Lecture 8: CANCER PHARMACOLOGY PART II: HORMONOTHERAPY & BIOLOGIC AGENTS

Legend

SECTION HEADER | Sub-topics | Important information
Concepts/topics | Drugs | Nursing capsules

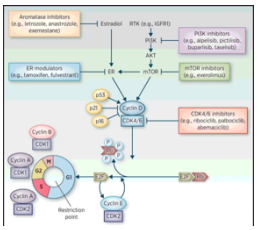
See glossary of abbreviations at the end of the document

HORMONOTHERAPY & BIOLOGIC AGENTS (CH. 103)

Hormonal Agents: Introduction

- Hormonotherapy only works on hormone-dependent tumors
    - Breast CA = estrogen dependent
        - Ex.: Antiestrogens / Aromatase Inhibitors
    - Prostate CA = testosterone dependent
        - Ex.: GnRH modulators / Androgen Antagonists / CYP17 Inhibitors
- Adjuvant therapy to surgery and radiation
    - Post-Surgery → ↓ Recurrence + Kill metastasized cells
    - Pre-Surgery → ↓ Tumor size
- Overall ↓ Recurrence rate & Prolong life

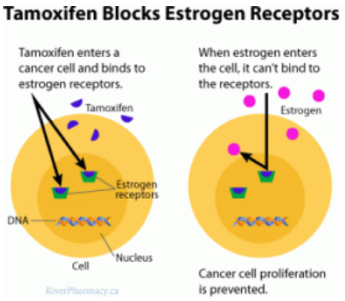
BREAST CANCER AGENTS



Tamoxifen, Anastrazole, Trastuzumab, Ado-Trastuzumab Emtansine, Palbociclib/Ribociclib, Anti Skeletal Events Rx

Estrogen for Breast CA targets a cyclin and this cyclin determines whether or not the cell cycle moves from stage G1 to the S phase. By depriving those cancers from the hormone, halt cell cycle, tumor not growing.

ANTIESTROGENS: Tamoxifen



Breast CA therapy

- CYP2D6 Inhibitors Interactions
- Long half-life → Single daily dose
- Recurrence decline after 5 years = 47%
- Fairly effective if you have an estrogen-dependent tumor

MOA

- Blocks estrogen receptors, estrogen doesn't act anymore.

AE

- Endometrial CA, Thrombosis, TERATOGENIC
- Others related to post-menopausal bcs you are kind of inducing menopause (ex. Hot flashes, irregular menstruation)

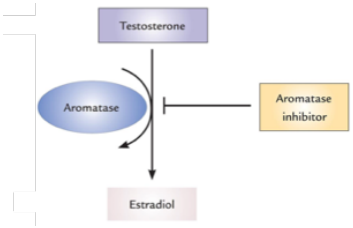
Breast CA prophylaxis

- Advantage: ↓ breast cancer development by 44% in 4 years
- Drawback: ↑ endometrial cancer development
- Appropriate only for high-risk women
    - Risk benefit: which CA are you more likely at risk of?

Drugs for Adjuvant Therapy of Breast Cancer

Generic Name	Brand Name	Route	Mechanism	Indications	Major Adverse Effects
HORMONAL THERAPIES					
Antiestrogens					
Tamoxifen	Soltamox	PO	Blockade of estrogen receptors	ER-positive breast cancer in pre- and postmenopausal women	Increased risk of endometrial cancer and thrombosis Hot flashes, fluid retention, vaginal discharge, nausea, vomiting, and menstrual irregularities
Toremifene	Fareston	PO	Blockade of estrogen receptors	ER-positive breast cancer in postmenopausal women only	

AROMATASE INHIBITORS: Anastrozole



MOA

- Aromatase = enzyme that transforms testosterone into estrogen
- Estrogen stays in form of testosterone
- Ultimately, you deplete tumor from estrogen

AE

- MSK pain, osteoporosis and related fractures

Indications

- Only use if ER-positive (estrogen-positive)
    - Take biopsy, if tumor expresses receptors for estrogen = tumor estrogen positive = ER dependent

<u>Compared to Tamoxifen</u>

- Advantages: Effectiveness > Tamoxifen
- No risk of cardiovascular events or endometrial cancer
- Disadvantage: only use in postmenopausal women only
    - 1st choice Rx for ER-positive breast cancer in postmenopausal women

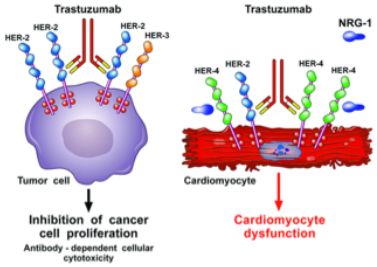
MSK pain + osteoporosis mngmt

- Bone pain in 50% of patients
- Management: Acetaminophen or Vit. D supplements

Drugs for Adjuvant Therapy of Breast Cancer

Generic Name	Brand Name	Route	Mechanism	Indications	Major Adverse Effects
HORMONAL THERAPIES					
Aromatase Inhibitors					
Anastrozole	Arimidex	PO	Inhibition of estrogen synthesis	ER-positive breast cancer in postmenopausal women only	Musculoskeletal pain, osteoporosis and related fractures
Letrozole	Femara	PO			
Exemestane	Aromasin	PO			

Trastuzumab (Anti-HER2)



- HER2 = Growth regulating receptor
    - Take biopsy, if HER2 positive = tumor expresses receptors
- High expression of HER2 associated with aggressive tumors
    - +++ HER2 = ++ aggressive tumor (growth + metastasize)
- Used alone or in combination with Paclitaxel

