Oncology Pharmacy Specialty Sessions, Part II

Wednesday, October 19
9:00 a.m.–noon
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 I will be presented on Tuesday, October 18, from 1:30 p.m. to 4:30 p.m. 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: Ryan N. Bookout, Pharm.D., BCOP
Clinical Pharmacist, Moffitt Cancer Center, Tampa, Florida

9:00 a.m.
Germ Cell Tumors (GCT): Beyond BEP
Activity No. 0465-9999-11-402-L04-P

Kellie L. Jones, Pharm.D., BCOP
Clinical Associate Professor, Purdue University School of Pharmacy and Pharmaceutical Sciences, Indianapolis, Indiana

10:00 a.m.
Chronic Lymphocytic Leukemia
Activity No. 0465-9999-11-303-L01-P

Ashley K. Morris Engemann, Pharm.D., BCOP
Clinical Associate, Division of Cellular Therapy, Duke University Medical Center, Durham, North Carolina

11:00 a.m.
Updates in the Treatment of Metastatic Breast Cancer
Activity No. 0465-9999-11-301-L01-P

Michael J. Berger, Pharm.D., BCOP
Specialty Practice Pharmacist, Arthur G. James Cancer Hospital, Dublin, Ohio

Faculty Conflict of Interest Disclosures

Michael J. Berger: no conflicts to disclose.
Kellie L. Jones: no conflicts to disclose.
Ashley K. Morris Engemann: consulting fees from Genzyme and sanofi Aventis.
Learning Objectives

1. Summarize the current standards of therapy for testicular cancer.
2. Evaluate the impact of stem cell transplant in the metastatic setting.
3. Compare different salvage therapies utilized in the management of metastatic testicular cancer based on efficacy and toxicity.
4. Construct treatment recommendations to manage supportive care issues that testicular cancer patients face during treatment.
5. Outline long-term toxicities associated with the treatment of testicular cancer.
6. Compare and contrast initial treatment strategies for symptomatic or advanced stage chronic lymphocytic leukemia (CLL).
7. Differentiate treatment options for management of relapsed or refractory CLL.
8. Justify the role of allogeneic stem cell transplantation in selected patients with CLL.
9. Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC).
10. Compare and contrast targeted therapies for the treatment of HER2(+) MBC.
11. Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability.
12. Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Germ Cell Tumors (GCT): Beyond BEP

Kellie L. Jones, Pharm.D., BCOP
Clinical Associate Professor
Purdue University College of Pharmacy
Salt Lake City, UT
Kellie Jones has no areas of conflict to disclose
Objectives

- Summarize the current standards of therapy for testicular cancer.
- Evaluate the impact of stem cell transplant in the metastatic setting.
- Compare different salvage therapies utilized in the management of metastatic testicular cancer based on efficacy and toxicity.
- Construct treatment recommendations to manage supportive care issues that testicular cancer patients face during treatment.
- Outline long-term toxicities associated with the treatment of testicular cancer.
Epidemiology of Testicular Cancer

- 1% of all cancers in men
- Most common carcinoma in men ages 15-35
- Estimated 8,480 cases in 2010
  - 350 estimated deaths
- Goal of therapy is cure
  - ~60% present with localized disease
  - ~15% present with metastatic disease
- Seminoma or non-seminoma GCT’s

Histology of Testicular Cancer

- Seminoma
  - Does not secrete alpha fetoprotein (AFP)
- Non-seminoma
  - Can secrete AFP and/or beta human chorionic gonadotropin (β-HCG)
  - Embryonal
  - Yolk sac
  - Choriocarcinoma
  - Teratoma

False elevations may occur with:
- Liver cancer
- Hepatitis/cirrhosis
- Alcohol abuse
- Marijuana use
# International Germ Cell Cancer Collaborative Group (IGCCCG) Risk Classification

