Oncology Pharmacy Specialty Sessions, Part I

Tuesday, October 18
1:30 p.m.–4:30 p.m.
Convention Center: Rooms 306 & 307

Part of the professional development program for the recertification of board-certified oncology pharmacists, approved by the Board of Pharmacy Specialties and cosponsored by ACCP, the American Society of Health-System Pharmacists (ASHP), and the Hematology/Oncology Pharmacy Association (HOPA). Part II will be presented on Wednesday, October 19, from 9 a.m. to noon. Participants must attend all 6 hours of programming to be eligible to complete the Web-based posttest for oncology recertification credit (the posttest must be completed by December 31, 2011). Partial BCOP recertification credit is not available. The posttest fee is $45. After the Annual Meeting, program participants will receive e-mail instructions for accessing the BCOP recertification posttest. Program participants wishing to receive continuing pharmacy education credit will receive an e-mail after the Annual Meeting with instructions about how to claim continuing education credit for these sessions.

Moderator: Christy S Harris, Pharm.D., BCPS, BCOP
Assistant Professor of Pharmacy Practice, School of Pharmacy-Boston
Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts

1:30 p.m. The Heart of the Matter: When Targeted Cancer Therapies Cause Off-Target Toxicities
Activity No. 0465-9999-11-302-L01-P

Courtney L. Bickford, Pharm.D., BCPS
Cardiology Pharmacy Clinical Specialist, University of Texas M.D. Anderson Cancer Center, Houston, Texas

2:30 p.m. Castration-Resistant Prostate Cancer
Activity No. 0465-9999-11-401-L01-P

Rebecca E. Greene, Pharm.D., BCOP
Clinical Pharmacy Specialist, Oncology, South Texas Veterans Health Care System, San Antonio, Texas

3:30 p.m. Vaccinations in Cancer
Activity No. 0465-9999-11-402-L01-P

Kamakshi V. Rao, Pharm.D., BCOP
Oncology/BMT Clinical Specialist, University of North Carolina Hospital, Chapel Hill, North Carolina

Faculty Conflict of Interest Disclosures

Courtney L. Bickford: no conflicts to disclose.
Rebecca E. Greene: no conflicts to disclose.
Kamakshi V. Rao: no conflicts to disclose.
Learning Objectives

1. Distinguish cardiac toxicities (heart failure, hypertension, QT prolongation) attributable to targeted cancer therapies.
2. Summarize the evidence regarding the pathophysiology of cardiotoxicities induced by targeted cancer therapies.
3. Develop evidence-based plans for monitoring and treating cardiovascular adverse reactions associated with targeted cancer therapies.
4. Develop a treatment algorithm for castration-resistant prostate cancer (CRPC) based on the efficacy of the therapies.
5. Analyze patient specific information to determine when a change in management is indicated in patients with CRPC.
6. Construct a treatment plan for a patient with CRPC based on prior therapy, comorbid illness and concomitant medications.
7. Differentiate the toxicities associated with various treatments for CRPC about which patients and caregivers should be educated.
8. Differentiate the changes in immune function and immunity that occur in patients undergoing therapy for cancer based on age, disease, and chemotherapy regimen.
9. Summarize the recommendations for vaccinations in oncology patients based on data and guidelines from the Centers for Disease Control, Infectious Disease Society of America, and the American Society for Blood and Marrow Transplantation.
10. Analyze limitations in the current available data and gaps in the current recommendations for vaccination in oncology patients.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
The heart of the matter: when targeted cancer therapies cause off-target toxicities

Courtney L. Bickford, Pharm.D., BCPS
Pharmacy Clinical Specialist, Cardiology
MD Anderson Cancer Center, Houston, TX

Objectives

- Distinguish cardiac toxicities (heart failure, hypertension, QT prolongation) attributable to targeted cancer therapies
- Summarize the evidence regarding the pathophysiology of cardiotoxicities induced by targeted cancer therapies
- Develop evidence-based plans for monitoring and treating cardiovascular adverse reactions associated with targeted cancer therapies

Introduction

- Increased use of targeted anticancer agents
  - Prolong survival and decrease cancer recurrence
- Targeted therapies aimed at molecules overexpressed in tumor cells
  - Receptor tyrosine kinases expressed in normal tissues \(\rightarrow\) Cardiotoxicity

Cancer and Cardiotoxicity

- Patients with cancer often excluded from studies of cardiovascular (CV) disease
- Patients with clinically significant CV disease excluded from studies of new cancer therapies
- Definitions of cardiotoxicity vary across studies
- Study durations variable
- Determining incidence/prevalence of cardiovascular side effects and their management limited

Types of Cardiotoxicity

- Arrhythmias
- Hypertension
- Myocardial ischemia
- Thromboembolism
- Left ventricular dysfunction (LVD), Heart failure (HF)
Inhibiting which of the following targets is implicated as a potential cause for the development of heart failure?

1. VEGF
2. ABL
3. HER2
4. All of the above

Classification of Chemotherapy-Related LVD

<table>
<thead>
<tr>
<th>Type I: myocardial damage</th>
<th>Type II: myocardial dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural damage</td>
<td>Reversible myocyte dysfunction</td>
</tr>
<tr>
<td>Irreversible myocyte damage</td>
<td>Reversibly recovers to baseline in 2-4 months</td>
</tr>
</tbody>
</table>

Response to HF therapy:
- Permanent: Some cases may improve
- Typically recovers to baseline in 2-4 months

Dose related:
- Yes
- No

Effect of rechallenge:
- High probability of recurrent dysfunction
- Increasing evidence for the relative safety of rechallenge

Targeted Therapies Associated with LVD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>2-28</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1.5-2.2</td>
</tr>
<tr>
<td>Imatinib</td>
<td>0.5-1.7</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>2</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2.7-11</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1-3.8</td>
</tr>
</tbody>
</table>

Trastuzumab and LVD

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>LVD (%)</th>
<th>NYHA Grade III/IV HF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACH</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>AC alone</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>TH</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>T alone</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

New York Heart Association (NYHA) Classification of Heart Failure

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No symptoms: No limitation in ordinary physical activity</td>
</tr>
<tr>
<td>II</td>
<td>Mild symptoms: Slight limitation during ordinary activity, Comfortable at rest</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation in activity due to symptoms during less than ordinary activity, Patient comfortable only at rest</td>
</tr>
<tr>
<td>IV</td>
<td>Severe limitations: Symptoms even while at rest</td>
</tr>
</tbody>
</table>

Adjuvant Trastuzumab and LVD

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arm</th>
<th>LVEF decline 15%</th>
<th>NYHA Grade III/IV</th>
<th>Trastuzumab Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-31</td>
<td>AC → T</td>
<td>34%</td>
<td>0.6%</td>
<td>Post 21 days</td>
</tr>
<tr>
<td></td>
<td>AC → TH</td>
<td>17%</td>
<td>4.1%</td>
<td>Post 21 days</td>
</tr>
<tr>
<td>NCCTG</td>
<td>AC → T</td>
<td>0.3%</td>
<td></td>
<td>Post 21 days</td>
</tr>
<tr>
<td>N9831</td>
<td>AC → T → H</td>
<td>2.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AC → TH → H</td>
<td>3.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HERA</td>
<td>Observation</td>
<td>2.1%</td>
<td>0%</td>
<td>Post 89 days</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>7%</td>
<td>0.6%</td>
<td></td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC → T</td>
<td>11%</td>
<td>0.7%</td>
<td>Post 21 days</td>
</tr>
<tr>
<td></td>
<td>AC → TH</td>
<td>19%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TCH</td>
<td>9%</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>FinHER</td>
<td>T, TH, V</td>
<td>No trastuzumab: 6%</td>
<td></td>
<td>Pre-anthracycline</td>
</tr>
<tr>
<td></td>
<td>or VH → FEC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FinHER reported incidence of LVEF decline ≥ 15%.

AC = Anthracycline; T = Trastuzumab; TH = Taxanes

**Adjuvant Trastuzumab with Chemotherapy**

- Lower incidence of trastuzumab-induced LVD in the adjuvant setting
- Factors affecting incidence in adjuvant trials
  - Prospective monitoring of cardiac function
  - Exclusion criteria
    - HERA: LVEF < 55%
    - Other trials: LVEF < 50%
  - Chemotherapy regimen
  - Time between anthracycline and trastuzumab

---

**Trastuzumab and Cardiotoxicity**

- Long-term cardiac tolerability of trastuzumab in HER2(+) metastatic breast cancer patients (n=173)
  - Overall incidence cardiac toxicity= 28%
  - Risk factors:
    - Age >50
    - Borderline LVEF prior to treatment
    - History of CV disease
    - Sequence of chemotherapy administration
    - Prior treatment with anthracyclines
      - Cumulative dose >300 mg/m²

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**Lapatinib and Incidence of Cardiac Events**

<table>
<thead>
<tr>
<th>Previous Cardiotoxic Therapy</th>
<th>Decreased LVEF (%)</th>
<th>Asymptomatic LVEF Decline (%)</th>
<th>Symptomatic LVEF Decline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline (n=552)</td>
<td>2.2</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Trastuzumab (n=828)</td>
<td>1.7</td>
<td>1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Neither (n=2311)</td>
<td>1.5</td>
<td>1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Total (n=3689)</td>
<td>1.6</td>
<td>1.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Defined as LVEF decrease ≥20% relative to baseline and below lower limit of normal
*Defined as National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or 4 left ventricular dysfunction

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**Mechanisms of Trastuzumab and Lapatinib-Induced LVD**

