Symptom Management of Oral Targeted Anti-cancer Agents

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Siu-Fun Wong, PharmD, FASHP, FCSHP
Associate Professor of Pharmacy Practice
Western University of Health Sciences
Pomona, California
Faculty-in-residence
Hematology Oncology Medical Group of Orange County, INC.
Center for Cancer Prevention and Treatment, St. Joseph Hospital
Orange, California
Associate Clinical Professor of Medicine
University of California, Irvine

Outline

- Overview of side effects associated with oral targeted anti-cancer agents
- Patient management and counseling of oral targeted agents
- Issues regarding safe handling of oral targeted anti-cancer agents

Approved Indication | Target | Drug Name
--- | --- | ---
EGFR Tyrosine Kinase Inhibitor
Lung Pancreas | EGFR | Gefitinib (Iressa™)
Erlotinib (Tarceva™)

Multi-kinase Inhibitor
Leukemias, Hematologic disorders, (GIST) | Bcr-Abl, PDGFR, SCF, c-KIT | Imatinib (Gleevec®)
Cediranib (Cediranib®)
Dasatinib (Sprycel®)
Nilotinib (Tasigna®)

Chronic and acute leukemias
Liver cancer | VEGFR1, VEGFR2, VEGFR3, PDGFRα, FLT3, SCFR, KIT, RET, intracellular RAF | Sorafenib (Nexavar®)
Sunitinib (Sutent®)

Gastrointestinal stromal tumor (GIST), Kidney cancer | VEGFR1, VEGFR2, VEGFR3, PDGFRα, FGFR3, C-SKI, FLT3, SCFR, KIT, RET | Lapatinib (Tykerb®)

Breast cancer | EGFR, HER2 | Lapatinib (Tykerb®)

HDAC inhibitor
CTCL | HDAC1, HDAC2 AND HDAC3 (class I) and HDAC6 (class II) | Vorinostat (Zolinza®)
Potential Side Effects of Oral Targeted Anti-cancer Agents

- Hematologic Complications
- Dermatologic toxicities
- Diarrhea
- Hand-foot syndrome
- Hypertension
- Fluid retention/Pleural effusion
- Lab Abnormalities

Hematologic Complications

<table>
<thead>
<tr>
<th>Drug</th>
<th>ANC</th>
<th>Plt</th>
<th>Hgb</th>
<th>Hemorrhage</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarceva</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>↑</td>
</tr>
<tr>
<td>Imatinib</td>
<td>15-64%</td>
<td>8-63%</td>
<td>4-53%</td>
<td>++</td>
<td>↑</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>49-83%</td>
<td>48-63%</td>
<td>18-70%</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>28-37%</td>
<td>28-37%</td>
<td>8-23%</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>5%</td>
<td>1%</td>
<td>2%</td>
<td>+</td>
<td>↑</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>10-12%</td>
<td>5-8%</td>
<td>3%</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vironostat</td>
<td>mild</td>
<td>6-21%</td>
<td>2-16%</td>
<td>esp in comb w/ valproic acid</td>
<td>↑</td>
</tr>
</tbody>
</table>

Management:
- Monitor CBC w/diff every 1-2 weeks x 2 months and then monthly
- Interrupt and reduce dose for grade 3 or 4 toxicity
- Hematopoietic growth factors have been used
- s/sx of DVT & PE should be reinforced in patients receiving Vorinostat
Dermatologic Toxicities

Two major classes
- EGFR Monoclonal Antibodies (IV formulation)
  - Cetuximab
  - Panitumumab
- EGFR Tyrosine Kinase Inhibitors (PO formulation)
  - Erlotinib
  - Lapatinib – HER1/EGFR & HER2
- A class to keep in mind - Multi-Kinase Inhibitors (PO)
  - Imatinib & Dasatinib & Nilotinib
  - Sorafenib & Sunitinib

EGFR Inhibitor – Induced Dermatologic Toxicity

Dermatologic toxicities include:
- Papulopustular (interfollicular and follicular-based erythematous papules and pustules) rash, xerosis, paronychial inflammation

**Papulopustular Rash:**
- Onset: 1-2 weeks
- Usually occur on face, scalp, and upper body
- Symptoms: dry skin, pain/tenderness and pruritus
- Inflammatory and infectious sequelae

Papulopustular Rash is common
- 35-88% (all grades)
- 16% (grade 3 or 4) - Dose reduction or discontinuation are recommended

Potential marker for drug activity and clinical outcome

EGFR Inhibitor-Induced Dermatologic Toxicity

Papulopustular rash on face
Papulopustular rash on chest

*Photos courtesy of Memorial Sloan-Kettering Cancer Center.*
What do we know about the pathophysiology of EGFR Inhibitor-Induced skin rash?