IF…

- ER+ and HER2+ = can combine both drugs (**Anastrozole + Trastuzumab)**
- ER- and HER2- = can't use these drugs = poor prognosis

Main Toxicities:

- Cardiotoxicity → Ventricular dysfunctions or Congestive Heart Failure
- Potentially fatal Flu-like syndrome → Develops within 12h of initial dose → SO monitor at first very closely

Drugs for Adjuvant Therapy of Breast Cancer

Generic Name	Brand Name	Route	Mechanism	Indications	Major Adverse Effects
OTHER DRUGS FOR BREAST CANCER					
Anti-HER2 Antibodies					
Trastuzumab	Herceptin	IV	Blockade of HER2 receptors	HER2-positive breast cancer in pre- and postmenopausal women	Cardiotoxicity and hypersensitivity reactions

Ado-Trastuzumab Emtansine

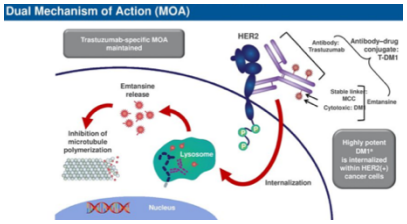
Improvement of trastuzumab

MOA

- Monoclonal Ab with emtansine (cytotoxic molecule)
- Binds to HER2 receptors on the tumor cell
    - Blocks the receptor
    - Releases the toxic molecule, which goes inside the tumor cell to inhibit microtubule polymerization
        - If you give only the toxic cytokine, it would be very harmful to the pt, but if you combine it with this MOA, the cytokine will only target the tumor cells (HER2+).
        - Doesn't always work 100%, can still target healthy cells in the liver (hepatoxicity) or in the brain (neurotoxicity)

Usage

- Used against HER2+ breast cancer resistant to Trastuzumab + Paclitaxel
- Dual action: ↓ Growth + ↑ Cell Death



Higher Toxicity:

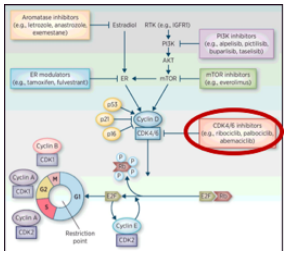
- Same as Trastuzumab
    - +Hepatotoxicity
    - +Neurotoxicity
    - +Teratogen

Drugs for Adjuvant Therapy of Breast Cancer

Generic Name	Brand Name	Route	Mechanism	Indications	Major Adverse Effects
OTHER DRUGS FOR BREAST CANCER					
Anti-HER2 Antibodies					
Ado-trastuzumab	Kadcyla	IV	Blockade of HER2 receptors	HER2-positive breast cancer	Hepatotoxicity, cardiotoxicity, neurotoxicity

CDK4/6 INHIBITORS: Palbociclib & Ribociclib

Drugs ending in -IB = inhibitors



MOA

- Act downstream = block cyclin dependent kinase (If estrogen were to be present, it would activate this molecule). Stop it!

Severe Toxicity:

- Palbociclib: Neutropenia & Infections
    - Preferred
- Ribociclib: Neutropenia & Infections + QT Prolongation & Hepatotoxicity
    - A bit more efficient but more toxic

Indications

- **ALWAYS** combined with the Aromatase Inhibitor Letrozole
    - Secondary pathways not shown in the diagram by which estrogen can still activate the cell cycle driven pathways. You want to block estrogen regardless, you're just adding an extra break to the system

Drugs for Adjuvant Therapy of Breast Cancer

Generic Name	Brand Name	Route	Mechanism	Indications	Major Adverse Effects
Palbociclib	Ibrance	PO	Inhibits cyclin-dependent kinase 4 and 6	ER-positive, HER2-negative breast cancer in pre- and postmenopausal women	Bone marrow suppression, pulmonary embolism, peripheral neuropathy
Ribociclib	Kisqali	PO	Inhibits cyclin-dependent kinase 4 and 6	ER-positive, HER2-negative breast cancer in pre- and postmenopausal women	Severe hypokalemia, neutropenia, hepatotoxicity

Anti Skeletal Events Rx
Cytotoxic Drugs & Adjuvants

Indications

- Given in addition to the other drugs mentioned
- Because estrogen is targeted, these drugs weaken bones as SE. Use these drugs to mitigate the toxicities on the bones.

Pre-Surgery: ↓ Tumor size
Post-Surgery: Kill leftovers & metastasized cells

Common Regimen:

- Doxorubicin + Cyclophosphamide + Paclitaxel
    - Review them from last week

Breast cancer ↑ Skeletal events risk

- Primary Metastasis site = Bones
- Antiestrogens ↑ Bone resorption

Drug therapy

- Zoledronate: ↓ Bone metastasis risk
- Denosumab: ↓ risk of skeletal related events (Review bone lecture)

PROSTATE CANCER AGENTS

Objective: Block Testosterone production from the 3 sites of synthesis:

1) Testes
2) Adrenal Glands
3) Prostate tumors

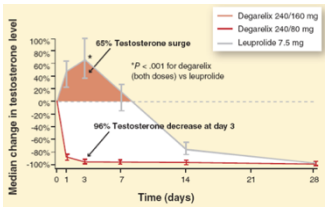
Castration Less effective than drug therapy because castration only removes the testes. If you have a prostate tumor, and normal functioning adrenal glands, castration doesn't decrease testosterone synthesis from those sites.