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Non-Seminoma</th>
<th>Seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good risk</strong></td>
<td>Testicular or retroperitoneal primary</td>
<td>Any site, no non-pulmonary mets</td>
</tr>
<tr>
<td></td>
<td>No non-pulmonary mets</td>
<td>Normal AFP</td>
</tr>
<tr>
<td></td>
<td>AFP &lt; 1,000 ng/mL</td>
<td>Any hCG</td>
</tr>
<tr>
<td></td>
<td>hCG &lt; 5,000 IU/L</td>
<td>Any LDH</td>
</tr>
<tr>
<td></td>
<td>LDH &lt; 1.5 x ULN</td>
<td></td>
</tr>
<tr>
<td>**Intermediate</td>
<td>Same as above with:</td>
<td>Same as above, with non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>risk**</td>
<td>AFP 1,000-10,000 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hCG 5,000-50,000 IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH 1.5-10 x ULN</td>
<td></td>
</tr>
<tr>
<td><strong>Poor risk</strong></td>
<td>Non-pulmonary visceral metastases present (i.e. bone, liver, brain):</td>
<td>No patients classified as poor risk</td>
</tr>
<tr>
<td></td>
<td>AFP &gt; 10,000 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hCG &gt; 50,000 IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH &lt; 10 x ULN</td>
<td></td>
</tr>
</tbody>
</table>

Staging

- **Stage I**
  - Confined to the testes

- **Stage II**
  - Involves the testes and the retroperitoneal and/or para-aortic lymph nodes

- **Stage III**
  - Spread beyond the retroperitoneal lymph nodes
  - Can spread to lymph nodes, lungs, brain, and liver
## Treatment Based on Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>Treatment modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Seminoma</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observation</td>
</tr>
<tr>
<td></td>
<td>Non-seminoma</td>
<td>Surgery (RPLND)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observation</td>
</tr>
<tr>
<td>2</td>
<td>Seminoma</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
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<tr>
<td></td>
<td>Non-seminoma</td>
<td>Surgery (RPLND)</td>
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<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>3</td>
<td>Seminoma</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Non-seminoma</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

Adapted from NCCN Guidelines. Testicular Cancer v.2.2010.
Question # 1

Which of the following is the standard treatment for good risk testicular cancer?

1. Bleomycin, epirubicin, prednisone
2. Busulfan, etoposide, cisplatin
3. Bleomycin, etoposide, cisplatin
4. Busulfan, epirubicin, paclitaxel
Management of Good Risk Disease

- BEP x 3 = BEP x 4 (SECSG)$^1$
- BEP x 3 superior to EP x 3 (ECOG)$^2$
- BEP x 3 = EP x 4 (EORTC)$^3$
- BEP superior to BE + (Carboplatin) (EORTC)$^4$
- EP x 4 superior to E + (Carboplatin) (Memorial)$^5$

BEP x 3 standard of care for good risk patients with > 90% cure rate

B = Bleomycin, E = Etoposide, P = Cisplatin; SECSG = South East Cancer Study Group; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer.

"HP3 use = here as in bullet 3

Kj: OK

"Clarian Health Partners, 11/11/2010
Poor Risk Disease

• Advanced disease
• Cure rate 40-60%
• Goal of therapy:
  ▪ Improve on the current cure rate
  ▪ Improve upon the standard BEP x 4 regimen
    – Use of different regimens such as VIP

VIP = Etoposide, Ifosfamide, and cisplatin
Poor Risk Disease

Advanced stage germ cell tumors

RAN DOMI ZED

Cisplatin 20mg/m² x 5
Etoposide 100mg/m² x 5
Bleomycin 30 units days 1, 8, 15
Given q 3weeks x 4 cycles
(BEP)

Cisplatin 20mg/m² x 5
Etoposide 75mg/m² x 5
Ifosfamide 1,200mg/m² x 5
Given q 3weeks x 4 cycles
(VIP)

## Poor Risk Disease Results

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>BEP x 4 (n= 141)</th>
<th>VIP x 4 (n = 145)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>31</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>PFS</td>
<td>58</td>
<td>64</td>
<td>NS</td>
</tr>
<tr>
<td>OS</td>
<td>67</td>
<td>69</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicities (%)</th>
<th>BEP x 4</th>
<th>VIP x 4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall toxicities*</td>
<td>79</td>
<td>93</td>
<td>P = 0.0002</td>
</tr>
<tr>
<td>Hematologic$^\psi$</td>
<td>76</td>
<td>90</td>
<td>P = 0.003</td>
</tr>
</tbody>
</table>

