Managing Common Toxicities with Tyrosine Kinase Inhibitor

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Overview

EGFR = Epidermal growth factor receptor, VEGFR = Vascular endothelial growth factor receptor, PDGFR = Platelet-derived growth factor receptor, HER2 = human epidermal growth factor receptor 2
Epidermal Growth Factor Receptors (EGFR)
EGFR expression

http://www.proteinatlas.org/ENSG00000146648-EGFR/tissue
Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities

Mario E. Lacouture · Milan J. Anadkat · René-Jean Bensadoun · Jane Bryce · Alexandre Chan · Joel B. Epstein · Beth Eaby-Sandy · Barbara A. Murphy · MASCC Skin Toxicity Study Group
Epidermal growth factor receptors

Skin reaction

• Incidence
  • All grade ≈ 80 – 86 %
  • ≥ grade III ≈ 5.2 - 18 %
Pathophysiology

EGFR inhibition

- Growth and migration arrest and apoptosis
- Chemokine expression
- Abnormal maturation and differentiation

Inflammatory cell recruitment

Cutaneous injury

- Tenderness
- Papulopustules
- Periungual inflammation

Xerosis and pruritus

Hair and nail plate disturbance

Grading EGFR TKIs induced acne rash

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10% BSA</td>
<td>10-30% BSA Effected to QOL</td>
<td>&gt;30% BSA Effected to QOL with local infection</td>
<td>+ associated superinfection</td>
</tr>
</tbody>
</table>

Maintain dose

- Maintain dose
- If prolonged >2wk temporarily hold until < grade 1, reintroduce same dose
- Temporary hold for 2–4 wks. Until <grade 2
- reintroduce lower dose. If toxicities do not worsen, escalate the dose. If no improvement, discontinue.

Topical corticosteroid

- Topical corticosteroid + Oral Antibiotic
- Topical corticosteroid + IV Antibiotic

Estimated BSA
Prevention

Protocol: Start on D-1 to week 6 of Panitumumab

- Skin moisturizer*(bid)
- Sunscreen (OD) (PABA free, SPF ≥15)
- 1% Hydrocortisone cream* (hs)
- Doxycycline (Doxy) 100 mg (BID)

*Applied to face, hands, feet, neck, back, and chest

## Treatment/Prevention Guideline

<table>
<thead>
<tr>
<th>Preventive (weeks 1–6 and 8 of EGFR initiation)</th>
<th>Recommend</th>
<th>Not recommended</th>
<th>Level of evidence</th>
<th>Recommendation grades</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td>Hydrocortisone 1% cream with moisturizer and sunscreen twice daily</td>
<td>Pimecrolimus 1% cream</td>
<td>II^a</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Minocycline 100 mg daily</td>
<td>Tetracycline 500 mg bid</td>
<td>II^a</td>
<td>A</td>
<td>Doxycycline is preferred in patients with renal impairment. Minocycline is less photosensitizing.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Alclometasone 0.05% cream</td>
<td>Vitamin K1 cream</td>
<td>IV^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Doxycycline 100 mg bid</td>
<td>Acitretin</td>
<td>IV^a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Gr.1:**
  - Tropical steroid + Cont. EGFR TKIs
- **Gr.2:**
  - Tropical steroid + Oral ATB + Cont. EGFR TKIs
- **Gr.3,4:**
  - Systemic Tx + Stop EGFR TKIs to ≤ Gr.1, reintroduce ↓ dose. If toxicities do not worsen, escalate the dose. If no improvement, discontinue.

Low dose Doxycycline

Erlotinib + Doxy 100mg OD ≥ 4 to 12 mo.

Non pharmacotherapy

**Prophylactic and general care**

- Counsel patient and provide educational materials to take home.
- Cleanse skin with a gentle, moisturizing soap. *Examples: Dove (Sensitive Skin Unscented), Head & Shoulders (be sure to rinse off completely), Aveeno Moisturizing Bar*
- Avoid alcohol-containing and other drying soaps and cleansers.
- Moisturize skin twice per day with a perfume-free emollient. *Examples: Nivea, Aquafor, Aveeno*
- Avoid excess sun exposure and wear sunscreen (SPF ≥ 15), preferably one containing titanium dioxide or zinc oxide. *Examples: Banana Boat Kids Tear Free Sunblock, Neutrogena Sensitive Skin Sunblock Lotion, Kiss My Face 100% Paraben-free Sunscreen*
- Avoid chemical irritants such as solvents, polishes, and chlorine.
- Avoid putting pressure on the nail folds.
- Avoid tight-fitting shoes
- Provide patient with prescription for an oral tetracycline antibiotic (doxycycline 100 mg PO BID).
Conclusion

