Evidence-Based Approach to Management of Common Chemotherapy Toxicities

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Presenter Disclosure

Presenter: Nureen Sumar

Relationships with financial sponsors:

- Any direct financial relationships, including receipt of honoraria: Not Applicable
- Membership on advisory boards or speakers' bureaus: Aga Khan University Cancer Center Scientific Review Committee (CCSRC)
- Patents for drugs or devices: None
- Other: Employee of Aga Khan University (Aga Khan University Hospital, Nairobi) and University of Calgary (Alberta Health Services). Sub-Investigator several clinical trials

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Disclosure of Financial Support

No external financial support

This program has received in-kind support from CFPC in the form of logistical support

Potential for conflict(s) of interest:
Not Applicable

Serve as: - Member of the Cancer care Member Interest Group (MIG) committee

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Presenter Disclosure

Presenter: Genevieve Chaput

Relationships with financial sponsors:

- No relationships to disclose

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Not Applicable

Serve as: - Chair of the Cancer care Member Interest Group (MIG)
- Member, CFPC MIG Council Committee

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Learning Objectives

At the conclusion of this activity, participants will be able to:

Identity common chemotherapy adverse toxicities

Assess the severity of common toxicities using CTCAE grading scale

Employ an evidence-based approach to the management of common chemotherapy toxicities.

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CTCAE:
Common Terminology Criteria for Adverse Events

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CTCAE Symptom	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
GENERAL	**Asymptomatic or mild symptoms;** clinical or diagnostic observations only; intervention not indicated.	**Moderate;** minimal, local or Non-invasive intervention indicated; **limiting age-appropriate instrumental ADLs.**	**Severe or medically significant but not immediately life-threatening;** hospitalization or prolongation of hospitalization indicated; **disabling; limiting self-care ADL**	**Life-threatening consequences;** urgent intervention indicated.	**Death related to AE.**

Common Terminology Criteria for Adverse Events (CTCAE)
Version 5.0
Published: November 27, 2017
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Table of Contents

- Presented by System Organ Class (SOC)
- i.e., identified by anatomical or physiologic system, etiology, purpose
- Subsequently described by severity or grade

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

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CTCAE grading Examples - Blood

Grading system
System Organ Class
Sub-category of anatomic / physiologic organ class
Definition / Navigation notes

Blood and lymphatic system disorders

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. **Navigational Note:** -					

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

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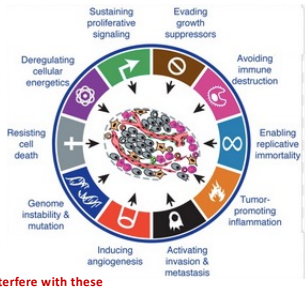
Hallmarks of Cancer Growth

Cancer cells develop mechanisms to:

- Evade growth suppressors
- Avoid death
- Proliferate rapidly and uninhibited
- Invade surrounding areas
- Spread to distant sites
- adapt / mutate to propagate the above



Thus, chemotherapy aims to interfere with these growth mechanisms

Adapted with permission from Dr. Nimia Alimohamed, Medical Oncologist (TBCC)

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Systemic Cancer Therapies fall into broad categories:

- Chemotherapy (cytotoxic)
  - Alkylators & Platinums
  - Antimetabolites
  - Antimicrotubule
  - Toperisomerase I & II Inhibitors
- Targeted Agents: "Nibs and Mabs"
  - TKIs
  - Monoclonal Abs
- Hormones
  - Antiestrogens
  - Androgen Deprivation Rx
- Immunologic agents
  - Vaccines
  - Novel, CAR-T Cell
- Supportive Medications

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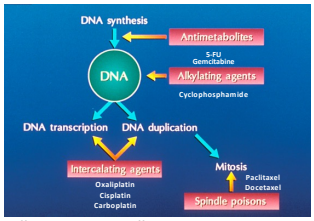
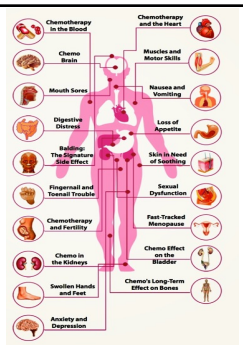
Cytotoxic Agents



Different agents target different parts of the cell cycle



Adverse toxicities can impact almost every organ system

Borrowed from Dr. Anna Wilkinson, GPO Ottawa Hospital Cancer Center

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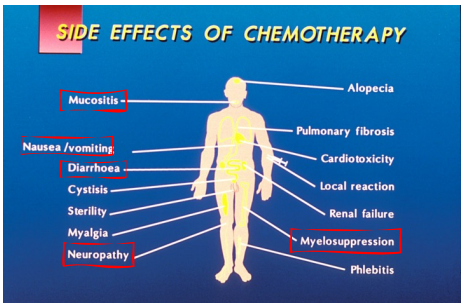