*Overall toxicities included: Nausea/vomiting, infection, bleeding, neurologic, respiratory, genitourinary, hepatic, and hematologic; $^\psi$ Hematologic toxicity was most common toxicity no matter the treatment arm


CR = Complete response; PFS = Progression free survival; OS = overall survival; NS = non-significant
Poor Risk Disease

- **Toxicities**
  - Increased with VIP
  - Because of this, BEP is standard of care

- VIP used to prevent pulmonary toxicities
  - Extensive mediastinal disease
  - Underlying pulmonary dysfunction
Post Treatment Resection

- Should be conducted on residual retroperitoneal masses
- RPLND should be considered in larger, persistent masses
  - Only by highly skilled surgeon
- Masses can comprise:
  - Necrosis, teratoma, malignant germ cells
  - Teratomas can transform to sarcoma


RPLND: Retroperitoneal lymph node dissection
# Post Treatment Follow Up

<table>
<thead>
<tr>
<th>Type</th>
<th>Tests</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>Tumor Markers</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; year: q 2 - 4 months&lt;br&gt;2&lt;sup&gt;nd&lt;/sup&gt; year: q 3 - 4 months&lt;br&gt;3&lt;sup&gt;rd&lt;/sup&gt; - 4&lt;sup&gt;th&lt;/sup&gt; year: q 4 - 6 months&lt;br&gt;Annually thereafter</td>
</tr>
<tr>
<td></td>
<td>Abdominal CT Scans</td>
<td>1. Annually if para-aortic radiotherapy&lt;br&gt;2. At each visit alternating with chest x-ray for up to 10 years</td>
</tr>
<tr>
<td>Non-seminoma</td>
<td>Tumor Markers</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; year: q 1- 2 months&lt;br&gt;2&lt;sup&gt;nd&lt;/sup&gt; year: q 2 - 4 months&lt;br&gt;3&lt;sup&gt;rd&lt;/sup&gt; - 4&lt;sup&gt;th&lt;/sup&gt; year: q 3 - 6 months&lt;br&gt;5&lt;sup&gt;th&lt;/sup&gt; year: q 6 months&lt;br&gt;Annually thereafter</td>
</tr>
<tr>
<td></td>
<td>Abdominal CT Scans</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; year: q 6 months&lt;br&gt;2&lt;sup&gt;nd&lt;/sup&gt; year: q 6 - 12 months&lt;br&gt;Annually up to 5 years, then as indicated</td>
</tr>
</tbody>
</table>

After surgery and chemotherapy, tumor markers should ↓

- AFP serum half life = 5 - 7 days
- $\beta$-HCG serum half life = 18 - 36 hours
- A plateau or slow decline suggests residual active disease
Testicular cancer

Second most curable cancer:
- Second line therapy for testicular cancer

Third most curable cancer:
- Third line therapy for testicular cancer
Question # 2

Which of the following is the best answer regarding the use of high dose chemotherapy and stem cell transplant in testicular cancer?

1. High dose chemotherapy with stem cell transplant prolongs DFS, but not OS.
2. Tandem stem cell transplant is standard of care for recurrent disease.
3. Induction chemotherapy prior to stem cell transplant includes VIP for 2 cycles.
4. Stem cell transplant is considered after failing 2 salvage chemotherapy regimens.
Prognostic Factors for Salvage Conventional Dose Chemotherapy (CDC)

Up to 70% who relapse or fail to achieve a CR can be cured

Good prognostic factors:
- Testis or retroperitoneal primary site and CR to initial therapy
- 35 - 40% 3 year survival with CDC

Poor prognostic factor:
- Incomplete response to initial therapy or relapsed mediastinal NSGCT
- < 10% 3 year survival with CDC

NSGCT = Non-seminomatous germ cell tumor
Prognostic Factors for High Dose Chemotherapy (HDC)

- Those less likely to benefit from HDC:
  - Primary mediastinal GCT refractory to initial and salvage chemotherapy
  - Refractory disease
    - Rising markers or radiographic evidence of progression within 4 weeks of cisplatin
    - High β-HCG levels (> 1,000 IU/L)