Protocol: Start on $D_{-1}$ to 1.5 mo (Min) 12 mo. (Max)

Skin moisturizer (bid)

+ Sunscreen (OD) (PABA free, SPF $\geq 15$

+ 1% Hydrocortisone cream (hs)

+ Doxycycline (Doxy) 100 mg (BID) or 100 mg OD hs

Applied to face, hands, feet, neck, back, and chest
Paronychia

(A)

(B)

(C)
Grading

Grade 1  • Nail fold edema or erythema; disruption of the cuticle.

Grade 2  • Nail fold edema or erythema with pain; associated with discharge or nail plate separation.
• Limits instrumental activities of daily living.
• Localized intervention indicated; oral intervention indicated (for example, antibiotic, antifungal, antiviral).

Grade 3  • Limits self-care activities of daily living.
• Surgical intervention or intravenous antibiotics indicated.

Grade 4  —

Grade 5  —
Treatment/Prevention

<table>
<thead>
<tr>
<th>Recommend</th>
<th>Not recommended</th>
<th>Level of evidence</th>
<th>Recommendation grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Wear protective footwear and avoid friction with fingertips, toes, and heals</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Thick moisturizers or zinc oxide (13–40%) creams Liquid glues or cyanoacrylate to seal cracks Steroids or steroid tape, hydrocolloid dressings, topical antibiotics Bleach soaks to prevent infection Zinc oxide</td>
<td>III&lt;sup&gt;a/b&lt;/sup&gt;</td>
<td>B</td>
</tr>
</tbody>
</table>

- **Gr.1-2:**
  - Treatment + Cont. EGFR TKIs

- **Gr.3:**
  - Stop EGFR TKIs to ≤ Gr.1, reintroduce ↓ dose. If toxicities do not worsen, escalate the dose. If no improvement, discontinue.
Diarrhea
# Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC CAE version 4.03</td>
<td>None</td>
<td>&lt; 4 stools/day</td>
<td>4-6 stools/day, or nocturnal stools</td>
<td>≥ 7 stools/day or incontinence or need for parenteral support for dehydration</td>
<td>Physiologic consequences requiring intensive care; or hemodynamic collapse</td>
<td>Death</td>
</tr>
</tbody>
</table>

CTCAE 4.03 - June 14, 2010
# Classifications

<table>
<thead>
<tr>
<th>Uncomplicated</th>
<th>Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>❑ Grade 1 or 2 diarrhea</td>
<td>❑ Grade 3 or more</td>
</tr>
<tr>
<td>❑ Conventional management</td>
<td></td>
</tr>
<tr>
<td>❑ Excepted should be classified as complicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>i. Moderate to severe cramping</td>
</tr>
<tr>
<td></td>
<td>ii. &gt; Grade 2 nausea and/or vomiting</td>
</tr>
<tr>
<td></td>
<td>iii. Decreased performance status</td>
</tr>
<tr>
<td></td>
<td>iv. Fever, sepsis, neutropenia</td>
</tr>
<tr>
<td></td>
<td>v. Frank Bleeding or dehydration</td>
</tr>
</tbody>
</table>
Uncomplicated diarrhea management

• Supportive care: Hydration, Electrolytes
• Exclude: Infection
• Medication:

Loporamide → Loporamide high dose → Octiroid

• Loperamine dose: 4 mg stat then 2 mg after each loose stool (Max dose 24 mg/day)
• loporamide high dose: 2 mg po q 2hr (Max dose 24 mg/day)
• Octreotide 100 to 150 mcg SC TID or IV (25 to 50 mcg/hour) if patient severely dehydrated, max dose 500 mcg.
Complicated diarrhea management

• Start Octreotide 100 to 150 mcg SC TID or IV (25 to 50 mcg/hour) if patient severely dehydrated, max dose 500 mcg.

