test should be performed

Primary Adrenal Insufficiency

Grade	ASCO Management
G1: asymptomatic or mild symptoms	Consider holding therapy until patient stabilized on replacement hormone; endocrine consult; replacement therapy with prednisone or hydrocortisone, may require fludrocortisone; titrate dose up or down as symptoms dictate
G2: moderate symptoms, able to perform ADLs	Consider holding therapy; endocrine consult; initiate outpatient therapy at 2-3x maintenance; taper stress dose steroids down to maintenance dose over 5-10 days
G3-4: severe symptoms, medically significant or life threatening consequences, unable to perform ADL	Hold therapy; endocrine consult; NS bolus (at least 2L), IV stress dose steroids; taper down to maintenance dose over 7-14 days after discharge

- Maintenance doses: prednisone 5-10 mg, hydrocortisone 10-20 mg in AM, 5-10 mg in afternoon, fludrocortisone 0.1 mg/day

Considerations

- Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol
 - If the ACTH is low with low cortisol then manage as hypophysitis
- Patients on steroids for management of other conditions will have low morning cortisol, ACTH will also be low
- Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed; if diagnosis is already confirmed, can use hydrocortisone 100mg

Symptoms of Hypophysitis

- Headache
- Visual field impairment
- Diagnosis based more so on laboratory testing

- A relatively rare side effect, hypophysitis is reported for ipilimumab 3mg/kg, 10mg/kg and in combination with nivolumab at 1%, 16% and 8% respectively

Hypophysitis

Grade	ESMO Management	ASCO Management
G1: asymptomatic or mild symptoms		Consider holding therapy until patient stabilized on replacement hormones; hormonal supplementation as needed; testosterone or estrogen therapy as needed in those without CI; endocrine consult; start steroids several days prior to thyroid hormone replacement to prevent precipitating adrenal crisis; follow FT4 for thyroid replacement titration (TSH not accurate)
G2: moderate symptoms, able to perform ADLs	Hold treatment; if headaches and other neurological problems, high-dose steroids should be given; however appears not to counteract the hormonal deficiency resulting from treatment	Consider holding therapy; endocrine consult; hormone supplementation as above
G3: severe symptoms, medically significant or life threatening consequences, unable to perform ADLs		Hold therapy; endocrine consult; hormone supplement as above; consider initial pulse dose therapy with prednisone 1-2mg/kg (or equivalent) orally daily tapered over at least 1-2 weeks

ESMO Pituitary Axis Lab

- 9 AM cortisol
 - Or random if unwell and treatment cannot be delayed
- ACTH
- TSH/FT4
- LH, FSH, oestradiol if premenopausal
- Testosterone in men
- IGF-1
- Prolactin

Replacement Advice

- If 9 AM cortisol <250 or random cortisol < 150 and vague symptoms:
 - Replace with hydrocortisone 20 mg/10 mg/10 mg
 - If thyroid function tests normal, 1-2 weekly monitoring initially
 - Always replace cortisol for 1 weeks prior to thyroxine initiation
 - If falling TSH +/- low FT4
 - Consider need for thyroxine replacement based on symptoms +/- check 9 am cortisol

Considerations

- Start steroids first, always
 - Even with multiple deficiencies
- All patients need instruction on doubling doses for illness and a medical alert bracelet should be worn
- Work up cannot be done with simple AM cortisol in a patient on steroids for other conditions

Your turn!

- JL, 61 yo male who finished course of ipilimumab, behavioral changes, sodium, cortisol and ACTH abnormalities.
- In your groups, discuss:
 - In your experience, have you seen something like this?
 - What treatment would you suggest for JL?

What treatment would you suggest for JL?

- A** Hold ICPI and resume once symptoms resolve
- B** Refer for endocrine assessment, continue ICPI for now
- C** Start hormonal replacement immediately
- D** Start steroid immediately

Patient Case

- RV is a 59 yo male diagnosed with stage IV squamous NSCLC in 2017. He was previously treated at another facility with atezolizumab, however treatment was discontinued due to progression of disease. Since that time patient has been in and out of the hospital due to hemoptysis, obstructive pneumonias and AKI. He has never received traditional chemotherapy for his cancer. Patient is seen by provider with his sister – who is pushing for the patient to go back on clinical trial with another immunotherapy agent, however the patient does not qualify for trial at this time.

Patient Case

- The sister calls the clinical trials nurse after appointment and is very upset. She has heard about the new 'Right to Try' legislation and would like to investigate getting the immunotherapy agent for her brother outside of a clinical trial
- The nurse comes to you, the pharmacist, for your advice

What advice do you give?