- Tumor cell growth and survival
- Cardiomyocyte development and survival

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**Trastuzumab and Antibody-Dependent Cell-Mediated Cytotoxicity**

- NK cell
- Tumor Cell
- Cardiac Myocytes
- Cardiomyocyte destruction

---

**Package Insert Guidelines for Monitoring LVEF**

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Baseline</th>
<th>During Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>✓</td>
<td>Every 3 months and upon completion</td>
<td>Every 6 months ≥ 2 years</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>✓</td>
<td>Periodically</td>
<td></td>
</tr>
</tbody>
</table>

---

Monitoring and Management of Trastuzumab in Asymptomatic Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>LVEF</th>
<th>Trastuzumab</th>
<th>LVEF monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ but normal</td>
<td>Continue</td>
<td>Repeat in 4 weeks</td>
<td>None</td>
</tr>
<tr>
<td>↓ &gt;10 points but normal</td>
<td>Continue</td>
<td>Repeat in 4 weeks</td>
<td>Consider beta-blockers</td>
</tr>
<tr>
<td>↓ 10-20 points and LVEF &gt;40%</td>
<td>Continue</td>
<td>Repeat in 2-4 weeks; if improved, then monitor, if not improved, then stop trastuzumab</td>
<td>Treat for LVD</td>
</tr>
<tr>
<td>↓ &gt;20 points to &lt;40% or LVEF &lt;30%</td>
<td>Hold</td>
<td>Repeat in 2-4 weeks; if improved to &gt;45%, then restart, if not improved then stop trastuzumab</td>
<td>Treat for LVD</td>
</tr>
</tbody>
</table>


Guidelines for Monitoring and Management of Trastuzumab in Adjuvant Breast Cancer

<table>
<thead>
<tr>
<th>Physical Status</th>
<th>LVEF</th>
<th>Trastuzumab</th>
<th>LVEF monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic Normal</td>
<td>Continue</td>
<td>As scheduled</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>↓ &lt;16 % but normal</td>
<td>Continue</td>
<td>As scheduled</td>
<td>If LVEF&lt;40% treat with ACEI</td>
<td></td>
</tr>
<tr>
<td>↓ ≥16 % or subnormal (regardless of the amount of reduction)</td>
<td>Hold temporarily</td>
<td>Repeat in 4 wk; if improved, then restart T; if not improved, then stop trastuzumab</td>
<td>If LVEF&lt;40% treat with ACEI</td>
<td></td>
</tr>
<tr>
<td>Symptomatic &lt;Normal</td>
<td>Hold permanently</td>
<td>Per cardiologist’s discretion</td>
<td>Treat for HF</td>
<td></td>
</tr>
</tbody>
</table>

ACEI = Angiotensin Converting Enzyme Inhibitor

Imatinib and Heart Failure

<table>
<thead>
<tr>
<th>Case Series</th>
<th>N</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerkela (case series)</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atallah*</td>
<td>1276</td>
<td>1.7%</td>
</tr>
<tr>
<td>Hatfield*</td>
<td>2327</td>
<td>0.5%</td>
</tr>
<tr>
<td>Trent*</td>
<td>219</td>
<td>0.4%</td>
</tr>
<tr>
<td>IRIS trial</td>
<td>553</td>
<td>1%</td>
</tr>
<tr>
<td>Verweij</td>
<td>942</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

*Retrospective studies

Mechanisms of Imatinib-Induced LVD

PDGF = platelet-derived growth factor
"PDGF receptors → may have cardioprotective role in response to stress"

Endoplasmic reticulum (ER) stress

Imatinib → ABL protein

2011 ACCP Annual Meeting
Oncology Pharmacy Specialty Sessions, Part I
Dasatinib

- Mechanism of dasatinib-induced cardiotoxicity:
  - Inhibition of ABL
  - Inhibits Src family kinases (SFK) and a number of other kinases, which may be involved in the development of cardiotoxicity as well
  - Leukemia patients (n=2182) across all dasatinib studies:
    - HF or LVD (all grades) occurred in 2%
    - Grade 3 or 4 HF: <1%

Leukemia patients (n=2182) across all dasatinib studies: HF or LVD (all grades) occurred in 2% Grade 3 or 4 HF: <1%


Sunitinib and LVD

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<th>MRCC</th>
<th>GIST</th>
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<tbody>
<tr>
<td>Treatment Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib-treated (n=375)</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>Interferon-alpha-treated (n=360)</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Sunitinib-treated (n=209)</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Placebo (n=102)</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Frequency of LVD</td>
<td>27%</td>
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SRCC = metastatic renal cell carcinoma; GIST = Gastrointestinal stromal tumor

Sunitinib and LVD

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Sunitinib: Mechanisms of cardiotoxicity

- Animal studies → Mitochondrial damage in cardiomyocytes
  - VEGF inhibition → Hypertension → HF
  - Ribosomal S6 kinase (RSK) inhibition
    - Activation of intrinsic apoptotic pathway and ATP depletion
  - Platelet-derived growth factor receptor (PDGFR)-β inhibition
    - PDGFRβ signaling - essential component of the mouse cardiac response to load-induced stress
  - Hypothyroidism
    - 4-16% in sunitinib-treated patients
    - Hypothyroidism associated with an increased risk of HF

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Guidelines for Monitoring and Management of Sunitinib

- Monitoring
  - Monitor for clinical signs and symptoms of HF
  - Baseline and periodic evaluations of LVEF

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Bevacizumab and HF

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<tr>
<th>Overall incidence (%)</th>
<th>Bevacizumab</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Low dose bevacizumab</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>2.5 mg/kg/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose bevacizumab</td>
<td>1.9</td>
<td>0.4</td>
</tr>
<tr>
<td>5 mg/kg/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>1.7</td>
<td>0.3</td>
</tr>
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<td>Capcitabine</td>
<td>1.9</td>
<td>0.8</td>
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<thead>
<tr>
<th>Overall incidence (%)</th>
<th>Bevacizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose bevacizumab</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>2.5 mg/kg/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose bevacizumab</td>
<td>1.9</td>
<td>0.4</td>
</tr>
<tr>
<td>5 mg/kg/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>2.8</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Mechanism of Bevacizumab Cardiotoxicity

- Uncontrolled hypertension and inhibition of VEGF/VEGFR signaling
- Animal studies → angiogenesis plays key role in normal adaptive response to pressure load
- Pressure overload → reduction of myocardial capillary density, global contractile dysfunction, cardiac fibrosis and decompensated HF

Methods for Evaluating LVD

- Endomyocardial biopsy
  - Traditionally viewed as gold standard for determining chemotherapy induced cardiac damage; Invasive
- Echocardiogram (ECHO) & Multi-Gated Acquisition (MUGA)
  - Most common methods used to monitor LV function
  - Non-invasive, cost-effective, high reproducibility
- Serial monitoring
  - Use the same method to facilitate comparison of LVEF

Biomarkers as a Monitoring Tool

- Biomarkers
  - Early identification, assessment and monitoring of cardiotoxicity
  - Minimally invasive and less expensive than ECHO and MUGA
  - Avoid interobserver variability
- Troponin
  - Predict future development of ↓ LVEF after chemotherapy
  - Identify patients at different risks of future cardiac events
- B-type natriuretic peptide
  - Positive correlation with cardiac events & subclinical cardiotoxicity
  - Correlates more with diastolic vs. systolic dysfunction

Troponin and Trastuzumab-Induced LVD

- 251 breast cancer patients
  - Adjuvant and metastatic
- Primary end point: occurrence of cardiotoxicity
  - ↓ LVEF of >10 units from baseline and LVEF<50%
- Results
  - Cardiotoxicity more frequent in patients with troponin increase
  - LVEF recovery occurred less frequently
  - ↑ troponin only independent predictor of trastuzumab-induced cardiomyopathy and lack of LVEF recovery

Guidelines for Monitoring LVEF

- Guidelines* suggest regular cardiac assessment by evaluation of LVEF by either ECHO or MUGA
  - > 1/3 of patients with HF have a normal EF
  - LVEF not sensitive or specific enough to predict late declines
  - Does not allow for early preventative strategy
- Symptoms are the mainstay of the diagnosis of HF
- No recommendation for biomarker testing or preventive therapy

*American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), and ASCO websites

Classification of Heart Failure

**ACC/AHA Treatment Guidelines For Heart Failure**

- **Stage A**: High risk with no symptoms
- **Stage B**: Structural heart disease, symptoms
- **Stage C**: Structural disease, presence or current symptoms
- **Stage D**: Refractory symptoms requiring special interventions

### Hospice
- VAD, transplantation
- Aldosterone antagonist, nesiritide
- Consider multidisciplinary team
- Revascularization, mitral valve surgery
- Cardiac resynchronization if bundle branch block

### Risk factor reduction
- Patient and family education
- Inotropes
- Aldosterone antagonist, nesiritide

### Inotropes
- Consider multidisciplinary team
- Revascularization, mitral valve surgery
- Cardiac resynchronization if bundle branch block

- **ACEI or ARB in all patients.**
- Beta blockers in some patients
- Dietary sodium restriction, diuretics, digoxin

### Treat hypertension, diabetes, dyslipidemia
- ACEI or ARB in some patients
- Treatment hypertension, diabetes, dyslipidemia.


**Anthracycline-Induced Cardiomyopathy Response to ACEI/BB**

**Percentage of Responders According to Time Elapsed from Anthracycline Administration and Start of HF Therapy**

**Reversibility of Trastuzumab following HF Therapy**

**Effects of Valsartan on Acute Cardiotoxicity after CHOP Chemotherapy**

**Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy**


---

Oncology Pharmacy Specialty Sessions, Part I
A 59 year old female with a history of breast cancer treated with anthracycline-based chemotherapy as well as trastuzumab developed HF (EF 35-40%) during chemotherapy. She was managed with carvedilol and enalapril. She returns for follow-up and her EF on ECHO is now 50-55%. Would you discontinue her cardiac medications now that her EF is normal?

