Beyond Chemotherapy:

AN UPDATED GUIDE FOR HOSPITALISTS ON TARGETED THERAPY AND IMMUNOTHERAPY

Disclosures

I have no relevant financial or nonfinancial relationships to disclose.

Learning Objectives

Upon completion of this program, the participate should be able to:

1. Understand how targeted therapies and immunotherapies work and how they differ from traditional chemotherapy.
2. Identify the most common complications and adverse effects you will see as a hospitalist and initial management strategies.
3. Recognize how these modalities are changing the treatment and prognosis of solid tumor malignancies.

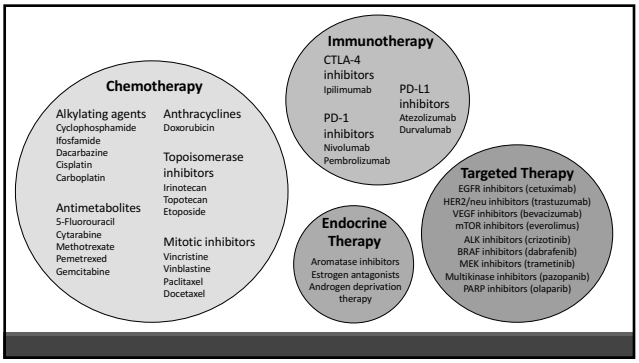
Case

"I have a 60 year old woman with lung cancer who is on chemotherapy. She has had one week of worsening diarrhea and Imodium isn't helping. She looks dehydrated and has an acute kidney injury. She isn't febrile or neutropenic. She needs to be admitted."

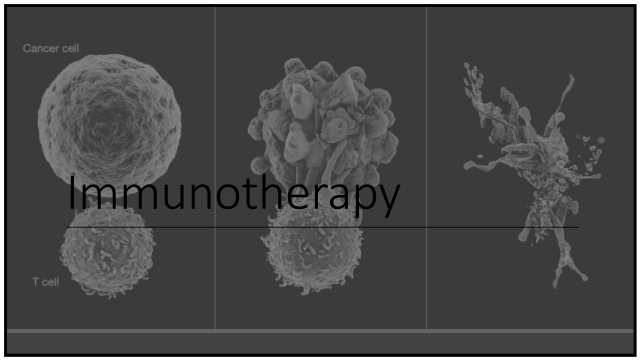
Case

This patient with lung cancer on "chemotherapy" could truly be on a traditional chemotherapy regimen. But she could also be on immunotherapy with a PD-1 inhibitor or targeted therapy with an ALK inhibitor.

All of these regimens can cause diarrhea but the etiology, evaluation, and management varies.



	Chemotherapy	Immunotherapy	Targeted therapy
Mechanism of Action	Kill or inhibit rapidly dividing cells	Activate the innate immune system to kill cancer cells	Inhibit specific pathways critical to tumor growth
Mechanism of Toxicity	Direct damage to healthy dividing cells	Autoimmune damage to healthy tissue	Disruption of physiologic pathways
Timing of Adverse Events	Generally cycle dependent	Delayed and variable	Variable, days to months
Management of Adverse Events	Supportive care	Immunosuppression	Supportive care, dose reduction



Immunotherapy

Immunotherapy – FDA approvals

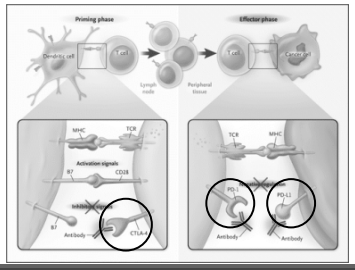
First line
- Metastatic melanoma
- Non-small cell lung cancer (in combination with chemotherapy)
- Microsatellite instability high (MSI high) site-agnostic cancer
- Advanced renal cell carcinoma
- Metastatic cutaneous squamous cell carcinoma

Second line or later
- Urothelial cell carcinoma
- Head and neck squamous cell carcinoma
- Hepatocellular carcinoma
- Gastric adenocarcinoma
- Merkel cell carcinoma
- Hodgkin lymphoma
- Small cell lung cancer
- Cervical cancer

Immunotherapy – Mechanism of Action

Immune Checkpoint Inhibitors target proteins in the T-cell activation pathway.

