Take the Lead: Pharmacists’ Growing Role in Managing Oral Oncologics

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Disclosures

Ashley Glode nor Megan May have anything to disclose.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

- Discuss tips for proper storage, handling, and disposal of oral oncologics.

- Recognize unique adverse effects associated with oral oncologics and assess and select appropriate management strategies.

- Identify appropriate patient and provider resources for adverse effect management.

- Describe challenges associated with managing oral oncologics, including adherence and persistence, managing multiple medications, potential drug interactions, and laboratory and toxicity monitoring.
1. Assessment Question

JT’s wife comes to the pharmacy to pick up her husband’s new prescription for brigatinib. He progressed on crizotinib and his wife states they have about 20 pills left. She asks you what they should do with the remaining medication? You respond:
A. Flush the pills down the toilet
B. Open up the capsules into the trash
C. Dissolve the capsules in water and pour down the drain
D. Bring them to your local drug take back program
WW is a 72 year old man who was placed on enzalutamide for his prostate cancer. He is also on warfarin for his atrial fibrillation. What is a concern you have when giving these 2 medications together?

A. I have no concerns
B. These medications are contraindicated to be given together and he should receive a different medication for his prostate cancer
C. WW may have an increased risk of bleeding due to a drug interaction and more frequent INR monitoring is indicated
D. WW’s warfarin may be less effective due to a drug interaction and this combination should be avoided
3. Assessment Question

Patient CG presents to your pharmacy to pick up a new prescription for capecitabine for treatment of his colorectal cancer. He has read information on hand foot syndrome and is wary of taking the medication. He asks you what he can do to prevent it from occurring. What do you tell him?

A. There are no ways to prevent its development. However, urea based moisturizers can be used for treatment if it develops.
B. Take hot showers.
C. Ask physician for tetracycline based cream to use preemptively.
D. Use shock absorbers in shoes and consider manicure/pedicure.
4. Assessment Question

Patient BK comes to your pharmacy to pick up his prescription for erlotinib. He says he has been struggling with the rash on his face. He asks you for some recommendations. Which of the following are appropriate resources for you to use to help BK?

A. Chemocare.com  
B. Natural Medicine Database  
D. Medication Adherence Toolkit
Proper Storage, Handling, and Disposal of Oral Oncologics
Oral Oncologics

- Anticancer agents: “chemotherapy”
  - Inclusive term encompassing all antineoplastic therapies
- Projected use of oral chemotherapy will more than double in next several years
  - Just over 50% of 2017 Food and Drug Administration (FDA) new oncology drug approvals were oral agents
  - 25% of anticancer agents in pipeline are oral
- Care moved from a medical facility to a patient’s home

Oral Medications

Advantages

- Increased patient control and convenience
  - Taken at home 😊
- Potential increase in quality of life
- Sustained medication exposure
- Potential reduction in travel costs and use of health care resources

Disadvantages

- Potential nonadherence
- Compromised patient safety
- Medication errors
- Inadvertent exposure of other individuals

Oral chemotherapy: not just an ordinary pill

- Not necessarily safer than IV chemotherapy
  - Just as potent
  - Narrow therapeutic index
  - Used in complex, multidrug regimens
  - Complex dose calculations and adjustments
  - Dose adjustments for organ function, toxicity, and other clinical parameters

- Mistakes can lead to serious side effects and death
Oral chemotherapy: not just an ordinary pill

- Can kill healthy cells as well as cancer cells
  - Mistakes more likely to cause harm
- Often prescribed in cycles
  - 2 weeks on 1 week off; repeat every 21 days
- Different dosing for different indications and even same indication
  - Temozolomide
    - Glioblastoma multiforme: 200 mg/m² once daily for 5 days every 28 days
    - Neuroendocrine tumors:
      - 150 mg/m² once daily for 7 days on, 7 days off in combination with thalidomide
      - 200 mg/m² once daily (at bedtime) on days 10-14 of a 28-day cycle in combination with capecitabine
- Harmful to individuals who do not have cancer
  - Safe storage, handling, and disposal
Chemotherapy Errors

- Overall chemotherapy error rate: 8.1 errors per 100 clinic visits
  - Adults: errors associated with 7.1% of clinic visits
  - Pediatrics: errors associated with 18.8% of clinic visits

- Common phase of errors
  - Administration: 56%
  - Ordering: 36%

- Oral chemotherapy
  - 9.9% error rate in pediatrics with acute lymphoblastic leukemia (ALL)

- Chemotherapy-related errors are intercepted at rates of 2-5%

Example Oral Chemotherapy Errors

- 60 year-old female, Ruth Ann Collins, with brain cancer died after taking all capsules of lomustine in the bottle she received from the pharmacy
  - Thought it was a single dose since that is how it had been filled before
  - Pharmacy dispensed enough medicine for 3 cycles
    - Intended dose: 150 mg every 6 weeks
    - Ingested dose: 450 mg in total
  - Package insert: “Only the appropriate number of lomustine capsules required for the administration of a single dose should be dispensed”
  - Lomustine carton label: “Caution: DO NOT DISPENSE ENTIRE CONTAINER. Dispense only enough capsules for one dose”