The case for HDC

- Poor risk patients do not have the same high rate of cure as good/intermediate risk (50%)
- GCT’s are highly responsive to chemo
- High dose chemo as 3rd line salvage therapy
  - 10 - 20% cure rate
- Improved supportive care
- Patient’s age permits use of high dose chemotherapy with improved safety profile
**History of High Dose Chemotherapy**

1986
- Phase I/II trial: 2 cycles of HDC with carboplatin/etoposide

1997
- 2 cycles of HDC with carboplatin/etoposide

2000
- Review of 65 patients with HDC at Indiana University Hospital

2000
- High dose carboplatin/etoposide/cyclophosphamide in poor risk patients

2007
- Review of 184 patients with HDC with carboplatin and etoposide at Indiana University Hospital
  - (2nd and 3rd line results)
High Dose Chemotherapy (HDC)

- Retrospective review of 184 patients with cisplatin-resistant, progressive GCT’s
- VelIP x 2 cycles ➔ HDC (n = 173)
- VelIP x 1 cycle ➔ HDC (n = 11)
- Primary endpoint
  - Disease Free Survival
- Secondary endpoint
  - Overall survival

VelIP = Vinblastine 0.11 mg/kg IV on days 1, 2
Ifosfamide 1200 mg/m² IV on days 1-5
Cisplatin 20 mg/m² IV on days 1-5

## Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of previous chemo regimens</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>135 (73.4)</td>
</tr>
<tr>
<td>2</td>
<td>45 (24.4)</td>
</tr>
<tr>
<td>3</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Response to initial chemotherapy</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>75 (40.8)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td>&lt; CR or PR with normal tumor markers</td>
<td>100 (54.3)</td>
</tr>
<tr>
<td>Initial IGCCCG stage (risk)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>71 (38.6)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>38 (20.7)</td>
</tr>
<tr>
<td>High</td>
<td>75 (40.8)</td>
</tr>
</tbody>
</table>


CR = complete remission; PR = partial remission
HDC consisted of:

- Carboplatin 700 mg/m² on days -5, -4, -3
- Etoposide 750 mg/m² on days -5, -4, -3

≥ 1 million CD34+ cells/kg were required for each cycle of HDC

No planned reductions/escalations of doses

2nd cycle given after recovery of counts, unless toxicities (grade 4 non-hematologic), or no response to the 1st cycle

Mobilization of peripheral blood stem cells (PBSC): G-SCF (10 µg / kg / d)

Apheresis (adequate number for 2 autologous transplants)

Cycle 1 high dose chemotherapy:
  Carboplatin days -5, -4, -3
  Etoposide days -5, -4, -3

PBSC re-infusion day 0 and Filgrastim starting day 0

Perform additional mobilization and PBSC collection if needed

Cycle 2 high dose chemotherapy as given in cycle 1

Results

- 40/184 (22%) were platinum refractory
- 116/184 (63%) were disease free at a median follow-up of 48 months
  - 104/116 (90%) were disease free > 2 years
- 6 patients = CR
  - 4 patients = CR after paclitaxel + gemcitabine
  - 2 patients = CR after resection

Results – Disease Free Survival


Figure 2. Disease-free Survival.

The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points for third-line chemotherapy, 2 points for platinum refractoriness, and 2 points for advanced International Germ Cell Cancer Collaborative Group stage. High scores indicated a low probability of disease-free survival.
Results

- Prognostic variables associated with statistical improvement in PFS
  - HDC as 2\textsuperscript{nd} line therapy vs. 3\textsuperscript{rd} line
  - Platinum sensitivity
  - Response to initial chemotherapy
  - Favorable prognosis
  - Favorable IGCCCG score

# Grade 3 and Higher Toxicities

<table>
<thead>
<tr>
<th>Total patients = 184</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic (leukemia)</td>
<td>3</td>
</tr>
<tr>
<td>Renal (creatinine ↑’d 3-6 x ULN)</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30</td>
</tr>
<tr>
<td>Hepatic</td>
<td>6</td>
</tr>
<tr>
<td>Neurologic</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
</tr>
</tbody>
</table>

