Managing the Toxicity of Sequencing-Guided Treatment

CASEY WILLIAMS, PHARMD, BCOP, DIRECTOR OF MOLECULAR AND EXPERIMENTAL MEDICINE, AVERA CANCER INSTITUTE
RACHEL ELSEY, PHARMD, CLINICAL ONCOLOGY PHARMACIST, AVERA CANCER INSTITUTE; ASSISTANT PROFESSOR, SOUTH DAKOTA STATE UNIVERSITY
SEPTEMBER 25, 2015

Learning Objectives

1. Discuss strategies to reduce the toxicities of MEK inhibitors, PI3K-AKT-mTOR pathway inhibitors, and checkpoint inhibitors when treating patients with cancer

2. Describe available literature that outlines the recommended doses and schedules of applicable drug combinations routinely used in sequencing guided therapy

Precision Medicine in Oncology

Avera Cancer Institute
There Is An Increasing Shift Toward Targeted Therapy In Cancer

Chemotherapy vs Targeted Therapy

- Anticancer drugs may be highly effective in some, but less effective in others.
- Patients are exposed to the risk of side effects.

In personalized medicine, clinicians use biomarkers to predict a patient’s response to therapy. Patients are more likely to get therapies with the greatest impact with fewer side effects.

Anticancer drugs may be highly effective in some, but less effective in others.

Patients are exposed to the risk of side effects.

Conventional Cancer Treatment

Patient’s tissue sample → Pathology grade, size, IHC → Chemotherapy

Personalized cancer treatment

Patient’s tissue sample → Molecular diagnostics → Pathway targeted combination therapy

which pathways are active?

Conventional View of Breast Cancer

ER+ HER2+
Solid Tumor Genomes Are Complex: Driver Alterations Must Be Separated from Passenger Alterations

Exposure
- UV light
- Tobacco smoke

Genomic Instability
- Pre-cancerous lesion
- In situ cancer
- Invasive cancer
- Metastatic cancer

Genetic Instability

<table>
<thead>
<tr>
<th>Genomic alterations</th>
<th>Number</th>
<th>Total</th>
<th>Biologically relevant</th>
<th>Clinically relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10,000s</td>
<td>5-10</td>
<td>1-2</td>
</tr>
</tbody>
</table>

The number of “clinically relevant” alterations in a single patient is LOW buried amongst 1,000s of passenger genomic alterations

Stupid and Smart Cancers

Stupid Cancers
- Single dominant mutation
- Small mutational load
- Monotherapy is often effective
- Resistance rare, late, same pathway

Smart Cancers
- Multiple mutational drivers
- Large mutational load
- Multi-targeted therapy required
- Resistance common, early
Somatic point mutations: varying rates across cancer (1035 WES)

Genomic Oncology Challenges

- Extremely complex in most cases
- Available assays all have significant weaknesses
  - Germline?
  - Quality and tumor content of sample
  - Quality of DNA, RNA, and protein
  - Storage and shipping methods
- Pharmacology of combination treatments needs to be critically evaluated

Results Review Process

- Standard review of each set of results can take up to 30 minutes or more of discussion with variable amounts of time spent by multiple individuals prior to meeting
- Balance of time divided between basic science pathway discussion, oncology issues, and pharmacology
ONCOLOGY HISTORY:

• In brief, 65 year old lady: diagnosed in 2009 with stage I T1cN0i+M0 invasive lobular carcinoma, Nottingham grade 2 for which she underwent right breast mastectomy with implant-based reconstruction. Tumor markers were ER 4+ positive, PR 4+ positive, and HER-2 not amplified by FISH with a ratio of 1.3. HER-2 copy number was 3.8. Oncotype was low risk at 12.