• Discontinue medication until all symptoms resolve and next cycle should be at a reduced dose
Conclusion

• Management
  – Uncomplicated (grade 1, 2)
    • Supportive care
    • Start loporamide → loporamide high dose → octiotide

  – Complicated
    • Start octiotide and titrated to 500 mcg if clinical not improved
    • Stop CMT and restart when clinical improved should be at a reduced dose
Human Epidermal growth factor Receptor Type2 (HER2)
## Her2-targeted agent

<table>
<thead>
<tr>
<th>Trastuzumab</th>
<th>Incidence</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>3%-7%</td>
<td>LV dysfunction, CHF, hypertension</td>
</tr>
<tr>
<td>+ paclitaxel</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>+ doxorubicin</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>
Management

**BASELINE ASSESSMENT**
- History, clinical exam, ECG, echocardiogram

**EF > 50%:** trastuzumab initiation

Re-evaluate at 12-week intervals

- **EF reduction >10% or EF <40% or Symptoms of heart failure**
  - Interrupt treatment
  - Introduce HF treatment
  - Re-evaluate EF and symptoms in 3 weeks

- **EF >50%**
  - Continue trastuzumab and introduce ACE inhibitors
  - Re-evaluate EF and symptoms in 3 weeks
  - Continue if EF stable and no symptoms

- **EF 45–50%**

ACE = angiotensin-converting-enzyme; EF = ejection fraction.
Vascular Endothelial Growth Factor (VEGF)
Anti-angiogenesis drugs

VSP Inhibitors
- Bevacizumab (Anti-VEGF)
- Afiberecept (VEGF Trap)
- Ramucirumab (Anti-VEGFR2)

TKI (with anti-VEGF Activity)
- FDA Approved: Sunitinib, Sorafenib, Pazopanib
- Under Investigation: Axitinib, Cediranib, Regorafenib, Semaxanib, Torceranib, Vandetanib, Brivanib
Hypertension
Hypertension

Mean ↑ systolic and diastolic BP
• 1\textsuperscript{st} wk: 14 and 11 mmHg
• 4\textsuperscript{th} wk: 22 and 17 mmHg

Proteinurea

## Incidence (Proteinurea)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Categories</th>
<th>No. of studies</th>
<th>Proteinuria events</th>
<th>Sample size</th>
<th>Incidence (%; 95%CI)</th>
<th>Relative risk (95%CI)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-grade</td>
<td>Overall</td>
<td>23</td>
<td>604</td>
<td>3701</td>
<td>18.7% (13.3–25.6%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Non-RCC</td>
<td>14</td>
<td>261</td>
<td>1635</td>
<td>18.5% (10.7–29.9%)</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>RCC</td>
<td>9</td>
<td>343</td>
<td>2066</td>
<td>18.4% (11.5–28.3%)</td>
<td>1.05 (0.88–1.25)</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
<td>4</td>
<td>108</td>
<td>715</td>
<td>11.6% (4.3–27.6%)</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Axitinib</td>
<td>4</td>
<td>97</td>
<td>535</td>
<td>20.2% (6.9–46.7%)</td>
<td>1.24 (0.92–1.68)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>5</td>
<td>131</td>
<td>761</td>
<td>13.5% (3.9–37.6%)</td>
<td>1.17 (0.88–1.54)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Vandetanib</td>
<td>1</td>
<td>23</td>
<td>231</td>
<td>10.0% (6.7–14.5%)</td>
<td>0.62 (0.39–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Regorafenib</td>
<td>1</td>
<td>35</td>
<td>500</td>
<td>7.0% (5.1–9.6%)</td>
<td>0.42 (0.28–0.63)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Cediranib</td>
<td>5</td>
<td>73</td>
<td>192</td>
<td>37.8% (27.5–49.3%)</td>
<td>3.45 (2.41–4.92)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Tivozanib</td>
<td>2</td>
<td>76</td>
<td>531</td>
<td>9.6% (0.9–54.3%)</td>
<td>0.94 (0.68–1.29)</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Linifanib</td>
<td>3</td>
<td>61</td>
<td>236</td>
<td>27.3% (18.6–38.1%)</td>
<td>1.96 (1.37–2.80)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
↑ risk of proteinurea ≈ 3 times
Cardiovascular toxicity

Number needed to harm [n]

- HTN: 6
- Severe HTN: 17
- Cardiac ischemia: 85
- ATE: 141
- Cardiac dysfunction: 139
- Clinical HF: 410

Hypertension

• In general BP target (JNC7)
  – ↓140/90 mmHg
  – ↓ 130/ 80 mmHg (DM +/- CKD)

JNC8:
• 150/90 mm Hg ≥60 years
• 140/90 mmHg <60 years
or with diabetes

Systolic Blood Pressure Intervention Trial (SPRINT)