CTLA-4
PD-1
PD-L1



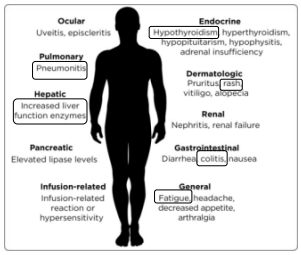
Immunotherapy – Mechanism of Action

Both the **antitumor effects** and **adverse effects** are caused by blocking the negative regulators of immunity that normally maintain immunologic homeostasis:

-> T-cells fight cancer cells

-> T-cells can start attacking healthy tissue

Immune-related Adverse Events (IrAEs)



Immune-related Adverse Events (IrAEs)

- **Rash** (40-60% overall, <10% grade 3-4)
- **Colitis** (8-23% overall, grade 3-4 rate is 2-7%)
- **Hepatitis** (more common in CTLA-4 inhibitors)
- **Hypophysitis, Hypothyroidism** (up to 10% with CTLA-4 inhibitors, 1-7% with PD-1)
- **Pneumonitis** (typically occurs later than other irAEs)

Immune-related Adverse Events (IrAEs)

Unlike with chemotherapy, onset is **not** cycle dependent (not related to drug half-life)

IrAEs can be quite delayed and the timing of onset varies by the affected tissue:

- Rash often occurs the earliest (3-6 weeks)
- Colitis, hypophysitis, and hepatitis typically occur later (5-10+ weeks)

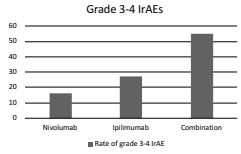
Given the delayed onset, IrAEs can even appear after discontinuation of therapy

Immune-related Adverse Events (IrAEs)

Combination regimens have the highest incidence of irAEs (Ipilimumab + Nivolumab)

For example, in a trial for melanoma patients receiving Nivolumab, Ipilimumab, or Combination therapy:

- Nivolumab – 16% had grade 3-4 irAEs
- Ipilimumab – 27% had grade 3-4 irAEs
- Combo – 55% had grade 3-4 irAEs



Larkin J, et al. *N Engl J Med.* 2015; 373: 23–34.

Treatment of IrAEs

In a word:

STEROIDS

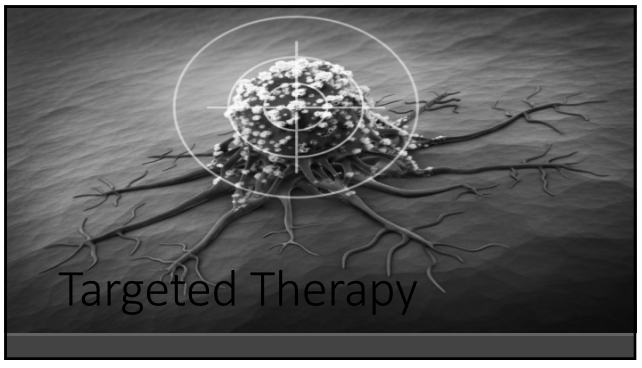
Treatment of IrAEs

High doses: prednisone 1-2 mg/kg daily

Long tapers: 4 to 8 weeks

Refractory cases may need alternative immunosuppressive agents: Infliximab, mycophenolate mofetil, tacrolimus, IVIG

In February 2018, the NCCN and ASCO released a joint guideline: Management of Immunotherapy-Related Toxicities (www.NCCN.org or www.asco.org)



Targeted Therapy

Non-small cell lung cancer
- ALK rearranged: Alectinib, Crizotinib
- EGFR mutated: Erlotinib, Afatinib, Osimertinib

Renal cell carcinoma
- Pazopanib, Sunitinib (mulitkinase inhibitor)

Breast cancer (HER2/neu positive)
- Trastuzumab

Hepatocellular carcinoma
- Sorafenib (multikinase inhibitor)

Metastatic melanoma (BRAF V600E mutated)
- Dabrafenib, Vemurafenib
- Trametinib

Colon cancer
- Bevacizumab (VEGF inhibitor)
- Cetuximab (EGFR inhibitor)

Pancreatic neuroendocrine tumors
- Everolimus (mTOR inhibitor)

Targeted Therapy – Mechanism of Action

These drugs **target** specific molecules along the signaling pathways of cell activities.
- They can target cell surface molecules (typically monoclonal antibodies) or intracellular molecules (small molecule drugs that can enter the cell).
- They can disrupt cell growth and reproduction, cell differentiation, or tumor metastasis by causing apoptosis or preventing angiogenesis or blocking intracellular communication pathways.