GNRH AGONISTS: Leuprolide

- ↓ Production at Testes only → Chemical Castration

MOA

- Pathway: GnRH is secreted from the hypothalamus to the anterior pituary glands, releases LH/FSH. LH/FSH travel to the testes to produce testosterone and sperm maturation.
    - This is done in a pulsatile way = short bursts
- Key = negative feedback
    - Large dose for a continuous amount of time = hypothalamus/pituary think that there's too much GnRH = shuts down the access completely
    - That's why not giving FSH/LH agonist bcs they would tell the testes to produce testosterone, whereas GnRH only tells the anterior pituary to produce LH/FSH. Bcs there's too much GnRH, the anterior pituary stops responding to it.
    - Initial flare-up bcs you give a boost of GnRH and it will increase production of testosterone bcs body thinks it's a normal pulsatile release. Once the dosage remains high, that's when the pathway shuts down.
        - Increase at first (flare-up), than decrease (see graph).



Indication

- Advanced prostate carcinoma

Action

- Initial flare-up followed by chemical castration

Toxicity Mngmt

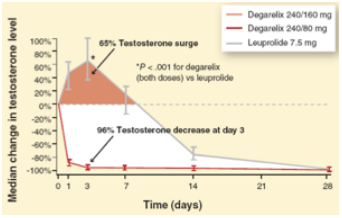
- Androgen Receptor Blocker combination for first weeks = ↓ Flare & Adrenal/Prostate synthesis
- Zolendronate or Denosumab or Vit. D supplements = Reduce skeletal-related events

Drugs for Prostate Cancer

Generic Name	Brand Name	Route	Major Adverse Effects
DRUGS FOR ANDROGEN DEPRIVATION THERAPY			
GnRH Agonists*			
Leuprolide	Lupron ◆, Lupron Depot	IM	Hot flashes, erectile dysfunction, decreased libido, decreased muscle mass, gynecomastia, osteoporosis
	Eligard	SubQ	

GNRH ANTAGONISTS: Degarelix

- Identical to Leuprolide but NO FLARE up
    - It immediately shuts down the access
- Same efficacy & toxicity = preferred!
- But careful with costs + dosage
    - Half-Life = 53 Days!!!

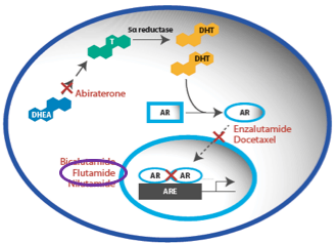


Drugs for Prostate Cancer

Generic Name	Brand Name	Route	Major Adverse Effects
DRUGS FOR ANDROGEN DEPRIVATION THERAPY			
GnRH Antagonist			
Degarelix	Firmagon	SubQ	Same as the GnRH agonists *plus* hepatotoxicity

ANDROGEN RECEPTOR BLOCKER: Flutamide

- Adjuvants to chemical or surgical castration
- ↓ Leuprolide Flares



MOA

- Inhibit adrenal/prostatic Testosterone
  - Blocks the androgen receptor so that even if testosterone is produced, it doesn't bind to the receptor
  - Inhibits adrenal and testosterone everywhere

Indications

- Discontinue after flare risk period
  - No further advantage + Increases toxicity

Main toxicities:

- Teratogen & Hepatotoxicity

Drugs for Prostate Cancer

Generic Name	Brand Name	Route	Major Adverse Effects
DRUGS FOR ANDROGEN DEPRIVATION THERAPY **Androgen Receptor Blockers**			
Flutamide	Generic only	PO	Same as the GnRH agonists *plus* hepatotoxicity
Bicalutamide	Casodex	PO	Same as the GnRH agonists *plus* hepatotoxicity

CYP17 INHIBITOR: Abiraterone

CYP enzymes don't always metabolize stuff like in this case.

MOA

- Blocks the action of testosterone but earlier in the pathway. Blocks the conversion of the precursor (you don't have testosterone, so you don't need to block its action)

Indications

- Metabolized by CYP3A4
- Inhibits **CYP2D6**

Usage

- Combined with Prednisone
  - Long term use of GCC causes immunosuppression = not good for cancers → keep as last resort
- Metastatic castration-resistant prostate cancer
- Increases survival ≈ 4 months

Main toxicities

Very efficient but also very toxic

- Glucocorticoid deficiency
- Hyperaldosteronism → Hypokalemia + HTN
- Hepatotoxicity → LFT every 2 weeks
- Teratogen

Drugs for Prostate Cancer

Generic Name	Brand Name	Route	Major Adverse Effects
DRUGS FOR ANDROGEN DEPRIVATION THERAPY **CYP17 Inhibitor**			
Abiraterone	Zytiga	PO	Same as the GnRH agonists *plus* hepatotoxicity, edema, hypertension, hypokalemia, glucocorticoid insufficiency

IMMUNOTHERAPY: Sipuleucel-T

Trying to harvest the power of the immune system. Fabricating the drug from pt's body.