1. Yes
2. No

Hypertension

- Hypertension (HTN) - one of the most frequent comorbid conditions found in cancer registry patients as well as observed side-effects of inhibiting VEGF signaling
- Risk factor for coronary heart disease, stroke, HF, and end-stage renal disease
- CV risk doubles for every 20/10 mmHg increase over 115/75 mmHg
- Higher incidence of intracerebral hemorrhage reported in patients with mRCC treated with agents targeting VEGF

Definition of Hypertension

CTCAE v4.02

- Grade 1: Prehypertension (systolic blood pressure (SBP) 120-139 or diastolic blood pressure (DBP) 80-89 mmHg)
- Grade 2: Stage 1 HTN (SBP 140-159 or DBP 90-99 mmHg); medical intervention indicated; recurrent or persistent (>24 hours); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated
- Grade 3: Stage 2 HTN (SBP >160 or diastolic blood pressure >100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
- Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
- Grade 5: death

Incidence of Hypertension

<table>
<thead>
<tr>
<th>Agent</th>
<th>Overall Incidence (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>4-35</td>
<td>5-18</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>40-47</td>
<td>0-4</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>5-47</td>
<td>4-13</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>17-43</td>
<td>1.4-38</td>
</tr>
</tbody>
</table>
Mechanism of Hypertension

- Effects of VEGF binding VEGFR2:
  - Increase capillary permeability
  - Production of nitric oxide (NO) and prostaglandin I2 → smooth muscle relaxation
  - Endothelial cell proliferation, migration, and survival under stress

- Effects of VEGF inhibition on vasculature → ↑BP
  - Decreased NO and prostaglandin I2 → Vasoconstriction
  - Rarefaction (decreased arteriole and capillary densities)

Hypertension as a biomarker of efficacy in patients with mRCC treated with sunitinib

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Max SBP &lt; 140 mmHg</th>
<th>OR (n = 441)</th>
<th>Max DBP &lt; 90 mmHg</th>
<th>OR (n = 362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>241 (54.6)</td>
<td>9 (9.7) &lt; 0.0001</td>
<td>207 (57.2)</td>
<td>43 (25.0) &lt; 0.0001</td>
<td>2.49 (0.94-6.59)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>12.5</td>
<td>2.5 &lt; 0.0001</td>
<td>13.4</td>
<td>5.3 &lt; 0.0001</td>
<td>0.66 (0.18-2.61)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>7.8 &lt; 0.0001</td>
<td>10.3</td>
<td>15 &lt; 0.0001</td>
<td>0.40 (0.17-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

Increased Risk of High-Grade HTN with Bevacizumab in Cancer Patients

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>B (events/SS)</th>
<th>Control (events/SS)</th>
<th>Incidence % (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>588/6754</td>
<td>75/5902</td>
<td>7.9 (6.1-10.2)</td>
<td>5.28 (4.15-6.71)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>278/3028</td>
<td>50/2969</td>
<td>8.6 (5.7-12.8)</td>
<td>5.24 (3.89-7.05)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>108/1230</td>
<td>9/841</td>
<td>9.0 (6.1-13.2)</td>
<td>7.06 (3.66-13.62)</td>
</tr>
<tr>
<td>RCC</td>
<td>55/779</td>
<td>2/893</td>
<td>7.1 (3.4-14.1)</td>
<td>8.99 (2.72-29.72)</td>
</tr>
<tr>
<td>Breast</td>
<td>103/1091</td>
<td>4/794</td>
<td>8.5 (3.1-21.2)</td>
<td>14.8 (0.92-238.51)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>32/663</td>
<td>5/550</td>
<td>5.5 (2.2-12.7)</td>
<td>5.52 (2.12-14.35)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>21/268</td>
<td>5/258</td>
<td>22.6 (13.3-35.8)</td>
<td>2.49 (0.94-6.59)</td>
</tr>
</tbody>
</table>

Management per Package Insert

- Bevacizumab: Monitor blood pressure (BP) and treat HTN. Temporarily suspend bevacizumab if not medically controlled. Discontinue if hypertensive crisis or hypertensive encephalopathy
- Pazopanib: BP should be well-controlled prior to initiating pazopanib. Monitor for HTN and treat as needed
- Sorafenib: Monitor BP weekly during the first 6 weeks and periodically thereafter and treat, as required. In cases of severe or persistent HTN consider temporary or permanent discontinuation of sorafenib
- Sunitinib: Patients should be monitored for HTN and treated as needed with standard and hypertension therapy. In case of severe hypertension, temporary suspension of sunitinib is recommended until HTN controlled

Compelling Indications and Recommended HTN Treatment

- HF
- Diabetes
- CKD
- Recurrent stroke prevention

Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee Recommendations

- Conduct formal risk assessment
- Identify preexisting HTN and address before initiation
- Monitor blood pressure throughout treatment
- Identify preexisting HTN and address before initiation
- Then at least every 2-3 weeks for the duration of treatment
- Target blood pressure: <140/90 mmHg
- Treat the goal immediately before initiating therapy
- Adjust lower for patients with multiple preexisting risk factors
- Manage blood pressure elevations aggressively
- Consult hypertension specialist if difficulty maintaining goal
Other Considerations for Management of HTN

- Mechanism of HTN associated with targeted therapy
  - ACEI – ↓ microcirculatory changes, ↑ release of endothelial NO
  - Calcium channel blockers – vasodilation, ↓ rarefaction
  - Nitrates – ↓ NO levels
  - Nebivolol – vasodilation through NO pathway

- Drug interactions – Avoid diltiazem and verapamil

- Prevention of HF – ACEI and BB

- Dose reduction/temporary cessation of targeted therapy


Types of Cardiotoxicity

- Arrhythmias
- Myocardial ischemia
- Hypertension
- Left ventricular dysfunction (LVD)/ Heart failure (HF)
- Thromboembolism

Risk Factors for QT Prolongation

- Female sex*
- 2/3 of all cases
- Elderly age*
- Hypokalemia (< 3.5 mEq/L)
- Severe hypomagnesemia (< 1.4 mEq/L)
- Congestive heart failure*
- Myocardial ischemia or infarction*
- Bradycardia
- Recent conversion from atrial fibrillation, especially with a QT-prolonging drug
- High drug concentrations
- Rapid rate of infusion of QT-prolonging medication
- Congenital long-QT syndrome*
- Baseline QT interval prolongation
- Ion-channel polymorphisms

Risk Factors in Cancer Patients

- Patients with cancer predisposed to QT prolongation
  - 36% have ECG abnormality at screening
  - ~15% patients have prolonged QT
  - High prevalence of comorbid diseases
  - Renal and hepatic dysfunction
  - Concomitant medications
    - Antiemetics, antihistamines, antibiotics, antifungals, antidepressants, antipsychotics, methadone, antiarrhythmics
  - Electrolyte disturbances


Targeted Therapies and QT Prolongation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>16</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>1-10</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>3.5-6</td>
</tr>
</tbody>
</table>

The mechanism underlying QT prolongation: UNKNOWN

When discussing drug-induced QT prolongation, it is now understood that the blockade of delayed rectifier potassium (IKr) current by medications is at least in part responsible for their pro-arrhythmic effect

2011 ACCP Annual Meeting

Oncology Pharmacy Specialty Sessions, Part I
Nilotinib Black Box Warning: QT Prolongation and Sudden Death

- Hypokalemia or hypomagnesemia must be corrected prior to nilotinib administration and should be periodically monitored
- Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided
- Avoid food 2 hours before and 1 hour after nilotinib
- Use with caution in patients with hepatic impairment
- ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

Nilotinib Dose Adjustment for QTc>480 msec

1. Withhold nilotinib, assess & supplement potassium / magnesium; review concomitant medications
2. Resume within 2 weeks at prior dose if QTc returns to <480 msec and to within 20 msec of baseline
3. If QTc 450-480 msec after 2 weeks reduce dose to 400 mg once daily
4. If QTc returns to >480 msec on 400 mg daily, nilotinib should be discontinued
5. ECG should be repeated 7 days after any dose adjustment

Monitoring Recommendations for QT Prolongation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Package Insert Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>ECG at baseline, 7 days after initiation, periodically thereafter, and following any dose adjustments. Avoid strong CYP3A4 inhibitors. Use caution in patients with hepatic impairment.</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>None</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Baseline and on-treatment ECGs; electrolyte monitoring.</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Baseline and periodic ECGs; maintain normal electrolytes.</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>No ECG monitoring recommendations. Avoid strong CYP3A4 inhibitors; consider dose reduction of sunitinib.</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>None</td>
</tr>
</tbody>
</table>

QT Prolongation Summary

- Identify risk factors
- Recognize drug-drug interactions
  - Pharmacodynamic
    - Other QT-prolonging medications
    - www.torsades.org
  - Pharmacokinetic
    - Strong 3A4 inhibitors + nilotinib
- Obtain baseline ECG in patients receiving QT-prolonging drugs and follow periodically

ARS

- Which of the following targeted therapies causes hypertension, heart failure, and QT prolongation?
  1. Bevacizumab
  2. Dasatinib
  3. Pazopanib
  4. Sunitinib

Summary of Cardiotoxicities Associated with Targeted Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Hypertension, Heart failure</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Heart failure, QT prolongation</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Hypertension, QT prolongation</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Hypertension, Heart failure</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Hypertension, Heart failure, QT Prolongation</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Heart failure</td>
</tr>
</tbody>
</table>
Conclusion

- Targeted therapies have made tremendous advances in oncology, but there is still inadequate understanding in regards to predicting, preventing, and reducing the occurrence of cardiotoxicity.