Targeted Therapy

Some targeted therapies are approved based on cancer site rather than identified molecular markers:
- Sunitinib, Pazopinib for Renal cell carcinoma
- Bevacizumab for Colon cancer
- Sorafenib for Hepatocellular carcinoma

Other targeted therapies are only indicated based on molecular testing of the tumor itself:
- ALK inhibitors and EGFR inhibitors in NSCLC
- BRAF/MEK inhibitors in Melanoma and other cancers
- HER2/neu inhibitors in Breast and Gastric cancers

Tumors are now commonly sent for full molecular testing to identify possible targets that might not be common and could open up treatment options that would not otherwise be available.

Targeted Therapy – Toxicities

On-Target
- Due to interference with a specific physiologic pathway
  - Hypertension, bleeding, clotting, poor wound healing with VEGF inhibitors
  - Acneiform rash with EGFR inhibitors
  - Pulmonary fibrosis with mTOR inhibitors
- **On-target toxicities often correlate with response so amelioration of the toxicity (rather than cessation of drug) is preferred**

Off-Target
- Due to the class of drug rather than the specific signaling pathway involved
  - Diarrhea with TKIs
  - Hepatotoxicity with TKIs
- Immune-reactions
- Toxic metabolites

Targeted Therapy – Toxicities

Important side effects:

Diarrhea – common, especially with tyrosine kinase inhibitors (vs monoclonal antibiodies)

Hepatic toxicity – with TKIs, three drugs have black box warnings (sunitinib, pazopanib, lapatinib)

Rash – Acneiform (erythematous and papulopustular) vs Hand-Foot syndrome

Blood clots, poor wound healing, bleeding – with VEGF inhibitors; take particular care with surgical procedures, typically hold bevacizumab for 6 weeks before and after elective surgery.

High blood pressure – common (20-40%) with VEGF inhibitors, associated with improved clinical outcomes.

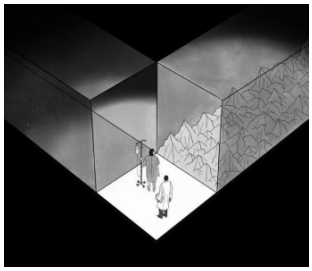
Bowel perforation – seen with VEGF inhibitors, uncommon but not exactly rare. For example, incidence of bowel perforation with bevacizumab was around 1% with mortality of 21%.

A Rapidly Changing Landscape

Immunotherapy and Targeted therapies have dramatically changed the prognosis of several types of solid cancers over the last 5-10 years (metastatic melanoma, NSCLC, RCC to name a few).

In general, they are well-tolerated – even in those patients who have relatively poor performance status and wouldn't necessarily tolerate traditional chemotherapy.

Limitations:
- Tumors mutate and eventually will evade targeted therapies; sometimes after only a few months and sometimes those mutations takes years.
- While there have been remarkable responses to immunotherapy across nearly all types of solid tumors, there is no way to predict who will respond and who will not.
- Immunotherapy typically takes months to show a response so when it is offered as a last resort it can significantly delay enrollment in palliative care and hospice services that have be proven to improve quality of life in the last weeks to months of a cancer patient's life.



The New York Times

The Problem With Miracle Cancer Cures

By Robert Wachter

Active Learning Questions

A 60 year-old woman with Non-small cell lung cancer on nivolumab for the past 3 months presents with intractable diarrhea for the last week. She has tried loperamide with no improvement. Her GI PCR was negative for infection. What is the most likely mechanism for her severe diarrhea?

A. Mucositis from rapid cell turnover

B. Increased gut motility

C. Autoimmune colitis

D. Insufficient exocrine secretions

Active Learning Questions

The correct answer is **Autoimmune colitis**.

The incidence of grade 3-4 colitis in nivolumab is 1-3%. The timing in this case is about right for onset of autoimmune colitis (typically around 5-10 weeks after initiation of treatment). After ruling out infectious etiologies it would be appropriate to initiate prednisone 1-2 mg/kg/day and assess for response.

Active Learning Questions

A 44 year-old man with metastatic colon cancer presents with acute abdominal pain. He is on treatment with FOLFOX (5-FU, oxaliplatin – traditional chemotherapy) and bevacizumab (a VEGF inhibitor). What life-threatening etiology of abdominal pain should be considered immediately based on his treatment regimen?

A. Neutropenic enterocolitis

B. Bowel ischemia from microvascular thromboses

C. Bowel perforation

D. All of the above

Active Learning Questions

The correct answer is **All of the above**.

Bevacizumab is a VEGF inhibitor and increases the risk of clotting (including arterial thromboses) and bowel perforation.

FOLFOX is associated with cytopenias, including neutropenia, and thus carries a risk of neutropenic enterocolitis (also known as typhlitis). Neutropenic enterocolitis is associated with increased mortality rates and is considered a oncologic emergency.

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