MOA

- Immune system is not good at killing cancer cells bcs they look like our normal cells. This drug tries to boost the immune system to attack the cancer cells.
    - Collect APC (antigen presenting cells) of the patient
    - Combine the APCs with antigen called PAP-GM CSF (found on prostate cancer), which stimulates the APCs into super antigen cells (which are more specific for prostate cancer)
    - You take those super-APCs and you inject them back into the patient to attack the tumor

Indications

- Moderate Efficacy & Very expensive $$$$
- 100% personalized → Can't use on other patients bcs foreign
- Interest because novel field/approach
- 3 doses 2 weeks apart

Usage

- Minimally symptomatic metastatic castration-resistant prostate cancer

Benefits

- Slight survival improvement over chemotherapy
- No tumor progression alteration
- Unknown beneficial mechanism of survival

Drugs for Prostate Cancer

Generic Name	Brand Name	Route	Major Adverse Effects
OTHER DRUGS FOR PROSTATE CANCER			
Immunotherapy			
Sipuleucel-T	Provenge	IV	Infusion reactions, fatigue, fever

Toxicity Management:

- NSAIDs + Anti-histamine pre-treatment ↓ Infusion reactions

TARGETED ANTICANCER DRUGS

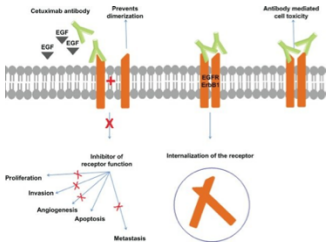
Not for specific type of cancer, specific process

Kinase inhibitors, CD-directed Ab, angiogenesis inhibitors, immunostimulants, glucocorticoids, novel immunotherapy agents.

Targeted Cancer Therapy: Intro

- Looking for a 'Magic Bullet' like antibiotics
    - Trying to find a drug that attacks something that cancer cells have but not human cells
    - Ex. Cell walls are specific to bacteria → abx
- Killing cancer cells with minimal harm to healthy cells
    - More specificity = decrease toxicity
- Success stories: ex.: Gleevec
- Many failures…
- Immunotherapy field born from this approach
- The future 'Cancer cure' will find roots here, chemotherapy is used in the meantime we have cure for cancer.

EGFR TK INHIBITORS: Cetuximab



Indication

- Epithelial growth factor molecule
- EPFR normally expressed by skin, hair, cells
- Overexpressed in many cancers (lung, colon, breast, prostate)

MOA (EGFR inhibitors ↓ growth + ↑ apoptosis)

- EGFR (growth factor) promotes division of the cell
- Cetuximab blocks this receptor and prevents the growth signal to be understood by the cells.
    - Triggers apoptosis: without the signal to grow, the cells become wrinkle and die
- Tirasine kinase (TK) is an enzyme that acts a lot like an on/off switch. EGFR activates TK. By turning on TK, the cell cycle proceeds. By giving cetuximab, you keep the switch off, which prevents the growth.
- Kinases = Phosphorylating proteins
- On-Off Switch analogy

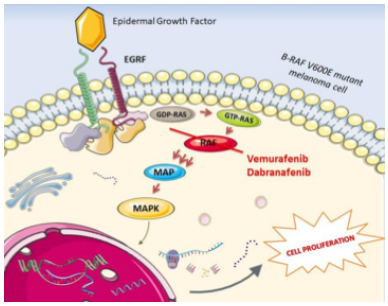
Toxicity management

- IV antihistamine: ↓ Infusion reactions
- Sunblock/Limit sun exposure: ↓ Acne-like rash
    - photosensitivity
- Considered teratogenic but still unproven

Kinase Inhibitors

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
EGFR TYROSINE KINASE INHIBITORS				
Cetuximab [Erbitux]	Inhibits EGFR	Antibody	EGFR-positive colorectal cancer and head and neck cancer	Rash, infusion reactions, interstitial lung disease

BRAF V600E INHIBITORS: Vemurafenib



MOA

- Inhibits a specific subtype of BRAF receptors
    - V600E = hyperactive version found on cancer cells
    - Difference between CA cells and healthy cells
        - Healthy cells also have BRAF molecules, but version V600E is mostly found on CA cells

Indication

- BRAF V600E mutant cells reproduce excessively
- Must confirm genetic profile pretreatment (biopsy)

Toxicity management

- Cutaneous squamous cell carcinoma → 24% patients!!
- **Hepatotoxicity & QT Prolongation** → Monitor
    - Worst toxicity so make sure good genetic profile
- Unpredictable interactions: P-Glycoprotein & CYP3A4

Kinase Inhibitors

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
BRAF V600E KINASE INHIBITORS				
Vemurafenib [Zelboraf]	Inhibits BRAF V600E kinase	Small molecule	BRAF V600E-positive melanoma	Cutaneous squamous cell carcinoma, arthralgia, QT prolongation, severe skin reactions, photosensitivity

BCR-ABL TK INHIBITORS: Imatinib

-IB = inhibitor

Usage

- CML Gold Standard!
    - BCR-ABL TK inhibitors are very specific to chromic myologic leukemia (CML)
- Only happens to patients that have a switch in their chromosome (9 & 22).
    - If you're born with this, you're born with a **fusion protein (BCR-ABL)**
        - ABL = tyrosine kinase = on/off switch
        - BCR = protein that keeps cell cycle open
    - When it's fused, it stays in ON position = cell cycle continues forever and forever

MOA

- Design a molecule that fuses perfectly and **irreversibly** in the ATP site preventing further ATP from coming = shuts off tyrosine kinase =cancer cell stops progressing
    - ATP is used to power the cell cycle

Resistance

- Imatinib-resistant CML subclones emergence = Switch to other BCR-ABL TK inhibitors

Most serious toxicity

A lot of toxicity, but efficacy so great that it's ok (risk benefit)

- Fluid retention / Hepatotoxicity / Neutropenia / Teratogen
- CYP3A4 metabolism & inhibitor of 2D6 & 2C9 → Drug Interactions

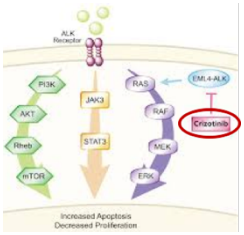
Kinase Inhibitors

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
BCR-ABL TYROSINE KINASE INHIBITORS				
Imatinib [Gleevec]	Inhibits BCR-ABL tyrosine kinase	Small molecule	Chronic myeloid leukemia, GI stromal tumors	Nausea, diarrhea, myalgia, edema, liver injury