- Patient taking capecitabine for bowel cancer
  - Supposed to have a drug-free period during her cycle
  - Admitted to the hospital and prescribed to continue
  - Instructed to take daily upon discharge as well
    - Patient never received “off” time
  - Readmitted 1 week later due to toxic effects

Steps to Prevent Errors

- Know the patient’s cancer type, height, weight, and ask them their planned schedule/cycle
- Review medication list (including over-the-counters/herbals) for potential drug interactions
  - Proton pump inhibitors (PPIs)/H2 blockers
- Thoroughly review the directions, even on refills
  - Dosing calendar
- Review medication appearance with each dispense

Minimize the risk of errors in chemotherapy ordering, preparation, and administration

Medication errors account for half of the preventable errors that occur in up to 25% of hospitalized patients

Many types of errors
  - Underdosing, overdosing, schedule and timing, administration of incorrect drugs, omission of drugs, etc.

Focus on 4 domains:
  1: Environment and routine procedures
  2: Treatment planning and patient education before initiating therapy
  3: Specific standards for ordering, preparing (including labeling), and administering chemotherapy
  4: Monitoring adherence to, and toxicity from, chemotherapy to promote safety both while on treatment and subsequent therapy
Pharmacy Storage

- Prevent accidental exposure and ensure medication integrity
- Designated area per manufacturer’s instructions
  - Separate from noncytotoxic agents
- Some agents are air-, moisture-, and/or light-sensitive
Pharmacy Handling

- Correct use of personal protective clothing and equipment
  - Disposable gloves
    - Wash hands before and after
- Dispose of as cytotoxic waste according to local regulatory guidelines
- Do not use automatic counting machines
  - Wash or decontaminate counting trays thoroughly after use
- Need written emergency plan in event of spill or accidental exposure

Oral Oncologic Manipulation

- Compounding, crushing, cutting, or splitting
- Use biological safety cabinet
- Disposable personal protective equipment
- Separate equipment for cytotoxic and noncytotoxic agents

Pharmacy Labeling Key Points

- Dosage form and strength
- Quantity dispensed within each container
- # of pills or mLs per dose if container holds > 1 dose
- Administration schedule
  - # of times/day and days on/off treatment
- Administration instructions
  - Food, other medicines
- Warning or precaution statement for storage and handling
- Caution statement
  - “Caution: chemotherapy” or “HAZARDOUS DRUG”
- Storage instructions
General Tips for Patients on Safe Storage

- Store separately from other family member’s medications
  - Separate shelf, cabinet, or drawer
- Store in a safe, cool, dry place out of the sight and reach of children and/or pets
  - Have local poison control center’s phone #
- Keep in a place with good lighting so able to read label
- Store medicine in the original container
  - If using a pill box, use a separate one and clearly label it
- Keep medication lid tightly closed
  - Child-proof if possible
- Keep printed information with prescription
General Tips for Patients on Safe Handling

- Administer the chemotherapy to themselves
  - Caregivers should wear gloves and wash hands thoroughly before and after glove application
    - If not using gloves, tip tablets/capsules from container/blister pack directly into a disposable medicine cup or cap of the pill bottle

- Administer medication as instructed
  - Do not chew, crush, cut, or dissolve

- Soiled linens should be cleaned separately
  - Caregivers should wear gloves

General Tips for Patients on Safe Disposal

- Local regulations on disposal
  - Drug Take Back Days
  - Manufacturer instructions with packaging material to return unused medications
  - Mail order or specialty pharmacies may accept returns
- Never throw out or flush leftover chemotherapy
- Empty containers or other chemotherapy waste

Clinical Case Vignette

- BB is a 41 year old male on ceritinib who lives in Arizona. On a hot summer day (high ~120F) he has his medication delivered to his home while he is at work. When he arrives home at night the medication wasn’t shipped “on ice” as he had requested.

- The package insert states: store at 25C (77F); excursions permitted between 15C to 30C (59F to 86F)

- What should he do?
Managing Oral Oncologics
Adherence and Persistence

- Adherence (compliance)
  - Apparent mg taken/mg prescribed

- Persistence
  - Time on therapy without significant gaps in refills

- Direct measurement methods
  - Observation, pharmacokinetic values

- Indirect measurement methods
  - Patient self-report, diaries, pill counts, rates of prescription refills, electronic medication monitors
The Case of Imatinib

- Chronic myeloid leukemia (CML)
  - Must take as chronic medication once daily
- Side effects manageable
  - Edema, fatigue, skin rash, GI upset, muscle cramps
- Adherence of 85% or less leads to a higher probability of losing response at 2 years (27% vs 2%)
Barriers to Adherence

- Cost
- Dosing complexity
- Forgetfulness
- Distractions of everyday life
- Inadequate social support
- Side effects
- Misinterpretation of instructions
- Poor communication with health care providers

How Can the Pharmacist Help?