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Case 1: Ida, Breast Cancer

- Ida is a 35-year-old woman who presented to your office because she had found a lump in her right breast.
- Imaging and core biopsy confirmed an ER/PR negative, Her2/Neu neg invasive ductal carcinoma
- Lumpectomy and sentinel lymph node biopsy. Surgical pathology revealed a Stage IIa right breast invasive ductal carcinoma with a 3cm grade 3 primary tumour, IHC confirming triple negative, with clear surgical margins and 1/6 sentinel nodes involvement.
- Staging investigations including a CT of the chest, abdomen and pelvis were negative for metastatic disease.

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Case 1: Ida, Chemotherapy Regimen

- Due to having high grade disease and being a triple negative breast cancer (hormone therapy is not an option), Ida is told by her oncologist that she has a 43% chance of recurrence in the next 10 years which could be reduced to 19% by adjuvant chemotherapy.
- She agrees to the recommended adjuvant chemotherapy protocol with **FEC-D Fluorauracil, Epirubicin & Cyclophosphamide x 3 cycles + 3 cycles of Docetaxel.**
- Ida's genetic testing revealed a pathogenic BRCA 1 mutation and thus she opted for complete mastectomy of the affected breast with contralateral prophylactic mastectomy +/- immediate reconstruction following completion of her chemotherapy.
- Ida is otherwise healthy with prior medical history and no allergies. She and her husband John, have no children as her husband is infertile.

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EMETOGENIC POTENTIAL OF CHEMOTHERAPY

- Combinations are more emetogenic than single drugs
- Often dose-dependent: As dose increases, emetogenicity increases
- Infusions are less emetogenic than bolus
- With repeated cycles, antiemetics are less successful

Emetogenicity: percentage of patients who will experience acute emesis if not treated

1) High = greater than 90%
2) Moderate = 30% to 90%
3) Low= 10% to less than 30%
4) Minimal (rare) = less than 10%

FEC-D is a highly emetogenic protocol

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Case 1: Ida – Nausea and Vomiting

Ida took all recommended medications as prescribed before and after her treatment

Despite this, she found herself with no appetite and unable to keep foods or liquids down.

She retches all day and vomits after every solid meal. At current, she sips on 1-2 high caloric, high protein meal replacement shakes per day.

She comments that even when she does eat, her food has an unpleasant metallic taste.

Questions

1) How would you grade Ida's nausea symptoms?
2) What are some strategies you would offer to help manage her symptoms?

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NCI CTCAE v5.0 nausea and vomiting

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feedings, TPN, or hospitalization indicated		
Vomiting	Intervention not indicated	Outpatient intravenous hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death

Nausea is characterized by a queasy sensation and/or the urge to vomit. Vomiting is characterized by the reflexive act of ejecting the contents of the stomach through the mouth.

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TPN: total parenteral nutrition.

Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute, Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed March 27, 2018).

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Case 1: Ida – Nausea and Vomiting

FEC given IV every 3 weeks x 3 cycles
F-5U, Epirubicin, Cyclophosphamide

- Nausea / Vomiting PREVENTION:
- Dexamethasone 8-12mg PO Daily for 1-3 days prior to chemotherapy
- PLUS NK1 RA (i.e. Aprepitant 125mg PO on D1, then 80mg PO on D2-3)
- AND 5-HT3 RA (i.e. ondansetron 8mg PO BID x 2-5 days)

Ida remains nauseated with ongoing emesis despite the above preventive antiemetic protocol.

Questions

1.What else can be used to manage her symptoms?
2.What else is on your differential diagnosis?

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APPROACH TO TREATMENT

- The goal is **NO** nausea or vomiting.
- Easier to **PREVENT** nausea and vomiting than to treat it.
- **ANTICIPATORY** nausea and vomiting is a conditioned response and happens after a negative past experience.
- Optimize antiemetic therapy for **EVERY** cycle of chemotherapy.

Why is this important?