ALK INHIBITORS: Crizotinib

Usage

- For a specific cancer
    - Type of fusion protein found in a subset of a subset of lung cancer
- Very effective if tumor is EML4-ALK-positive
    - A lot of smokers are EML4-ALK negative, whereas non-smokers are usually EML4-ALK positive
- Overactive variant of ALK kinase found in normal cells



Toxicity management

- Pneumotitis → Rare but potentially fatal
- Hepatotoxicity & QT Prolongation → Monitor
- Substrate & Inhibitor of CYP3A4 → Interactions

Kinase Inhibitors

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
ANAPLASTIC LYMPHOMA KINASE (ALK) INHIBITORS				
Crizotinib [Xalkori]	Inhibits ALK	Small molecule	ALK-positive non-small cell lung cancer	Pneumonitis, hepatotoxicity, QT prolongation

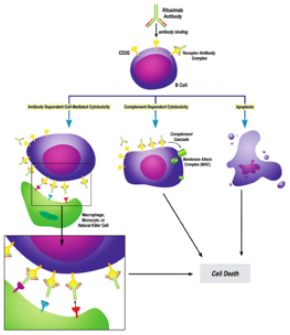
CD-DIRECTED ANTIBODIES: Rituximab

Rituximab also used in rheumatoid (see bone lecture)

Usage

- Effective for B-cell related cancer. Potentially curative
    - Might kill all your B-cells (susceptible to infection), but when your body creates some more, the likelihood that new b-cells are healthy is very high

MOA



- Anti CD antibody (CD is located on B-cells)
- Triggers immune attack vs healthy & malignant B-Cells
    - Blocking the activation of B-cell inhibits proliferation of WBCs
- CD20 is located on some B-cells. Blocking B-cells decreases proliferation of WBC.

Significant Toxicity!

- Tumor Lysis Syndrome = Acute renal failure + Hyperkalemia

Toxicity management

- Infusion reactions → Slowing or Discontinuation
- Tumor Lysis Syndrome → Dialysis & Electrolyte correction
    - If you kill a lot of WBCs at once, you might need dialysis
- PML & Hep. B reactivation → Monitor immune functions
    - If you have a dormant infection, bcs your immune system is weaken, risk that those infections reactivate.

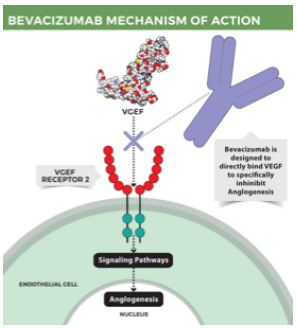
Other Targeted Drugs

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
CD-DIRECTED ANTIBODIES				
Rituximab [Rituxan]	Binds CD20 antigen, causing apoptosis and immune attack	Antibody	B-cell chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma	Severe infusion reactions, severe mucocutaneous reactions, tumor lysis syndrome, PML

ANGIOGENESIS INHIBITORS: Bevacizumab

MOA

- Blocks actions of VGEF (vascular growth epithelial factor).
    - When it binds to receptors on blood vessels, it signals the vessels to grow (angiogenesis)
- Prevent the growth of blood vessels to limit the growth of the tumor.
- Only delay tumor progression / No cell killing
    - Add other drugs to kill the cells
- Benefits: Overall life prolongation
- Most Common usage: Colon cancer Tx with IV 5-FU



Life-threatening toxicity management

- GI Perforation → 2% of patients / monitor abdominal pain
- Hemorrhage → Common in NSCLC patients
- Thromboembolsim → ↑ risk when combined with 5-FU
- Impaired healing → Cannot use for 4 weeks post-surgery
- Severe HTN months post-Tx → Monitor BP
- Nephrotic Syndrome → Monitor Proteinuria

Other Targeted Drugs

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
ANGIOGENESIS INHIBITORS				
Bevacizumab [Avastin]	Binds VEGF and thereby inhibits angiogenesis	Antibody	Colorectal cancer, non–small cell lung cancer, glioblastoma, renal cell carcinoma, cervical cancer, epithelial cancers	Hypertension, GI perforation, impaired wound healing, hemorrhage, thromboembolism, nephrotic syndrome

Immunostimulants & Glucocorticoids
2 extremes = behaviours are similar but different mechanisms

Immunostimulants
- Enhanced host immune response
    - Using interferons = immune promoting cytokines = boost immune response to cancer
- Direct Antiproliferative Effects

Most common Toxicity:
- Flu-like Syndrome / Hepatotoxicity / Nephrotoxicity

Glucocorticoids
- Effective against. lymphoid CA (CLL, Multiple myelomas, etc.)
- Used specifically for blood CA bcs they decrease the population of immune cells. DON'T use for other types of CA

Most used:
- Prednisone
- Dexamethasone

Other benefits:
- Nausea-Vomiting management
- Pain management
- ↑ Appetite & Weight gain

Immunostimulants

Generic Name	Brand Name	Route	Indications
Interferon alfa-2b	Intron A	SubQ IM, IV	Melanoma, hairy cell leukemia, chronic myelogenous leukemia, follicular lymphoma, AIDS-related Kaposi's sarcoma
Peginterferon alfa-2b	Sylatron	SubQ	Melanoma
Aldesleukin (interleukin-2)	Proleukin	IV	Metastatic renal cell cancer, metastatic melanoma
BCG vaccine	TICE BCG	Intravesical	*In situ* bladder cancer