- A** Wow, that seems like a lot of work
- B** We can inquire to the drug company to see if the medication is available compassionate use
- C** It is up to the patient's sister to investigate
- D** I have no idea what to do either

Right-To-Try Laws

- The idea behind the ‘right-to-try’ allows terminal patients earlier access to drugs that are being developed for market
- Proponents of these laws cite the average time to market for a drug is around 15 years
 - These laws allow patients access to therapies once they have passed phase I trials
 - Also may benefit patients who do not qualify for or have access to clinical trials

Right-To-Try

- About 40 US states have enacted laws
- Federally, was signed by the president on May 30, 2018
- This is separate from established compassionate use or expanded access programs

Is this a good thing?

- On the surface, this sounds like a good idea
 - Critics worry that the laws generally don't require:
 - Physicians to prescribe experimental therapies
 - Insurance companies to pay for them
 - Manufacturers to provide them
 - Could this then be offering false hope?

Informed Consent

- Patients in clinical trials have to sign informed consent
 - These patients are usually fit for treatment
 - Unknown how a terminally ill patient would tolerate treatment based on available data (phase I trial)
 - No clause to promote efficacy, only safety in right-to-try
 - How would a provider adequately obtain informed consent for right-to-try patients?

Inequitable Access

- The laws are triggered based on a terminal illness
- What about patients that have exhausted available options but are not imminently dying?

FDA's Expanded Access Program

- Separate from right-to-try laws
- Programs also can be called 'Compassionate Use'
 - The patient's provider contacts the drug manufacturer to enroll the patient
 - If the company agrees, they provide the product
 - An investigational new drug (IND) form is filed with the FDA
 - On average, approval is granted within 4 days, 24 hours if need is critical
 - The provider's institutional review board (IRB) must also approve protocol and informed consent forms

FDA's Expanded Access Program

- Puthumana et al, looked at manufacturers offering expanded access programs in the past 2 decades, the majority of drugs that offered programs, did so within 6 months of time of the application for FDA approval
 - The authors suggest that with this approach, safety and efficacy has been established
 - 99% of applications to the FDA for expanded access have been approved

Right-To-Try

- Currently, no substantiated cases of a patient actually receiving a drug through these laws
 - One facility in Texas claims 80 patients were able to access an agent through right-to-try, however the medication has an expanded access program

Your Turn!

- In your groups, discuss:
 - Are we offering false hope with right-to-try?
 - Have you been involved with obtaining medication through compassionate use?

Have you been involved in helping someone get a medication through the Right to Try Act?

A Yes

B No

Patient Case Revisited

- An email was sent to the drug manufacturer on behalf of RV to see if he would qualify for expanded access of the medications in the trial for which he was being considered
- The manufacturer refused to provide the therapy as they do not currently have a compassionate use program for these agents as there was not enough data supporting favorable risk benefit profile

Direct To Consumer (DTC) Advertising

- Any unsolicited promotional endeavor by a pharmaceutical company or other provider of medical services to present information about medicine or medical services to the public
- Includes television, radio, newspaper, magazine, billboard, and direct mailing advertisements; drug company brochures
- FDA requires balanced representation of possible benefits, risks, and side effects

DTC Advertising

- The United States and New Zealand are the only two countries in the world that allow DTC advertising of prescription drugs.
- 30% increased spending in the last two years to \$4.5 billion



DTC Advertising

- Go-to strategy for the drug with the most to gain
 - Brand teams are trying to create awareness of a new market or new type of drug
 - If the therapy has a stronger clinical profile than its competitors
- Average American TV viewer watches 9 drug ads a day = 16 hours a year

- Op-ed in *The New York Times* criticized the ad, saying that the drug's “velvet-voice narrator” and “actors portraying lung cancer patients playing with babies and watching Little League games” would be uplifting “if it weren't so utterly misleading and exploitative.”
 - Matt Jablow, lost his wife to stage 4 lung cancer.

Regulations

- FDA Amendments Act of 2007
- FDA drafted guidance on standardized appearance of drug names, clarified points of fair and balanced presentations of risks/benefits, specified regulatory guidelines for online advertisements
- Pharmaceutical Researchers & Manufacturers of America (PhRMA) 2005 & 2008
 - Information should be clear, accurate, evidence-based
 - Responsible education about the medicine and condition; promote disease awareness, inform about alternatives
 - Denounce the promotion of off-label uses/benefits, clearly identify actor and celebrity endorsers, reiterate FDA guidance on language