- From a pharmacological perspective, eventual understanding of primary mechanisms responsible for cardiotoxicity is essential.

- From a clinical perspective, there is a need to define clinical endpoints of cardiotoxicity and harmonize cardiac monitoring.

- Case-by-case: therapeutic gain vs. cardiovascular risks.

- Multidisciplinary approach encompassing basic science and oncology/cardiology expertise in order to minimize CV risks associated with targeted therapy.

The heart of the matter: when targeted cancer therapies cause off-target toxicities

Courtney L. Bickford, PharmD, BCPS
Pharmacy Clinical Specialist, Cardiology
MDAnderson Cancer Center, Houston, TX
Castration Resistant Prostate Cancer

Rebecca E. Greene, Pharm.D., BCOP
Clinical Pharmacy Specialist, Oncology
South Texas Veterans Health Care System

Learning Objectives

At the completion of this presentation, the participant should be able to:

• Develop a treatment algorithm for castration-resistant prostate cancer (CRPC) based on the efficacy of the therapies
• Analyze patient specific information to determine when a change in management is indicated in patients with CRPC
• Construct a treatment plan for a patient with CRPC based on prior therapy, comorbid illness and concomitant medications
• Differentiate the toxicities associated with various treatments for CRPC about which patients and caregivers should be educated

Prostate Cancer (PCa)

• Most common cancer in men in US

2010 estimates

• Cases: 217,730 (28%)
• Deaths: 32,050 (11%)

• Hormone dependent

Initial Therapy of Advanced PCa

• Deprive cancer cell of androgen
  • Castration (Serum testosterone < 50 ng/dL)
    ▪ Surgical
    ▪ Chemical
  • CRPC
    ▪ Serum testosterone < 50 ng/dL
    ▪ Rising PSA
    ▪ Metastatic disease
**Adrenal Cortex**

- Cholesterol
- Pregnenolone
- Progesterone
- Corticosterone
- Aldosterone

**CRPC**

- Cholesterol
- Pregnenolone
- Progesterone
- DHEA
- Androstenedione
- DHT-AR

CYP: cytochrome; DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; AR: androgen receptor

---

**Therapy for CRPC in 2009**

- Ensure castration (testosterone < 50 ng/dL)
- Add antiandrogen
- Antiandrogen withdrawal
- First line chemotherapy
  - Docetaxel based
- Second line chemotherapy
  - Mitoxantrone/prednisone
  - Ketoconazole/hydrocortisone
- Clinical trial

---

**Audience Response Question #1**

WG is a 63 yo male with metastatic prostate cancer. WG has been receiving leuprolide IM Q3 months for the past 2 years. WG returns to clinic today for follow up and it is noted that PSA has increased from 3.5 ng/mL to 5 ng/mL to 9 ng/mL over the past 6 months. Testosterone is < 50 ng/dL and CTs confirm new bone lesions. Which therapy would you recommend?

A. Docetaxel 75 mg/m² q 3 weeks + prednisone 5 mg po bid
B. Sipuleucel-T infused every 2 weeks x 3 treatments
C. Cabazitaxel 25 mg/m² q 3 weeks + prednisone 10 mg po daily
D. Mitoxantrone 12 mg/m² q 3 weeks + prednisone 5 mg po bid

---

**Docetaxel Based Therapy**

<table>
<thead>
<tr>
<th>SWOG 9916</th>
<th>TAX 327</th>
<th>TAX 327 Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>DE (n=286)</td>
<td>MP (n=384)</td>
<td>D3P (n=334)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>17.5</td>
<td>15.6</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>6.3</td>
<td>3.2</td>
</tr>
<tr>
<td>50% decrease in PSA</td>
<td>50%</td>
<td>27%</td>
</tr>
</tbody>
</table>

* p<0.05; DE: docetaxel/estramustine; MP: mitoxantrone/prednisone; D3P: Q3-week docetaxel/prednisone; D1P: Q1-week docetaxel/prednisone; NR: not reported

---

**Phase III Trial of Bevacizumab with Docetaxel/Prednisone in First Line Treatment of CRPC (CALGB 90401)**

<table>
<thead>
<tr>
<th>PCa • uCRPC • Chemotherapy naive • ECOG PS ≤ 2</th>
<th>R A N D O M I Z E T • I</th>
<th>R A N D O M I Z E T • I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint • OS</td>
<td>DP: Docetaxel 75 mg/m² q 3 weeks + prednisone 5 mg po bid + placebo</td>
<td>DP + B: Bevacizumab 15 mg/kg + Docetaxel 75 mg/m² q 3 weeks + prednisone 5 mg po bid</td>
</tr>
<tr>
<td>Stratification • 24 month survival probability • Age • Prior arterial thrombotic event</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group
Kelly WK, et al. ASCO abstract LBA4511, 2010

---

**Phase III Trial of Bevacizumab with Docetaxel/Prednisone in First Line Treatment of CRPC (CALGB 90401)**

<table>
<thead>
<tr>
<th></th>
<th>DP (n=526)</th>
<th>DP + B (n=524)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>21.5</td>
<td>22.6</td>
<td>0.181</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.5</td>
<td>9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ Grade 3 adverse events</td>
<td>55.3%</td>
<td>74.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment related deaths</td>
<td>1.1%</td>
<td>4.4%</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

Kelly WK, et al. ASCO abstract LBA4511, 2010
Bevacizumab Summary

- Not approved for first line therapy
- OS in control group was longer than seen in previous studies
- Several phase II trials evaluating bevacizumab with docetaxel/prednisone after progression on docetaxel/prednisone

Treatment of CRPC in 2011

- Asymptomatic
  - Sipuleucel-T
- First line
  - Docetaxel
- Second line
  - Cabazitaxel
  - Satraplatin
- Third line
  - Clinical trial

Sipuleucel-T

- Active cellular immunotherapy
- Stimulate T-cell immunity against prostatic acid phosphatase (PAP)
- Preparation
  - 1.5-2 blood volume mononuclear cell leukapheresis
  - Antigen presenting cells (APCs) isolated
  - APCs cultured with fusion protein of PAP-GMCSF (PA2024)

Integrated Data of 2 Phase III Trials of Sipuleucel-T (D9901 + D9902A)

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Sipuleucel-T (n=147)</th>
<th>Placebo (n=78)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to progression</td>
<td>11.1 weeks</td>
<td>9.7 weeks</td>
<td>0.111</td>
</tr>
<tr>
<td>Hazard ratio (CI)</td>
<td>1.26 (0.05-1.68)</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Median survival</td>
<td>23.2 months</td>
<td>18.9 months</td>
<td>0.011</td>
</tr>
<tr>
<td>Hazard ratio (CI)</td>
<td>1.5 (1.10-2.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Events</td>
<td>7.5%</td>
<td>2.6%</td>
<td>NR</td>
</tr>
</tbody>
</table>

Integrated data of 2 Phase III trials of Sipuleucel-T (D9901 + D9902A)

- 1.5-2 blood volume mononuclear cell leukapheresis
- Antigen presenting cells (APCs) isolated
- APCs cultured with fusion protein of PAP-GMCSF (PA2024)

Phase III Trial of Sipuleucel-T for Asymptomatic mCRPC (IMPACT)

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Sipuleucel-T infused every 2 weeks x 3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratified</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>OS</td>
</tr>
</tbody>
</table>


NR: not reported


**Phase III Trial of Sipuleucel-T for Asymptomatic mCRPC (IMPACT)**

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sipuleucel-T (n=341)</th>
<th>Placebo (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease location - %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone only</td>
<td>50.7</td>
<td>43.3</td>
</tr>
<tr>
<td>Soft tissue only</td>
<td>7.0</td>
<td>8.2</td>
</tr>
<tr>
<td>Bone and soft tissue</td>
<td>41.9</td>
<td>48.5</td>
</tr>
<tr>
<td>Previous prostate cancer therapy - %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgen-deprivation therapy</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>19.6</td>
<td>15.2</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>15.5</td>
<td>12.3</td>
</tr>
</tbody>
</table>


### HR (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Median survival</th>
<th>Time to objective disease progression</th>
<th>Antibody &gt; 400 titers against PA2024 after baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T (n=341)</td>
<td>25.8 months</td>
<td>3.7 months</td>
<td>66.2%</td>
</tr>
<tr>
<td>Placebo (n=171)</td>
<td>21.7 months</td>
<td>3.6 months</td>
<td>2.9%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.61-0.98)</td>
<td>0.95 (0.77-1.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR: not reported</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>


**Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Sipuleucel – T (N=338) No (%)</th>
<th>Placebo (N=168) No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>183 (54.1)</td>
<td>21 (12.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>99 (29.3)</td>
<td>23 (13.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>54 (16)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>33 (9.8)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>33 (9.8)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (7.4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Groin pain</td>
<td>17 (5)</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>8 (2.4)</td>
<td>3 (1.8)</td>
</tr>
</tbody>
</table>


**Phase III Trial of Sipuleucel-T for Asymptomatic mCRPC (IMPACT)**

**Sipuleucel-T Summary**

- Patients with antibody > 400 titers against PA2024 or PAP lived longer
- Benefit primarily in asymptomatic, docetaxel-naïve patients
- OS different despite no difference in TTP
  - Delayed onset of antitumor response
  - TTP not appropriate endpoint for immunotherapy in CRPC
- Access issues