- 30% refuse further treatment
- 20% self-induced delays
- Causes suffering

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Possible additional ongoing antiemetics to use if patient is:

vomiting	nauseated*
haloperidol 0.5 to 2 mg PO/IV every 4 to 6 hours[18]	olanzapine 2.5 to 10 mg PO daily (if not previously given and if not using metoclopramide, prochlorperazine or haloperidol)[17,18,30,31]
~~nabilone 1 to 2 mg PO bid~~[18]	dimenhyDRINATE 100 mg PO every 12 hours alternating with prochlorperazine 10 mg PO every 12 hours (for a q6h regimen)[3]
	prochlorperazine 25 mg PR every 12 hours or 10 mg PO/IV every 6 hours[18]
	metoclopramide 10 to 20 mg PO every 4 to 6 hours[18]
	~~nabilone 1 to 2 mg PO bid~~[18]

*5-HT$_3$ antagonist plus dexamethasone if above choices are ineffective[3]

Dronabinol capsules 5–10 mg, or dronabinol PO solution 2.1–4.2 mg/m2, PO 3–4 times daily

Consider using an H2 blocker or proton pump inhibitor (PPI) to prevent dyspepsia, which can mimic nausea.

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BREAKTHROUGH TREATMENT FOR ANTICANCER THERAPY-INDUCED NAUSEA/VOMITING[h,hh]

The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen.

Any nausea/ vomiting

- Atypical antipsychotic[i]:
  - Olanzapine 5–10 mg PO daily (preferred, category 1)[cc]
- Benzodiazepine[j]:
  - Lorazepam 0.5–1 mg[j] PO/sublingual (SL)/IV every 6 h
- Cannabinoid[i]:
  - Dronabinol capsules 5–10 mg, or dronabinol PO solution 2.1–4.2 mg/m², PO 3–4 times daily[dd]
- Other:
  - Haloperidol 0.5–2 mg PO/IV every 4–6 h[i]
  - Metoclopramide 10–20 mg PO/IV every 4–6 h[i]
  - Scopolamine 1.5 mg transdermal patch 1 patch every 72 h
- Phenothiazine[i]:
  - Prochlorperazine 25 mg suppository (supp) PR every 12 h or 10 mg PO/IV every 6 h[i]
  - Promethazine 25 mg supp PR every 6 h or 12.5–25 mg PO every 4–6 h[h]
- 5-HT3 RA[i]:
  - Dolasetron 100 mg PO daily
  - Granisetron 1–2 mg PO daily or 1 mg PO two times per day (BID) or 0.01 mg/kg (maximum 1 mg) IV daily or 3.1 mg/24-h transdermal patch every 7 days
  - Ondansetron 8 mg PO/IV every 8–12 h (16–24 mg total daily dose)
- Corticosteroid[i]:
  - Dexamethasone 12 mg PO/IV daily

RESPONSE

Nausea and vomiting controlled → Continue breakthrough medications, on a schedule, not PRN

Nausea and/ or vomiting uncontrolled → Re-evaluate and consider dose adjustments and/ or sequentially add one agent from a different drug class

SUBSEQUENT CYCLES

Consider changing antiemetic therapy to higher level primary treatment for next cycle

Antiemesis

Consider using an H2 blocker or proton pump inhibitor (PPI) to prevent dyspepsia, which can mimic nausea.

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TREATMENT FAILURES
If a patient experiences nausea or vomiting despite optimal prophylactic therapy:

- Rule out or treat other causes of nausea and vomiting:
  - Intestinal obstruction
  - Gastroparesis
  - Gastritis
  - Medications (pain meds (opioids), bronchodilators)
  - Consider brain metastases
  - Vestibular dysfunction
  - electrolyte imbalance
  - Uremia
  - Infection.

→ Give additional antiemetic agent from a **different class** if vomiting/retching while on antiemetics.
→ Give 5-HT3 Receptor Antagonist +/- dexamethasone if vomiting/retching after antiemetics are finished.
→ Use **rectal, parenteral or sublingual route** of administration.
→ Use around-the-clock dosing rather than PRN until vomiting stops.
→ Monitor and correct dehydration and electrolytes as required. Consider admission to hospital.

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Other Considerations

Manage Anticipatory Nausea:
- Lorazepam pre-treatment
- Behavioral strategies

Lifestyle measures may help to alleviate nausea/vomiting, such as eating small frequent meals, choosing healthful foods, controlling the amount of food consumed, and eating food at room temperature. A dietary consult may also be useful.

NCI's "Eating Hints: Before, During, and After Cancer Treatment" (https://www.cancer.gov/publications/patient-education/ eating-hints).

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Case 1: Ida, CIPN, Mucositis, Febrile neutropenia

Ida does well with the remainder of her FEC combination chemotherapy.

On initiation of Docetaxel, she starts to experience significant and prolonged periods of low neutrophils (ANC 0.6-0.8).

This has resulted in some treatment delays (despite the use of GCSF).

She is exhausted and wants to quit chemotherapy: "My hands hurt, I can't find my balance, nausea is better, but now it is painful to eat."

