Learning Objectives - Pharmacists

1. Describe trends in oncology drug approvals and prescription patterns.
2. Compare activity of targeted anticancer agents to traditional cytotoxic chemotherapy.
3. Recall how to identify and manage side effects associated with targeted oral anticancer agents.
4. Recognize modifications to medication profiles to resolve drug-drug interactions with targeted anticancer agents.
5. Explain safe handling and compounding instructions for oral anticancer agents.

Learning Objectives: Technicians

1. Describe trends in oncology drug approvals and prescription patterns.
2. Compare activity of targeted anticancer agents to traditional cytotoxic chemotherapy.
3. Identify side effects associated with targeted oral anticancer agents.
4. Recognize modifications to medication profiles to resolve drug-drug interactions with targeted anticancer agents.
5. Explain safe handling and compounding instructions for oral anticancer agents.

Disclosure

☐ I have no conflict of interest to disclose in relation to this activity.

Trends in anticancer therapies

Learning Objectives - Pharmacists

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5. Explain safe handling and compounding instructions for oral anticancer agents.

Trends: Drug approvals

Annual targeted oral anticancer agents FDA approvals

### Trends: Treatment Costs

![Graph showing trends in treatment costs](image)

Insurance payments for oncology therapy


### Activity: Anticancer agents

<table>
<thead>
<tr>
<th>Traditional chemotherapy</th>
<th>Targeted agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td></td>
</tr>
<tr>
<td>Interfere with cellular metabolism and growth, causing apoptosis (cell death)</td>
<td>Block specific signaling proteins</td>
</tr>
<tr>
<td><strong>Affected cells</strong></td>
<td></td>
</tr>
<tr>
<td>Any rapidly dividing cells:</td>
<td></td>
</tr>
<tr>
<td>• Tumor cells</td>
<td>• Tumor cells</td>
</tr>
<tr>
<td>• Bone marrow and blood cells</td>
<td>• Some specialized healthy cells</td>
</tr>
<tr>
<td>• Skin and mucous membranes</td>
<td></td>
</tr>
<tr>
<td>• Gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects (selected)</strong></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Rash</td>
</tr>
<tr>
<td>Myelosuppression (neutropenia, anemia, thrombocytopenia)</td>
<td>Hand-foot skin reaction</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Thyroid disorders</td>
</tr>
<tr>
<td></td>
<td>QTc prolongation</td>
</tr>
</tbody>
</table>

### Personalizing cancer treatment


### Activity: Traditional chemotherapy


### Activity: Targeted agents

![Diagram showing anticancer mechanism](image)

Anticancer mechanism of action


Patient case MG

- MG is a 77 y/o male with relapsed non-small cell lung cancer following first-line treatment with cisplatin and pemetrexed.
- PMH: Lung cancer, renal impairment, coronary artery disease
- Medication list:
  - Lisinopril 20 mg PO qday
  - Simvastatin 40 mg PO qhs
  - Carvedilol 6.25 mg PO BID
  - Aspirin 81mg POI qday
  - Tums (calcium carbonate) 750mg PO prn (most evenings) heartburn

Side effects: EGFR inhibitors

- EGFR = epidermal growth factor receptor
- EGFR mutations increase kinase signaling activity and confer sensitivity to targeted agents
- Common in non-small cell lung cancer (NSCLC)
- Especially common among Asian female non-smokers
- Present in 10% of non-Asian, 50% Asian NSCLC patients

Side effects: EGFR inhibitors

- Populopustular (acneiform) rash

Table: Rash incidence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>90%</td>
<td>16%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>85%</td>
<td>14%</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>47%</td>
<td>2%</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>28-44%</td>
<td>2%</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>41%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Side effects: EGFR inhibitors

**Prevention**
- Topical: Hydrocortisone 1% cream with moisturizer and sunscreen twice daily
- Systemic: Minocycline 100 mg daily

**Treatment**
- Topical: Alclometasone 0.05% cream
- Fluocinonide 0.05% cream bid
- Clindamycin 1%
- Systemic: Doxycycline 100 mg bid (preferred in renal impairment)
- Minocycline 100 mg daily
- Isotretinoin at low doses (20–30 mg/day)


Side effects: VEGF inhibitors

- VEGF = vascular endothelial growth factor
- VEGF signaling promotes angiogenesis
  - Solid tumors subvert the VEGF signaling pathway to form new vessels and create their own blood supply
  - Activity in a variety of solid tumors:
    - Colorectal cancer
    - Kidney cancer
    - Ovarian cancer
    - Thyroid cancer