Treatment History:

• The patient was treated with anastrozole from March 2010 to 2012. When she discontinued this due to joint arthralgias in June 2012
• The patient was started on Tamoxifen in July 2012 and was maintained on this without difficulty
• In her 4 year follow up appointment there was a dime-sized identified lump found in the right axilla. Core biopsy confirmed recurrent invasive lobular carcinoma grade 2 (3/2/1), ER positive with 90% of cells staining strongly, PR positive with 50% of cells staining strongly, and HER-2 FISH not amplified with a ratio of 1.4, copy number 3.7.
• July 2014, excisional biopsy of the right axilla lump was performed. Final pathology from this showed a 1.5 X 1.5 cm invasive lobular carcinoma grade 2. Medial, anterior, and deep margins are positive and the tumor was sent for Theralink and Foundation One testing after consultation with MEM team.
25 Patients with HER2 Somatic Mutations

- Each blue circle represents a patient.
- From 8 publications with a total of 1,499 patients.
- 20% of patients have mutations at amino acids 309 or 310.
- 68% of patients have mutations at amino acids 755-781.

**HER2 Somatic Mutations identified by Breast Cancer Genome Sequencing**

<table>
<thead>
<tr>
<th>HER2 mutation</th>
<th>Stage</th>
<th>ER</th>
<th>PR</th>
<th>HER2 Status</th>
<th>HER2 IHC</th>
<th>HER2 FISH Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>G309A</td>
<td>IIB</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>R678Q and L755S</td>
<td>IIB</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>L755S</td>
<td>IIA</td>
<td>+</td>
<td>+</td>
<td>Negative*</td>
<td>2+</td>
<td>Not available</td>
</tr>
<tr>
<td>L755S</td>
<td>I</td>
<td>+</td>
<td>-</td>
<td>Negative*</td>
<td>2+</td>
<td>2.05</td>
</tr>
<tr>
<td>Del.755-759</td>
<td>IIB</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>D769H</td>
<td>IIB</td>
<td>+</td>
<td>-</td>
<td>Positive</td>
<td>3+</td>
<td></td>
</tr>
<tr>
<td>V777L</td>
<td>IIA</td>
<td>+</td>
<td>+</td>
<td>Negative*</td>
<td>2+</td>
<td>1.0</td>
</tr>
<tr>
<td>V842I</td>
<td>IIB</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>1+</td>
<td></td>
</tr>
</tbody>
</table>

* Confirmed by SNP chip and/or exome sequencing read number.

**HER2 mutations V777L, D769H, V842I, G309A induce gain-of-function over HER2 WT in MCF10A mammary epithelial cells.**

Recommended Therapy

- Neratinib compassionate use is best available therapy
- May possibly try trastuzumab or lapatinib, but overall benefit of each unclear
  - Insurance is requiring that patient must fail trastuzumab before trying alternative treatments

---

Distribution of nonsynonymous mutations in A, PIK3CA, B, PIK3R1, and C, PIK3R2.

1. Hypermorphic mutation
   • Activation of PI3K Pathway –
     Everolimus ok
2. Hypomorphic mutation
   • No true activation of PI3K
     pathway.
3. Neomorphic mutation
   • Activation of RAS-MAPK
     Pathway initiated – Need to use
     in concert with MEKi

Cancer Cell 26, 479–494, October 13, 2014

"... patients who benefit from chemotherapy (in the metastatic setting) may be treated
successfully with other regimens at the time of progression. However, the chance of
response decreases by about half with each subsequent treatment." DeVita VT.

