ORAL CHEMOTHERAPY: SETTING EXPECTATIONS FOR PATIENTS AND PROVIDERS

Douglas Hackenyos, PharmD
Clinical Pharmacy Specialist
Tufts Medical Center
Unclear expectations…

- DN, a 62 M w/ refractory multiple myeloma prescribed:
  - Ixazomib (Ninlaro) 4 mg PO days 1, 8, 15
  - Lenalidomide (Revlimid) 25 mg PO days 1-21
  - Dexamethasone 40 mg PO weekly

- Call received in clinic c/o sleeplessness, jitteriness, and extreme hunger
  - Complete course of dexamethasone finished over 4 days
- On day 8, DN calls to report that he broke one of his ixazomib capsules while trying to open the packaging
Unclear expectations…

• CL, a Cantonese-speaking 42 F w/ advanced gastric cancer prescribed adjuvant therapy with intravenous cisplatin, trastuzumab, and:
  • **Capecitabine (Xeloda)** 1000 mg/m² twice daily for two weeks, followed by one week off
    • 1300 mg per dose = two 500 mg tablets and two 150 mg tablets
    • Restricted to fill prescription through outside specialty pharmacy

• After 3 cycles:
  • Patient found to have taken only half of the intended daily dose
  • Patient believed capecitabine was an antibiotic rather than chemotherapy
Objectives

• Describe current trends in oral chemotherapy drug development and approvals
• Analyze complexities in initiating treatment with oral chemotherapy
• Apply evidence-based supportive care strategies for the prevention and management of unique oral chemotherapy toxicities
• Evaluate opportunities for pharmacist involvement in the care of patients receiving oral chemotherapy
Oral Chemotherapy Approvals

1950s
- Mercaptopurine
- Methotrexate
- Busulfan
- Chlorambucil
- Cyclophosphamide

1960s
- Melphalan
- Thioguanine
- Procarbazine

1970-80s
- Lomustine
- Etoposide

1990s
- Capecitabine
- Thalidomide
- Temozolomide

Early 2000s
- Imatinib
- Gefitinib
- Erlotinib
- Sorafenib

Recent Approvals

New Oral Agents Approved

New Oral Agents Approved

Year


## 2015-2016 Approvals

<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib (Lenvima)</td>
<td>Metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer</td>
</tr>
<tr>
<td>Panobinostat (Farydak)</td>
<td>3rd-line treatment of multiple myeloma, in combination with bortezomib &amp; dexamethasone</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>Metastatic non-small cell lung cancer (NSCLC) with select EGFR deletions/mutations</td>
</tr>
<tr>
<td>Trifluridine/tipiracil</td>
<td>Metastatic colorectal cancer following 5-FU, oxaliplatin, irinotecan,</td>
</tr>
</tbody>
</table>

Looking ahead...~35% of antineoplastic agents in development are oral

<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib (Tagrisso)</td>
<td>Metastatic EGFR T790M mutation (+) NSCLC</td>
</tr>
<tr>
<td>Ixazomib (Ninlaro)</td>
<td>2nd-line treatment of multiple myeloma, in combination with lenalidomide &amp; dexamethasone</td>
</tr>
<tr>
<td>Alectinib (Alecensa)</td>
<td>ALK-positive metastatic NSCLC following progression or intolerance to crizotinib</td>
</tr>
<tr>
<td>Venetoclax (Venclexta)</td>
<td>Relapsed/refractory chronic lymphocytic leukemia, 17p deletion</td>
</tr>
<tr>
<td>Rucaparib (Rubraca)</td>
<td>3rd-line treatment of advanced ovarian cancer with BRCA mutation</td>
</tr>
</tbody>
</table>