You see her in your office today. Her vitals are stable ***except*** from a temperature of 38.1 degrees Celsius. You proceed with a physical exam.

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Case 1: Ida, Physical Exam

Vitals: Normal limits except temperature **38.1 degrees Celsius**
HEENT: conjunctival pallor, no thrush, **erythematous / weeping aphthous oral lesions**
CV: B1B2 N
RESP: Clear bilaterally
Abdo: Soft, non tender
Neuro: Grossly intact, **painful tips of fingers and toes**
Extremities: nil acute bilaterally

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Chemotherapy-induced Peripheral Neuropathy (CIPN)

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NCI CTCAE v5.0 neurotoxicity

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL*		-
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL*	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL*	Life-threatening consequences; urgent intervention indicated	-

- Paresthesia is characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.
- Peripheral motor neuropathy is characterized by inflammation or degeneration of the peripheral motor nerves.
- Peripheral sensory neuropathy is characterized by inflammation or degeneration of the peripheral sensory nerves.

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Taxanes

- E.g., paclitaxel, docetaxel, nab-paclitaxel, cabazitaxel
- Interferes with microtubule depolymerization
- Common uses: breast, ovarian, prostate, lung

Common Toxicities

–**Peripheral neuropathy,** myelosuppression, myalgias, fluid retention, mucositis, fatigue, hair loss, nausea and vomiting

–Hypersensitivity reactions (due to Cremaphor in paclitaxel)

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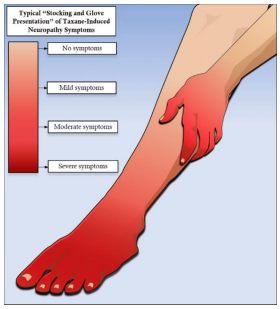
Taxanes: Stocking and Glove Sensory Neuropathy



- Often causes a pain syndrome that occurs in the days following each dose
- "arthralgias and myalgias" – newer data supports manifestation of acute neuropathy
- Peaks 2-3 days post infusion
- Pain tends to resolve between cycles
- Can become chronic, but doesn't typically get exponentially worse with every cycle (*vs. oxaliplatin neuropathy)*
- SENSORY neuropathy (numbness, tingling)
- Stocking-Glove distribution
- Lower > Upper

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Platinum Agents

- E.g., cisplatin, carboplatin, oxaliplatin
- Forms DNA cross-links, prevents DNA synthesis
- Common uses: testicular, ovarian, lung, Head & Neck, colon

Common toxicities

–Highly emetogenic, myelosuppression, nephrotoxicity, ototoxicity

–Cisplatin – nausea and vomiting

–**Oxaliplatin – COLD-INDUCED NEUROPATHY**

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Oxaliplatin-induced neuropathy

- Cold sensitivity
- Throat discomfort
- Difficulty swallowing cold liquids
- Muscle cramps
- Can occur at the time of drug infusion, however, usually peaks 2-3 days after
- Severity increases with subsequent cycles
- Primarily SENSORY vs motor or autonomic
- Upper > Lower

Coasting phenomenon – worsens 2-3 months post treatment

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Characteristics of peripheral neuropathy associated with cytotoxic chemotherapy agents

Drug	Clinical manifestations				Recovery
	Sensory	Motor	Reflexes	Autonomic	
Paclitaxel Docetaxel	Mild distal loss of sensation to all modalities, feet greater than hands, painful paresthesias	Occasional mild weakness in foot muscles; myalgia, myopathy	Reduced ankle reflexes	Rare	Usually improves after treatment, but persistent symptoms in about 50% of patients one year later
Oxaliplatin					
Acute	Cold-induced dysesthesias in mouth, throat, and upper limbs	Cramps and/or muscle spasm in throat muscles	Usually normal	None	Gets better within one week, but persists between two-week cycles; improves after chemotherapy is completed
Chronic	Similar to cisplatin; symptoms worse in upper extremities during active therapy, but upper extremity neuropathy improves faster than lower extremity neuropathy after treatment completion. One year after treatment completion, there is more neuropathy in lower extremities.	Normal	Usually normal	Rare	Generally starts to improve approximately three months after completion of chemotherapy; can be a chronic problem for some patients.