- It is NOT acne or acne vulgaris which has both:
  - Non-inflammatory lesions (comedones)
  - Inflammatory papules, pustules, and nodules caused by bacterial colonization

- It is a secondary inflammatory response
  - Inhibition of EGFR in basal keratinocytes leads to follicular degeneration and destruction

Published Treatment Recommendations for Papulopustular Rash

- Mild to moderate:
  - Cover make-up without worsening the existing rash
  - Standard analgesic for pain
  - Oral antihistamine for pruritus
  - High-potency topical corticosteroids
  - Topical immunomodulatory agent (e.g., pimecrolimus aka Elidel)
  - Avoid topical retinoids and benzoyl peroxide due to skin drying effect

- Secondary infection:
  - Prophylactic intranasal mupirocin
  - Oral antibiotic

- Severe:
  - Systemic corticosteroids
  - Interruption of treatment

Published Treatment Recommendations for Papulopustular Rash

- General:
  - Maintain maximal hydration using emollient cream
  - Sunblock - Sunlight can exacerbate any skin reactions
  - Avoid topical or systemic corticosteroids

- Grade 1:
  - Topical anti-acne products

- Grade 2:
  - Oral minocycline or doxycycline
  - Oral antihistamine or topical menthol cream for pruritus

- Grade 3 or 4:
  - Dosage adjustments
  - Higher doses of oral antimicrobials

**Principles of Skin Rash Treatment**

- Elimination of skin rash is not necessarily desirable!
- Perhaps maintaining a grade 2 rash is most optimal?
- Criteria for optimal supportive treatment:
  - Treatments should not interfere with the anti-tumor effects of EGFR inhibitors
  - Maintain low side effect profile
  - Ease of administration with rapid results to ensure patient compliance
  - Individualize treatment according to presenting signs and symptoms
  - Keep costs at minimal

**The Other Dermatologic Toxicities**

- **Sunitinib**
  - Skin discoloration (yellow)
  - Skin and hair depigmentation
  - Management: ??
- **Non-papulopustular skin rash**
  - Symptomatic control

**Diarrhea**

- All the oral targeted agents discussed can cause diarrhea
- Incidence:
  - All grade = 40-65%
  - Grade ¾ = 2-6 %
- Gradual onset in 7-10 days
- Management:
  - Other etiologies, especially infectious
  - Start with loperamide
  - Monitor for fluid and electrolytes
  - Dose reduction or temporary interruption of oral targeted therapy in severe cases
Hand-Foot Syndrome

- aka palmar-plantar erythrodysesthesia
- Incidence:
  - Sorafenib 30%, Gr 3 6%
  - Sunitinib 21%, Gr 3 5%
  - Lapatinib + capecitabine 53%, Gr 3 12%
- Onset can be from 2 to 12 days after initiation of therapy
- May progress 3 to 4 days later into symmetrical edema and erythema of the palms and soles

Hand–Foot Syndrome

Grading

Grade 1  
Numbness, dysesthesia or paresthesia, tingling, painless swelling or erythema, and/or discomfort of hands or feet not disrupting normal activities

Grade 2  
Painful erythema and swelling of hands or feet and/or discomfort affecting ADLs

Grade 3  
Moist desquamation, ulceration, blistering or severe pain of hands or feet, or severe discomfort preventing work or performance of ADLs
Hand-Foot Syndrome Management

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Any event</th>
<th>Continue tx and initiate topical agent for sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>1st event</td>
<td>Continue tx and initiate topical agent for sx</td>
</tr>
<tr>
<td></td>
<td>No improvement of 1st event in 7 days; 2nd or 3rd event</td>
<td>6x support tx</td>
</tr>
<tr>
<td></td>
<td>4th event</td>
<td>d/c treatment drug</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1st or 2nd event</td>
<td>6x support tx</td>
</tr>
<tr>
<td></td>
<td>3rd event</td>
<td>d/c treatment drug</td>
</tr>
</tbody>
</table>

Systemic Agents
- Pyridoxine or vitamin B6
- Dexamethasone
- Amifostine
- COX-2 inhibitors

Topical agents
- Bag Balm, a topical petroleum-lanolin-based ointment with the antiseptic ingredient hydroxyquinoline sulfate.
- Emollients, e.g. Biafine, Carmol 46
- Aloe vera lotion
- Moisturizing creams.