*Graph was NOT taken from DeVita but is provided to illustrate the effects of the quote above and assumes an initial response of 60%.
Phase III Trials of Capecitabine With or Without Ixabepilone in Pretreated Advanced Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>CA163-046</th>
<th>CA163-048</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cape + Ixa</td>
<td>Cape</td>
</tr>
<tr>
<td></td>
<td>n = 375</td>
<td>n = 377</td>
</tr>
<tr>
<td>ORR</td>
<td>36%</td>
<td>14%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.0 mo</td>
<td>4.2 mo</td>
</tr>
<tr>
<td>HR, P value</td>
<td>HR 0.75; P = 0.0003</td>
<td>HR 0.79; P = 0.0005</td>
</tr>
<tr>
<td>Median OS</td>
<td>12.9 mo</td>
<td>11.1 mo</td>
</tr>
<tr>
<td>HR, P value</td>
<td>HR 0.90; P = 0.1936</td>
<td>HR 0.90; P = 0.1162</td>
</tr>
</tbody>
</table>

*N = 462 for each arm; † N = 480 for each arm.
- Pooled analysis of patients with triple-negative breast cancer: Combination showed 2.5 months improvement in median PFS (4.2 vs 1.7 mo) compared to capecitabine alone
- Doubled ORR (31% vs 15%)


Phase II Trial: Weekly Nab-Paclitaxel in MBC Previously Treated With a Taxane

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Nab-Paclitaxel 100 mg/m² (n = 106)</th>
<th>Nab-Paclitaxel 125 mg/m² (n = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>15 / 106 (14%)</td>
<td>12 / 75 (16%)</td>
<td>0.7309</td>
</tr>
<tr>
<td>Prior paclitaxel</td>
<td>4 / 30 (13%)</td>
<td>4 / 20 (20%)</td>
<td>NR</td>
</tr>
<tr>
<td>Prior docetaxel</td>
<td>7 / 34 (21%)</td>
<td>6 / 28 (21%)</td>
<td>NR</td>
</tr>
<tr>
<td>Prior paclitaxel and docetaxel</td>
<td>2 / 29 (7%)</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Median PFS</td>
<td>3.0 mo</td>
<td>3.5 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Median OS</td>
<td>9.2 mo</td>
<td>9.1 mo</td>
<td>NR</td>
</tr>
</tbody>
</table>


EMBRACE: Best Overall Response

<table>
<thead>
<tr>
<th></th>
<th>ORR, % Eribulin</th>
<th>ORR, % TPC Eribulin</th>
<th>CBR, % Eribulin</th>
<th>CBR, % TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>12.2% 4.7%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CB</td>
<td>-</td>
<td>-</td>
<td>22.6% 16.8%</td>
<td></td>
</tr>
<tr>
<td>Receptor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER / PgR+ (n = 326 / 152)</td>
<td>14.7 3.3</td>
<td>25.5 15.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER / PgR- (n = 111 / 50)</td>
<td>2.7 6.0</td>
<td>8.9 16.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2+ (n = 77 / 34)</td>
<td>6.5 2.9</td>
<td>14.3 17.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2- (n = 342 / 162)</td>
<td>13.2 4.3</td>
<td>23.1 14.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 unknown (n = 49 / 18)</td>
<td>14.3 11.1</td>
<td>32.7 38.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER / PgR / HER2+ (n = 54 / 49)</td>
<td>3.6 5.0</td>
<td>11.9 10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral (n = 391 / 181)</td>
<td>11.0 5.0</td>
<td>21.7 16.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-visceral (n = 77 / 33)</td>
<td>18.2 5.0</td>
<td>27.3 18.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR = CR + PR; CBR = CR + PR + SD ≥ 6 months.
SABC Poster 2015 – Abstract 850649
Title: Implementation of Routine Genomic and Proteomic Profiling of Metastatic Breast Cancer Patients in a Community Cancer Center

Body: **Background:** The optimal treatment strategy for patients with metastatic breast cancer (MBC) is currently unknown. Resistance to standard therapies, including anthracyclines and taxanes, limit the number of treatment options in many patients to a small number of non-cross resistant regimens. Rational combination approaches that are selected based upon genomic and proteomic analysis represents a possible advance that warrants extensive exploration.

**Methods:** Single center analysis of 77 consecutive metastatic breast cancer patients seen over a 12 month period (June 2014 through May 2015). All patients were seen in consultation and metastatic tissue obtained. All samples were sent for standard pathologic, genomic (FoundationOne), and proteomic (TheraLink) analysis.