The oral chemotherapy landscape

<table>
<thead>
<tr>
<th>Afatinib</th>
<th>Cobimetinib</th>
<th>Hydroxyurea</th>
<th>Mercaptopurine</th>
<th>Ponatinib</th>
<th>Thioguanine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>Crizotinib</td>
<td>Ibrutinib</td>
<td>Methotrexate</td>
<td>Procarbazine</td>
<td>Topotecan</td>
</tr>
<tr>
<td>Altretamine</td>
<td>Cyclophosphamide</td>
<td>Idelalisib</td>
<td>Mitotane</td>
<td>Regorafenib</td>
<td>Trametinib</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Dabrafenib</td>
<td>Imatinib</td>
<td>Nilotinib</td>
<td>Rucaparib</td>
<td>Tretinoin</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Dasatinib</td>
<td>Ixazomib</td>
<td>Olaparib</td>
<td>Ruxolitinib</td>
<td>Trifluridine/Tipiracil</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Erlotinib</td>
<td>Lapatinib</td>
<td>Osimertinib</td>
<td>Sonidegib</td>
<td>Vandetanib</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Estramustine</td>
<td>Lenalidomide</td>
<td>Palbociclib</td>
<td>Sorafenib</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Etoposide</td>
<td>Lenvatinib</td>
<td>Panobinostat</td>
<td>Sunitinib</td>
<td>Venetoclax</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Everolimus</td>
<td>Lomustine</td>
<td>Pazopanib</td>
<td>Temozolomide</td>
<td>Vismodegib</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Gefitinib</td>
<td>Melphalan</td>
<td>Pomalidomide</td>
<td>Thalidomide</td>
<td>Vorinostat</td>
</tr>
</tbody>
</table>

Explaining the Paradigm Shift

- Cytostatic nature of recently developed drugs requires continuous administration
- Sensitive monitoring techniques detecting minimal residual disease, requiring chronic therapy
- Drug companies incentivized by the introduction of Medicare Part D
- Patient preference
  - 63-89% of patients prefer PO vs IV therapy (assuming equal efficacy)

Perceived Advantages

- Avoidance of infusion port placement or frequent IV access
- Fewer clinic visits
- Reduced demand on hospital staff and less resource-intensive therapy
- Patient empowerment
Multidisciplinary discussion regarding the impact of increasing oral chemotherapy use, including:

- Common misconceptions
  - Not “real” chemotherapy; convenience; easier to administer; fewer side effects
- Patient selection criteria
  - Adherence, compliance, and monitoring concerns
- Safety issues
  - Medication errors, communication issues, biohazard issues
- Factors affecting oncology practice
  - Changes in the process of care, potential financial impacts
- Distribution
  - Impact on mail order, specialty, hospital, and community pharmacies
- Financial concerns
  - Prescription insurance and formulary management issues
INITIATING TREATMENT WITH ORAL CHEMOTHERAPY
Patient Case & Audience Response

DN, our 62 YOM, meets with the pharmacist to review his treatment with ixazomib, lenalidomide, & dexamethasone. Which of the following counseling points must the pharmacist make at the start of every cycle?

a) Capsules must not be broken, chewed, or opened

b) Female partners must contact their healthcare provider immediately if they become pregnant

c) Blood and sperm may be donated during “off-weeks” only

d) A and B only

e) A, B, and C
Establishing Standards in Oral Chemotherapy

• 2013 American Society of Clinical Oncology (ASCO)/Oncology Nursing Society (ONS) Chemotherapy Administration Safety Standards
  • Addressed trends by publishing standards for the safe administration and management of oral chemotherapy
    • 2016 Update focusing on pediatric oncology

• Chemotherapy: All antineoplastic agents used to treat cancer, given through oral and parenteral routes or other routes as specified in the standard
  • Includes “traditional chemotherapy” and targeted agents, monoclonal antibodies, and biologics
  • Excludes hormonal therapies

2013 ASCO/ONS Chemotherapy Administration Safety Standards Relating to Oral Chemotherapy

Oral chemotherapy planning:
• Outline frequency of visits/monitoring in treatment plan
• Document ability to obtain and administer oral chemotherapy agent in treatment plan