**Treatment for CRPC in 2011**

- Asymptomatic
  - Sipuleucel-T
- First line
  - Docetaxel
- **Second line**
  - **Cabazitaxel**
  - **Satraplatin**
- Third line
  - Clinical Trial

**Cabazitaxel**

- Approved second line after docetaxel
- Novel taxane
- Antitumor activity in paclitaxel and docetaxel resistant models
- Low affinity for multi-drug resistance transporter, p-glycoprotein
# Phase III Trial of Cabazitaxel for Second Line Treatment of CRPC (TROPIC)

### Inclusion
- mCRPC
- ECOG PS 0-2
- Progression during or after docetaxel
- *Received > 225 mg/m² docetaxel

### Exclusion
- Cardiovascular risk factors
- > Grade 2 neuropathy or stomatitis

### Primary Endpoint
- OS

### Stratified
- Disease measurability
- ECOG PS

### Randomize 1:1

### MP: Mitoxantrone 12 mg/m² every 3 weeks + prednisone 10 mg/day

### CP: Cabazitaxel 25 mg/m² every 3 weeks + prednisone 10 mg/day


* Amendment to protocol after 59 patients enrolled

### Primary Endpoint
- OS

### Stratified
- Disease measurability
- ECOG PS

### Median PFS, months
- MP: 1.4
- CP: 2.8
- HR: 0.74 (0.64-0.86)

### Median TTP, months
- MP: 5.4
- CP: 8.8
- HR: 0.61 (0.49-0.76)

### Dose reductions, # patients
- MP: 15 (4%)
- CP: 45 (12%)

### OS: overall survival; PFS: progression-free survival; TTP: time to progression; NR: not reported

### Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>MP (n=377)</th>
<th>CP (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>325 (86)</td>
<td>215 (58)</td>
</tr>
<tr>
<td>Anemia</td>
<td>302 (81)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 (11)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12 (3.2)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

### Grade 3-4 n (%)

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<th>CP (n=378)</th>
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<tbody>
<tr>
<td>Neutropenia</td>
<td>347 (94)</td>
<td>303 (82)</td>
</tr>
<tr>
<td>Anemia</td>
<td>361 (97)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>173 (47)</td>
<td>23 (6)</td>
</tr>
</tbody>
</table>

### Death due to causes other than disease progression within 30 days of last dose
- 18 (5%) cabazitaxel patients
- 3 of 131 (2%) of patients <65 years old
- 15 of 240 (6%) of patients > 65 years old

### Fatal adverse reactions
- Infections (n=7)
- Cardiac (n=5)
- Renal failure (n=3)

### Cabazitaxel Summary
- First agent to show OS benefit for second line therapy of CRPC
- Majority of study patients ECOG 0 or 1
- Caution in elderly patients
- Patient education
  - Febrile neutropenia
  - Diarrhea

---

Satraplatin

- Oral platinum
- Activity in cell lines resistant to taxanes
- Phase II trial results - Activity in CRPC
- Not susceptible to some cisplatin mechanisms of resistance

Phase III Trial of Satraplatin for Second Line Treatment of CRPC (SPARC)

Inclusion
- mCRPC
- Disease progression after 1 prior chemotherapy regimen
- ECOG ≤ 2

Stratified
- ECOG PS
- Mean baseline Present Pain Intensity score
- Type of disease progression

Primary Endpoints
- OS
- PFS

Satraplatin 80 mg/m² po daily on days 1-5 every 35 days + prednisone 5 mg po bid
Placebo po daily on days 1-5 every 35 days + prednisone 5 mg po bid

Phase III Trial of Satraplatin for Second Line Treatment of CRPC (SPARC)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Satraplatin (n=635)</th>
<th>Placebo (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 and 4</td>
</tr>
<tr>
<td>Neutropenia %</td>
<td>62.8</td>
<td>22.3</td>
</tr>
<tr>
<td>Thrombocytopenia %</td>
<td>87.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Anemia %</td>
<td>96.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Diarrhea %</td>
<td>24.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Vomiting %</td>
<td>16.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>


Audience Response Question #2

Primary prophylaxis with colony stimulating factors should be considered in all patients receiving which chemotherapy?

A. Docetaxel
B. Cabazitaxel
C. Sipuleucel-T
D. None of the above

Satraplatin Summary

- Not approved due to lack of improvement in OS
- Longer than expected OS in placebo group
- Study started prior to docetaxel/prednisone becoming standard of care for first line
  - Only 50% of patients received docetaxel prior to satraplatin

**Toxicity Comparison of FDA Approved Agents**

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Docetaxel</th>
<th>Sipuleucel-T</th>
<th>Cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>38*</td>
<td>42*</td>
<td>28.1</td>
<td>34</td>
</tr>
<tr>
<td>Vomiting</td>
<td>*</td>
<td>*</td>
<td>17.8</td>
<td>23</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td>29.3</td>
<td>12</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
<td>3</td>
<td>NR</td>
<td>8</td>
</tr>
<tr>
<td>Myalgias</td>
<td>13</td>
<td>14</td>
<td>9.8</td>
<td>11</td>
</tr>
<tr>
<td>Chills</td>
<td>NR</td>
<td>NR</td>
<td>54.1</td>
<td>NR</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22</td>
<td>32</td>
<td>NR</td>
<td>82</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>7</td>
<td>30</td>
<td>NR</td>
<td>14</td>
</tr>
</tbody>
</table>

* Combination of nausea and/or vomiting reported; NR: not reported


**Treatment for CRPC in 2011**

- Asymptomatic
  - Sipuleucel-T
- First line
  - Docetaxel
- Second line
  - Cabazitaxel
- **Third line**
  - Clinical Trial

**Audience Response Question #3**

WG received docetaxel/prednisone x 8 cycles. PSA prior to cycle 9 shows an increase from 6 ng/dL to 20 ng/dL. Restaging CTs showed a new lung lesion. Which therapy is most appropriate?

A. Sipuleucel-T  
B. Mitoxantrone/prednisone  
C. Cabazitaxel/prednisone  
D. Ketoconazole/hydrocortisone

**MDV3100**

- AR antagonist  
- Prevents nuclear translocation and DNA binding  
- Higher affinity for AR than bicalutamide  
- No agonist activity

**Novel Agents**

- MDV3100  
- Abiraterone

**MDV3100 Model**

<table>
<thead>
<tr>
<th>Cholesterol → Pregnenolone</th>
<th>Adrenal Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 11A1 → 17αHydroxypregnenolone</td>
<td>17αHydroxyprogesterone</td>
</tr>
<tr>
<td>CYP 11A1 → DHEA</td>
<td>Androstenedione</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cholesterol → Pregnenolone</th>
<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 11A1 → 17αHydroxypregnenolone</td>
<td>DHEA → 5Androstenediol</td>
</tr>
<tr>
<td>Progesterone → 17αHydroxyprogesterone</td>
<td>androstenedione → Testosterone</td>
</tr>
</tbody>
</table>

CYP: cytochrome; DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; AR: androgen receptor
**MDV 3100 Phase I/II Study**

- CRPC with progressive disease (n = 140)
- 54% had previous chemotherapy

<table>
<thead>
<tr>
<th>Previous chemotherapy</th>
<th>Previous hormones</th>
<th>Previous ketoconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% PSA decrease</td>
<td>No (n=65)</td>
<td>Yes (n=75)</td>
</tr>
<tr>
<td></td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td>≥30-50% PSA decrease</td>
<td>≥2 (n=74)</td>
<td>≥3 (n=56)</td>
</tr>
<tr>
<td></td>
<td>61%</td>
<td>50%</td>
</tr>
<tr>
<td>≥70% PSA decrease</td>
<td>No (n=77)</td>
<td>Yes (n=63)</td>
</tr>
<tr>
<td></td>
<td>71%</td>
<td>37%</td>
</tr>
</tbody>
</table>


**MDV 3100 Toxicities**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>


**Phase III Trial of MDV 3100 in Docetaxel Refractory mCRPC (AFFIRM)**

**Inclusion**
- mCRPC
- Disease progression after 1-2 prior chemotherapy regimens (1 regimen with docetaxel)
- ECOG PS ≤ 2

**Primary Endpoint**
- OS

**Abiraterone**

- Oral irreversible inhibitor of CYP17A
- More selective and specific than ketoconazole

**Abiraterone**

- Phase II data shown response in chemotherapy-naive and docetaxel treated patients
- Two Phase II trials in CRPC after progression on docetaxel
- Abiraterone 1000 mg po daily

Abiraterone

<table>
<thead>
<tr>
<th>PSA Decrease</th>
<th>≥ 30% PSA Decrease</th>
<th>≥ 50% PSA Decrease</th>
<th>≥ 90% PSA Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>47%</td>
<td>43%</td>
<td>16%</td>
</tr>
<tr>
<td>Previous ketoconazole-naive</td>
<td>58%</td>
<td>55%</td>
<td>9%</td>
</tr>
<tr>
<td>Reid AH, et al (n=47)</td>
<td>68%</td>
<td>51%</td>
<td>15%</td>
</tr>
</tbody>
</table>


Phase III Trial of Abiraterone in Docetaxel Refractory mCRPC (COU-AA-301)

**Inclusion**
- ≥mCRPC
- Disease progression after 1-2 prior chemotherapy regimens (1 regimen with docetaxel)
- ECOG PS ≤ 2

