Management of the Adverse Effects Associated with Mammalian Target of Rapamycin (mTOR) Inhibitors

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God Bless These United States of America

Learning Objectives

- Describe the mechanism of action(s) of mTOR inhibitors
- Identify the common and dose limiting side effects associated with mTOR inhibitors
- Describe interventional strategies for the prevention or management of mTOR adverse effects.
52 year old Caucasian male with metastatic renal cancer is receiving IV temsirolimus, weekly. Pertinent history includes nephrectomy (Scr 1.1 mg/dl), bilateral adrenalectomy (Rx: fludrocortisone), and hypercholesterol/triglyceridemia (Rx: diet; gemfibrozil). Labs prior to 2\textsuperscript{nd} course WNL except: HbA1c 9\% (ref value > 6\%), FPG 208 mg/dl (ref value < 100 mg/dl). Which of the following would you recommend for glycemic control?

A. Intermediate or long-acting insulin
B. GlipiZide (Glucotrol) – Sulfonamide
C. Pioglitazone (Actos) – Thiazolidinedione
D. Metformin (Glucophage) – Biguanide
E. Repaglinide (Prandin) - Meglitinide

**Temsirolimus & Glycemic Control**

Correct Answer(s) A or D (Insulin or Metformin)

- **Metformin** (typically lowers A1c by \~ 1.5\% points, generally well tolerated (GI effects – So titrate; renal excretion- (Contraindicated GFR < 30 ml/min), Anticancer Effect ?
- **Insulin** - Considered 2\textsuperscript{nd} line to metformin for Type 2 (Diabetes Care 32:193,2009)
- (B,C,E) glipizide [CYP2C8/9], pioglitazone [CYP2C8/9], repaglinide [CYP2C8;OATP1B1] – Gemfibrozil inhibits UGT1A1/1A3, CYP2C8; SLCO1B1 (OATP1B1).
  (Clin Pharmcol Ther 84:403,2008)
- Consider alternative to gemfibrozil ?
Potential Alternatives to Gemfibrozil

- Statin (HMGCR genotype A/A)*
- Fenofibrate
- Fenofibrate + Simvastatin
- Omega 3 (Loraza) - RX (4Gm/d)
- Omega 3 + Simvastatin


Metformin’s Anticancer Effect?

Circulating insulin levels
Metformin
Gluconeogenesis
AMPK
Liver

*OCT1-420 del (20% Caucasians)

J Clin Oncol 27: 3271, 2009
Clin Cancer Res 16: 1695, 2010
Inhibitors of Mammalian Target of Rapamycin (mTOR)

- **USAN nomenclature**
  - **imus**, immunosuppressant; **rolimus**, rapamycin derivative
  (ama-assn.org/ama/pub/aboutama/.../approved stems.shtml)

**Approved Rapalogs**
- Sirolimus (Rapamycin) – bacteria in soil of Easter Island, fungicide
- Temsirolimus (Torisel; CCI779, IV) Advanced Renal Cell
- Everolimus (Afinitor; RAD001, oral) Advanced Renal Cell

**Investigational**
- Ridaforolimus (Deforolimus; AP2353) phase III in sarcomas (SUCCEED)
- BEZ235; EX147 – Dual P13K / mTOR inhibitors
- TOR-Kinibs eg. OSI-027 (mTORC1/mTORC2 kinase inhibitor)
- Combination of targeted agents...(breast, lung, etc.)

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![Diagram showing inhibition of AKT expression and related pathways.](Clin Cancer Res 16:1348, 2010)

**Increased Expression of AKT**

- mTOR, mTORC1/mTORC2, PDK1, S6K, 4E-BP1, HIF-1α, VEGF/PDGFR

- **Loss of Function**
  - p53
  - p53

- Treatment:
  - VEGF/FGFR

- **Mutated/Amplified in Tumor:**
  - PTEN, Cowden's disease
  - LKB1, Peutz-Jeghers syndrome
  - TSC1/2, tuberous sclerosis
  - VHL, von Hippel-Lindau disease

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J Clin Oncol 27:2278, 2009
Cancer Cell 16:21, 2009
Phase III Trials of Rapalogs in Metastatic Renal Cell Cancer

<table>
<thead>
<tr>
<th></th>
<th>Temsirolimus</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>626</td>
<td>410</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Poor Risk Untreated</td>
<td>Failed TKIs</td>
</tr>
<tr>
<td>Comparator</td>
<td>Interferon – alpha</td>
<td>Placebo</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Overall Survival (OS)</td>
<td>Progression-Free Survival (PFS)</td>
</tr>
<tr>
<td></td>
<td>Median OS (months) 10.9 vs 7.3 (0.73, 0.58 – 0.92)*</td>
<td>Median PFS (months) 4 vs 1.9 (0.30, 0.22 – 0.40)*</td>
</tr>
</tbody>
</table>