Oral chemotherapy order/prescription standards:
• Procedures for communicating discontinuation of oral chemotherapy, including patient education on stopping and disposing
• It may be appropriate to alert the dispensing pharmacy when the oral chemotherapy is discontinued
2013 ASCO/ONS Chemotherapy Administration Safety Standards Relating to Oral Chemotherapy

Patient consent and education:

- Informed consent
- Written or electronic patient education materials, which includes:
  - Storage, handling, preparation, administration, and disposal information
  - Concurrent cancer treatment/supportive care medications/measures (if applicable)
  - Possible drug/drug and drug/food interactions
  - Plan for missed doses

Monitoring and assessment

- Policy and/or procedure to complete an initial adherence assessments, including plans to address identified issues.

- Adherence assessments should include:
  - Confirmation that the patient filled the prescription as written.
  - Inquiry regarding concerns about treatment costs.
  - Verification that the patient understands how to take the prescribed oral chemotherapy.
  - Verification that the patient understands what to do in case of missed doses.
  - Assessment for potential toxicity.
Access Concerns

• Average wholesale price for monthly supply:
  • Tarceva (erlotinib)—150 mg (30 tablets): $8,694.85
  • Ninlaro (ixazomib)—4 mg (3 capsules): $10,404
  • Imbruvica (ibrutinib)—140 mg (90 capsules): $12,291.06
  • Revlimid (lenalidomide)—25 mg (21 capsules): $13,529.22
  • Pomalyst (pomalidomide)—4 mg (21 capsules): $15,669.67

• Medicare Part D Coverage Gap—the “donut hole”
  • For 2017, after $3,700 paid by patient and plan (combined), patient responsible for 40% of plan’s cost for brand-name drugs
  • “Catastrophic coverage” reached after $4,950 in out-of-pocket spending, patient responsible for paying 5% co-insurance

Human capital costs of obtaining oral anticancer medications

• Quantified staff effort in initiating on-label oral anticancer medications for kidney/prostate cancer (8/1/14-8/31/15)

<table>
<thead>
<tr>
<th>Results (116 patients, 149 unique prescriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average/median monthly copay</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Average days from prescribing to starting treatment</strong></td>
</tr>
<tr>
<td><strong>Calls made by staff to obtain medication</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
INITIATING TREATMENT WITH ORAL CHEMOTHERAPY

Administration and Adherence
## With food? Or not with food?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Instructions</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>Take within 30 minutes of a meal</td>
<td>Cmax ↑ 2.47-fold and AUC ↑ 1.51-fold w/o food</td>
</tr>
<tr>
<td>(Xeloda)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>Take with food</td>
<td>Avoids stomach irritation (iron in caps)</td>
</tr>
<tr>
<td>(Gleevec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Take after a low-fat meal (&lt;600 calories &amp; &lt;30% fat)</td>
<td>Mean AUC ↑ 36% for low-fat meal vs ↑ 48% with high-fat</td>
</tr>
<tr>
<td>(Stivarga)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Take w/o food (≥1 hr before or ≥2 hrs after a meal)</td>
<td>Bioavailability ~100% w/ vs 60% w/o food</td>
</tr>
<tr>
<td>(Tarceva)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Take on an empty stomach (≥1 hr before or ≥2 hrs after a meal)</td>
<td>Bioavailability ↑82% w/in 30 min of a high-fat meal</td>
</tr>
<tr>
<td>(Tasigna)</td>
<td></td>
<td><strong>Black Box Warning &amp; REMS Program</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• QT prolongation and sudden death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↑ absorption w/ food = ↑ risk</td>
</tr>
</tbody>
</table>

Controversy with Abiraterone

- Recommended to take on an empty stomach
  - Low-fat meal: $C_{\text{max}}$ ↑ 7-fold and systemic exposure ↑ 5-fold
  - High-fat meal: $C_{\text{max}}$ ↑ 17-fold and systemic exposure ↑ 10-fold
Foods to avoid altogether