**Stratified**
- ECOG PS
- Number of lines of prior chemotherapy
- Pain score
- Type of disease progression

**Primary Endpoint**
- OS

Abiraterone 1000 mg po daily + prednisone 5 mg po bid

Placebo daily + prednisone 5 mg po bid


| Phase III Trial of Abiraterone in Docetaxel Refractory mCRPC (COU-AA-301) |
|---------------------------------|-----------------|-----------------|-----------------|
| Placebo + prednisone            | Abiraterone + prednisone | P value         |
| OS, months                      | 10.4            | 14.8            | <0.0001         |
| Time to PSA progression, months | 6.6             | 10.2            | <0.0001         |
| PSA response rate               | 5.5%            | 29.1%           | <0.0001         |


**Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>55%</td>
<td>5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17%</td>
<td>&lt;5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>15%</td>
<td>9%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>14%</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34%</td>
<td>31%</td>
<td>NR</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>NR</td>
<td>NR</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

NR: not reported

Summary

Symptomatic, visceral metastases

Asymptomatic or minimally symptomatic, ECOG 0-1

mCRPC

Phase III Trial of Abiraterone in Docetaxel Refractory mCRPC (COU-AA-301)

**Inclusion**
- ≥mCRPC
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- ECOG PS ≤ 2

**Stratified**
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- Pain score
- Type of disease progression

**Primary Endpoint**
- OS

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- Pain score
- Type of disease progression

**Primary Endpoint**
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mCRPC

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- ECOG PS ≤ 2

**Stratified**
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- Number of lines of prior chemotherapy
- Pain score
- Type of disease progression

**Primary Endpoint**
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Summary

Symptomatic, visceral metastases

Asymptomatic or minimally symptomatic, ECOG 0-1

mCRPC
**Summary**

- New options for treatment of mCRPC
  - Docetaxel-refractory
  - Asymptomatic
- CRPC remains hormone dependent despite castrate serum levels of testosterone

**Castration Resistant Prostate Cancer**

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South Texas Veterans Health Care System
Vaccinations in Cancer

Kamakshi V. Rao, Pharm.D., BCOP, CPP
BMT Clinical Pharmacist Practitioner
University of North Carolina Hospitals and Clinics
Chapel Hill, North Carolina

Objectives

- Differentiate the changes in immune function and immunity that occur in patients undergoing therapy for cancer based on age, disease, and chemotherapy regimen
- Summarize the recommendations for vaccinations in oncology patients based on data and guidelines from the Centers for Disease Control, Infectious Disease Society of America, and the American Society for Blood and Marrow Transplantation
- Analyze limitations in the current available data and gaps in the current recommendations for vaccination in oncology patients

Cancer and the Immune System

- Historically, theory suggested that the presence of cancer itself depletes immunity
  - Numerous studies have demonstrated that children with cancer have normal levels of immunoglobulins and antibodies at the time of disease presentation
- Specific diseases where immune function may be compromised upfront
  - Leukemias
  - Sarcomas
  - Untreated Hodgkin’s lymphoma
  - Burkitt’s lymphoma

Cancer Therapy and the Immune System

Numerous chemotherapy and immunotherapy agents can induce varied levels of immune suppression and dysfunction

Traditional Chemotherapy
- Cyclophosphamide
- Fludarabine
- Mercaptopurine
- Corticosteroids

Immunotherapy
- Rituximab
- Alemtuzumab
- Anti-thymocyte globulin

Faculty Disclosure

- Kamakshi Rao has no areas of conflict to disclose
Cancer Therapy and the Immune System

- Lymphocyte depletion is the most significant cause of immunosuppression from chemotherapy
  - **T cells**
    - Profound and prolonged decrease in circulating CD3+ and CD4+ cells
    - Increased susceptibility of T cells to activation-induced apoptosis
  - **B cells**
    - Minor decrease in Immunoglobulin G levels
    - Significant decrease in Immunoglobulin M and A levels
    - Immunoglobulin levels tend to increase when therapy moves to less intensive phases of treatment

Loss of Immunity – The Data

- Numerous studies have evaluated the presence and persistence of antibody titers in patients at the end of chemotherapy
- Evidence exists with a number of vaccine preventable diseases
  - Hepatitis B (HBV), Measles-mumps-rubella (MMR), tetanus, polio, influenza, pneumococcal disease

Loss of Immunity – The Data

- 192 pediatric patients completing first-line therapy for malignancy, who attained a CR
  - 70.3% hematologic malignancies
- Evaluated for immunity to Hepatitis B, measles, mumps, rubella, tetanus, and polio

Loss of Immunity – The Data

- Success of booster vaccinations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Successful revaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>29/32 (91%)</td>
</tr>
<tr>
<td>Measles</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>Mumps</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Rubella</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>10/10 (100%)</td>
</tr>
<tr>
<td>Polio</td>
<td>6/6 (100%)</td>
</tr>
</tbody>
</table>

Loss of Immunity – The Data

- Predictive factors for loss of immunity
  - Against mumps, rubella, and tetanus
    - younger age (p=0.021)
  - Against measles
    - female gender and younger age
  - Underlying disease not predictive

“Lack of Immunity”

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>53/116 (46%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>35/138 (25%)</td>
</tr>
<tr>
<td>Mumps</td>
<td>35/127 (28%)</td>
</tr>
<tr>
<td>Rubella</td>
<td>31/131 (24%)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>22/162 (14%)</td>
</tr>
<tr>
<td>Polio</td>
<td>19/137 (7%)</td>
</tr>
</tbody>
</table>

“Loss of Immunity”

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>35/67 (52%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>23/92 (25%)</td>
</tr>
<tr>
<td>Mumps</td>
<td>16/77 (21%)</td>
</tr>
<tr>
<td>Rubella</td>
<td>14/76 (18%)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>13/102 (13%)</td>
</tr>
<tr>
<td>Polio</td>
<td>6/77 (8%)</td>
</tr>
</tbody>
</table>

Pre-therapy

- Confirm vaccination and exposure history
- Evaluate immunity
- Obtain baseline antibody titers

Post-therapy

- Assess antibody titer changes in order to determine immunity
- In cases of lack of loss, attempt to vaccinate and determine response

Success of booster vaccinations

<table>
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<td>Tetanus</td>
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</tr>
<tr>
<td>Polio</td>
<td>6/6 (100%)</td>
</tr>
</tbody>
</table>
Immune Reconstitution following Therapy

- In children
  - Neutrophils
  - NK-cells
  - T-cells
  - B-cells

- In adults
  - Neutrophils
  - NK-cells
  - B-cells
  - T-cells

Affected Populations

- Pediatric oncology patients
  - Greatest likelihood of cancer diagnosis and chemotherapy interrupting routine childhood vaccination schedules
  - Younger children are at even greater risk because of chemotherapy effects on B-cell development and bone marrow plasma cell development

- Adult oncology patients
  - Lack data to determine utility of re-vaccination for childhood immunizations
    - Efficacy of immunization is difficult to quantify because most studies use surrogate endpoints
      - does antibody titer = clinical prevention?
  - Variable immunocompetence
    - Tumor type, therapy type, duration of therapy, and response to therapy

- Stem cell transplant recipients
  - More data for re-vaccination with childhood immunizations
  - Wide variability in time to immune reconstitution
    - transplant type (autologous vs. allogeneic)
    - duration of immunosuppressive therapy
    - need for further immunosuppression for graft versus host disease


ARS Question #1

- Which of the following patients is likely the most immunosuppressed?
  A. A 54 year old female with locally advanced breast cancer, receiving cycle #2 of doxorubicin + cyclophosphamide
  B. An 16 year old male with osteosarcoma, currently undergoing cycle #6 with doxorubicin and cisplatin
  C. A 2 year old with ALL 4 months into maintenance therapy with methotrexate/vincristine
  D. A 62 year old male with CLL, undergoing cycle #4 of therapy with fludarabine, cyclophosphamide, and rituximab

Horwitz SM et al. Blood 2004;103:777-83
Nordoy T et al. BMT 2001;28:681-7

2011 ACCP Annual Meeting
Oncology Pharmacy Specialty Sessions, Part I
**Guidelines**

- Recommendations regarding immunizations can be found from:
  - CDC
  - IDSA
  - ASBMT – provides specific recommendations
- Outside of the SCT population, most data regarding pediatric and adult oncology patients comes from small trials, anecdotal experience, and evaluations of antibody titers in these populations

**CDC guidelines**

- Provide all indicated vaccines to all persons before initiation of therapy
- No Live-attenuated vaccines administered until 3 months after therapy
- Re-immunization may be required for inactivated vaccines
  - ALL > AML, lymphoma, other malignancies, or radiation
- Revaccination of a person after chemotherapy or radiation therapy is not necessary if the vaccination occurred before therapy
  - exception = SCT
- Determination of the level of immune memory and the need for revaccination should be made by the treating physician.