- Mitigate cost
  - Insurance plans, prior authorizations, patient assistance programs, grant funding
- Streamline dosing
  - Create a calendar, consider timing of all other medications
- Address adherence
  - Apps, pill boxes, incorporate into daily routine
- Side effect management
  - Recognize side effects early
- Be a patient resource/line of communication
- Educate, educate, educate!
Educate to Different Learning Styles

- Use of a calendar with days and times to take oral chemotherapy
- Smartphone apps with reminders
- 1 page summary of important issues related to specific regimen
  - Medication specific information and administration instructions
  - Blood monitoring
  - Frequency of provider visits
- Other precautions
  - Drug-drug or drug-food interactions
- Dispensing pharmacy information
Management of Multiple Medications

- May be prescribed as part of a multi-drug regimen
  - Other IV medication(s)
  - Other oral medication(s)
    - Corticosteroids
- Pre-medications and supportive care medications
  - Anti-emetics
  - Anti-infectives

Drug, Herb, Supplement, and Food Interactions

- CYP inducers, inhibitors, and substrates
  - Grapefruit, grapefruit juice and grapefruit products, star fruit, Seville oranges
  - St. John’s Wort
  - Lapatinib dose adjustments for CYP 3A4 inducers (strong) and inhibitors (strong)
  - Tamoxifen efficacy with antidepressants (CYP2D6)

- P-gp inducers, inhibitors, and substrates
  - Ibrutinib: may inhibit P-gp in GI tract; monitor P-gp substrate medications with narrow therapeutic index (eg, digoxin)

- Worsened side effects
  - Bleeding risk: garlic, ginseng, fish oil, milk thistle, turmeric, St. John’s Wort

Drug, Herb, Supplement, and Food Interactions

- **Anticoagulants**
  - Increased effect of warfarin: capecitabine, vemurafenib, vorinostat
  - Decreased effect of warfarin: dabrafenib, enzalutamide

- **Antacids and PPIs**
  - Antacids containing aluminum cations may increase concentration of capecitabine
  - Crizotinib solubility pH dependent; PPI, H2 blockers, and antacids may decrease bioavailability of crizotinib
  - H2 antagonists and PPIs decrease absorption of dasatinib; use antacids in place of H2 blockers and PPIs; antacids should be taken 2 hours before or after dasatinib

- **Food**
  - Imatinib: take with food to decrease GI upset
  - Sorafenib: take on an empty stomach, high-fat food reduces absorption

Laboratory Monitoring

- Blood counts
- Blood glucose
- Lipid panel
- Liver enzymes and bilirubin
- Renal function

Patients need to know:
- What testing is required
- When to have blood work done
- If fasting is required
EKG Monitoring

- Oral oncologics
  - Crizotinib
  - Lapatinib
  - Pazopanib
  - Sorafenib
  - Sunitinib
- With or without concomitant use of QTc prolonging medications
- Electrolyte management

Toxicity Monitoring

- Hypertension
  - Pazopanib, regorafenib
- Nausea/vomiting
  - Crizotinib, lenvatinib, temozolomide
- Diarrhea
  - Idelalisib, capecitabine,
- Mouth sores
  - Everolimus
- Skin rash
  - Erlotinib
Patient Reported Outcomes (PROs)

- Patient reports via internet, automated phone systems, or apps
  - Engaged in care
  - Reflection of how a patient feels and functions
- 80-85% of patients will regularly self report symptoms
- Quickly identify severe or worsening symptoms
- Some data to support decreased ER visits, longer persistence on therapy, and improved survival
Oral Oncologic Follow-up

- Assess for side effects
- Reinforce side effect management
- Obtain required laboratory monitoring
- Ensure adherence to dosing regimen
- Answer patient and caregiver questions

Clinical Case Vignette

- TP is a 57 year old male who was recently started on Cap/ox. He is supposed to take capecitabine 1500 mg (3-500mg tabs) by mouth twice daily with food on days 1-14 of a cycle and receive oxaliplatin by IV infusion on day 1 of a cycle.

- He presents to clinic to begin cycle 2 and states he is currently taking capecitabine. He has been taking it continuously since he received it and has about a week left in his bottle.

- How can this error be prevented?
Adverse Effects of Oral Oncologics
Oral Targeted Agents Versus Traditional Chemotherapy

- Do not attack all rapidly dividing cells
- Side effect profiles can be different
- Toxicity profile differs based on drug target
- May be able to target more than one domain within the cancer cell, potentially increasing the side effect profile

Common Terminology Criteria for Adverse Events (CTCAE)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild, asymptomatic or with mild symptoms; clinical or diagnostic observation, no need for intervention</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate, minimal, limits normal activities of daily living for that age group; noninvasive intervention indicated</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe, disabling, or medically significant without being life threatening; however, hospitalization is indicated</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening, urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to the adverse event</td>
</tr>
</tbody>
</table>

As side effect severity increases, more likely to consider dose reduction/dose interruption.