- Blood pressure target <140/90 mm Hg
- Preferred antihypertensive agents:
  - ACE inhibitors
  - Dihydropyridine calcium channel blockers (amlodipine or nifedipine)
- Monitor closely with anticancer regimens requiring “off” periods – some agents may cause rebound hypotension and increase stroke risk


Hand-foot skin reaction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (Cometriq)</td>
<td>50%</td>
<td>13%</td>
</tr>
<tr>
<td>Regorafenib (Stivarga)</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Axitinib (Inlyta)</td>
<td>27%</td>
<td>5%</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>21%</td>
<td>8%</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>11%</td>
<td>2%</td>
</tr>
</tbody>
</table>


Prevention of HFSR

- Reduce exposure of hands and feet to hot water (washing dishes, long showers, hot baths)
- Avoid constrictive clothing, wear comfortable well-fitting shoes
- Avoid vigorous exercise or friction on hands and feet
- Apply moisturizer after bathing and at night, under cotton gloves and socks
- A pedicure before treatment may be effective for patients with plantar hyperkeratosis

Side effects: VEGF inhibitors

- Treatment of HFSR
  - Use a pumice stone to gently exfoliate lesions
  - Apply topical corticosteroids BID
  - Apply a petroleum-based ointment (Vaseline) and bandage blisters
  - Apply urea- or salicylic acid-containing topical treatments
    - Urea: Kerassal ultra20, Udderly Smooth Extra Care Cream
    - Salicylic acid: CeraVe Renewing SA
- Consider oral analgesics to relieve pain
- May require dose-reduction or delay of anticancer therapy

Side effects: ALK inhibitors

- ALK = anaplastic lymphoma kinase
- ALK gene rearrangement occurs in 4% of lung cancers
  - 33% among never or light smokers without EGFR mutation

Drug-drug interactions

- CYP interactions
  - Axitinib (Inlyta)
  - Crizotinib (Xalkori)
  - Dasatinib (Sprycel)
  - Erlotinib (Tarceva)
  - Gefitinib (Iressa)
  - Imatinib (Gleevec)
  - Lapatinib (Tykerb)
  - Nilotinib (Tasigna)
  - Olaparib (Lynparza)
  - Pazopanib (Votrient)
  - Regorafenib (Stivarga)
  - Ruxolitinib (Jakafi)
  - Sunitinib (Sutent)
  - Vemurafenib (Zelboraf)

To review...

- MG has been prescribed erlotinib (Tarceva) 150 mg PO qAM for his lung cancer. Which of the following supportive care regimens should MG receive?
  - Ointment containing salicylic acid
  - Sunscreen only
  - Sunscreen, hydrocortisone 1% topical, doxycycline 100 mg PO BID
  - None, MG does not require any up-front supportive care medications.

Drug-drug interactions

Visual disturbances

<table>
<thead>
<tr>
<th></th>
<th>Any grade</th>
<th>Grade 3/4</th>
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</thead>
<tbody>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>71%</td>
<td>1%</td>
</tr>
<tr>
<td>Alectinib (Alecensa)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Ceritinib (Zykadia)</td>
<td>&lt;10%</td>
<td>Not reported</td>
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Management

- Resolves after discontinuation of ALK inhibitor

Drug-drug interactions

Visual disturbances

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  - None, MG does not require any up-front supportive care medications.
Drug-drug interactions

- CYP Interaction management
  - Obtain complete medication list, including prescription, OTC, and herbal supplements
  - Common CYP3A4 interactions:
    - Substrates
      - Clarithromycin
      - Erithromycin
      - Verapamil
      - Diltiazem
      - Levotratin
      - Simvastatin
      - Dexamethasone
    - Inhibitors
      - Clarithromycin
      - Erithromycin
      - Ketoconazole
      - Verapamil
      - Diltiazem
      - Cinetidine
      - Antidolazine
      - Variconazole
    - Inducers
      - Carbamezapine
      - Modafinil
      - Oxcarbazepine
      - Phenytoin
      - Rifabutin
      - Rifampin

- Avoid concomitant use with acid-suppressing medications
  - Erlotinib (Tarceva)
  - Dasatinib (Sprycel)
  -Nilotinib (Tasigna)
  - Vismodegib (Erivedge)
  - Pazopanib (Votrient)
  - Bosutinib (Bosulif)
  - Dabrafenib (Tafinlar)

