Multikinase Inhibitors: Dermal Toxicities and Implications for Oncology Nursing Care
Tyrosine Kinases

• Highly regulated enzymes that carry out protein phosphorylation
• Important in cellular signal transduction in pathways that control cell proliferation, differentiation, migration, metabolism, and apoptosis
• Some are implicated in tumor growth and metastatic progression of cancer
Tyrosine Kinases are Classified in Two Groups

- Receptor tyrosine kinases (RTK)
  - Transmembrane receptor-linked kinases
  - Ligand binding to the extracellular region causes a series of structural rearrangements in the RTK that lead to its enzymatic activation
  - **Solid malignancies EGFR, PDGFR, VEGFR**

- Cellular tyrosine kinases
  - Cytoplasmic
  - **Hematologic malignancies: ABL/JAK**

Multikinase Inhibitors (MKI)

• Inhibit *multiple intracellular and cell surface kinases* thus decreasing tumor growth and replication
  – Increase efficacy
  – Reduce resistance

• Kinase inhibitors have specific toxicities
  – Related to the primary target kinase(s)
  – Related to an off-target effect
  – Caused by a specific metabolite of the kinase inhibitor
    – Hepatotoxicity?

## Oral Multikinase Inhibitors (MKIs)*

<table>
<thead>
<tr>
<th>MKI</th>
<th>Target Receptor/Pathway</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>c-KIT, PDGFR, VEGFR-1, VEGFR-2, VEGFR-3</td>
<td>RCC</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>ABL, SRc</td>
<td>CML</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK, EGFR</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Bcr-ABL, SRc</td>
<td>Adult CML, Pcp ALL</td>
</tr>
<tr>
<td>Imatinib</td>
<td>ABL, Kit, PDGFR</td>
<td>CML, ALL, GIST</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>ABL, Kit, PDGFR</td>
<td>CML, Pcp ALL, HS, SM</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>c-KIT, PDGF, VEGFR family</td>
<td>RCC</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>c-KIT, PDGF, RAF, RET, VEGFR family</td>
<td>Metastatic CRC, GIST</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>c-KIT, PDGFR, RAF, RET, VEGFR-1, VEGFR-2, VEGFR-3</td>
<td>HCC, RCC, thyroid</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>c-Kit, FLT3, M-CSFR-1, PDGFR, RET, VEGFR</td>
<td>RCC</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>EGFR, RET VEGFR-1, VEGFR-2 [melanoma]</td>
<td>Thyroid</td>
</tr>
</tbody>
</table>


*Generic names of agents approved by the US FDA.
Side Effects Associated with TKIs

- Fatigue
- Diarrhea
- Functional mucositis
- Nausea
- Vomiting
- Dyspepsia
- Taste changes
- Anorexia
- Hypertension
- Hand-Foot Skin Reaction
- Rash
- Pruritus
- Skin color changes
- Alopecia
- Hair depigmentation
- Neutropenia
- Thrombocytopenia
- Hypothyroidism
Drug-Induced Dermatologic Reactions

Nursing Considerations

• One of the most common types of adverse reaction to drug therapy
• Most drug-related skin eruptions are not serious, however some are severe and potentially life-threatening (e.g., Stevens-Johnson)
• Healthcare professionals should carefully evaluate all drug-associated rashes
• A cutaneous drug reaction should be suspected in any patient who develops a rash during a course of drug therapy
• Skin reactions should be identified and documented in the patient record so that their recurrence can be avoided
Dermatologic Toxicities

- Dry skin
- Rash
- Pruritus/Urticaria
- HFS/HFSR
- Bullous dermatitis
- Erythroderma
- Stevens-Johnson syndrome

HFS, hand-foot syndrome; HFSR, hand-foot skin reaction

# Selected MKIs and Dermatologic Toxicities

<table>
<thead>
<tr>
<th>MKI</th>
<th>Target Receptor/Pathway</th>
<th>Toxicity</th>
</tr>
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<tr>
<td>Axitinib</td>
<td>c-KIT, PDGFR, VEGFR-1, VEGFR-2, VEGFR-3</td>
<td>HSFR, Rash</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>ABL, SRc</td>
<td>Rash</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK, EGFR</td>
<td>Rash</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Bcr-ABL, SRc</td>
<td>Rash&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Imatinib</td>
<td>ABL, Kit, PDGFR</td>
<td>Rash</td>
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<td>Rash</td>
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<td>Pazopanib</td>
<td>c-KIT, PDGF, VEGFR family</td>
<td>HFSR, Rash</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>c-KIT, PDGF, RAF, RET, VEGFR family</td>
<td>HFSR, Rash&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>c-KIT, PDGFR, RAF, RET, VEGFR-1, VEGFR-2, VEGFR-3</td>
<td>HFSR&lt;sup&gt;3&lt;/sup&gt;, Rash</td>
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<td>Sunitinib</td>
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<tr>
<td>Vandetanib</td>
<td>EGFR, RET, VEGFR-1, VEGFR-2</td>
<td>Rash&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