American Medical Association Ban

- *...reflects concerns among physicians about the negative impact of commercially-driven promotions, and the role that marketing costs play in fueling escalating drug prices...*
- *DTC advertising also inflates demand for new and more expensive drugs, even when these drugs may not be appropriate*
 - AMA Board Chair-elect Patrice A. Harris, M.D., M.A. (November 7, 2015)
- Prohibiting DTC advertising would require an act of Congress and would raise complex freedom of speech issues

Analysis of DTC Advertisements

- Now and Then (2016 vs. 2004)
 - Longer ad length - 7.4 sec vs 51.8 sec
 - Less information on biologic nature, risk factors or causes, prevalence
 - Used qualitative descriptions vs quantitative evidence
 - More positive emotional appeal; decreased negative appeal (50.8% vs. 75.3%)
 - For medications with associated behavioral change – no mention of options
 - Depicted patients with improved social acceptance and renewed control over their disease – doubled in rate of increased endurance from 2004
- Conclude: self-regulation by industry may need to be more regulatory in nature

Critiques of DTC Advertising

- Misinforms patients
- Overemphasizes drug benefits
- Promotes new drugs before safety profiles are fully known
- Manufactures disease and encourages drug over-utilization
- Leads to inappropriate prescribing
- Strains relationships with health care providers
- Wastes appointment time
- Is not rigorously regulated
- Increases costs

Positives of DTC Advertising

- Informs, educates, empowers patients
- Encourages patients to contact a clinician
- Promotes patient dialogue with health care providers
- Strengthens a patient's relationship with a clinician
- Encourages patient compliance
- Reduces under-diagnosis and under-treatment of conditions
- Removes stigma associated with certain diseases
- Encourages product competition and lower prices

It's Your Turn!

- Have you heard feedback from patients about DTC for cancer treatments?
- Debate!
 - Split into two groups
 - Pro- DTC Advertising for oncologic medications
 - Con- DTC Advertising for oncologic medications
 - Volley back and forth to support your assigned position.

What percent of patients may benefit from immunotherapy?

- A** <10%
- B** 12-20%
- C** 20-30%
- D** 40-50%

Prognostication

- Clinicians are only accurate when the patient is actively dying
- Oncologists tend to overestimate prognosis by 4-5 times
- Ability to prognosticate gets worse with longer therapeutic relationships
- ‘no one should die without a dose of immunotherapy’

Prognostication

- 12-20% of cancer patients may benefit from therapy
- Patients expectations – closer to 90% efficacy
- Need for concordant value-based care
- Being willing to say “I don’t know”
- “Super-responders”

Patient Education

- Should include:
 - Assess illness understanding and how best learn information
 - Time to efficacy and true likelihood of response
 - Possible complications in the mean time
 - May need to repeat conversation at different junctures

‘Desperation Oncology’

- If patients are dying and there’s a remote chance that the drug will help, then why not?
 - Is more always better?
 - Historical examples
- Ethical conundrum: when knowledge is insufficient to drive decision-making
- Balancing hope with reality
- Consider home-based palliative care

Price Tag

- “Approximately 4000 times the cost of gold” – Dr. Saltz
- Widespread use could cost the U.S. \$174 billion annually
- Price per milligram:
 - Nivolumab: \$28.78; Pembrolizumab : \$51.79; Ipilimumab: \$157.46.
- Ipilimumab, nivolumab – \$100,000 – \$150,000/course
 - ~\$300,000 for dual-treatment
 - \$60,000 out-of-pocket at a 20% copay
- Pembrolizumab - \$46,000-\$83,500 monthly

Initial Considerations

Patient considering immunotherapy:

- Overall condition
- Symptom burden, possibility of side effects
- Pre-existing conditions (IBS, Crohn's, etc.)
- Cost (co-pay?)
- Possibility of % “response”
- What does response mean?

On-going Considerations

Patient condition declining despite immunotherapy:

- Symptom burden, side effects
- Have side effects been treated appropriately?
- Overall condition
- Hopes, goals
- How many treatments?

Rules of *Immuno*-cation

- Meet the patient where they are
- Discuss all of the options
- Assess YOUR understanding
- Accept the possibilities- Respect the excitement
- Assess their understanding of diagnosis, prognosis and treatment
- Assess their understanding of possible side effects
- “What are you willing to pay?”

Key Takeaways

- There are now guidelines that can help with therapeutic decision-making in the management of adverse drug effects related to treatment with ICPI
 - Apply them to clinical decision-making in a team-based approach as a standard of care
- Steroids may not have an impact on the clinical outcomes of treatments with ICPI's
 - Careful discussion with oncologists and patients and their families can help guide treatment options
- Patients are exposed to DTC Advertising on a daily basis and it may impact care
 - Explore patient's knowledge and predisposition toward therapies as they are offered

Questions?

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