- **Grapefruit or grapefruit juice**
  - Strong, irreversible 3A4 inhibitor by furanocoumarins (e.g. bergamottin) in GF juice—numerous interactions
  - 200 mL of GF juice (one grapefruit) enough to cause clinically relevant changes in drug concentrations

- **Seville (bitter) oranges**
  - Moderate 3A4 inhibitors—Ibrutinib package insert

- **Starfruit (Carambola)**
  - Strong 3A4 inhibitor—Ibrutinib and venetoclax PIs

- **Pomelos, limes, pomegranate, hops**
  - Reports of varying impact on CYP 3A activity

- **Tyramine-rich foods** with procarbazine
  - Aged meats and cheeses, beer, wine, dried fruits

References:
### pH-Dependent Absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosutinib (Bosulif)</td>
<td>Single-dose Cmax ↓46% and AUC ↓26% with PPI</td>
</tr>
<tr>
<td>Dasatinib (Sprycel)</td>
<td>Dose-adjusted AUC ↓ 58% with PPI/H2RA</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)*</td>
<td>Cmax ↓~61% and AUC ↓46% with PPI</td>
</tr>
<tr>
<td>Nilotinib (Tasigna)*</td>
<td>Single-dose Cmax ↓27% and AUC ↓ 34% with PPI</td>
</tr>
<tr>
<td>Others: gefitinib, dabrafenib</td>
<td></td>
</tr>
</tbody>
</table>

# pH-Dependent Absorption: Management

<table>
<thead>
<tr>
<th>Interacting Agent</th>
<th>General Management Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitors</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Histamine$_2$ Receptor Antagonists</td>
<td>Give oral chemo dose ≥2 hours before or 10 hours after H2RA</td>
</tr>
<tr>
<td>Antacids</td>
<td>Separate by ≥2 hours before or after dose</td>
</tr>
</tbody>
</table>

**When Acid Suppression is Required:**
- **Treatment alternatives**
  - e.g. afatinib in place of erlotinib
- **Gastric re-acidification?**
  - Reversal of rabeprazole-induced hypochlorhydria with betaine HCl for improved dasatinib absorption demonstrated in healthy volunteers

Importance of adherence

6-Mercaptopurine (6MP) non-adherence in pediatric acute lymphoblastic leukemia

- Daily 6-MP over 2 years a key component of maintenance therapy
- 20.5% of patients took <90% of prescribed 6-MP doses
  - 3.9-fold more likely to relapse vs those with ≥90% adherence

Predictors of non-adherence

- Age ≥12 years
- Hispanic or African American
- Parental education ≤ high school
- Annual household income <$50,000
- Involvement of >2 adults in 6MP supervision
- Failure of caregivers to understand the purpose of 6MP
- Failure to take 6MP at the same time each day
- Taking 6MP with milk/dairy

Patient Case and Audience Response

JT is a 64 YOM with newly diagnosed EGFR-positive metastatic non-small cell lung cancer. JT is on the following medications:

- Amlodipine 10 mg PO QDay
- Atorvastatin 20 mg PO QDay
- Docusate 100 mg PO QDay
- Levothyroxine 75 mcg PO QDay
- Omeprazole 20 mg PO QDay
- Oxycodone 5 mg PO Q4-6H PRN pain
- Senna 17.2 mg PO QDay PRN constipation

JT’s oncologist plans to start him on erlotinib (Tarceva). Which of JT’s current medications would be most important to discuss before starting erlotinib?
Patient Case and Audience Response

JT cannot remember why he is taking omeprazole and says that he’s been on it for more than a year. There are no supporting indications in his medical record. **Which of the following is a reasonable recommendation given his upcoming erlotinib (Tarceva) start?**

a) Take erlotinib in the morning & omeprazole in the evening

b) Switch to famotidine 40 mg PO QHS & take erlotinib in the morning

c) Take erlotinib with a 8 oz of orange juice

d) Hold omeprazole & have JT report any new reflux symptoms
UNIQUE TOXICITIES OF ORAL CHEMOTHERAPY
CL has been counseled on the correct capecitabine dose and returns to clinic after her next cycle noting new redness and sensitivity on her palms and soles. Which of the following would be an appropriate recommendation?