<sup>2</sup>Includes rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.

<sup>3</sup>Palmar plantar erythrodysaesthesia syndrome in MedDRA

<sup>4</sup>Includes rash, rash (erythematous, generalized, macular, maculo-papular, papular, pruritic, and exfoliative), dermatitis, dermatitis bullous, generalized erythema, and eczema.
Initiating Therapy
Patient Case (1)

• Mrs. L is a 70-year-old female with stage III metastatic colorectal cancer, KRAS wild-type
• She was treated initially with FOLFOX (5-FU/ocaliplatin) and bevacizumab and was subsequently treated with irinotecan and cetuximab
• Her oncologist is now starting her on regorafenib
Why Should Oncology Nurses Care About Skin Structure?

“The ability to diagnose and manage dermatologic toxicities can be improved by understanding the structure and function of the integumentary system.”

-E Graber, MD, Boston University School of Medicine
-A Garg, MD, Hofstra School of Medicine, North Shore-LIJ Health System
Epidermis (1)

• Continually renewing structure of keratinocytes attached to the basement membrane
• Keratinocytes migrate from the basement membrane to the stratum corneum as they differentiate and mature
• Epidermal barrier regulates
  – Desquamation
  – Permeation of water and environmental solubles
  – Initiation of cytokine-mediated inflammation
Epidermis (2)

• Corneocytes (mature keratinocytes) comprise the lipid and protein-rich epidermal barrier

• Epidermal barrier regulates
  – Desquamation
  – Permeation of water and environmental solubles
  – Initiation of cytokine-mediated inflammation
Skin Structure

Key Clinical Point:
If grade 3 toxicities destroy the barrier it can’t regenerate sufficiently to allow the patient to resume therapy

Patient Case (2)

- Mrs. L lives with her husband.
- Her husband and adult daughter are at the appointment and will be at all appointments.
- Her treatment plan is as follows:
  - Regorafenib 160 mg daily for 21 days, then off treatment for 7 days
  - Drug formulation: 40-mg tablet
  - Dosing:
    • 4 tablets (160-mg dose) with low-fat breakfast
    • Take all tablets at the same time
Stop and Think

• What patient education materials would you provide for Mrs. L?
Patient Education

• What patient education materials would you provide for Mrs. L?
  
  – Mrs. L should receive a diary sheet to help with correct dosing
  
  – Provide an additional copy of patient education materials to the daughter since her parents live on their own
Stop and Think

• What side effects should you discuss with Mrs. L?
Patient Education and Nursing Actions

• What side effects should you discuss with Mrs. L?
• Discuss possible side effects of treatment including hypertension and dermal toxicities
  – Mrs. L’s baseline BP is 128/72 mmHg
  – Her daughter offers to take her blood pressure Mon-Wed-Fri on her way home from work for the first several weeks
  – The frequency of subsequent BP assessments can be determined based on blood pressure readings during the 1st few weeks of therapy
• Discuss possible dermatologic side effects
Stop and Think

• What would you do after discussing possible dermatologic side effects?
Patient Education and Nursing Actions

• What would you do after discussing possible dermatologic side effects?
  – Prior to starting therapy examine the soles of Mrs. L’s feet for calluses
  – Recommend beginning skin care now with a urea-based cream (e.g., Udderly Smooth)

• Schedule a clinic visit with lab tests on Day 22
Stop and Think

• Why is it important that Mrs. L or her family be vigilant about communicating possible side effects as soon as they notice them?
Early Communication

• Why is it important that Mrs. L or her family be vigilant about communicating possible side effects as soon as they notice them?