<table>
<thead>
<tr>
<th>ER+/HER2-</th>
<th>ER+/HER2+</th>
<th>ER-/HER2+</th>
<th>Triple Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>PR</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Total evaluable patients = 40
Overall CR = 13%
Overall PR = 33%
Overall SD = 43%
Overall PD = 13%
Total Not Evaluable = 37 pts (48%)

**Results:** Genomic and proteomic analysis yielded actionable targets in a majority of cases (89%). The most common pathways involved were the following: PI3K/Akt/mTOR (73%), MAPK (46%), ERBB (36%), FGFR (25%), and Jak/STAT (11%). Over 100 unique molecular aberrations were identified in 40 evaluable patients. Current outcomes are summarized in Table 1. The overall response rate was 45%, with another 43% of patients with stable disease. Average number of prior therapies was over 4, with a range of 1-11.

**GENOMIC MEDICINE IS THE INEVITABLE FUTURE: CHALLENGES??**

1. **BURDEN ON PATHOLOGY** and Biobank/ Histology
2. **INSURANCE COVERAGE:** TESTING/ DRUGS
   - Some insurance companies are covering basically most/all recommended treatments
   - Some companies are not covering anything
   - Patients that live longer cost more
3. **BUILDING THE DRUG UMBRELLA**
4. **DRUG COMBINATIONS:** N OF ONE TRIALS
5. **SHIFT TO NEOADIUVANT CARE**
6. **REPEAT TUMOR BIOPSIES or REPEAT LIQUID BIOPSIES**
7. **IMMUNOLOGY**
8. Data now shows a prognostic value to sequencing upfront at a minimum
Questions?

Targeted Medications
- MEK inhibitor
  - Trametinib (Mekinist)
- mTOR inhibitors
  - Everolimus (Afinitor)
  - Temsirolimus (Torisel)
- Checkpoint inhibitor
  - Palbociclib (Ibrance)
  - CDK 4/6

Preventing and Managing Toxicities
DOSING
Dosing of Combination Therapy

Clinical Trials

Drug-Drug Interactions

Toxicity Profiles

Clinical trials

Everolimus and Trametinib

Phase Ib
Advanced solid tumors
- pancreas, colorectal, melanoma, breast, neuroendocrine, other

Maximum tolerated dosing
- Everolimus 5 mg M/W/F
- Trametinib 1 mg daily

Dose limiting toxicities:
- Stomatitis
- Mucositis
- Thrombocytopenia
- Fatigue
- Dermatitis acneiform

**Everolimus and Pazopanib**

Phase I

Advanced solid tumors
- Urothelial, SCLC, Adrenal cortex, NSCLC, Atypical carcinoid of lung

Maximum tolerated dose
- Everolimus 5 mg daily
- Pazopanib 400 mg daily

Pharmacokinetics
- No increase in pazopanib
- Everolimus levels 41% increased

Dose limiting toxicities
- Rash and thrombocytopenia


---

**Everolimus and Sorafenib**

Phase Ib

Maximum Tolerated Dose
- Everolimus 2.5 mg daily
- Sorafenib 600 mg daily

Advanced solid tumors

Grade 3 toxicities
- Hypophosphatemia
- Increased alanine aminotransferase (ALT) levels
- Asthenia
- Anorexia


---

**Everolimus, Vinorelbine, and Trastuzumab**

Phase I

Pre-treated patients with HER2-overexpressing metastatic breast cancer

Maximum tolerated dosing (Q.21 D regimen)
- Everolimus 5 mg/day
- Vinorelbine 25 mg/m2 D1, D8
- Trastuzumab 2 mg/kg D1, D8, D15

Dose limiting toxicities
- Neutropenia
- Fever neutropenia
- Stomatitis
- Fatigue
- Anorexia
- Acneiform dermatitis