a) CL should be more cautious in touching the capecitabine tablets to reduce her symptoms

b) CL is having an atypical allergic reaction and should permanently discontinue capcetibine therapy

c) CL should be continue on her current regimen and be reassessed in two weeks

d) CL should have her treatment with capecitabine held until all redness has resolved
Unique Toxicities: Hand-Foot Syndrome

Hand-Foot Syndrome (HFS; palmar-plantar erythrodysesthesia)

**Offending agents** (incidence):
- Capecitabine (54-60%, all grades)
- Various IV (e.g. Doxil)

**Theorized Pathogenesis**
- Direct toxic effect on eccrine sweat gland cells of palms/soles
- ↑ sensitivity due to ↑ proliferative rate of epidermal basal cells
- Inflammation due to ↑ COX-2
- ↑ expression of thymidine phosphorylase

Hand-Foot Skin Reaction (HFSR)

**Offending agents** (incidence):
- Multikinase inhibitors
  - Sorafenib (21-69%)
  - Regorafenib (45-67%)
  - Sunitinib (23-29%)
  - Axitinib (27%)
  - Pazopanib (6%)

**Theorized Pathogenesis**
- Loss of endothelial cell/fibroblast repair mechanisms + daily trauma

HFS and HFSR: Presentation

Hand-Foot Syndrome

- Onset: Variable (days-months)

Hand-Foot Skin Reaction

- Onset: ~2-4 weeks following initiation

HFS and HFSR: Prevention

Self-care recommendations:
• Removal of calluses prior to treatment
• Avoid:
  • Excessively hot water
  • Friction/trauma for first 2-4 wks of therapy
  • Tight-fitting shoes
  • Excessive pressure when applying lotion
• Wear:
  • Thick cotton gloves +/- slippers or socks
• Use:
  • Heavy moisturizer (petroleum-lanolin based ointments) or ammonium lactate 12% cream BID
HFS: Pharmacologic Prevention

2014 Meta-analysis featuring 10 trials (N=1963) evaluating 4 preventative agents

- Grade 1 HFS:
  - No difference in risk with any strategy
- Grade 2-3 HFS:
  - **Celecoxib** 200-400 mg BID shown to significantly reduce risk in patients receiving capecitabine for colorectal cancer ($P=0.003$)
    - NNT = 7
    - No reported adverse effects

Prophylactic steroids, regional cooling strategies not widely supported

HFS and HFSR: Suggested Management

- **Grade 1**: Minimal skin changes or dermatitis without pain
  - Continue at current dose and monitor
  - Reassess in 2 weeks and proceed to next grade of treatment if not improved/worse

- **Grade 2**: Skin changes with pain; limiting instrumental ADLs
  - Continue at current dose and monitor
  - Urea 20% cream BID and clobetasol 0.05% cream QDay/BID; pain control as indicated
  - Reassess in 2 weeks and proceed to next grade of treatment if not improved/worse

- **Grade 3**: Severe skin changes with pain; limiting self care ADLs
  - Hold antineoplastic therapy until recovery to Grade 0 or 1
  - Clobetasol 0.05% cream BID and pain control
  - Reassess in 2 weeks for improvement and dose reduce or discontinue therapy as indicated

Stomatitis

**Incidence**

- Mammalian target of rapamycin (mTOR) inhibitors associated stomatitis (mIAS)
  - **Everolimus (Afinitor):** 44-78%
  - Temsirolimus IV (Torisel): 41%
  - [Sirolimus (Rapamune): 3-10%]
- Associated with other tyrosine kinase inhibitors to a varying degree

**Pathogenesis**

- Theorized to involve direct epithelial injury, increased apoptosis, and release of pro-inflammatory cytokines