Non-pharmacologic Interventions
- Avoid undue pressure or rubbing of the skin
- Avoid blood vessel dilation induced by hot showers or sun exposure
- Cooling with cold water


Hypertension

MOA: Not completely known
- ? abnormal endothelial function (RAF kinase inhibition) and angiogenesis (VEGF inhibition)

Incidence:
- Sorafenib 17% (Gr ¾ 3%)
- Sunitinib 30% (Gr ¾ 20%)

Onset usually within first 6 weeks after initiation of therapy

Management:
- Monitor BP q week for first 6 week after initiation of therapy
- Interruption and/or dose reduction should be considered
- Permanent discontinuation is rare
- Standard antihypertensive agents can be selected with caution to avoid agents with potential for CYP450 drug-drug interaction (e.g. verapamil, diltiazem)
**Fluid Retention**

- Overall <10%: Pleural, pericardial, ascites, & generalized edema
- Dasatinib, Imatinib, Nilotinib
  - Appears dose-related

**Management:**
- Monitor weight for sudden weight changes
- Diuretic & corticosteroid as needed

**Pleural Effusion**

- Check chest x-ray at baseline and 2 months after starting dasatinib
- If new or worsening grade 3 pleural effusion, interrupt dasatinib therapy and spironolactone 50 mg QD
- Increase diuretic & corticosteroid as needed

**Laboratory Abnormalities/Monitoring**

<table>
<thead>
<tr>
<th>Drug</th>
<th>TScr</th>
<th>TLT</th>
<th>Metabolic Panel</th>
<th>Blood Glucose</th>
<th>Thyroid</th>
<th>Lipase/amy lase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarceva</td>
<td>+</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>+</td>
<td>+++</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td></td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nilotinib</td>
<td></td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>x/e</td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td></td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinostat</td>
<td></td>
<td>+++</td>
<td>+++</td>
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</tr>
</tbody>
</table>
Laboratory Abnormalities

Management

- Monitor for abnormality and corrected as appropriate
- Electrolyte (potassium, magnesium, phosphate, and calcium) should be evaluated prior to administration and replace accordingly, especially in patients at risk of or suffering from diarrhea, dehydration, or ECG changes (e.g. QT prolongation)
- Dasatinib, Nilotinib, Vorinostat, Lapatinib
  - Risk of QT prolongation
  - ECG at baseline, day #7, and then periodically
- Vorinostat
  - Risk of dehydration (Gr ¾ 8%) and N/V, monitor electrolytes (e.g. Mg, Ca), serum creatinine. Encourage 2 liters of fluid replacement
  - Blood glucose q 2 weeks x 1 month, then q monthly

Potential Drug-Drug Interactions

<table>
<thead>
<tr>
<th>CYP3A4 Inhibitors</th>
<th>CYP3A4 Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents</td>
<td>dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital</td>
</tr>
<tr>
<td>ketoconazole, itraconazole, erythromycin, clarithromycin, rifonavir, atazanavir, indinavir, nefazodone, nefluramine, saquinavir, telithromycin</td>
<td></td>
</tr>
</tbody>
</table>
| Action            | Adjust dose of targeted drug if possible
|                   | Seek alternative agents
|                   | Monitor for toxicity or suboptimal response |

Others:
- Dasatinib – antacids, H2 blocker, PPI
- Sorafenib – irinotecan (increase SN-38AUC), increase AUC doxorubicin

General Risk Factors for Altered Adherence

- Advanced age
- Chronic condition
- Cognitive impairment
- Depression
- Low literacy
- Lack of social support
- Cultural barriers
- Cost
How to Improve Adherence?

- Good patient education
  - Side effect management
  - Proper administration instructions
- Identify patients at risk of poor adherence and conduct more close monitoring
- Education caregivers to enhance patient’s support system away from the health care facility

Safe Handling of Oral Cytotoxic Agents

- All oral antineoplastic agents must be packaged by the Pharmacy
- Crushing or breaking of the oral dosage form should be conducted in the Class II Type A biological safety cabinet
- Separate equipment for dispensing or administration
- Never use the automated machine for counting

Exposure During Disposal of Contaminated Material

- Body fluids: vomitus, urine, ascitic fluid, pleural fluid, blood, excreta containing high concentrations of cytotoxic drugs and their metabolites for 48 hours after patient receives chemotherapy
- Contaminated linen should be placed in designated and clearly marked laundry bags
- Linen should be washed separately
- Provide gloves when dispense meds
**Should Oral targeted agents be handled the same manner?**

- Pharmacokinetic data for imatinib, dasatinib, sorafenib, sunitinib, and lapatinib were all conducted in health subjects.
- The carcinogenesis, mutagenesis, or teratogenic effects in humans and animals were not clearly defined. Data were derived from animal models where higher doses were administered.
- Imatinib package insert did not have strong exclusive statement for use in pregnancy.
- Dasatinib package insert discourage crushing or breaking the tablet.

**What are my humble recommendations?**

- Should oral targeted agents be handled using the “ganciclovir”-type precautions?
- Do not crush or break the tablets or capsules in unprotected area
- Do not use automated machine for dispensing
- Keep out of reach of children
- Wash hand before and after handling (for health care practitioners, patients, and caregivers)

**Summary**

- Oral targeted anti-cancer therapy is not as “benign” as we initially thought.
- Many of these agents are administered on chronic continuous schedule where adherence is critical to achieve optimal disease control.
- Empowering patients with good education to manage adverse effects can promote and enhance adherence.
- Safe handling education is essential to protect patients and caregivers in their home setting.