Systolic BP
Intensive: <120 mmHg
Standard: <140 mmHg

Hypertension management

Risk factors for hypertension and events:
- Uncontrolled BP
- Organ damage, e.g. LVH
- Established CVD
- CKD ≥ Stage 3
- Diabetes mellitus
- ≥ 3 CV risk factors
- Obstructive sleep apnea
- Obesity
- Age ≥ 60-65

Therapy initiation or intensification (<130 mmHg systolic goal, <120 mmHg ideal)

Blood pressure (BP) assessment preferably daily with first cycle, then weekly

Risk/benefit assessment

Cancer therapy options:
High hypertension risk: VEGF inhibitors, mTOR inhibitors, Ponatinib, Cisplatin

Prohibitive risk:
- Poorly controlled angina
- ACS within 6 months
- Uncontrolled heart failure
- Uncontrolled blood pressure
- Uncontrolled arrhythmia
- Significant QTc prolongation

Temporary hold or dose reduction of cancer therapy if BP >180/110 mm Hg or prohibitive risks as above

Mechanism VEGF induced hypertension vs Anti-hypertensive drug (AHD)

- **CCB**
  - Non-DHP-CCB (X(CYP3A4))
  - DHP (Nifedipine, Amlodipine)
- **Nitrates**

- **ACEI/ARB**
  - Ex. bosentan, macitentan etc.

Sunitinib + AHD in mRCC

Sunitinib + ACEI or ARB in mRCC

Beta-blocker and anti-tumor effect

Anti-hypertensive drugs

Anti-hypertensive strategies for BP goal of <130 mmHg systolic (<120 mmHg ideal)

**STEP 1** – treatment of contributing factors
- pain, emotional stress, etc.
- Obstructive sleep apnea, myocardial ischemia

**STEP 2** – anti-hypertensive drugs by comorbidities:
- Volume overload => diuretics
- Heart failure => ACE-I/ARB, carvedilol
- Myocardial ischemia => carvedilol/nebivolol
- Diabetes mellitus => ACE-I/ARB
- CKD Stage ≥3 => ACE-I/ARB
- None of the above => ACE-I/ARB +/- amlodipine or nifedipine XL +/- carvedilol
- Resistant cases => + long-acting nitrate

Home BP OD was recommended
Proteinurea (Grading and Incidence)

### Incidence
- All gr. ≈ 20%
- Gr. 3 ≈ 0.7-7%
- Gr. 4 <1%

### Onset and Time to resolution
≈ 6 mo.

40% didn't resolve after 11 mo.

---

Proteinuria management

- **≤1+**
  - Negative Proteinuria
  - Continue anti-VEGF agents
  - Blood Pressure
    - BP > 130/80 or uncontrolled hypertension
    - Antihypertensive treatment until BP control (initiate ACE or ARA as first-line treatment)
    - Persistent proteinuria
      - Proteinuria + microscopic hematuria
        - Referral to nephrologists for possible kidney biopsy
        - ≥1 g/l
          - ≥1 g/l, continue anti-VEGF agents and
    - isolated proteinuria
      - <1 g/l

- **≥2+**
  - Positive Proteinuria
  - 24-hour urine collection
  - Hold ≥2 g/24 hr → resume <2 g/24 hr.
  - Discontinue VEGF inh. in patients who develop nephrotic syndrome

Hand-Foot Skin Reaction

• “Hand-Foot syndrome (HFS)” vs “Hand-Foot Skin Reaction (HFSR)”

• HFS ass. with conventional cytotoxic agent
  – HFS are also called Palmar-plantar erythrodysesthesia (PPE)
  – HFSR is seen with multikinase inhibititon
# Rate of HFSR

<table>
<thead>
<tr>
<th>Oral Anti-VEGFr TKI</th>
<th>FDA-Approved Indications</th>
<th>All Grades HFSR (%)</th>
<th>Grades 3-4 Severe HFSR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Renal cell carcinoma, hepatocellular carcinoma</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Renal cell carcinoma, GIST, PNET</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Renal cell carcinoma, advanced soft-tissue sarcoma</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Renal cell carcinoma</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Advanced medullary thyroid cancer</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Advanced medullary thyroid cancer</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Metastatic colon cancer, GIST</td>
<td>45</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, US Food and Drug Administration; HFSR, hand-foot skin reaction; GIST, gastrointestinal stromal tumor; PNET, pancreatic neuroendocrine tumor; TKI, tyrosine kinase inhibitor; VEGFr, vascular endothelial growth factor receptor.
Symptom