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Treatment of Chemotherapy-induced Peripheral Neuropathy

ASCO 2020 Guidelines

Treatment of chemotherapy-induced peripheral neuropathy for patients who have completed neurotoxic chemotherapy	For cancer patients experiencing painful CIPN, clinicians may offer duloxetine.	Type: Evidence based; benefits equal harms Evidence quality: Intermediate Strength of recommendation: Moderate
	Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the treatment of CIPN: • Exercise therapy • Acupuncture • Scrambler therapy • Gabapentin/pregabalin • Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine • Tricyclic antidepressants • Oral cannabinoids	Type: No recommendation Evidence quality: Low Strength of recommendation: Not applicable
	Note: While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample sized definitive studies are needed to confirm efficacy and clarify risks.	

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Mucositis

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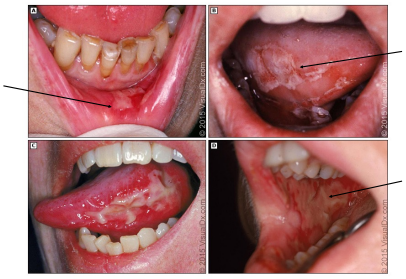
Chemotherapy-related mucositis



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NCI CTCAE v5.0 mucositis oral

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain, interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Mucositis oral is characterized by ulceration or inflammation of the oral mucosa.

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed March 27, 2018).

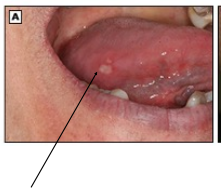

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Table 4. Management of chemotherapy-related mucositis and diarrhea

NONPHARMACOLOGIC MANAGEMENT	PHARMACOLOGIC MANAGEMENT
Mucositis	
Optimize routine oral hygiene (regular brushing, flossing, denture cleaning and fitting)	Monitor for oral candidiasis, xerostomia, and HSV. Treat where appropriate
Avoid foods that may irritate mucosa (hard, acidic, spicy)	Mucosal coating agents • Use antacid solutions (aluminum or magnesium hydroxide)
Use nonmedicated rinses (club soda rinses and diluted sodium bicarbonate rinses [1 tbsp sodium bicarbonate to 2 cups water])	Water-soluble lubricating agents • Use artificial saliva, benzocaine
Use high-fluoride-content toothpaste (5000 ppm)	Topical anesthetics • Administer 10 to 15 mL of 2% viscous lidocaine every 4 h as needed, but no more than 60 mL in 24 h; if swallowing, no more than 30 mL in 24 h
Switch to sponge brushing if toothbrushes are painful	Magic mouthwash* • A compounded formula; constituents vary but typically include anticholinergics (eg, diphenhydramine), topical anesthetics (eg, viscous lidocaine), and antacids or mucosal coating agents (eg, aluminum or magnesium hydroxide). May also contain nystatin, tetracycline, and hydrocortisone. Swish or gargle 15 to 30 mL every 4 h as needed
If receiving 5-FU bolus chemotherapy, consider cryotherapy—ice cubes or cold water in the mouth during chemotherapy administration (preventive)	Use systemic analgesics if needed (oral, subcutaneous)
Acquire nutritional support if required	

5-FU—5-fluorouracil; BRAT—bananas, rice, applesauce, toast; HSV—herpes simplex virus.
*Level 1 evidence for use of multidrug rinses is limited by heterogeneity of solutions.
Data from Elad et al,[11] Alberta Health Services,[12] Cancer Care Ontario,[13,14] and BC Cancer.[15]

Wilkinson AN, Sumar N. Chemotherapy basics for family physicians. Can Fam Physician. 2022 Jan;68(1):30-34. doi: 10.46747/cfp.680130. PMID: 35063980; PMCID: PMC9810051

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Febrile Neutropenia

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Febrile Neutropenia

Classic definition:

- any documented fever of 38.3 degrees Celsius or higher,
- or a fever of ≥ 38.0 degrees sustained for 1 hour or repeated over a 12-hour period, occurring in a patient who is receiving myelosuppressive chemotherapy.
- Sometimes present with SIRS: tachypnea, tachycardia, hypotension
- Some report dizziness, pre-syncope or syncope, shortness of breath, or, in the elderly, being bedridden and unable to walk or stand due to extreme weakness.

→ **Initiate investigations: CBC and chemistry, blood cultures, urine culture**

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Febrile Neutropenia

Neutrophils are critical components in the system of defense against bacterial infection.

The normal range for the ANC is 1.5 to 8.0 (or 1500 to 8000 per cubic mm of blood).

Chemotherapy causes the neutrophils to decrease following each treatment (Nadir often 7-10 days following treatment) and the neutrophils may remain critically low for many days to weeks.

The degree and duration of neutropenia is specific to each chemotherapy protocol.