**IDSA guidelines**

- Full guidelines for vaccination in immunocompromised hosts due to be published in spring 2011
  - Will address specific considerations to be made in administration of immunizations to immunocompromised patients, including cancer patients

**IDSA Guidelines**

- 2009 Immunization Programs for Infants, Children, Adolescents, and Adults – comprehensive immunization recommendations
  - Immunocompromised individuals can safely receive inactivated vaccines
    - response may be suboptimal
    - higher doses or additional doses may be needed
  - Live, attenuated vaccines are not recommended
    - known or theoretical risks of disseminated infection due to the vaccine virus

**ASBMT Guidelines**

- Specifically address vaccinations in patients after stem cell transplantation
- Guidelines divide recommendations into 3 parts
  - Vaccinations with good evidence for safety and immunogenicity, recommended in all SCT patients
  - Vaccinations in special situations (i.e., exposure, travel), lacking or limited data available
  - Vaccination of family members, household contacts and healthcare workers to minimize exposure

**Individual Vaccinations**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Inactivated vaccines</th>
<th>Live attenuated vaccines</th>
<th>Conjugate vaccines</th>
<th>Polysaccharide vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Td/pO/Tdap</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hib</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Meningococcal</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
**Influenza**

- Consequence of susceptibility
  - Upper/lower respiratory tract symptoms
  - Secondary bacterial pneumonia, sinusitis, otitis media
  - Infection can lead to delays in therapy
  - Mortality rate = 9% in oncology patients


**Influenza**

- Since the early 1970’s, >20 studies have evaluated the utility and effectiveness of influenza vaccination in a variety of oncology populations
  - Pediatrics
  - Adult hematologic malignancy
  - Adult solid tumors
  - Stem cell transplantation


**Influenza - Pediatrics**

- 2009 Cochrane review evaluated 9 trials
  - 1 RCT, 8 case-controlled trials
  - N=708
  - Clinical outcomes were not reported in any studies
  - All reported on immunity to influenza
    - Variability in measurement of immunity

Results
- % of patients with adequate immune response to influenza vaccination
  - Current chemotherapy = 25-52%
  - Completed chemotherapy = 50-86%
  - Healthy children = 71-89%

Goossen GM et al. Cochrane Review 2009

**Influenza - Adults**

- Solid Tumors
  - Most data in patients not currently receiving chemotherapy
    - Detectable, albeit diminished response to vaccination
    - 1225 colorectal cancer patients
    - 40% received influenza vaccination
    - Decreased rates of influenza, pneumonia and trend towards decreased morbidity and mortality

- Hematologic Malignancies
  - Respond more poorly to vaccine than solid tumor patients
    - Use of immunosuppressive agents and/or rituximab
  - 34 patients with lymphoproliferative diseases
    - >60% response, compared to 80% in normal healthy controls


**Influenza - Adults**

- Vaccination during chemotherapy
  - Solid and hematologic malignancies
    - Vaccinated patients
      - Concurrently with administration of chemotherapy or between cycles, at the nadir of blood counts
    - Immunologic response seen in
      - 50% for concurrent administration
      - 93% for in between cycle administration
    - Consider administration of vaccination in between chemotherapy cycles if possible


**Influenza - Stem Cell Transplant**

- Data not uniform in relation to time from transplant for vaccination
  - No benefit from immunization within the first 6 months of SCT
  - Longer interval between SCT and immunization correlates with improved responses
  - Two-shot series may be recommended in times of high risk

Ljungman P et al. BMT 2009;44:521-6

**Oncology Pharmacy Specialty Sessions, Part I**

30
**Recommendation - Influenza**

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>Inactivated virus vaccination upon completion of chemotherapy or between chemotherapy cycles</td>
<td>Strong</td>
</tr>
<tr>
<td>Adult</td>
<td>Solid Tumors: Inactivated virus vaccination during active chemotherapy. Consider live attenuated vaccination if chemotherapy completed &gt;4-6 months Hematologic Malignancy: Inactivated virus vaccination between chemotherapy cycles or after completion of chemotherapy</td>
<td>Strong</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
<td>Inactivated virus vaccination no sooner than 6 months after SCT. If high risk season occurs prior to 6 months, consider 2-shot series 3 months after SCT</td>
<td>Strong (All)</td>
</tr>
</tbody>
</table>


**ARS Question #2**

- RP is a 54 year old man with stage III colorectal cancer. He is undergoing therapy with Fluorouracil, Leucovorin, and Oxaliplatin. He arrives to clinic for cycle #3 in November, and wants to know if he can receive an influenza vaccination at his visit today
  A. Wait until 4 months after chemotherapy ends to vaccinate
  B. Administer inactivated vaccine now
  C. Administer live attenuated vaccine now
  D. Administer inactivated vaccine between cycles 3 and 4

**Hepatitis B**

- Infection is associated with serious consequences in immunosuppressed patients, including liver failure and death
- Risk of reactivation or infection in cancer patients is highest in those with hematologic malignancies
  - Greater need for transfused blood products
  - Greater degree of immunosuppression to allow reactivation
- Stem cell transplantation often leads to reactivation
  - Lack of surface antibody in donor
  - Graft versus host disease requiring immunosuppression


**Recommendation - Hepatitis B**

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Pediatrics            | Data demonstrates positive response to vaccination during and after chemotherapy  
  - Children who have not started or completed standard series at diagnosis: standard vaccination at 0, 1, and 6 months  
  - Children who have completed vaccination schedule at diagnosis: 2 booster doses 3 months apart after the completion of chemotherapy | Moderate |
| Adult                 | Immunize with at least 2 doses within a 3-4 week interval  
  Third dose can be given after chemotherapy is completed | Moderate |
| Stem Cell Transplant  | 3-dose series beginning 6-12 months after transplant | Moderate (BII) |

Measles, Mumps, and Rubella (MMR)

- Measles in immunocompromised patients may have atypical presentation with prolonged viral shedding
  - Pneumonitis, encephalitis
- Vaccine details
  - In combination MMR, as a live attenuated vaccine
  - 1-2 doses
  - Should not be administered while patient is heavily immunosuppressed

Recommendation - MMR

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>Not vaccinated: 2 doses separated by 3 months in patients off therapy for 6 months Prior vaccination: single booster dose in patients off therapy for 6 months</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adult</td>
<td>Insufficient data to recommend routine reimmunization. Consider checking serostatus and vaccinating if negative. For leukemia patients, consider booster vaccination &gt;3 months after end of chemotherapy</td>
<td>Poor</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
<td>Pediatrics: 2 doses, starting 24 months post transplant Seronegative adults: 1 dose 24 months post transplant</td>
<td>Moderate (BII)</td>
</tr>
</tbody>
</table>

DTaP/Tdap

- Pertussis: gram negative coccobacillus can cause acute respiratory illness
- Vaccination typically provides protection for approximately 5 years, necessitating booster vaccination in healthy adolescents and adults
- Vaccine details
  - DTaP: 3-dose series recommended in children through age 6
  - Tdap: recommended single dose post therapy, then Q10 year dose in adolescents and adults

DTaP/Tdap in Pediatric / Adult

- Data on immunity
  - Pediatric data: response to DTP booster vaccine given 6, 8, and 10 months after completion of chemotherapy
  - Low rates of seronegativity at baseline
  - 16.4%, 3.9% and 3.5% for D, P, and T, respectively
  - 100% were able to respond adequately to immunization
  - Adult data: adult cancer patients, especially hematologic malignancies, have been shown to have a higher rate of tetanus seronegativity than healthy controls
  - Greater in lymphoid malignancies than myeloid malignancies

DTaP/Tdap in SCT

- Response to Tdap following auto-SCT
  - Median of 3 years post transplant
  - 86.5% of patients had suboptimal anti-P and anti-T titers
  - >90% had undetectable titer
  - 28/57 patients were re-vaccinated
  - 26 failed to attain adequate anti-P titers
  - Slightly better response to tetanus and diphtheria, but still high rate of failure
  - Patients receiving post-transplant rituximab uniformly failed to respond to re-vaccination, regardless of time after transplant

Recommendation – DTaP/Tdap

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>Not vaccinated: standard 3-dose schedule DTaP starting 3 months after completion of therapy Prior vaccination: administer booster dose after off therapy for 3 months (less data re: pertussis)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adult</td>
<td>Same schedule as healthy persons. Limited data on loss of immunity, but good data to show response to vaccination</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
<td>3-dose DTaP series for all SCT recipients beginning 6-12 months after transplant If DTaP unavailable, can administer Tdap x 2 annual doses beginning 6-12 months after transplant</td>
<td>Moderate (BII)</td>
</tr>
</tbody>
</table>
Varicella

- Varicella zoster and herpes zoster infections pose serious and life-threatening risks to immunocompromised hosts
  - Dermatologic complications, pneumonitis, encephalitis, hepatitis
- Vaccine details
  - Varivax: prevention of chickenpox, live attenuated vaccine with low viral titers
    - Dose recommendations for children, adolescents, and adults
  - Zostavax: prevention of shingles, live attenuated vaccine with high viral titers
    - Recommended only for those >60 years of age

Efficacy/safety

- Pediatrics: 437 VZV seronegative children with ALL received 2 doses of varicella vaccine (Varivax®) separated by 3 months
  - Patients with CRx1 year, ALC>700/uL, platelet >100,000/uL, with all maintenance therapy held for 1 week before and 1 week after vaccination
  - 85% developed antibody response
  - 75% of nonresponders responded to second dose.
  - Long term follow up showed 36 cases of varicella – 35 were mild/moderate, indicating attenuation by vaccine

Varicella

Efficacy/Safety

- Adults: case reports of patients developing disseminated zoster infections following administration of VZV (Zostavax) vaccine
  - Reports in solid tumors and hematologic malignancies
- SCT: high viral titers in VZV vaccines (Zostavax) pose high risk of disease activation
  - Consideration for use of chickenpox vaccine (Varivax) if benefit outweighs risk

Recommendation - Varicella

<table>
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<tbody>
<tr>
<td>Pediatrics</td>
<td>Not vaccinated: 2 doses separated by 3 months in patients meeting criteria for ability to receive live attenuated vaccines Prior vaccination: single booster dose in patients meeting same criteria above</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adult</td>
<td>Not recommended in immunocompromised patients (symptoms, receiving immunosuppression). Solid Tumors: Consider allowing a minimum of 3 months from last chemotherapy Hematologic Malignancy: Consider allowing a minimum of 3 months from last chemotherapy, given disease in remission</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
<td>In general, not recommended until at least 24 months, off immunosuppression Consider using Varivax over Zostavax because of lower varicella titer, decreasing risk of activation</td>
<td>Strong (CIII/EIII)</td>
</tr>
</tbody>
</table>