Oral Chemotherapy: Adverse Effects

- Alopecia
- Anemia
- Cardiotoxicity
- Constipation/diarrhea
- Delayed wound healing
- Fatigue
- Fluid retention
- Flu-like symptoms
- GI perforation
- Hand-foot syndrome
- Hearing changes
- Hepatotoxicity
- Hot flashes
- Hypertension
- Hypothyroidism
- Interstitial pneumonitis
- Metabolic abnormalities
- Mucositis/stomatitis
- Nail changes
- Nausea and vomiting
- Neuropathy
- Ocular toxicities
- Organ changes
- Osteoporosis
- Pulmonary toxicity
- Sex/sexuality
- Skin toxicities
- Thrombocytopenia
- Thrombosis

Hematologic Toxicities

- Anemia
- Fatigue
- Neutropenia
- Thrombocytopenia
Anemia

- Definition: hemoglobin less than normal
- Most common hematologic complication of chemotherapy
- Type and duration of therapy and stage of malignancy
- Potential causes
  - Treatment, GI bleed, nutrient deficiency (e.g. iron, folate), bone marrow involvement
- Symptoms
  - Fatigue
- Evaluate underlying cause
# Cancer- and Chemotherapy-Induced Anemia (CIA)

<table>
<thead>
<tr>
<th>NCI Common Toxicity Criteria</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>Mild (Hgb &lt; WNL - 10 g/dL)</td>
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</tbody>
</table>

Hgb: hemoglobin  
WNL: within normal limits  
NCI: National Cancer Institute
Management of Anemia

1. Patient is identified as having anemia
2. Determine if packed red blood cell (RBC) transfusion is needed
3. Determine cause of anemia
4. If nutritional deficiency is not cause, the primary way to increase hemoglobin is transfusion or erythropoiesis stimulating agents (ESAs)
5. If needed, administer iron or folate supplementation
## Risks/Benefits: ESA vs RBC Transfusion

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESAs</strong></td>
<td>Prevent transfusions</td>
</tr>
<tr>
<td></td>
<td>Gradual improvement in fatigue</td>
</tr>
<tr>
<td></td>
<td>Shortened time to tumor progression</td>
</tr>
<tr>
<td></td>
<td>Increased risk of thromboembolism</td>
</tr>
<tr>
<td></td>
<td>Risk of hypertension</td>
</tr>
<tr>
<td></td>
<td>Possible decreased survival</td>
</tr>
<tr>
<td><strong>Transfusions</strong></td>
<td>Rapid increase of Hgb</td>
</tr>
<tr>
<td></td>
<td>Rapid improvement in anemia related symptoms</td>
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<tr>
<td></td>
<td>Transfusion reactions</td>
</tr>
<tr>
<td></td>
<td>Virus transmission</td>
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<tr>
<td></td>
<td>Bacterial contamination</td>
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<tr>
<td></td>
<td>Iron overload</td>
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</tbody>
</table>

## ESA Use in Patients with Cancer

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Cancer &amp; chronic kidney disease</td>
<td>Consider ESA with kidney dosing</td>
</tr>
<tr>
<td>Myelosuppressive chemotherapy with <strong>curative</strong> intent</td>
<td>ESAs not recommended</td>
</tr>
<tr>
<td>Patient undergoing palliative treatment</td>
<td>ESAs or RBC transfusion</td>
</tr>
<tr>
<td>All other patients with anemia on chemotherapy without other causes of anemia</td>
<td>ESAs or RBC transfusion or clinical trial</td>
</tr>
</tbody>
</table>

Transfusion Goals in Patients with Cancer

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Target Hgb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>7 – 9 g/dL</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>8 – 10 g/dL</td>
</tr>
<tr>
<td>Symptomatic with ACS or MI</td>
<td>Unclear</td>
</tr>
<tr>
<td>Acute hemorrhage with evidence of hemodynamic instability</td>
<td>Transfuse to correct and maintain $O_2$ delivery</td>
</tr>
</tbody>
</table>

ACS: Acute coronary syndrome  
MI: Myocardial infarction

Fatigue

- Multifactorial
  - Thyroid function, insomnia, depression, pain, underlying malignancy
- Impairs quality of life, relationships, mood, commitment to therapy
- Lifestyle interventions
- Complementary therapies
- CAUTIOUS use of ESAs in anemic patients
- CNS stimulants
  - Methylphenidate: 5 mg PO BID; max 40 mg/day
  - Corticosteroids - short term
    - Dexamethasone 4-8 mg/day

Neutropenia

- Definition: absolute neutrophil count (ANC) < 1500/mm³
  - Severe: ANC < 500/mm³
- Risk of infection: neutropenia duration and severity
  - Integrity of physical defense barriers
  - Functional integrity of leukocytes
- Neutropenia vs febrile neutropenia
- Most important hematologic toxicity
  - Sepsis and death
Thrombocytopenia

- Definition: platelets < 100,000/mm³
- Risk for bleeding
- Symptoms
  - Bleeding
  - Bruising
- Concomitant medications or conditions
Management of Thrombocytopenia

- Counseling on bleeding precautions
- Dose reductions
- Platelet transfusions
  - < 10,000 cells/mm³
- Oprelvekin (IL-11): 50 mcg/kg SQ daily
  - Nonmyeloid malignancies
  - Significant toxicities: fluid retention, cardiac toxicity
  - More expensive than platelet transfusions

Hematologic Toxicity

- Safe treatment parameters
  - ANC $\geq 1500$/mm$^3$
  - Hemoglobin $\geq 8$ g/dL
  - Platelets $\geq 100,000$/mm$^3$
- Disease and regimen specific

https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=160&ContentID=34
Gastrointestinal Toxicities