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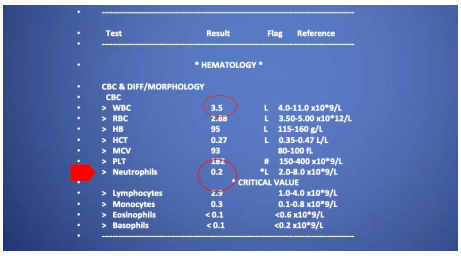

Test	Result	Flag	Reference
* HEMATOLOGY *			
CBC & DIFF/MORPHOLOGY			
CBC			
> WBC	3.5	L	4.0-11.0 x10*9/L
> RBC	2.88	L	3.50-5.00 x10*12/L
> HB	95	L	115-160 g/L
> HCT	0.27	L	0.35-0.47 L/L
> MCV	93		80-100 fL
> PLT	182	#	150-400 x10*9/L
> Neutrophils	0.2	*L	2.0-8.0 x10*9/L
	* CRITICAL VALUE		
> Lymphocytes	2.9		1.0-4.0 x10*9/L
> Monocytes	0.3		0.1-0.8 x10*9/L
> Eosinophils	< 0.1		<0.6 x10*9/L
> Basophils	< 0.1		<0.2 x10*9/L

ANC < 0.5 in a cancer patient (with or without infectious symptoms) is a MEDICAL EMERGENCY

The neutrophil count is part of the differential white blood cell count (WBC) on a CBC. The total WBC count may be only slightly low in a chemotherapy patient, but the neutrophils can be critical.

Always use the neutrophil count on the differential WBC for management decisions!

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MASCC Score

Characteristic	Score
Burden of illness:[1] • No or mild symptoms • Moderate symptoms • Severe symptoms	 5 3 0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour or haematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient at presentation	3
Age <60 years	2

[1]Only one score for this characteristic (5, 3 or 0 – points are not cumulative).
A score of 21 or more points is predictive of low-risk febrile neutropenia.

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Clinical pearls for practice

Sepsis in the context of a cancer patient on myelosuppressive chemotherapy can develop **RAPIDLY.**

The earliest warning of sepsis in a patient with neutropenia may be **fever**.

Neutropenic patients have **NO** immune capability against bacterial infections. Their only defense is rapid administration of broad-spectrum antibiotic.

These patients require **urgent admission** for work up and initiation of broad-spectrum antibiotics and other supportive management.

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Case 2: Max, Colorectal Cancer

58-year-old male, recent diagnosis sigmoid colon adenocarcinoma

Staging CT/PET scans: single metastatic lesion in one lobe of the liver

Elevated CEA
Molecular assessment of colon ca revealed EGFR expressing and wild-type KRAS

History of hypertension, under good control
No personal or family history of colon cancer

Feels well aside from some RUQ pain
Strong, fit, good performance status (ECGO/PS = 0)

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Case 2: Max, Colorectal Cancer

Young and fit patient, with a single metastatic lesion to the liver

Treatment planning with a multidisciplinary team recommended first-line:
FOLFIRI + CETUXIMAB +/- Surgical resection
**** High toxicity, but potential for R0 resection***

CRYSTAL Trial: Liver Resection Increased With Addition of Cetuximab

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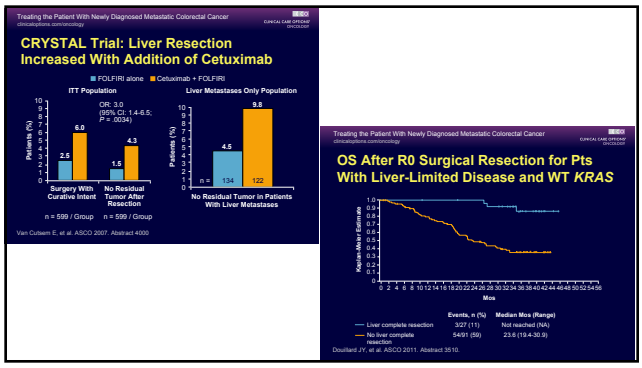

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Case 2: Max, Colorectal Cancer

Question

1.What potential chemotherapy-related toxicities does Max face?

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FOLFIRI + CETUXIMAB q 2 weekly

Cetuximab: Moderately Emetogenic
FOLFIRI: High Emetogenic
F5U + Irinotecan: Culprits for high grade chemo-related diarrhea
Cetuximab: Rash
F-5U: Stomatitis, Myocardial spasms

DPD Deficiency: Rapid progression to grade 2-4 toxicity and risk of **death**. Close monitoring with first cycle of any F5U containing regimen is necessary.