Temsirolimus, Carboplatin and Paclitaxel

**Phase I**
- Advanced solid tumors
  - endometrium, ovary, head and neck, other
- Maximum tolerated dosing (Q21D)
  - Temsirolimus 25 mg D1, 8
  - Carboplatin AUC 5 D1
  - Paclitaxel 175 mg/m² D1

**Dose limiting toxicities**
- Thrombocytopenia
- Fatigue

**Adverse events occurring in >20%**
- Fatigue, mucositis, alopecia, neuropathy, nausea, neutropenia, thrombocytopenia, infection


---

Temsirolimus and Pegylated Liposomal Doxorubicin

**Phase I**
- Refractory solid malignancies
- Maximum tolerated dose (Q 28 D)
  - Temsirolimus 25 mg D1, 8, 15, 22
  - Liposomal Doxorubicin 25 mg/m² D1

**Pharmacokinetics**
- Increased systemic exposure of doxorubicin when used in combination

**Common treatment-related adverse events (AEs)**
- Mucositis/stomatitis
- Anorexia
- Thrombocytopenia
- Fatigue


---

Temsirolimus and Pazopanib

**Phase I**
- Advanced solid tumors: RCC, Soft tissue sarcoma, adrenal cortical carcinoma, colorectal, head and neck
- Dosing considered not feasible at clinically significant doses
  - Temsirolimus 10 mg weekly
  - Pazopanib 200 mg daily

**Dose limiting toxicity**
- Fatigue
  - Grade ≥3 AEs
  - Neutropenia
  - Hypophosphatemia

Palbociclib Combinations
Has yet to be studied in combination with other targeted agents
On-going clinical trials
  - ClinicalTrials.gov

Drug Metabolism

<table>
<thead>
<tr>
<th></th>
<th>Trametinib</th>
<th>Everolimus</th>
<th>Temirolimus</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolized by:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Sul724A</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inhibits or induces</td>
<td>Weakly inhibits CYP2C8</td>
<td>N/A</td>
<td>Weakly inhibits CYP2D6</td>
<td>Weakly inhibits CYP3A4</td>
</tr>
</tbody>
</table>

+++: primarily metabolized by enzyme
+: secondary pathway
0: not metabolized by enzyme

Adverse Effect Profiles

<table>
<thead>
<tr>
<th></th>
<th>Trametinib All grades; grades ≥3</th>
<th>Everolimus All grades; grades ≥3</th>
<th>Temirolimus All grades; grades ≥3</th>
<th>Palbociclib All grades; grades ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>N/A</td>
<td>14-31%; &lt;1-5%</td>
<td>14-31%; &lt;1-5%</td>
<td>79%; 62%</td>
</tr>
<tr>
<td>Anemia</td>
<td>38%; 2%</td>
<td>41-61%</td>
<td>230%</td>
<td>35%; 6%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>N/A</td>
<td>19-54%; 0-3%</td>
<td>19-54%; 0-3%</td>
<td>19%; 2%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>13%; &lt;1%</td>
<td>3%</td>
<td>1%</td>
<td>11%</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST elevations</td>
<td>60%</td>
<td>20-56%; 1-4%</td>
<td>20-56%; 1-4%</td>
<td>N/A</td>
</tr>
<tr>
<td>ALT elevations</td>
<td>39%</td>
<td>18-51%; 0-1%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>ALP elevations</td>
<td>24%</td>
<td>32-74%; 1%</td>
<td>68%; 3%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Adverse Effect Profiles