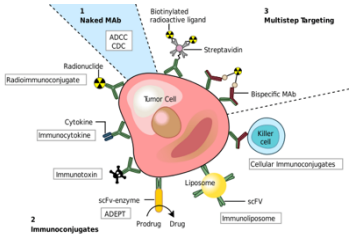
Toxicity
- Toxicity manageable if short-term use

HOPE FOR THE FUTURE? YES
- Immunotherapy & Targeted Antineoplastic Agents already available
- New Developments Underway

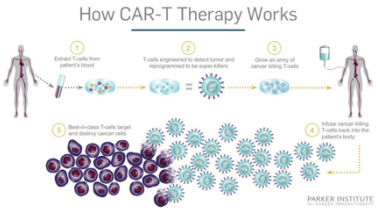
https://www.bestmedicaldegrees.com/experimental-cancer-treatments/

SPECIAL TOPIC: NOVEL IMMUNOTHERAPY AGENTS

1) Offensive immunotherapy and vaccines
- Improving monoclonal Ab to make them more toxic to cancers
- MAB+ radioactive : Combining monoclonal Ab and radioactive molecules
    - Monoclonal AB bring the radioactive molecules specifically to the cancer cells
    - Inspired by thyroid cancer with radioactive iodine (very specific + low toxicity)

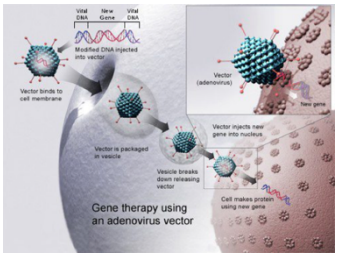


2) CAR = Chimeric Antigen Receptor



- Boost immune cells outside the body
    - Take a biopsy of the tumor
    - Take t-cells from the patient
    - In-lab = gene editing to make them express different receptors for antigens expressed on the cancer
    - Reinject the new t-cells in the patient
    - Create an army of cancer killing T-cells

3) Gene therapy



- Cancer is a genetic disease = dysfunction in the genetic material
    - Key: It used to be a healthy cell
- Gene therapy: change the gene back to the version before it was cancerous. The make the cells behave the way they did before → easier said than done

CANCER PAIN MANAGEMENT

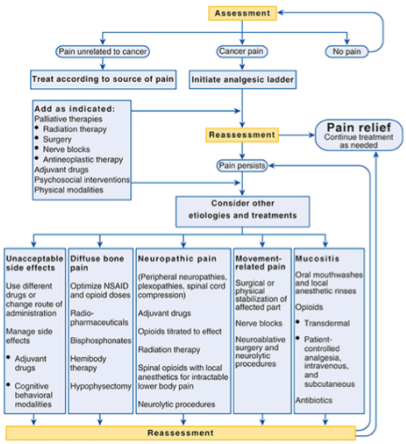
Cancer Pain Management: Intro

- Nociceptive Pain → Direct pressure / Metastatic invasions
    - Management: Opioids Analgesics
- Neuropathic Pain → Nerve infiltration
    - Cancer cells infiltrate nerves to use them as travel roads
    - Management: Anticonvulsants & Antidepressants
- Treatments themselves can cause pain!
    - Radiation → Peripheral neuropathies
    - Chemotherapy → Painful mucositis
    - Surgery → Phamtom limb pain
- Pain incidence & intensity is often proportional to stage/progression of cancer
    - The larger the tumor, the more pain
- A lot of barriers to cancer pain management. Our relationship with pain is complicated. Some say to tough it out and others can't support pain.
    - Barriers include: poor assessments, fear of addiction, concern about not being a good pt.

Barriers to Cancer Pain Management	
Barriers Related to Healthcare Professionals	
Inadequate knowledge of pain management	Reluctance to take pain medication
Poor assessment of pain	Fear of addiction or being thought of as an addict
Concerns stemming from regulations on controlled substances	Worries about unmanageable side effects
Fear of patient addiction	Concern about becoming tolerant to pain medications
Concern about side effects of analgesics	Inability to pay for treatment
Concern about tolerance to analgesics	Barriers Related to the Healthcare System
Barriers Related to Patients	Low priority given to cancer pain management
Reluctance to report pain	Inadequate reimbursement: The most appropriate treatment may not be reimbursed
Fear of distracting physicians from treating the cancer	Restrictive regulation of controlled substances
Fear that pain means the cancer is worse	Treatment is unavailable or access is limited
Concern about not being a "good" patient	

Management Strategies

- Flexible treatment plan
- Adapt to changing needs of the patients
- Seek active involvement of patient and relatives
    - Key point: be flexible in your tx plan bcs pain may fluctuate



<u>Continuous cycles</u>: assessment → intervention → reassessment

Comprehensive initial assessment

Patient Self-Report → Cornerstone of pain assessment

- Personal Pain Description → Crucial subjective component
- Ask about PQRSTIUA: Onset / Location / Quality / Intensity / Modulating Factors / etc…

Physical + Neurological Examinations → HPA stuff

- Look for inflammation / neuron involvement / etc…

Diagnostic Tests → To identify underlying cause of pain

- Ex.: Imaging / Tumor markers / Neurophysiologic tests
- Anticipate pain

Psychosocial Assessment → For both the patient & the family

- Pain history
- Personal preference in terms of management
- Concerns about opioids
- Potential involvement of family as care providers

Pain Intensity Scales

Useful for:

1) Pain intensity assessment
1) Setting Pain Relief Goals
2) Evaluating Treatment Efficacy