- Diarrhea
- Mucositis/Stomatitis
- Nausea/Vomiting
Diarrhea

- Moderate to severe
  - 14% of chemotherapy agents
- Causes
  - Direct and indirect toxic effects of treatment
  - Abdominal/pelvic radiation
  - Surgical intervention of GI tract
  - Malignancy
  - Infection

http://www.cancer.gov/about-cancer/treatment/side-effects/constipation/GI-complications-hp-pdq#link/stoc_h2_1
Diarrhea Management

- **Treatment**
  - **Loperamide**
    - 4mg PO at the first sign of diarrhea
    - 2mg PO q 2h until diarrhea free for 12 hours
    - Do not take > 12 tablets/day
  - **Diphenoxylate/atropine**
    - 5 mg PO QID
    - May alternate with loperamide
  - **Octreotide**
    - 50-150 mcg SQ q 8h; up to 500 mcg SQ q8h

- **General Supportive Care**
  - Hydration
  - Electrolytes
  - Diet modification-BRAT
  - Probiotics?

http://www.cancer.gov/about-cancer/treatment/side-effects/constipation/GI-complications-hp-pdq#link/stoc_h2_1
Mucositis (Stomatitis)

- Inflammation of GI mucosa
- Onset: 5-10 days
- Duration: 1-6+ weeks
- Complications
  - Pain, nutrition, infection
- Risk Factors
  - Poor oral health
  - Tobacco and alcohol
  - Females > Males
  - Dehydration
  - Chemotherapy regimen: especially high doses
  - Radiation

http://www.oralcancerfoundation.org/complications/mucositis.php
http://www.cancernetwork.com/cancer-management/dermatologic-adverse-events-associated-systemic-anticancer-agents#sthash.T3Cy5yTU.dpuf

cabozantinib, ponatinib, sorafenib, pazopanib, axitinib, regorafenib, sunitinib, temsirolimus, everolimus, erlotinib, lapatinib, imatinib
Mucositis (Stomatitis) Management

- **Prevention**
  - Good oral hygiene
  - Baking soda and salt rinses; saline rinses swish/spit QID
    - 1 tsp salt, 2 tsp baking soda, 8 oz warm water
  - MTOR inhibitors: dexamethasone mouth rinse swish/spit QID

- **Treatment: supportive management**
  - Oral hygiene
  - Topical/systemic analgesics
  - “Magic” mouthwash
  - Anti-infectives
    - Candida
    - HSV

http://www.oralcancerfoundation.org/complications/mucositis.php
Nausea and Vomiting

- **Treatment options**
  - 5-HT₃ receptors
  - Dexamethasone
  - Aprepitant
  - Promethazine
  - Metoclopramide
  - Olanzapine

- **Counseling Pearls**
  - Eat small, frequent bland meals
  - Avoid greasy, fried, salty, sweet, or spicy foods
  - Maintain adequate hydration
  - Nausea onset may take a week or more
  - Take medication at first sign of nausea

Dermatological Toxicities

- Hand and Foot Syndrome
- Nail Toxicity
- Photosensitivity
- Rash
Hand Foot Skin Reaction (HFSR) and Hand Foot Syndrome (Palmar-plantar erythrodysesthesia (PPE))

- Distinct in cause and presentation
- **HFSR**
  - 10% - 60% of patients on multi-kinase inhibitors
  - Localizes to areas of pressure or friction
- **PPE**
  - 30% of patients treated with capecitabine
  - Rupture of small capillaries
  - Diffuse edema and redness on palms and soles of feet

sorafenib, sunitinib, pazopanib, axitinib, regorafenib, cabozantinib, erlotinib, lapatinib, capecitabine, BRAF inhibitors

HFSR and PPE

- Mechanism
  - Immune response, damage blood vessels in hands and feet, or lower temperature in these areas
- Dose and exposure related
- Onset: 2-4 weeks after initiation
- Resolves over 1-2 weeks after drug discontinuation
- Surfaces exposed to repetitive friction or pressure
- Redness and swelling of palms and soles, may progress to dryness, scaling, pain, itching, blisters, and ulceration

HFSR and PPE Management

- **Prevention**
  - Remove pre-existing hyperkeratotic areas
  - Manicure/pedicure prior to and during treatment if develop
  - Shock absorbers in shoes
  - Avoid hot water and direct sunlight
  - Avoid undue pressure or rubbing of skin during initial 2-4 weeks

- **Treatment**
  - Opioids or NSAIDs
  - Topical high potency steroid creams
  - Ice packs/refrigerate creams for comfort
  - Keratolytic/urea moisturizers

Nail Toxicity

- Mee’s lines: transverse white lines
- Beau’s lines: transverse grooves or lines
- Melanonychia: melanin pigmentation of nail plate
- Paronychia: periungual inflammation
  - Epidermal growth factor receptor (EGFR) inhibitors and capecitabine
  - Management: moisturizing creams, topical/systemic antibiotics
- Subungual hemorrhages
  - 60% sorafenib, 30% sunitinib

Photosensitivity Management

- **Prevention**
  - Use sunscreen or protective clothing, even on cloudy days
  - Sunblock with a physical barrier (zinc oxide)
  - Avoid tanning booths

- **Treatment**
  - Use cool wet dressings
  - Apply lotions
  - Topical or oral steroids if severe