• Onset: first 3-6 weeks after start medication

• Symptom
  – dysesthesia, erythema, paresthesia involving the palms and soles with blister which are followed by thick hyperkeratotic, tender lesions
MANAGEMENT OF HFSR

Preemptive strategies are CRUCIAL in the management

- Hyperkeratotic regions on palms / soles and removal of all calluses
- Wearing thick cotton gloves and / or slippers or socks
- Using moisturizing creams that contain keratolytics such as ammonium lactate or urea prior to and during treatment
- Avoiding
  - hot water
  - Rigorous exercise (especially during first 4 weeks of therapy)
  - Tight fitting shoes
  - Excessive pressure
Grading severity of HFSR

**grade I:** painless erythema or dysesthesia, no impairment

**grade II:** painful erythema, swelling, tingling, numbness, dryness, cracking, desquamation, activity is impaired

**grade III:** strong pain, ulceration, blistering, erythema, self-sufficiency is at risk
Severity (CTCAE v.4.0) | Intervention
--- | ---
Grade 0 | Prophylaxis with ammonium lactate 12% cream twice daily or heavy moisturizer (e.g., petroleum jelly) twice daily
Grade 1 | Continue treatment at current dose and monitor for change in severity
| Treat with urea 20% cream twice daily and clobetasol 0.05% cream once daily
| Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to next step
Grade 2 | Continue treatment at current dose and monitor for change in severity
| Treat with urea 20% cream twice daily and clobetasol 0.05% cream once daily and control pain with NSAIDs/GABA agonists/narcotics
| Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to next step
Grade 3 | Interrupt treatment until severity decreases to grades 0–1
| Continue treatment with clobetasol 0.05% cream twice daily and control pain with NSAIDs/GABA agonists/narcotics
| Reassess after 2 weeks; if reactions worsen or do not improve, dose interruption or discontinuation per PI may be necessary

Balagula Y, ey J Support Oncol 2010;8:149-61
BCR-ABL

Irvine E, Williams. Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with TKIs for the Treatment of CML. Pharmacotherapy 2013 Apr 3.
Specific adverse drug reaction

Kinase Targets of TKIs

<table>
<thead>
<tr>
<th>Target (IC50)</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL1</td>
<td>122-466</td>
<td>20-60</td>
<td>&lt; 1</td>
<td>1</td>
<td>0.37</td>
</tr>
<tr>
<td>BCR-ABL1 (T315I)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>C-Kit</td>
<td>96</td>
<td>200</td>
<td>5</td>
<td>-</td>
<td>12.5</td>
</tr>
<tr>
<td>PDGFR</td>
<td>74</td>
<td>71</td>
<td>28</td>
<td>-</td>
<td>1.1</td>
</tr>
<tr>
<td>Src</td>
<td></td>
<td></td>
<td>0.5</td>
<td>1.2</td>
<td>5.4</td>
</tr>
<tr>
<td>YES</td>
<td></td>
<td></td>
<td>0.5</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>LCK</td>
<td></td>
<td></td>
<td>0.4</td>
<td>1.3</td>
<td>-</td>
</tr>
</tbody>
</table>

• Platelet-derived growth factor receptor (PDGFR), lymphocyte-specific protein tyrosine kinase (LCK), 50% inhibitory concentration (IC50)

Irvine E, Williams. *Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia.* Pharmacotherapy 2013 Apr 3.
## Adverse events associated with TKIs in studies of 1\textsuperscript{st} and 2\textsuperscript{nd} line treatment

<table>
<thead>
<tr>
<th>Adverse(%)</th>
<th>1\textsuperscript{st} line Imatinib 400 mg OD (IRIS study n = 553)</th>
<th>1\textsuperscript{st} line (ENESTnd study)</th>
<th>2\textsuperscript{nd} line(2101) Nilotinib 400 mg OD (n=321)</th>
<th>2\textsuperscript{nd} line (NCT00261846) Bosutinib 500 mg OD (n=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1\textsuperscript{st} line (ENESTnd study)</td>
<td>2\textsuperscript{nd} line</td>
<td>2\textsuperscript{nd} line</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imatinib 400 mg OD (N=283)</td>
<td>Nilotinib 300 mg bid (n=282)</td>
<td>Nilotinib 400 mg bid (n=281)</td>
<td>Imatinib 400 mg OD (N=283)</td>
</tr>
<tr>
<td>Non hematologic(all grade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraficial edema</td>
<td>56</td>
<td>7</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>44</td>
<td>11</td>
<td>19</td>
<td>31</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>37</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>11</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>34</td>
<td>31</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>8</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Headache</td>
<td>31</td>
<td>14</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>NR</td>
<td>5</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>QTcF &gt; 500 msec</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Irvine E, Williams. Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Pharmacotherapy 2013 Apr 3.
## Adverse events associated with TKIs in studies of 1<sup>st</sup> and 2<sup>nd</sup> line treatment