* Hazard ratio & 95% CI

Anti-Cancer Drugs 20:893, 2009

Targeting mTOR in Renal Cell Carcinoma (RCC)

**Drug**
- Temsirolimus
  - CYP3A4/Pgp substrate; $t_{1/2}$ 17 hrs; metabolite sirolimus 55 hrs
  - (Adv Ther 26: 55, 2009)
- Everolimus
  - 10 mg PO daily c / s food
  - (Be consistent! AUC $16\%$ c high fat meal) caution: grapefruit, St. John’s Wort, Starfruit

**Dosing**
- Temsirolimus: 25mg IV over 30-60 min, wkly premed-diphenhydramine (Hypersensitivity Reaction 9%)
- Everolimus: 10 mg PO daily c / s food

**Class Dose Adjustments**
- Concomitant CYP3A4 inducers / inhibitors
- Hepatic impairment (Child-Pugh class B- score 7-9, eg bill 2-3 mg/dl + albumin 3.5 – 2.8 mg/dl)
- Severe (Gr 3/4 intolerable adverse events)

Torisel® [package insert]

Afinitor ® [package insert]
New Jersey: Novartis, 2009
Clin Cancer Res 16: 1368, 2010
### Adverse Effects of mTOR Inhibitors

#### Cardio
- **Temsirolimus** (n=208): 35% (3%), 25% (<1%)
- **Everolimus** (n=274): 25% (<1%)

#### Derm
- **Temsirolimus** (n=208): 47% (5%)
- **Everolimus** (n=274): 29% (1%)

#### Metabolic
- **Temsirolimus** (n=208):
  - Hyperglycemia: 89% (16%)
  - Hypercholesterolemia: 87% (2%)
  - Hypertriglyceridemia: 83% (44%)
- **Everolimus** (n=274):
  - Hyperglycemia: 57% (15%)
  - Hypercholesterolemia: 77% (4%)
  - Hypertriglyceridemia: 73% (<1%)

#### Electrolyte
- **Temsirolimus** (n=208): 49% (18%)
- **Everolimus** (n=274): 37% (6%)

#### GI
- **Temsirolimus** (n=208): 41% (3%)
- **Everolimus** (n=274): 44% (4%)

#### Hem
- **Temsirolimus** (n=208): 94% (20%)
- **Everolimus** (n=274): 92% (13%)

#### Thrombocytopena
- **Temsirolimus** (n=208): 40% (1%)
- **Everolimus** (n=274): 23% (1%)

#### Neutropenia
- **Temsirolimus** (n=208): 19% (5%)
- **Everolimus** (n=274): 14% (<1%)

#### Infections
- **Temsirolimus** (n=208): 20% (3%)
- **Everolimus** (n=274): 37% (10%)

#### Hepatic
- **Temsirolimus** (n=208): 38% (2%)
- **Everolimus** (n=274): 25% (1%)

#### Renal
- **Temsirolimus** (n=208): 57% (3%)
- **Everolimus** (n=274): 50% (1%)

#### Neuro/Phys
- **Temsirolimus** (n=208): 51% (11%)
- **Everolimus** (n=274): 64% (8%)

#### Respiratory
- **Temsirolimus** (n=208): 2%
- **Everolimus** (n=274): 14%

*(Grade 3/4) * Patients with RCC

NCI CTC v 3.0

Torisel/Afinitor Package Insert
## Monitoring and Managing Side Effects of mTOR Inhibitors

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Prevention</td>
<td>Avoid “Live” (attenuated) vaccines (intranasal influenza, MMR, Varicella/Zoster) or contact with recently vaccinated (least 7d) MMWR 57:27,2008</td>
</tr>
<tr>
<td>Hypersensitivity Rxn</td>
<td>Monitoring</td>
<td>Interrupt, H₁ and/or H₂ antagonist, restart slower rate 30-60 min later</td>
</tr>
<tr>
<td>Wound healing</td>
<td>Caution</td>
<td>Major surgery-adequate time for healing</td>
</tr>
<tr>
<td>Neutropenia / Thrombocytopenia</td>
<td>CBC Diff</td>
<td>Interrupted / Dose adjusted</td>
</tr>
<tr>
<td>Anemia *(Gr 3/4 13-20%)</td>
<td></td>
<td>Transfusion</td>
</tr>
<tr>
<td>*(6.5 – 7.9g); Gr 4</td>
<td></td>
<td>ESA / Iron guidelines</td>
</tr>
<tr>
<td>(&lt; 6.5 g Hgb)</td>
<td></td>
<td>(NCCN V.3.2009)</td>
</tr>
</tbody>
</table>

"Fatigue is something (oncologists) get tired of hearing about, because it is the most common symptom patients complain about."