- **UV Recall Reaction**
  - May occur within 1 week of sunburn and may be more severe than primary sunburn

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Shields KM. Pharmacist’s Letter 2004 (May); 20: 200509
Papulopustular Rash (acneiform)

- EGFR-“turns off the signal" for skin cells to grow normally
- Onset: 7-10 days; Peak: 2nd week
- Usually mild to moderate in severity, can progress to life threatening
  - Resolves within 1-2 weeks after drug discontinuation
- Patient counseling: rash may be surrogate marker of response

Rash Toxicity Prevention

- Mild soap, free from alcohol and perfume, in addition to moisturizing with emollient to area at least twice a day
- Avoid hot baths or showers, loose or soft clothing
- Preemptive skin examination
- Avoid skin exposure
  - SPF >15, with UVA and UVB protection
- Emollients
- Topical/oral antibiotics
  - Minocycline, doxycycline, clindamycin 1%
- Antihistamines
  - Hydroxyzine, diphenhydramine, loratadine

Mild – Grade 1
Localized, mildly symptomatic, No impact on Quality of Life (QOL)

- No treatment
- Topical hydrocortisone or clindamycin

Moderate – Grade 2
Mild symptoms, minimal impact on QOL

- Topical hydrocortisone or clindamycin +
- Doxycycline 100 mg po daily
- Consider discontinuing EGFR

Severe – Grade 3 / 4
Severe symptoms, potential for super infection

- Hydrocortisone or clindamycin +
- Doxycycline + Methylprednisolone dose pack

References:
Maculopapular Rash (morbilliform eruption)

- Typically starts on trunk, may involve extremities
- Onset: ~ 2 weeks
- Management:
  - Moisturizing creams, gentle skin care, steroid cream

http://www.cancernetwork.com/cancer-management/dermatologic-adverse-events-associated-systemic-anticancer-agents
Cardiovascular Toxicities

- Hypertension
- QT Prolongation
- Ventricular Dysfunction
- Venous Thromboembolism
Hypertension

- Occurs in up to 30% of patients on vascular endothelial growth factor (VEGF) inhibitors
  - Normally, VEGF works to produce nitric oxide (NO)
  - NO is crucial in vascular homeostasis, leading to increased vascular dilation, permeability and decreased vascular resistance
- Evaluate patients prior to starting anti-VEGF therapy then periodically thereafter
  - Start antihypertensive therapy per general guidelines
- Guidelines follow that of the general population
  - Reduce sodium intake
  - Weight loss
  - Exercise
  - Medications

QT prolongation

- Primarily with multi-target kinase inhibitors
  - Thought to be due to inactivation of the PI3K/AKT/mTOR pathway or EGFR
- Black box warning for nilotinib and vandetanib
- Consider patient specific risk factors
  - Hypokalemia and hypomagnesaemia
  - Underlying cardiovascular disease
  - Concurrent QT prolonging drugs
- Consider baseline ECG and periodic monitoring

Ventricular Dysfunction

- Thought to be type II cardiotoxicity
  - Stems from decreased myocardial coordination
  - Most likely does NOT result in myocardial death
- Multifactorial cause
  - Inhibition of receptors that affect cardiac contractility
    - May be direct or bystander “target” of oral chemotherapy
- Review patient for underlying risk factors and correct if possible
  - Consider baseline LVEF monitoring and periodic follow-up per manufacturer recommendation

Venous Thromboembolism

- **Risk Factors:**
  - Specific cancer
  - Tumor burden
  - Anticancer treatment
    - Angiogenesis inhibitors, immunomodulatory agents
  - Surgery
  - Familial thrombophilia
  - Previous venous thromboembolism
  - Immobilization
  - Age
  - Central lines/catheters

- **Management:**
  - Routine primary prophylaxis not recommended
    - Exceptions: post major surgery up to 4 weeks, immunomodulatory agents
  - **Treatment:**
    - Low molecular weight heparin
      - Dalteparin 200 units/kg SQ once daily x 30 days, then 150 units/kg SQ once daily
      - Enoxaparin 1 mg/kg SQ BID
    - Monitoring: severe renal impairment, low body weight, thrombocytopenia
    - Warfarin and other oral anticoagulants are not recommended
    - Duration: 3-6 months to indefinite

### Miscellaneous Toxicities

- Alopecia
- Arthralgias/Myalgias
- Hepatic
- Hypothyroidism
- Metabolic
- Ocular
- Pulmonary
Alopecia

- Head, face, arms, legs, underarms, pubic area
- May fall out entirely, gradually, or in sections/patches
- Onset: 7-10 days, increase 1-2 months
- Regrow 1-3 months after, completely 6-12 months
  - Texture, color changes
- Grade 1: < 50% hair loss
- Grade 2: ≥ 50% hair loss, wig or hair piece necessary

http://www.cancer.net/navigating-cancer-care/side-effects/hair-loss-or-alopecia
Alopecia Management

- Expectations
- Hair and scalp care
  - Scalp sunscreen
- Wigs and hairpieces
- Mild shampoos
- Soft hairbrush
- Low heat when drying hair
- Do not use rollers to set hair
- Do not color hair or get a permanent
- Short hair cut
- Sunscreen SPF 15, sun block, hat or scarf to protect scalp

http://www.cancer.net/navigating-cancer-care/side-effects/hair-loss-or-alopecia
Arthralgias/Myalgias