<table>
<thead>
<tr>
<th></th>
<th>Trametinib</th>
<th>Everolimus</th>
<th>Temsirolimus</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades; grades ≥3</td>
<td>All grades; grades ≥3</td>
<td>All grades; grades ≥3</td>
<td>All grades; grades ≥3</td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>84-85%; 4-8%</td>
<td>22-59%; &lt;1-5%</td>
<td>22-59%; &lt;1-5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Acneiform eruption</td>
<td>19%; &lt;1%</td>
<td>3%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Palmar-plantar erythrodesia</td>
<td>N/A</td>
<td>5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>15%</td>
<td>41-78%; 3-8%</td>
<td>41-78%; 3-8%</td>
<td>25%</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>42-46%; &lt;1-1%</td>
<td>14-50%</td>
<td>27%</td>
<td>23%; 4%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>N/A</td>
<td>25%</td>
<td>32%</td>
<td>16%; 1%</td>
</tr>
</tbody>
</table>

### Preventing and Managing Toxicities

**THERAPEUTIC STRATEGIES**
Determining treatment of toxicity

What is the causative agent?

Management of toxicity?

- Pharmacologic and non-pharmacologic treatments vs. dose adjustment

Which agents have the greatest potential efficacy based on tumor genomics?

Which agent(s) can be adjusted?

### MEK Inhibitors

#### Dermatologic Toxicities

<table>
<thead>
<tr>
<th>Morbilliform Eruption</th>
<th>Papulopustular Eruption</th>
<th>Xerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment:</strong></td>
<td><strong>Prevention:</strong></td>
<td><strong>Treatment:</strong></td>
</tr>
<tr>
<td>- Topical steroids</td>
<td>- Similar strategies to EGFR inhibitors may be considered</td>
<td>- Gentle skin care</td>
</tr>
<tr>
<td>- Short course of systemic steroids</td>
<td>- Low potency topical steroids</td>
<td>- Emollients</td>
</tr>
</tbody>
</table>

#### Dermatologic Toxicities

<table>
<thead>
<tr>
<th>MEK Inhibitors</th>
<th>Dermatologic Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEK Inhibitors</td>
<td>Dermatologic Toxicities</td>
</tr>
</tbody>
</table>

#### Dermatologic Toxicities

- **Morbilliform Eruption**
  - Treatment: Topical steroids, short course of systemic steroids

- **Papulopustular Eruption**
  - Prevention: Similar strategies to EGFR inhibitors may be considered
  - Treatment: Low potency topical steroids, clindamycin 1% topical

- **Xerosis**
  - Treatment: Gentle skin care, emollients, antipruritic creams

---

### mTOR Inhibitors

#### Dermatologic Toxicities

<table>
<thead>
<tr>
<th>Stomatitis</th>
<th>Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment:</strong></td>
<td><strong>Treatment:</strong></td>
</tr>
<tr>
<td>- Use mouthwashes (without alcohol or peroxide)</td>
<td>- Gentle skin care</td>
</tr>
<tr>
<td>- Topical steroids (class I-III)</td>
<td>- Wet dressings</td>
</tr>
<tr>
<td>- Anesthetics</td>
<td>- Emollients</td>
</tr>
<tr>
<td>- Antiseptic washes</td>
<td>- Topical steroids (class III/IV)</td>
</tr>
<tr>
<td>- Dietary management</td>
<td></td>
</tr>
</tbody>
</table>

---


Hematologic Toxicities
Increase frequency of monitoring
Hold the medication
Dose reduce

Noninfectious Pneumonitis
Median onset
- 2 - 6 months
Need to rule out infectious causes
Clinical picture can be clouded by:
- Lung metastasis
- Pleural effusion
- Dyspnea
- Cough

Treatment
- Grade 1:
  - Additional monitoring
- Grade 2-3:
  - Temporary dose interruption
  - Reinitiate at a lower dose
  - Consider corticosteroid treatment
- Grade 4:
  - Discontinue everolimus
  - Consider corticosteroid treatment

Clinical Takeaways
Be more, not less, vigilant about dosing for sequencing-guided treatment regimens
Dosing adjustments occur frequently
- Medication reconciliation
Be very cognizant about toxicity
- Ask questions
- Minor adverse effects may turn into serious problems
Questions?

Additional References