-Lowell Anthony, MD

Oncology & Biotech News 3:16,2009
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<th>Management</th>
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</thead>
<tbody>
<tr>
<td>Fatigue (Asthenia) (Gr 3/4 8-11%)</td>
<td>Rule Out: anemia, hypothyroidism, Adrenal fatigue, hypophosphatemia</td>
<td>NCCN V.1.2009 Non/Pharmacologic Interventions</td>
</tr>
</tbody>
</table>

### Screening
Fatigue Analogue Scale (FAS)

<table>
<thead>
<tr>
<th>No Fatigue</th>
<th>Worst Possible</th>
</tr>
</thead>
</table>

Fatigue (Chp 9), Portenoy RK (http://symptomresearch.nih.gov)

## mTOR Skin Rashes

- **Herpetic (viral +)**
- **Maculopapular**
- **Papulopustular**

**Rash:** typically Gr 1-2 maculopapular, H/N region, 1st week of Rx  
**Management:** Supportive (lotions, sun screens), resolves spontaneously or with brief course of topical steroid or antibiotics

J Clin Oncol 22:2336, 2004
Stomatitis/Mucositis Associated with mTOR Inhibitors

- **Distinct** from radiation/chemo (no pseudomembrane)
- Mild to moderate severity
- **Rapid** onset (≤ 5 days)
- Mucosa of lips, lateral tongue, buccal mucosa, soft palate (unlike viral, not on hard palate)
- Management: improves/resolves with continued Rx; reversible by interruption

Symptom **palliation**: bland foods, mucosal pain-coating agents

**Caution**: Azoles even troches; fluconazole > 200 mg/d, Oral OPC-nystatin; esophageal- echinocandin

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Dyspnea, Dry Cough, Fatigue, Fever on Presentation?

- **Ground glass opacities**
- **Lung parenchymal Consolidation**

**PFT: DLCO**

*Eur J Cancer 42: 1875, 2006*  
*DLCO- diffusing lung capacity to carbon monoxide*
Monitoring and Managing Side Effects of mTOR Inhibitors

**Toxicity**
- Pneumonitis

**Monitoring**
- PFT (DLCO), Chest X-ray, CT

**Management**
- Asymptomatic – continuation
- **Symptomatic** – depending on severity: dose interruption, discontinuation, high dose steroids

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**Lab Abnormality**
- **Hypophosphatemia** (normal 2.5 – 4.5 mg/dl)

**Monitoring**
- Gr 2/3 (1-2.5 mg/dl)
- † G4 (<1 mg/dl)

**Management**
- PO phosphate 250 – 500 mg TID/QID; † IV 15 mM Na or K phosphate in 100 – 250 ml NS over 2-4hrs

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### Content of Various Phosphate Preparations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Phosphate (mM/ml)</th>
<th>Potassium (meq/ml)</th>
<th>Sodium (meq/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Phosphate</td>
<td>3 mM/ml</td>
<td>4.4 meq/ml</td>
<td></td>
</tr>
<tr>
<td>Sodium Phosphate</td>
<td>3 mM/ml</td>
<td></td>
<td>4 meq/ml</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fleets Phospho-Soda per ml</td>
<td>150 mg (4.8 mM)</td>
<td></td>
<td>4.8 meq</td>
</tr>
<tr>
<td>K-Phos Neutral tablet</td>
<td>250 mg (8.1 mM)</td>
<td>1.1 meq</td>
<td>13 meq</td>
</tr>
<tr>
<td>Neutra-Phos Powder</td>
<td>250 mg (8.1 mM)</td>
<td>7.1 meq</td>
<td>7.1 meq</td>
</tr>
<tr>
<td>Neutra-Phos K Powder</td>
<td>250 mg (8.1 mM)</td>
<td></td>
<td>14.25 meq</td>
</tr>
</tbody>
</table>

31 mg elemental phosphate = 1 mM phosphate
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<tr>
<td>Hyperlipidemia</td>
<td>• Fasting lipid panel (cholesterol, triglycerides)</td>
<td>• Diet modification, initiation of lipid-lowering agents based on profile</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>• Fasting blood sugar, Hemoglobin A1c</td>
<td>• Insulin, oral agents for glycemia control (e.g. metformin)</td>
</tr>
</tbody>
</table>

*Eur Urol 53:917,2008*

### Mammalian Target of Rapamycin (mTOR)

- **Validated** target in Renal Cell Carcinoma
- **Common toxicities** associated with mTOR inhibitors: fatigue, stomatitis, dyspnea, neutropenia / thrombocytopenia, increases in glucose, triglycerides, cholesterol
- Aggressive toxicity **management** with Supportive care can delay burden of disease while maximizing QOL.