- **Arthralgias**: symmetrical joint aches
- **Myalgias**: muscle pains
  - Improves with use and exercise
- **Abiraterone**: joint swelling/discomfort/muscle discomfort
- **Aromatase inhibitors**: 10-15%
  - Higher incidence than with tamoxifen
  - Cause: estrogen depletion?; Vitamin D deficiency
  - Risk factors: obesity, prior hormone replacement therapy, previous chemotherapy, baseline arthralgias or osteoarthritis
  - Treatment: exercise, acupuncture, yoga, weight loss, simple analgesics to high dose NSAIDs, aromatase inhibitors/tamoxifen rotation

Hepatic Toxicity

- Includes asymptomatic LFT elevations, chronic hepatitis with or without necrosis, cholestasis, sinusoidal obstruction and acute liver failure
- Causes
  - Direct tumor effects
  - Direct therapy-induced hepatotoxicity
  - Prothrombotic effects
- Usually not fatal, reversible
- Types of injury
  - Ductal injury with cholestasis
  - Parenchymal cell injury with steatosis
  - Sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD)
  - Fibrosis or necrosis

Hepatic Toxicity

- Risk Factors
  - Preexisting liver disease
  - Chemotherapy agents
  - Concomitant hepatotoxic medications
  - Infection or reactivation of infections
  - Coexisting medical conditions

- Evaluation
  - Synthetic function: serum albumin, prothrombin time
  - Estimates of cellular injury: AST, ALT
  - Cholestasis or duct injury: ALK phos, GGT, direct bilirubin

- Management
  - Dose reductions
  - Hold therapy
  - Permanent discontinuation

### CTCAE Liver Toxicity Grading

<table>
<thead>
<tr>
<th>AE</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin increased</td>
<td>&gt; ULN to 1.5 X ULN</td>
<td>&gt; 1.5 to 5 X ULN</td>
<td>&gt; 3 to 10 X ULN</td>
<td>&gt; 10 X ULN</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>&gt; ULN to 2.5 X ULN</td>
<td>&gt; 2.5 to 5 X ULN</td>
<td>&gt; 5 to 20 X ULN</td>
<td>&gt; 20 X ULN</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>&gt; ULN to 3 X ULN</td>
<td>&gt; 3 to 5 X ULN</td>
<td>&gt; 5 to 20 X ULN</td>
<td>&gt; 20 X ULN</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>&gt; ULN to 3 X ULN</td>
<td>&gt; 3 to 5 X ULN</td>
<td>&gt; 5 to 20 X ULN</td>
<td>&gt; 20 X ULN</td>
</tr>
</tbody>
</table>

NCI CTCAE can be accessed at http://evs.nci.nih.gov/ftp1/CTCAE
Hypothyroidism

- Seen primarily with agents for renal cell carcinoma
- Includes subclinical lab abnormalities
- Multiple proposed mechanisms
  - VEGF inhibition/destructive thyroiditis
  - Increased $T_3$ and $T_4$ metabolism
  - Competitive inhibition with iodine
- Assess TSH/$T_3$/T$4$ at baseline
  - Consider TSH at the beginning of each cycle and T$4$ supplementation if symptoms present
- Patient should have routine thyroid assessment
- Thyroid replacement (if warranted)

Metabolic Abnormalities

- Includes hyperglycemia and dyslipidemias
  - Thought to be due to PI3K/AKT/mTOR inhibition
- Assess labs at baseline and periodically thereafter
  - Treat with medication as indicated
- Guidelines for treatment follow that of general population
  - Diet
  - Exercise
  - Medications

Ocular Toxicity

- Includes a wide range of ocular disorders
- Thought to be due to EGFR, PDGF, and c-Kit inhibition
- Use with caution in patients with dry eyes, contact use, or a history of ocular disorders
- Temporarily discontinue use for eye pain, swelling, redness, blurred vision or other visual impairment
  - Refer to ophthalmologist if symptoms do not resolve or for severe pain or sensory defects

Erlotinib, vandetanib, vemurafenib, dabrafenib, trametinib, crizotinib

Pulmonary Toxicity

- Includes pneumonitis, interstitial lung disease, pleural effusions
- Occurs from numerous agents with multiple mechanisms of action
  - Black box warning with idelalisib, methotrexate
- Multiple proposed mechanisms
  - Cell mediated autoimmune response
  - Apoptosis of type I and II pneumocytes
  - Reduction of lung structure remodeling
  - Decreased alveolar regeneration from EGFR inhibition
- No good monitoring or prevention guidelines
  - Use caution in patients with underlying lung disease or previous lung radiation

## Long Term Side Effects

- Fertility
- Neuropathy
- Organ Damage
- Secondary Malignancies
- Sensorial Losses
Teratogenicity

- Factors in fetal risk
- Ethical issues
- Precautions
- Risk dependent on gestational age
- Methotrexate: greatest risk of fetal loss
- Other considerations:
  - Supportive care agents
  - Maternal toxicity
  - Altered kinetics
  - Risk of late effects