<table>
<thead>
<tr>
<th>Adverse(%)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; line (DASISION study)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; line (START-R study)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; line (BELA study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dasatinib 100 mg OD (n=101)</td>
<td>Dasatinib 70 mg OD (n=101)</td>
<td>Bosutinib 500 mg OD (n=248)</td>
</tr>
<tr>
<td></td>
<td>Imatinib 400 mg OD (n=101)</td>
<td>Imatinib 400 mg bid (n=49)</td>
<td>Imatinib 400 mg OD (n=251)</td>
</tr>
<tr>
<td><strong>Non hematologic (all grade)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraficial edema</td>
<td>9</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>11</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>QTcF &gt; 500 msec</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>NR</td>
</tr>
</tbody>
</table>

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### Adverse events associated with TKIs in studies of 1\textsuperscript{st} and 2\textsuperscript{nd} line treatment

<table>
<thead>
<tr>
<th>Adverse(%)</th>
<th>1\textsuperscript{st} line imatinib 400 mg OD (IRIS study n = 553)</th>
<th>1\textsuperscript{st} line (ENESTnd study)</th>
<th>2\textsuperscript{nd} line (2101) Nilotinib 400 mg OD (n=321)</th>
<th>2\textsuperscript{nd} line (NCT00261846) Bosutinib 500 mg OD (n=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nilotinib 300 mg bid (n=282)</td>
<td>Nilotinib 400 mg bid (n=281)</td>
<td>Imatinib 400 mg OD (N=283)</td>
<td></td>
</tr>
<tr>
<td>Hematologic(all grade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Laboratory abnormalities(grade 3,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT/AST level</td>
<td>5</td>
<td>4/1</td>
<td>9/3</td>
<td>2/1</td>
</tr>
<tr>
<td>Elevated bilirubin level</td>
<td>NR</td>
<td>4</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Elevated lipase level</td>
<td>NR</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Elevated glucose level</td>
<td>NR</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

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## Adverse events associated with TKIs in studies of 1st and 2nd line treatment

<table>
<thead>
<tr>
<th>Adverse(%)</th>
<th>1st line (DASISION study)</th>
<th>2nd line (START-R study)</th>
<th>1st line (BELA study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dasatinib 100 mg OD (n-101)</td>
<td>Imatinib 400 mg OD (n=101)</td>
<td>Dasatinib 70 mg OD (n-101)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21</td>
<td>20</td>
<td>63</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
<td>7</td>
<td>20</td>
</tr>
</tbody>
</table>

### Hematologic(all grade)

### Laboratory abnormalities(grade 3,4 )

<table>
<thead>
<tr>
<th></th>
<th>1st line (DASISION study)</th>
<th>2nd line (START-R study)</th>
<th>1st line (BELA study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ALT/AST level</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Elevated bilirubin level</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Elevated lipase level</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Elevated glucose level</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Adverse drug reaction summary

• Class effect
  – Fatigue $\rightarrow$ QOL ($2^{nd}$ Ima $>$ $1^{st}$ Ima $>$ Nilo $>$ Dasa $>$ Bosu)
  – Rash: Nilo $>$ Bosu $>$ Ima $>$ Dasa
  – Cardiac event: $\leq$ 1%, Can present any time clinical like heart failure.
  – Altered glucose metabolism
    • Hypoglycemia, Hyperglycemia

Irvine E, Williams. Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Pharmacotherapy 2013 Apr 3.
Specific adverse drug reaction

IRIS study 56%, DASISION study 42%

- **Imatimib**: Fluid retention may be related from inhibited PDGFR.

- **Dasatinib**: Pleural effusion occurred in 10% with 1st line dasatinib (The DASISION study) and 25% with 2nd line (START-R study).

More than 60 cases of pulmonary arterial hypertension (PAH) have been reported and 18 cases suspected with dasatinib use after prior imatinib treatment. In nearly all cases, patients were diagnosed with pleural effusion while receiving dasatinib before developing PAH, suggesting a related mechanism of cause.