- Acid suppressant therapy interaction management
  - Obtain complete medication list, including prescription, OTC, and herbal supplements
  - Recommend as needed antacids, separated from administration of oral anticancer agent
    - Calcium carbonate (Tums), aluminum hydroxide (Mylanta), etc
  - Some anticancer agents may be used with H₂ receptor antagonists
    - Fomotidine (Pepcid), ranitidine (Zantac), etc

- May cause QTc prolongation
  - Crizotinib (Xalkori)
  - Gefitinib (Iressa)
  - Idelalisib (Zydelig)
  - Lapatinib (Tykerb)
  - Nilotinib (Tasigna)
  - Pazopanib (Votrient)
  - Sorafenib (Nexavar)

- Food-drug interactions
  - Must be taken on an empty stomach
    - Erlotinib (Tarceva)
    - Sorafenib (Nexavar)
    - Lapatinib (Tykerb)
    - Nilotinib (Tasigna)
    - Pazopanib (Votrient)
    - Cabozantinib (Cometria)
    - Dabrafenib (Tafinlar)
    - Trametinib (Mekinist)
    - Afininib (Gilotrif)

- Must be taken with food
  - Imatinib (Gleevec)
  - Regorafenib (Stivarga)
  - Bosutinib (Bosulif)
  - Palbociclib (Ibrance)
To review…

- Which of MG’s current medications is the most concerning drug-drug interaction with erlotinib?
  1. Lisinopril 20 mg PO qday
  2. Simvastatin 40 mg PO qhs
  3. Carvedilol 6.25 mg PO bid
  4. Aspirin 81 mg PO qday
  5. Tums (calcium carbonate) 750 mg PO qday prn heartburn

Compounding

- Targeted oral anticancer agents = hazardous drugs
  - NIOSH List of Antineoplastic and Other Hazardous Drugs 2014
  - Tablet crushing and opening capsules may expose preparer to harm
  - Approximately 50% of oral chemotherapy medications have published compounding recipes

Handling & compounding

- Keep the tablets away from children and pets
- Store in a labeled childproof container
- Wash hands before and after handling the tablets
- Do not crush, chew, cut or disrupt tablets unless directed otherwise
- Caregivers who are pregnant, trying to become pregnant, or breast-feeding should not handle these medications

Targeted oral anticancer resources

- Oncology Nursing Society “Oral Adherence Toolkit”
- Multinational Association of Supportive Care in Cancer “Oral Agent Teaching Tool”®
  http://www.mascc.org/MOAATT

Handling & administration

- Keep the tablets away from children and pets
- Store in a labeled childproof container
- Wash hands before and after handling the tablets
- Do not crush, chew, cut or disrupt tablets unless directed otherwise
- Caregivers who are pregnant, trying to become pregnant, or breast-feeding should not handle these medications

Targeted oral anticancer resources

To review...

- Which of the following counseling points on handling & administration of erlotinib is NOT necessary to provide to MG?
  - A. Wear gloves and mask when taking erlotinib
  - B. Wash hands before and after handling
  - C. Keep the tablets in a labeled, secure container
  - D. Do not crush or chew tablets

Conclusions

- Targeted oral anticancer agents account for a substantial portion of new oncology drug approvals and rising costs of cancer care.
- New agents act on specific molecular targets, making them unique in mechanism and place in therapy as compared to older traditional chemotherapies.

To review...

1. In 2011, the class of oncology drugs which accounted for the largest portion of insurance payments was:
   - A. Non-targeted agents
   - B. Targeted oral agents
   - C. Targeted IV agents
   - D. Immunotherapies

Conclusions, continued

- The side effects of targeted anticancer therapies vary widely, depending on the molecular target(s).
- Drug-drug interactions, especially CYP interactions, acid-suppressing medications, and QTc prolongation, may be problematic with some targeted oral anticancer agents.
- These are hazardous medications and require adequate education of patients, caregivers, and health care providers on safe handling and administration.

References

16. 1. In 2011, the class of oncology drugs which accounted for the largest portion of insurance payments was:
   - A. Non-targeted agents
   - B. Targeted oral agents
   - C. Targeted IV agents
   - D. Immunotherapies

2. Which of the following oncology medications has activity against specific signaling proteins which are overexpressed in lung cancer cells?
   - A. Capecitabine
   - B. Crizotinib
   - C. Methotrexate
   - D. Oxaliplatin
Questions?
Megan Hartranft, PharmD, BCPS, BCOP
megan.hartranft@osu.edu