Supportive medications include:

H1 Agonist (pre-treatment, cetuximab, rash
Atropine (cholinergic symptoms from Irinotecan)
Loperamide (5FU / Irinotecan-related diarrhea)

MEC-HEC Nausea Protocol

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NCI CTCAE v5.0 diarrhea

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL*	Increase of seven or more stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL*	Life-threatening consequences; urgent intervention indicated	Death

Diarrhea is characterized by an increase in frequency and/or loose or watery bowel movements.

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Diarrhea and Cholinergic Symptoms

Diarrhea CAN BE LIFE THREATENING

Fluorouracil / Capecitabine: Have DPD Deficiency on your radar!

- **Early diarrhea** within 24 hours of treatment: consider atropine prophylactically for future cycles (0.3-1.2mg IV or SC)
- **Late diarrhea** onset 5-11 days post cycle: treat promptly with Loperamide (4mg Stat, then 2mg q2h prn)
- ORAL **REHYDRATION**
- Monitor for other **cholinergic symptoms**: rhinorrhea, salivation, lacrimation, diaphoresis, flushing.
- HIGH risk of **Febrile Neutropenia & Sepsis**

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Table 4. Management of chemotherapy-related mucositis and diarrhea

NONPHARMACOLOGIC MANAGEMENT	PHARMACOLOGIC MANAGEMENT
Diarrhea	
Use probiotics (preventive)	Consider infectious workup and ensure no recent immunotherapy
Oral hydration	Intravenous hydration
Dietary modifications might be needed—use BRAT diet. Avoid high osmolarity supplements, sweeteners, and alcohol	Administer 2 mg of loperamide by mouth after each loose stool. Do not use more than 16 mg in 24 h
Avoid lactose (chemotherapy can cause temporary lactase deficiency)	If not adequately controlled, add 2 tablets of diphenoxylate hydrochloride–atropine sulfate by mouth every 6 h. If still not controlled, add 50 to 600 µg/d of subcutaneous octreotide (given 2 times/d or 3 times/d)

5-FU—5-fluorouracil; BRAT—bananas, rice, applesauce, toast; HSV—herpes simplex virus.
*Level 1 evidence for use of multidrug rinses is limited by heterogeneity of solutions.
Data from Elad et al,[17] Alberta Health Services,[18] Cancer Care Ontario,[19,20] and BC Cancer.[21]

Wilkinson AN, Sumar N. Chemotherapy basics for family physicians. Can Fam Physician. 2022 Jan;68(1):30-34. doi: 10.46747/cfp.680130. PMID: 35063980; PMCID: PMC9810051.

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Hand-Foot Syndrome

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Hand-Foot Syndrome

- Also known as acral erythema, hand-foot skin reaction, palmar-plantar erythrodysesthesia
- ~ 60% incidence with capecitabine use / 5-FU
- Presentation
  - Initially tingling in palms / soles
  - Edema, tenderness over fat pads
  - Pallor, blister, desquamation
- Pain can be severely limiting affecting grasping, walking

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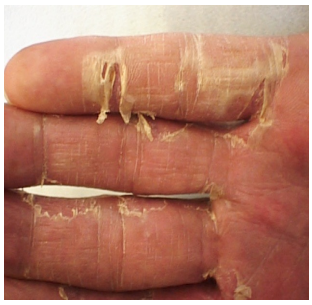
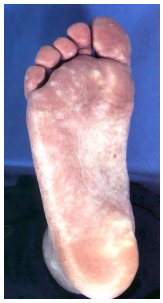
Hand-Foot Syndrome





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Rash

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EGFR Expression and RASH

- Antibodies: Cetuximab (Erbitux), Panitumumab
  Used in colon cancer → only in K-ras wt tumors
- TKI: Erlotinib (Tarceva), Gefitinib (Iressa), Afatinib (Gilotrif)
  Used in lung cancer → EGFR mutation

Toxicity

- Hypomagnesemia, hair and nail changes, diarrhea
- **ACNEIFORM RASH**

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Targeted Therapies/Biologics: Mab's and Nib's

Signal Transduction Pathways Involved in Cancer: EGFR and EGF

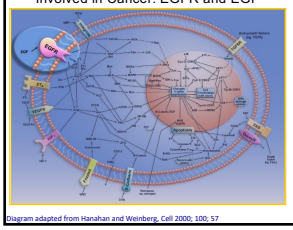
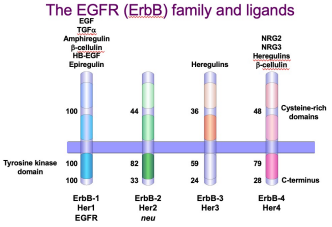


Diagram adapted from Hanahan and Weinberg, Cell 2000; 100; 57

The EGFR (ErbB) family and ligands



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EGFR expression in human tumors