---

Sonis S, Adreotta PW, Lyng G. Oral Dis. 2016 Nov 29 [Epub ahead of print]
mTOR Inhibitor-associated Stomatitis

• **Onset**
  • Median time to ulcer development: 10 days (range 4-25 days)
    • Faster than conventional chemotherapy

• **Presentation**

• **Impact**
  • 24% of patients required dose interruptions/reductions on everolimus & exemestane (BOLERO-2 Trial)

mIAS: Nonpararmacologic Prevention

- Patient counseling and diligent monitoring
- Good oral hygiene
  - Regular brushing with a soft-bristled toothbrush
  - Avoid alcohol-containing rinses & toothpastes with sodium lauryl sulfate
  - Frequent rinses with bland mouth rinses
- Consider oral moisturizers
- Avoid acidic/spicy/crunchy foods
2016 SWISH Trial: Prevention of everolimus/exemestane (EVE/EXE) stomatitis in metastatic breast cancer using a dexamethasone-based mouthwash

| **Patients (N=86)** | Postmenopausal women with hormone-receptor+ metastatic breast cancer  
• EVE 10 mg and EXE 25 mg daily |
|---------------------|-------------------------------------------------------------------|
| **Intervention**     | Dexamethasone oral solution (0.5 mg/5 mL)  
• Swish 10 mL x 2 min, then spit QID for 8 wks starting on day 1 of EVE/EXE therapy |
| **Results**          | Stomatitis rate at 8 wks, SWISH vs BOLERO-2 (historical control)  
• Grade 1: 17.4% vs 34%  
• Grade 2: 2.4% vs 25%  
• Grade 3: 0% vs 8%  
Mean pain score <1 at all visits  
86% of patients reported a normal diet at 8 weeks |
Management

Everolimus: Stomatitis dose adjustment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal</td>
<td>No adjustment</td>
</tr>
<tr>
<td>2</td>
<td>Moderate, can tolerate modified diet</td>
<td>Hold dose until ≤ grade 1, then resume same dose</td>
</tr>
<tr>
<td>3</td>
<td>Severe, interfering w/ PO intake</td>
<td>Hold and reduce dose upon recovery</td>
</tr>
<tr>
<td>4</td>
<td>Life threatening</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

Pharmacologic interventions

- Pharmacologic interventions
  - Topical anesthetics (e.g. lidocaine)
  - Topical corticosteroids (e.g. dexamethasone)
  - Compounded mouth rinses (e.g. Magic Mouthwash)
  - Systemic corticosteroids for severe resistant mIAS (prednisone 5 mg Qday-BID)

- Grade 3 mIAS typically resolves to grade ≤1 in ~3 wks with complete resolution in ~7 wks

Unique Toxicities: Acneiform Rash

Offending Agents (Incidence)

- Epidermal growth factor receptor (EGFR) inhibitors
  - Erlotinib (49-85%)
  - Afatinib (90%)
  - Gefitinib (58%)
  - Osimertinib (41%)
  - [Cetuximab, panatumumab, necitumumab (IV)]
- Multikinase inhibitors
  - e.g. sunitinib, sorafenib (20-40 %, lesser severity)

Lacouture ME. ASCO Post 2013;4(8).
Acneiform Rash: Pathogenesis

Lacouture ME. ASCO Post 2013;4(8).
Acneiform Rash: Presentation

- **Onset:**
  - Typically within the first 2 weeks of treatment

- **Distribution:**
  - Seborrheic areas (primarily the face, scalp; upper trunk)
  - Most cases mild/moderate; however, up to 76% will hold therapy and 32% will discontinue therapy

Lacouture ME. ASCO Post 2013;4(8).
Boone SL et al. Oncology 2007;72(3-4):152-159.
Correlation between rash and response