Pneumococcal, Meningococcal, and Hib vaccines

- Risks from infection with Streptococcus pneumoniae, Neisseria meningitides, and Haemophilus influenza is highest in asplenic patients due to reduced capacity to clear encapsulated bacteria from bloodstream

Vaccine details

- Pneumococcal (3 types)
  - Conjugate 7-valent (PCV7) - now unavailable
  - Conjugate 13-valent (PCV13) – 3 shot series recommended in children <5 years old, has replaced PCV7
  - Polysaccharide 23-valent (PPSV23) – 1-2 shot series recommended in adults >65 and in all ages at high risk for disease
- Meningococcal
  - Conjugate vaccine (MCV4) – recommended for adults <55 years old
  - Polysaccharide vaccine (MPSV4) – recommended for adults >58 years old
  - MCV4 booster dose recommended 3-5 years after initial dose
- Hib
  - Conjugate polysaccharide vaccine – not generally recommended for those >5 years old
  - In children <5 years old, 3-shot series recommended
Pneumococcal vaccine

- Adults
  - Patients with solid tumors typically respond similar to healthy adults
  - Patients with lymphoma and myeloma respond at much lower rates than healthy controls
- SCT
  - PCV7 shown to elicit better responses than PPSV23 despite narrower spectrum of protection
  - Little to no benefit seen when PPSV23 administered within one year of SCT

Schildt RA et al. Med Pediatr Oncol 1983;11;305
Schildt RA et al. J Infect Dis 1981;143:590

Schildt RA et al. Med Pediatr Oncol 1983;11;305
Schildt RA et al. J Infect Dis 1981;143:590

Timing of vaccination in relation to SCT
- Multicenter, randomized noninferiority study in allogeneic transplant recipients

**Early Vaccination (n=75)**
- Primary Endpoint: % with adequate antibody titers to 7 PCV7 serotypes 1 month after 3rd dose

<table>
<thead>
<tr>
<th>Arm</th>
<th>Response</th>
<th>Antibody titer 0.15 mcg/ml</th>
<th>Prevacination</th>
<th>1 month post dose 3</th>
<th>24 months post SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>45/57 (79%)</td>
<td>33/74 (45%)</td>
<td>45/57(79%)</td>
<td>26/44 (59%)</td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>47/57 (82%)</td>
<td>6/64 (9%)</td>
<td>47/57(62%)</td>
<td>35/42 (83%)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.001</td>
<td>0.64</td>
<td>0.013</td>
<td></td>
</tr>
</tbody>
</table>

- Prior to PPV23 vaccination, % of patients with adequate titers was similar between groups (59% vs 66%). One month after administration, % of patients with adequate response was significantly higher in the late group (88% vs 69%, p=0.02)
- Differences between study and nationally accepted definitions of adequate titer

Cordonnier C et al. CID 2009;48:1392

**Late Vaccination (n=83)**
- Primary Endpoint: % with adequate antibody titers to 7 PCV7 serotypes 1 month after 3rd dose

<table>
<thead>
<tr>
<th>Dose 1 @day +100</th>
</tr>
</thead>
<tbody>
<tr>
<td>47/57 (82%)</td>
</tr>
<tr>
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</tr>
<tr>
<td>47/57(62%)</td>
</tr>
<tr>
<td>35/42 (83%)</td>
</tr>
</tbody>
</table>

**Primary Endpoint:**

- N=158
- Early Vaccination (n=75) Dose 1 @day +100
- Late Vaccination (n=83) Dose 1 @day +9 months

- Vaccination consisted of 3 doses of PCV7 at one month intervals, followed by a single dose of PPSV23 7 months after last PCV7

Recommendation – Pneumococcal vaccine

**Population**

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>Poor</td>
</tr>
<tr>
<td>Adult</td>
<td>Poor</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
<td>Moderate (B)</td>
</tr>
</tbody>
</table>

**Evidence**

- Not vaccinated: primary schedule once patient is off therapy for 3 months
- Prior vaccination: consider booster dose in patients off therapy for 3 months
- Administer 23-valent vaccine to any nonimmune cancer patient, especially lymphoma or myeloma
- Prior to splenectomy, >10d before start of chemotherapy, or 3 months after completion of chemotherapy
- Administer booster dose 3-5 years later because of high rate of antibody titer loss
- Administer 4 shot series (3xPCV13 followed by 1xPPSV23), beginning 3-6 months after SCT

Recommendation – Meningococcal Vaccine

**Population**

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<td>Poor</td>
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<td>Stem Cell Transplant</td>
<td>Moderate (B)</td>
</tr>
</tbody>
</table>

**Recommendation**

- Not vaccinated: primary schedule once patient is off therapy for 3 months
- Prior vaccination: booster dose in patients off therapy for 3 months
- Not vaccinated: 3 shot series after patient off therapy for 3 months
- Prior vaccination: booster dose in patients off therapy for 3 months

**Evidence**

- Administer prior to splenectomy, especially in lymphoma patients
- Consider reimmunization 3-5 years after initial dose because of frequency of loss of adequate titers
- Administer single dose 6-12 months after SCT
- Recommended in lymphoma patients undergoing staging splenectomy
- Prior to splenectomy, >10d prior to start of chemotherapy, or 3 months after completion of chemotherapy
- 3-shot series starting 6-12 months after SCT

**Population**

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric</td>
</tr>
<tr>
<td>Adult</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
</tr>
</tbody>
</table>

**Evidence**

- More studies required to validate this recommendation


- 2011 ACCP Annual Meeting

Oncology Pharmacy Specialty Sessions, Part I
**BMT Specific Recommendations**

- Household contact and healthcare worker vaccinations
- Donor vaccination
- Optional vaccinations/Contraindicated vaccinations

**Household Contact and HCW Vaccinations**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendations</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Recommended for children 12y and those at risk for Hepatitis A</td>
<td>BIII</td>
</tr>
<tr>
<td>Inactivated influenza</td>
<td>Annual vaccination is strongly recommended <em>Intranasal vaccination is contraindicated</em></td>
<td>All</td>
</tr>
<tr>
<td>Polio</td>
<td>If necessary, should use inactivated polio vaccine</td>
<td>All</td>
</tr>
<tr>
<td>MMR (live)</td>
<td>Recommended for all ≥12 months old who are not pregnant or immunocompromised. No evidence to show transmission from person to person</td>
<td>All</td>
</tr>
<tr>
<td>Pertussis</td>
<td>DTaP for children &lt;7 years old, Tdap for adolescents and adults</td>
<td>BIII</td>
</tr>
<tr>
<td>Varicella (live)</td>
<td>Recommended for all ≥12 months old who are not pregnant or immunocompromised. Minimal risk of transmission person to person</td>
<td>All</td>
</tr>
</tbody>
</table>

**Donor Vaccinations**

- Vaccination of stem cell donors has been shown to improve the post-transplant immunity of the recipient in certain situations
  - Tetanus toxoid, PCV-7, Hib vaccines
- No current recommendations given practical and ethical issues surrounding vaccination in patients who do not need them

**Optional and Contraindicated Vaccines in SCT Patients**

- Data is largely lacking for many immunizations
  - Hepatitis A (CIII)
  - HPV (CIII)
  - Yellow fever (EIII) ≥24 months, CIII >24 months
  - Rabies (CIII)
  - BCG (EII)
  - OPV (EII)
  - Intranasal influenza (EIII)
  - Cholera (DIII)
  - Typhoid (PO/IM) (EII/DIII)
  - Rotavirus (EIII)
  - Zoster vaccine (EIII)

**Drug-Based Recommendation**

- Results in B-cell depletion for at least 6-9 months, during which time humoral response to antigens is reduced significantly
- Evaluation of effect of rituximab on humoral immunity in RA patients

**Van Assen S et al. Arthritis and Rheumatism 2010; 62(1):75-81**

**Rituximab early**

- Influenza vaccination 4-6 weeks post treatment

**Rituximab late**

- Influenza vaccination 6-10 months post treatment

**MTX**

- Standard seasonal vaccination

**Healthy controls**

- Standard seasonal vaccination
Drug-Based Recommendation
Rituximab

- Results showed markedly decreased response to immunizations in both rituximab arms
- Between early and late rituximab arms, late arm showed consistently higher geometric mean titers of antibody (p<0.05 for all influenza strains)
- Based on these results, consider delaying immunizations in patients receiving rituximab therapy to at least 6 months after the completion of therapy rather than the typically recommended 3 months

ARS Question #3

- Limitations of data regarding vaccination include
  A. Recommendations are many times based on expert opinion or case reports
  B. Evidence of efficacy or lack thereof is often not conclusive
  C. Populations studied sometimes do not match actual patient populations
  D. All of the above

Limitations to Recommendations

- Extremely limited data for children who have received partial immunization series at time of cancer diagnosis
- Questions regarding timing of administration
- Limited or lacking data regarding newer vaccinations (e.g. HPV)
- Variable definitions of immunity
- Largely retrospective data
- Lack of reporting of incidence of some vaccine preventable diseases

Conclusions

- Alterations in immunity are highly variable among the wide spectrum of oncology patients
- Current guidelines provide some basis to determine the need for vaccination in specific patients
- Research still needed to more clearly define time to vaccination, real need for booster therapy, and appropriate ways to assess immunity

Vaccinations in Cancer

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