Ongoing Evaluation & Barriers to Assessment

<u>Ongoing Evalauation</u>

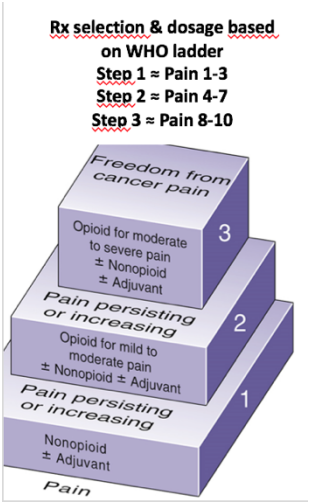
- Reassess pain intensity everytime new analgesic added
- Teach patients & caregivers to document & evaluate pain
- New pain usually = new cause → Rigorous diagnostic work-up

<u>Barriers to Assessment</u>

- Inaccuracy of self-report → Interview patients thoroughly
    - Underreporting → 'Tough it out' mentality / fear of opioids / etc..
    - Overreporting → Fear of insufficient dosage
- Language & Cultural Barriers
- Facial & Behavioral expression = Poor status indicators → use as last resort

Drug Therapy

- Successful pain relief in 90% of patients with 3 drug groups
- Non-Opioids → NSAIDs / Acetaminophen
- Opioids → Fentanyl / Morphine
- Adjuvant → Amitriptyline (TCA) / Carbamazepine (Anticonvulsant)



Drugs That Are Not Recommended for Treating Cancer Pain

Drug Class	Drug	Why the Drug Is Not Recommended
OPIOIDS		
Pure agonists	Meperidine	A toxic metabolite accumulates with prolonged use
	Codeine	Maximal pain relief is limited owing to dose-limiting side effects
Agonist-antagonists	Buprenorphine Butorphanol Nalbuphine Pentazocine	Ceiling to analgesic effects; can precipitate withdrawal in opioid-dependent patients; cause psychotomimetic reactions
Opioid Antagonists	Naloxone Naltrexone	Can precipitate withdrawal in opioid-dependent patients; limit use to the reversal of life-threatening respiratory depression caused by opioid overdose
Benzodiazepines	Diazepam Lorazepam others	Sedation from benzodiazepines limits opioid dosage; no demonstrated analgesic action
Barbiturates	Secobarbital others	Sedation from barbiturates limits opioid dosage; no demonstrated analgesic action
Miscellaneous	Marijuana	Side effects (dysphoria, drowsiness, hypotension, bradycardia) preclude routine use as an analgesic

Nonopioid Analgesics

- Benefits = Analgesia + Anti-Inflammation + Antipyretic
    - Opioid + NSAIDs = Synergistic Interaction
        - Start with nonopioid analgesics until no longer efficient → switch to opioid

Primary toxicity:

- Gastric Ulcers & Acute renal failure
- ↑ risk of thrombotic events (except Aspirin!!)

Disadvantage vs. Opioids

- Ceiling pain relief power → Do not exceed recommended dosage
    - Should not increase the dose over the limit bcs toxicity outweighs the benefits.

Advantage vs. Opioids

- No tolerance & physical/psychological dependence

Anticancer Rx → Thrombocytopenia → ↑ Bleeding

- Avoid all NSAIDs except Acetaminophen or COX-2 selective or Magnesium salicylate
    - To minimize risk of bleeding

Opioid Analgesics: Drug Selection

Pain intensity-dependent

- Moderate → Weaker opioid (ex.: oxycodone)
- Intense → Strong opioid (ex.: morphine)

Opioid Rotation → ↓ Adverse effects
- Good technique to decrease AE
- Abrupt stop and switch (no tapering)

Opioids to use with caution or avoid
- Codeine → Dose-limiting adverse effects / Poor analgesia:toxicity ratio
- Methadone → Long half-life makes dosage titration difficult
- Meperidine → Severe CNS adverse effects with long-term use
- Agonist-antagonists opioids (ex.: buprenorphine) → Poor analgesia:toxicity ratio

Dosage
- Individualised / Increase until pain relief or until toxicity is unbearable
    - Individualised bcs not same amount of pain + response to the drug is different
- Dosing schedule depends on pain pattern
    - Best = Fixed schedule around-the-clock → Avoids subtherapeutic concentrations
- Use equianalgesics tables when switching between opioids & routes

Opioid Analgesics: Tolerance and addiction

Tolerance = ↓ Efficacy for a same dose
- During cancer pain management:
    - Opioid analgesia ↓ could mean Tolerance developing OR Pain intensity ↑
        - Need frequent assessments to make sure you have the correct interpretation
    - Cross-tolerance between opioids
        - You can switch one to the next
    - No tolerance to constipation & miosis

Abstinence syndrome = Rebound effects if abrupt withdrawal
- Worst with short T1/2 opioids
- Mitigation: Withdraw slowly

Addiction = Rare during pain management
- Inappropriate fear = Undertreatment problem!
- Need to educate Patient, HCP & Family about low risk of addiction

Opioid Analgesics: Routes of Administration

Ladder of preference → based on convenience, cost & invasiveness

1) PO
    - Favor long-acting formulations
2) Rectal or Transdermal
    - Rectal → Avoid if diarrhea or anal lesions
    - Transdermal → Fentanyl patches = Only option
3) IV or Subcut = usually last resort
    - Quick onset & dosage adjustments / Possibility of Patient-controlled analgesia device
    - Drawbacks: Uncomfortable + inconvenient + expensive
4) Intraspinal → Epidural or subaracnoid space
    - Only when other routes have failed
    - ↑ risk of respiratory depression & infections bcs u put directly in nervous system