2013 Meta-analysis featuring 33 trials (N=6798) evaluating the predictive value of rash with EGFR-TKIs in NSCLC prognosis

|                                | Rash       | No Rash    | Relative risk
|--------------------------------|------------|------------|----------------
| Objective response rate        | 21.08%     | 6.06%      | (RR = 3.28, 95% CI 2.41-4.47; P=0.228) |
| Disease control rate           | 64.51%     | 32.82%     | (RR = 1.96, 95% CI 1.58-2.43; P=0.003) |
| Progression-free survival      | Relative risk of disease progression ↓ 55% with rash (HR 0.45, 95% CI 0.37-0.53; P=0.001) |
| Overall survival               | Relative risk of death ↓ 60% with rash (HR 0.40, 95% CI 0.28-0.52; P=0.001) |

EGFR Inhibitor Acneiform Rash: Prevention

2010 Skin toxicity evaluation protocol with panitumumab (STEPP) phase II, open-label randomized trial (N=95)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Pre-emptive treatment (starting 1 day prior to first panitumumab dose and continuing through week 6 of treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Skin moisturizer QAM</td>
</tr>
<tr>
<td></td>
<td>• Sunscreen (PABA free, SPF ≥15 UVA/UVB)</td>
</tr>
<tr>
<td></td>
<td>• Topical hydrocortisone 1% cream QHS</td>
</tr>
<tr>
<td></td>
<td>• Doxycycline 100 mg PO BID</td>
</tr>
<tr>
<td>Reactive skin care regimen</td>
<td>• Investigator’s choice</td>
</tr>
<tr>
<td>Results</td>
<td>Incidence of Grade ≥2 skin toxicities</td>
</tr>
<tr>
<td></td>
<td>• Pre-emptive 29% vs Reactive 62% (OR, 0.3; 95%CI 0.1-0.6)</td>
</tr>
<tr>
<td></td>
<td>• Less QOL impairment with pre-emptive treatment</td>
</tr>
</tbody>
</table>

EGFR Inhibitor Acneiform Rash: Guideline Recommendations

Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group

Guideline Recommendations

- **Prevention recommended for all patients**
  - Hydrocortisone 1% combined with a moisturizer, sunscreen, and doxycycline 100 mg BID for the first 6 weeks
    - Benefit associated with anti-inflammatory vs antibiotic effects

- **Reactive management**
  - Medium- to high-potency topical corticosteroids (alclometasone 0.05% cream or fluocinonide 0.05% cream BID)
  - Topical clindamycin 1%
  - Oral antibiotics (doxycycline or minocycline)

- Avoid topical astringents/alcohol-based acne products

Patient Case and Audience Response

Two weeks after starting erlotinib (Tarveca), JT is seen in clinic with an acne-like rash on his face and chest. The oncology fellow asks you to see JT with him. Which of the following recommendations is the most appropriate in regards to managing JT’s rash?

a) JT should try to pop any visible whiteheads and apply benzoyl peroxide to the affected areas daily
b) JT should take his erlotinib with food to reduce its bioavailability and side effects
c) JT should stop taking erlotinib since his rash likely indicates that he’ll respond poorly to the drug
d) JT should begin using topical steroids, topical clindamycin and oral doxycycline
## Other Unique Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Associated Agents</th>
</tr>
</thead>
</table>
| **Visual/Ophthalmic SEs**            | • EGFR Inhibitors  
• ALK inhibitors                                         |
| **Dysphonia**                        | Associated with VEGF inhibition  
• e.g. regorafenib                                                  |
| **Nail toxicity**                    | Numerous offending agents  
• Imatinib, capecitabine  
• Gefitinib, erlotinib, capecitabine  
• Imatinib, sorafenib, sunitinib |
| **Hair depigmentation & texture changes** | C-Kit inhibition  
• Sunitinib  
• Sorafenib,  
• pazopanib |

Many insidious side effects that are less unique:  
• Metabolic syndromes (hypertension, hyperlipidemia, hypothyroidism, electrolyte abnormalities), QTc prolongation, hepatotoxicity, etc.
ORAL CHEMOTHERAPY AND PHARMACIST OPPORTUNITIES
Pharmacy & Oral Chemotherapy