Tumors showing high EGFR expression	High expression generally associated with
• NSCLC 40-80% • Prostate 40-80% • Gastric 33-74% • Breast 14-91% • Colorectal 25-77% • Pancreatic 30-50% • Ovarian 35-70%	• Invasion • Metastasis • Late-stage disease • Chemotherapy resistance • Hormone-therapy resistance • Poor outcome

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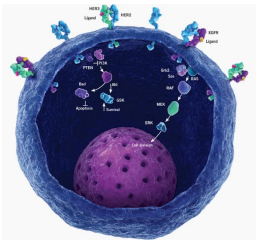
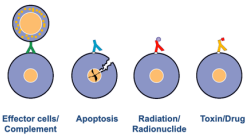
Monoclonal Antibodies "Mabs"



Cytotoxic Mechanisms of MoAbs



- Rituximab (Rituxan) Lymphoma
- Trastuzumab (Herceptin) Breast
- Pertuzumab (Perjeta) Breast
- **Cetuximab (Erbitux) Colon, Head & Neck**
- Panitumumab (Vectibix) Colon
- Bevacizumab (Avastin) Colon, GBM, Lung
- Ipilumumab (Yervoy) Melanoma

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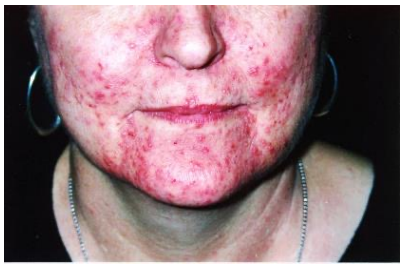
Cetuximab: Acneiform Rash



- Associated with tumor response
- Management: sunscreen, topical combination steroid-antibiotic cream, oral minocycline.
- Typically resolves afterwards

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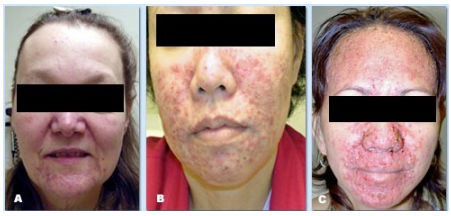
Acneiform Rashes



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Other potential side effect: Hypertension

- Hypertension: reported 17-80%
- Both MoAbs and Tyrosine Kinase Inhibitors ("nibs")
- Also related with tumor response and improved OS if hypertension optimized
- Sunitinib in RCC and Bevacizumab (Colon and Lung)
- **Recommendation:**
  - **Treat as per HTN guidelines (CCB (Norvasc), ACE-Inhibitor, Diuretics)**

Other potential toxicities to monitor for:

- Hyperglycemia, cardiac dysfunction, proteinuria, stroke, bleeding, delayed wound healing

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Cancer Care Ontario: Summary of Toxicities from Folfiri and Cetuximab

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Rash (may be severe) • Fatigue • Increased LFTs (may be severe) • Nausea, vomiting • Anorexia • Alopecia • Abdominal pain • Constipation • Diarrhea (may be severe) • EKG changes	• Neuropathy • Cough, dyspnea • Hypomagnesemia • Infection (may be severe) • Headache • Mucositis • Insomnia • Myelosuppression +/- bleeding, infection (may be severe) • Nail disorders	• Hand-foot syndrome • Dizziness • Musculoskeletal pain • Paronychia • Infusion reaction • Mood changes • Rhinitis • Dry mouth • Edema • Somnolence	• Arterial / venous thromboembolism • Arrhythmia • Cardiotoxicity • GI obstruction / perforation • Hypersensitivity • Pancreatitis • Pneumonitis • Renal failure • Keratitis, optic neuritis • Tumour lysis syndrome • Hemolysis

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Clinical Pearl: Common chemotherapies and related toxicities

Drug	Toxicity
Doxorubicin	Cardiomyopathy
Cisplatin	Nausea/Vomiting
Oxaliplatin	Cold Induced Neuropathy
Cyclophosphamide	Second Malignancies
5FU	Diarrhea
Capecitabine	Hand Foot Syndrome
Vincristine	Peripheral Neuropathy
Paclitaxel	Hypersensitivity Reaction
Traztuzumab (Herceptin)	Cardiomyopathy
Erlotinib (Tarceva), Cetuximab	Acneiform Rash
Bevacizumab (Avastin)	Bowel Perforation

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Conclusions

- CTCAE plays a major role in guiding systemic treatment recommendations
- Evidence-based recommendations facilitate management plans for chemotherapy-related toxicities
- Family physicians are essential providers to cancer patients

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