Thalidomide, antimetabolites, hormonal agents
Secondary Malignancies

- Most common
  - AML (acute myeloid leukemia) and MDS (myelodysplastic syndrome)
- Secondary leukemias
  - PARP inhibitors
- Solid tumors
  - Vemurafenib and dabrafenib: squamous cell carcinoma of skin
When to Contact the Physician

- A fever of 100.4°F or greater (taken by mouth)
- Bleeding or unexplained bruising
- A rash or allergic reaction, such as swelling of the mouth or throat, sudden severe itching, trouble breathing or swallowing
- Intense chills
- Pain or soreness at the chemo injection site or catheter site
- Unusual or new kind of pain, including intense headaches
- Shortness of breath or trouble breathing
- Diarrhea that lasts 2-3 days
- Vomiting that lasts more than a day or two
- Bloody stool or blood in your urine
- Any new or unusual problem that is causing concern
Clinical Case Vignette

- KP is a 49 year old female on everolimus for treatment of renal cell cancer. She has been using the baking soda/salt/warm water mouth rinses at least 4x/day as recommended but is getting more patches along her tongue and gum. She is no longer eating and only drinking cold beverages due to the pain.

- What should she do next?
Resources for Oral Oncology
Patient Education

- Development of multidisciplinary education and monitoring program
- Pharma Patient Support Programs
  - Drug information brochures, phone support, emails -> adherence
- Oncology Nursing Society (ONS)
  - Oral adherence toolkit
  - Association of Community Cancer Centers (ACCC)/Hematology Oncology Pharmacy Association (HOPA)/ONS/National Community Oncology Dispensing Association (NCODA) oral chemotherapy education initiative

Patient Resources

- **Adherence**
  - Top Rates Medication Reminder Apps: MyMedSchedule, MyMeds, RxmindMe, MediSafe, Care4Today, Mango Health

- **Financial Assistance**. www.needymeds.org

- **Side Effect and Cancer Education**
  - Chemocare.com
  - HOPA website: Time to Talk CINV Toolkit http://www.hoparx.org/patient-education/time-to-talk-cinv
  - Cancer.Net
    - ASCO Answers Taking Medications Correctly/Nausea and Vomiting/What is Chemotherapy/Safe Handling and Disposal of Chemotherapy

- **Drug Interactions**
  - Lexicomp® Clinical Drug Information, Micromedx, package insert
  - About Herbs Memorial Sloan Kettering Cancer Center’s Guide to Botanicals, Supplements, Complementary Therapies, and More
  - Natural Medicine Database
Summary

- Important to discuss proper storage, handling and disposal of oral oncologics
- Many challenges exist for patients while taking oral oncologics
- Essential to counsel patients on adverse effects and their management
- Several resources available for patient and providers on adverse effect management
Clinical Case Vignette

- NT is a 48 year old female diagnosed with metastatic colorectal cancer. She has progressed on previous treatment and is about to start regorafenib. She is very anxious that this therapy won’t work too and has been seeking advice from other patients and the internet on supplements she can take.

- She is interested in taking:
  - Immune Force: Mushroom & Oil Combination - Helps Strengthens the Body’s Natural Defense System; Core Liver Replenishment - Enhances Liver/Gut/Brain Communication; Minerals & Herbs - Support Healthy Circulation and Cellular Regeneration; Liposomal Delivery - Optimizes Cellular Detoxification

- How do you respond?
- What resources could you use?
1. Assessment Question

JT’s wife comes to the pharmacy to pick up her husband’s new prescription for brigatinib. He progressed on crizotinib and his wife states they have about 20 pills left. She asks you what they should do with the remaining medication? You respond:

A. Flush the pills down the toilet
B. Open up the capsules into the trash
C. Dissolve the capsules in water and pour down the drain
D. Bring them to your local drug take back program
2. Assessment Question

WW is a 72 year old man who was placed on enzalutamide for his prostate cancer. He is also on warfarin for his atrial fibrillation. What is a concern you have when giving these 2 medications together?

A. I have no concerns
B. These medications are contraindicated to be given together and he should receive a different medication for his prostate cancer
C. WW may have an increased risk of bleeding due to a drug interaction and more frequent INR monitoring is indicated
D. WW’s warfarin may be less effective due to a drug interaction and this combination should be avoided
3. Assessment Question

Patient CG presents to your pharmacy to pick up a new prescription for capecitabine for treatment of his colorectal cancer. He has read information on hand foot syndrome and is wary of taking the medication. He asks you what he can do to prevent it from occurring. What do you tell him?

A. There are no ways to prevent its development. However, urea based moisturizers can be used for treatment if it develops.
B. Take hot showers.
C. Ask physician for tetracycline based cream to use preemptively.
D. Use shock absorbers in shoes and consider manicure/pedicure.
4. Assessment Question

Patient BK comes to your pharmacy to pick up his prescription for erlotinib. He says he has been struggling with the rash on his face. He asks you for some recommendations. Which of the following are appropriate resources for you to use to help BK?

A. Chemocare.com
B. Natural Medicine Database
D. Medication Adherence Toolkit
The Rise in Oral Oncologic Medications: New Opportunities for Pharmacists

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Megan May, Pharm.D., BCOP