**Prescription**
- Improvements in order forms/care plans
- Incorporation of safety standards

**Medication Access**
- Prior authorization
- Financial assistance
- Dispensing (specialty pharmacy)

**Education**
- New-start counseling by pharmacist
- Verbal and written instructions per ASCO/ONS standards

**Monitoring**
- Pharmacy oversight and monitoring
- Access, adherence, toxicity

Oral Chemotherapy Education

- MASCC Oral Agent Teaching Tool (MOATT©)
  - Constructed via expert consensus and evaluated in the education of 635 patients/caregivers by 114 nurses

<table>
<thead>
<tr>
<th>MOATT© Sections</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Key Assessment Questions</td>
<td>Assesses knowledge of treatment plan, current medications, and ability to obtain and take oral agent</td>
</tr>
<tr>
<td>II. Patient Education</td>
<td>General teaching: Storage, handling, disposal, actions to take in event of problems</td>
</tr>
<tr>
<td>III. Drug Specific Information</td>
<td>Name, dose, schedule, potential side effects and management, interactions</td>
</tr>
<tr>
<td>IV. Evaluate</td>
<td>Assesses patient/caregiver understanding of information provided</td>
</tr>
</tbody>
</table>

Setting expectations

• DN, prescribed **Ixazomib (Ninlaro), Lenalidomide (Revlimid)** and dexamethasone with confusion in dexamethasone dosing and broken ixazomib capsule…

**Access**
- Initial prior authorization and copay assistance (in-house)
- Ongoing assistance (replacement capsule)

**Education**
- New-start counseling (including REMS requirements) by pharmacist
- Oral chemotherapy calendars
Setting expectations

• CL, a Cantonese-speaking 42 F w/ advanced gastric cancer prescribed adjuvant therapy with intravenous cisplatin, trastuzumab, and capecitabine (Xeloda), found to be taking only half of her intended dose

• Education and monitoring
  • Pharmacist counseling with Cantonese-speaking patient navigator
  • Review of all prescription vials and translation of instructions
  • Reinforced counseling at prescription refills and clinic visits
Pharmacy & Oral Chemotherapy Programs

- **University of Iowa Holden Comprehensive Cancer Center**
  - Pharmacist consultation and enrollment of patients in Celgene® REMS program for immunomodulatory agents
    - Prescription review, prior authorization, assistance, counseling, etc

- **Froedtert Clinical Cancer Center**
  - Development of oral chemotherapy protocols in the EMR
  - In-house pharmacist review upon prescription approval
  - Prior authorization, financial assistance, teaching visit scheduling

- **James Cancer Center – The Ohio State University**
  - In-house pharmacist notification and review upon oral chemo prescription entry in EMR
  - Disease-specific prior authorization coordinators
  - Patient counseling and follow-up

Pharmacy & Oral Chemotherapy Programs

University of North Carolina MC – ASHP Best Practice Award 2015

- Integrated, closed-loop, pharmacy-led oral chemotherapy program
- Education, adherence monitoring, and adverse effect management via clinical pharmacist with collaborative practice agreements

**Program Outcomes:**
- 107 patients enrolled, 350 patient encounters in the first year
- Adherence (patient-reported & medication possession ratio [MPR]):
  - GI/Breast = 86% and 85% (MPR)
  - Malignant hematology = 94.7% and 93.9% (MPR)
- Oral chemo understanding ↑ from 43% pre-test to 95% post-test
- CML major molecular response (MMR) rates (83%) compared to published averages of 40-60%
- Actual revenue >$4 million estimate for oral chemotherapy dispensed by specialty pharmacy

Conclusions

• Trends in oral chemotherapy approval and prescribing have increased the responsibility of the patient in cancer care
• The unique toxicities of many oral chemotherapies require awareness of both the patient and cancer care team for appropriate prevention and management
• Pharmacist involvement in oral chemotherapy education and monitoring has the potential for positive clinical and financial impacts at many institutions