Avoid IM → Painful & unpredictable/inconsistent absorption

Opioid Analgesics: Pain & Adverse Effects Management

Breakthrough Pain	Pain sensation despite sufficient opioid concentration **Management:** Short duration strong opioid rescue dose
Respiratory Depression	Risk greatest upon initiation → Tolerance develops with time Avoid other CNS depressants **Monitoring:** Sedation usually preceded respiratory depression **Management:** Naloxone titration
Constipation	Avoid anticholinergic Rx (ex.: TCAs) → Worsen constipation **Mitigation:** ↑ Fluid & Fiber intake **Management:** Stool softener & laxatives
Sedation	Risk greatest upon initiation → Tolerance develops with time **Mitigation:** Smaller doses more frequently **Management:** CNS stimulants (ex.: caffeine, ADHD medications)

- Despite having a high concentration of opioid, you may have peaks of pain → give rescue dose for a short period of time
- Sedation tends to precede resp depression = warning sign
- Naloxone = antidote
- Always constipation → give regular laxatives/stool softener

Adjuvant Analgesics

- ALWAYS combine with analgesics
    - These drugs are very specific, so they won't help for other kind of pain
- Inform patient of their use in cancer pain management vs. Original purpose
- Tricyclic antidepressants, other antidepressants, antiseizure drugs → reduce neuropathic pain
- CNS stimulants enhance analgesia and reduce sedation from opioid
- Glucocorticoids reduce pain associated with brain metastases and epidural spinal cord compression

3 main benefits

1) ↑ Opioid analgesia
2) Other Sx management
3) Opioid toxicity management

Nondrug Invasive Therapies

When all other options have failed!!

Neurolytic Nerve Block → Destruction of nociceptive neurons

- Allows ↓ opioid dosage → ↓ Toxicity
- Possible Complications: Incontinence / Paralysis / Hypotension

Neurosurgery (less than 10% of cancer patients)

- Implant releasing opioids OR stimulating endogenous opioid release (when implant put in the brain)
- Possible complications: New pain & neurologic deficits (when you put the implant in the brain)

Partial Tumor Surgery

- Only temporary relief → Remaining cells grow back

Palliative Radiation Therapy → Tumor regression

    - Done pre surgery → easier for surgeon to remove the tumor
- Dose-limiting toxicity → Skin & GI lesions
- Late-onset fibrosis is severe but limited concern due to impeding death of patient

Other Interventions
Limited efficacy/adjuvant to drug therapy

Psychosocial Interventions
- Relaxation & Imagery : Meditation / Rhythmic breathing / Visualisation
- Cognitive Distractions: Turn attention away from pain
- Peer Support Groups: Emotional support & Practical advice

Physical interventions
- Heat: Vasodilation + ↑ muscle elasticity
- Cold: ↓ Inflammation & muscle spasms
- Massage: Distraction + releaxation
- Exercise: Do I need to sell it?
- Acupuncture & Transcutaneous Electrical Nerve Stimulation (TENS)
    - Activation of modulating pain pathways
    - Unclear/conflicting scientific evidence

Special Populations: Elderly Patients
Main Issues: ↑ Rx Sensitivity leads to ↑ toxicity AND/OR undertreatment

↑ Drug Sensitivity
- Decline of Hepatic Metabolism & Renal Functions

Pain Undertreatment
- Cognitive Impairments → Difficult/ Inaccurate Pain Assessment
- Misconceptions → Elderly are less sensitive to pain & tolerate pain better

↑ Adverse Effects Risks
- Monitor more closely & Avoid Rx with longer half-life
- ↑ risk of NSAIDs toxicity → Ulcers & Renal toxicity
    - Mitigate Ulcers vis PPIs or Misoprostol / Nothing to do for kidneys □ → Monitor
- Polypharmacy → ↑ risk of Drug Interactions

Special Populations: Pediatric Patients
Main Issues: Pain mostly from chemotherapy & Difficult assessment

Assessment
- Must adapt to children's age & developmental stage
- Verbal Children: Frequent underreporting due to fear of needles & protecting parents
- Nonverbal Children: Behavioral assessment (ex.: crying, facial expressions)

Treatment
- Same as adult → WHO ladder / Prefer PO Admin / Etc.
- Neonate = ↑ Drug Sensitivity → Intensive respiratory function monitoring

Special Populations: Opioid Users

Main issues: Provide pain relief without promoting drug abuse

Treatment

- Provided by HCP trained in substance abuse management
- Pre-existing tolerance → Higher initial dosage
- Avoid opioid agonist-antagonists → Trigger withdrawal syndrome

Pain Undertreatment

- Relief-seeking behavior vs. Drug-seeking behavior confusion
- 'Innocent until proven guilty' → Treat unless 100% certain of abuse behavior
- PCA can avoid conflicts between patient & HCP → Adjust time limit to ↓ abuse risks

Patient Education

General Issues

- Nature & Causes of Pain
- Importance of pain assessment & honest self-report
- Establish therapeutic plan & communication line between HCP & patient

Drug Therapy

- Provide complete information on each drug & rationale behind the decision
- Explain difference between PRN & around-the-clock dosing schedules
- Teach patients about breakthrough pain management
- Reassure patients about tolerance/addiction/toxicity misconceptions

Nondrug Therapy

- Psychosocial intervention teaching & explanations

ABBREVIATIONS

Abx: antibiotics
CA: cancer
ER: estrogen
HCP: health care professionals
HPA: health and physical assessments
LFT : liver function test
MOA: mechanism of action
PA: pathway
VS: versus
WBC: white blood cells