Irvine E, Williams. Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Pharmacotherapy 2013 Apr 3.
Specific adverse drug reaction

– Nilotinib: Abnormal laboratory abnormalities
  • ↑ ALT/AST level (Nilo > Ima)
  • ↑ lipase level
  • Hyperbilirubinemia (Gr. 3,4)
    – 4–8% (Nilo), <1%(Imati)
  • Peripheral arterial occlusive disease (PAOD): 1.1% vs 0.5% vs 0.6% (Nilo vs Ima vs Placebo)
    – if PAOD is confirmed, permanently discontinued.

Irvine E, Williams. Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Pharmacotherapy 2013 Apr 3
Specific adverse drug reaction

• Bosutinib:
  – GI disorders Ex. diarrhea, nausea, abdominal pain, and vomiting.
  – In the BELA study: Laboratory ab. Gr3 or 4 [Bosutinib vs Imatinib]
    • ↑ ALT (22% vs 3%)
    • ↑ AST (11% vs 3%)
    • ↑ Lipase levels (9% vs 5%)

Diarrhea (all grades)
84% in 2\textsuperscript{nd} line and 68% in 1\textsuperscript{st} line

Irvine E, Williams. Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Pharmacotherapy 2013 Apr 3.
Managements

NCCN Task Force Report: Tyrosine Kinase Inhibitor Therapy Selection in the Management of Patients With Chronic Myelogenous Leukemia

Managing Side Effects of Tyrosine Kinase Inhibitor Therapy to Optimize Adherence in Patients with Chronic Myeloid Leukemia: The Role of the Midlevel Practitioner

Susan O’Brien, MD; Jerald P. Radich, MD; Hema M. Sundar, MD

Megan Cornelison, MS, PA-C; Elias J. Jabbour, MD; and Mary Alma Welch, MS, PA-C
Managements

1. Have to educated patients about benefit and adverse reaction from TKIs.

2. Goal to improved.
   1. Adherence to TKIs therapy.
   2. Quality Of Life (QOL)
   3. Reduced event to dose interruption.

If we can choose TKIs that suitable for patient 's co-morbidity
Table 2. Six-Year Probability of MMR, 4-Log Reduction in Transcript Levels, and CMR and Degree of Adherence

<table>
<thead>
<tr>
<th>Adherence Rate (%)</th>
<th>No. of Patients</th>
<th>MMR</th>
<th>4-Log Reduction</th>
<th>CMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 90</td>
<td>23</td>
<td></td>
<td>4.3</td>
<td>0</td>
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<td>≤ 90</td>
<td>69</td>
<td></td>
<td>≤ .001</td>
<td>.007</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>18</td>
<td></td>
<td>.692</td>
<td>.001</td>
</tr>
<tr>
<td>≤ 85</td>
<td></td>
<td></td>
<td>.98</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>75</td>
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<td>.813</td>
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<tr>
<td>≤ 80</td>
<td>12</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. The median adherence rates for patients with a rate of ≤ 99%, ≤ 95%, ≤ 90%, ≤ 85%, and ≤ 80% were 93.5%, 81.7%, 76.0%, 73.9%, and 63.1%, respectively.

Abbreviations: MMR, major molecular response; CMR, complete molecular response.
### Management of adverse drug reactions