• Catching side effects before they become serious may allow Mrs. L to continue her treatment without interruption.
Assessing Emergent Side Effects
Emerging Side Effects

- On Day 7, Mrs. L’s daughter calls to report that her mother has mild tenderness on the soles of her feet
- Her BP is about blood pressure is 134/78 mmHg
- She also has a mild rash on her chest and upper back – it does not itch
Stop and Think

• What would you do next?
Emerging Side Effects

- What would you do next?
  - Schedule a follow-up call in 2 days
  - Tell Mrs. L’s daughter to call immediately if the side effects worsen
# CTCAE Version 4.0

## Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain</td>
<td>Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL</td>
<td>Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or soles of the feet.

*CTCAE Version 4.0 (v4.03: June 14, 2010).*
Day 9

• Follow-up call in 2 days reveals that HFSR is worse, BP and rash are stable
Stop and Think

• What would you do next?
Day 9

• What would you do next?
  – Have Mrs. L come into the clinic
Clinic Visit

- Mrs. L’s BP is 138/82 mmHg
  - BP is stable and does not require intervention
- She has grade 2 HFSR on the soles of both feet
  - Grade 1 pain associated with the HFSR and grade 1 non-pruritic rash
- Rash is stable, no new areas of involvement, no pruritus
- She does not have constipation or diarrhea
<table>
<thead>
<tr>
<th>Skin Toxicity Grade</th>
<th>Occurrence</th>
<th>Suggested Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Any</td>
<td>Maintain dose level and immediately institute supportive measures for symptomatic relief.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Decrease dose by 40 mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the physician.</td>
</tr>
<tr>
<td>No improvement within 7 days or 2&lt;sup&gt;nd&lt;/sup&gt; or 3&lt;sup&gt;rd&lt;/sup&gt; occurrence</td>
<td>Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.</td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; occurrence</td>
<td>Discontinue treatment with regorafenib permanently</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence</td>
<td>Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; occurrence</td>
<td>Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet).</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; occurrence</td>
<td>Discontinue treatment with regorafenib permanently</td>
<td></td>
</tr>
</tbody>
</table>
Stop and Think

• What would you do next?
What Would You Do Next?

• Grade 2 HFSR (erythema, calluses, pain) means that Mrs. L’s regorafenib dose should be reduced to 120 mg daily for 7 days

• Review new dose and write instructions on her diary sheet (3 tablets)
Stop and Think

• When would you schedule her next visit?
When would you schedule her next visit?

• Schedule return clinic visit in 7 days to reassess HFSR
• Instruct Mrs. L and her daughter to call if the HFSR worsens prior to her next appointment
Managing Grade 2 HSFR
Stop and Think

• What supportive care would you suggest for Mrs. L?
The "3C" Approach to Manage MKI-HFSR

• **Control calluses**
  – Prophylactic removal of hyperkeratotic areas before & during treatment
  – Pumice stone, Ped Egg pedicure, podiatrist

• **Comfort with cushions**
  – Protect pressure-sensitive areas of hands & feet
    • Well-padded, well-fitting, soft shoes
    • Insole cushions or inserts

• **Cover with creams**
  – Frequent use of emollient creams
  – Keratolytic agents on callused areas of palms & soles

Clinic Visit 7 Days Later

- Mrs. L’s BP is 128/68 mmHg
- There is no improvement in her HFSR
- The rash is stable
- Plan:
  - Interrupt regorafenib therapy for continued grade 2 HFSR
  - Schedule follow-up call in approximately 5 days to check on improvement in HFSR
- Phone call in 5 days reveals significant improvement in HFSR and resolution of rash
Clinic Visit 7 Days Later

• Day 22 clinic visit demonstrates:
  – Lab tests (CBC Diff, Comprehensive Metabolic Panel) results are within normal limits
  – HFSR and pain have resolved
Stop and Think

• What are next steps for Mrs. L?
Clinic Visit 7 Days Later

• What are next steps for Mrs. L?
  – Begin Cycle 2 regorafenib in 1 week with a dose reduction to 120 mg
  – Review dosing (3 tablets)
  – Schedule phone call for side effect update in 7 days
  – Remind patient, husband, and daughter that Mrs. L can be seen anytime if HFSR recurs

• Phone calls on Day 7 and Day 15 reveal grade 1 HFSR, no rash, no constipation or diarrhea. BP 128/74 mmHg on Day 7, 126/70 mmHg on Day 15.

• Outcome: Patient tolerates regorafenib 120 mg dose for Cycle 2

• CT scans demonstrate stable disease.