**Imatinib:**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>• Grade 3/4 neutropenia (absolute neutrophil count [ANC] 1,000/mm³)</td>
</tr>
<tr>
<td></td>
<td>- Dose interruption until ANC 1,500/mm³</td>
</tr>
<tr>
<td></td>
<td>• Grade 3/4 thrombocytopenia (platelet count 50,000/mm³)</td>
</tr>
<tr>
<td></td>
<td>- Dose interruption until platelet count 75,000/mm³</td>
</tr>
<tr>
<td></td>
<td>- Growth factors can be used in combination with imatinib for patients</td>
</tr>
<tr>
<td></td>
<td>with resistant neutropenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
</table>
| Nonhematologic Specific interventions (Grade 2 or 3 severity) | ● Diarrhea: Supportive care  
● Edema: Diuretics, supportive care  
● Fluid retention (pleural effusion, pericardial effusion, edema, and ascites): Diuretics, supportive care, dose reduction, interruption, or discontinuation. Consider echocardiogram to check left ventricular ejection fraction.  
● GI upset: Take medication with a meal and large glass of water  
● Muscle cramps: Calcium supplement, tonic water  
● Rash: Topical or systemic steroids, dose reduction, interruption, or discontinuation  
If any of the grade 2 or 3 toxicities are not responsive to symptomatic measures, treat as grade 4. |
| Nonhematologic—Grade 4                            | Hold drug until grade 1 or better, then consider resuming dose at 25%–33% dose reduction (not less than 300 mg). Consider change to dasatinib, nilotinib, or clinical trial.                                    |
| Nonhematologic — Liver                            | ● Grade 2: Hold drug until grade 1. Resume at 25%–33% dose reduction (not less than 300 mg). Evaluate for other hepatotoxic drugs that may be contributing to toxicity, including acetaminophen. Consider change to dasatinib, nilotinib, or clinical trial.  
● Grade 3/4: Consider change to dasatinib, nilotinib, or clinical trial. |
### Nilotinib:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>● Grade 3/4 neutropenia (absolute neutrophil count [ANC] 1,000/mm³)</td>
</tr>
<tr>
<td></td>
<td>➢ Dose interruption until ANC 1,000/mm³</td>
</tr>
<tr>
<td></td>
<td>● Grade 3/4 thrombocytopenia (platelet count 50,000/mm³)</td>
</tr>
<tr>
<td></td>
<td>➢ Dose interruption until platelet count 50,000/mm³</td>
</tr>
<tr>
<td></td>
<td>➢ Growth factors can be used in combination with imatinib for patients with resistant neutropenia and thrombocytopenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT Interval prolongation</td>
<td>ECGs with a QTc 480 msec: Hold drug. ECG should be obtained to monitor the QTc at baseline, 7 days after initiation and periodically thereafter as well as following any dose adjustments.</td>
</tr>
</tbody>
</table>
| Nonhematologic Specific        | ● Headache, nausea (ondansetron), diarrhea: Supportive care  
● Rash: Topical or systemic steroids, dose reduction, interruption, or discontinuation  
If any of the grade 2 or 3 toxicities are not responsive to symptomatic measures, treat as grade 4. |
| interventions (Grade 2 or 3    |                                                                                                                                                                                                          |
| severity)                      |                                                                                                                                                                                                          |
| Nonhematologic Grade 4         | Hold drug until grade 1 or better, and then resume at reduced dose level (400 mg once daily). If clinically appropriate, consider escalating dose to 300–400 mg twice daily, depending on starting dose.               |
| Nonhematologic Liver           | ● Elevated serum levels of lipase, amylase, bilirubin, and/or hepatic transaminases (grade 3): Hold drug until serum levels return to grade 1. Resume nilotinib at 400 mg once daily.                                  |
Dasatinib:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>• Grade 4 neutropenia (ANC 500/mm³)</td>
</tr>
<tr>
<td></td>
<td>• Dose interruption until ANC 1000/mm³</td>
</tr>
<tr>
<td></td>
<td>• Grade 3–4 thrombocytopenia (platelet count 50,000/mm³)</td>
</tr>
<tr>
<td></td>
<td>• Dose interruption until platelet count is 50,000/mm³</td>
</tr>
<tr>
<td></td>
<td>• Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Nonhematologic Specific interventions** (Grade 2 or 3 severity)        | Fluid retention (ascites, edema, and pleural and pericardial effusion): Diuretics, supportive care  
● Pleural/pericardial effusion: Diuretics, dose interruption. If the patients has significant symptoms, consider short course of steroids (prednisone 20 mg/day x 3)  
● Headache, diarrhea: Supportive care  
● GI upset: Take medication with a meal and large glass of water.  
● Rash: Topical or systemic steroids, dose reduction, interruption, or discontinuation  
If any of the grade 2 or 3 toxicities are not responsive to symptomatic measures, treat as grade 4. |
| **Nonhematologic Grade 4**                                               | Hold drug until grade 1 or better, and then consider resuming at reduced dose level depending on the severity of the initial event, or change to nilotinib or imatinib. |

Conclusion

• TKIs class effect: fatigue, Rash, cardiac event and abnormal laboratory (Blood sugar, liver function, lipase)

• Specific effect:
  – Imatinib: Superficial edema
  – Nilotinib:
    • Abnormal laboratory abnormalities (AST, ALT, bilirubin, lipase). Should be monitor is recommended.
  – PAOD
    – Dasatinib: Pleural effusion may related to PAH
    – Bosutinib: GI side effect → Diarrhea (Most)
Conclusion

• Management
  – Educated patients about benefit and adverse drug reaction
  – Improve patients ‘s adherence (Related to efficacy)
  – Dose interruption is recommended when patients have grade 3,4 side effect and try to restart as fast as if possible.