2 deaths were associated with leukemia  
2 deaths were associated with hepatic dysfunction  
1 death was associated with pulmonary toxicities

**HDC with PBSCT can cure metastatic GCT’s when used as 2nd line and even as 3rd line therapy**

ULN = Upper limit of normal
**HDC – Supportive Care - Prophylaxis**

Indiana University

<table>
<thead>
<tr>
<th>Start on:</th>
<th>Day -1</th>
<th>Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin 500 mg po BID</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fluconazole 400 mg po daily</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Acyclovir 400 mg po BID</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vancomycin 1500 mg IV Q12 hours</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Use once daily in outpatient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filgrastim subcutaneously daily</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Stop: ANC is = or > 2000/mm³ x 2 days
Stop: ANC = or > 10,000/mm³ x 1 day
Adequate hydration

- **ASCO Guidelines: Stem Cell Transplant**
  - Highly emetogenic regimen
    - 5-HT$_3$ serotonin receptor antagonist
    - Dexamethasone
    - Aprepitant
      - Should be considered although evidence to support its use specifically in these patients is lacking

- **NCCN Guidelines: Stem Cell Transplant**
  - Aprepitant may be used for multiple day regimens. Based on phase II data, the drug has been safely given on days 4 and 5

### HDC – Supportive Care- Antiemetics
Indiana University

<table>
<thead>
<tr>
<th>Day</th>
<th>- 5</th>
<th>- 4</th>
<th>- 3</th>
<th>- 2</th>
<th>- 1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant 125 mg po</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprepitant 80 mg po</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ondansetron 24 mg po</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone 12 mg po</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone 8 mg po</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Lorazepam 1mg IV/PO q 4 hour PRN**
Maintenance Etoposide

- Maintenance oral etoposide
  - Platinum refractory, high risk disease
  - 50 mg/m² daily every 3 weeks, with 1 week off
    - Repeat x 3 cycles

Saxman S. *Drugs.* 1999;58(3):31-34.
HDC vs. CDC

- Retrospective review of 1,594 patients
  - 773 received conventional chemotherapy
  - 821 received HDC
- Evaluated use of second line therapy in patients who received prior cisplatin
- Patients were classified according to risk:
  - Very low, low, intermediate, high, very high
- Estimated 2 year PFS and 5 year OS

## HDC vs. CDC

<table>
<thead>
<tr>
<th>(Number of patients)</th>
<th>2 yr PFS (%)</th>
<th>5 yr OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (1594)</td>
<td>HDC vs. CDC</td>
<td>49.6 vs. 27.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Very low risk (76)</td>
<td>HDC vs. CDC</td>
<td>91.6 vs. 58.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.008</td>
</tr>
<tr>
<td>Low risk (257)</td>
<td>HDC vs. CDC</td>
<td>64.3 vs. 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Intermediate risk (546)</td>
<td>HDC vs. CDC</td>
<td>53.5 vs. 31.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>High risk (351)</td>
<td>HDC vs. CDC</td>
<td>33.3 vs. 17.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Very high risk (105)</td>
<td>HDC vs. CDC</td>
<td>22 vs. 1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Which of the following is the most effective salvage chemotherapy regimen for patients with recurrent disease?

1. TIP
2. Etoposide
3. PVB
4. VelIP
Salvage Chemotherapy - VeIP

- Vinblastine, Ifosfamide, and Cisplatin
  - 135 patients who progressed on cisplatin based chemotherapy
  - Included both gonadal (n=100) and extragonadal tumors (n=35)
- Patients received VeIP every 3 weeks x 4

<table>
<thead>
<tr>
<th>VeIP</th>
<th>Vinblastine</th>
<th>Ifosfamide</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.11 mg/kg IV on days 1, 2</td>
<td>1200 mg/m² IV on days 1-5</td>
<td>20 mg/m² IV on days 1-5</td>
<td></td>
</tr>
</tbody>
</table>

Salvage Chemotherapy - VeIP

- 67 (50%) achieved a CR after chemotherapy with or without surgery
- 42 (32%) were alive at 6 years
- 32 (24%) were NED at 6 years
  - No patients with extragonadal tumors were NED compared to 30% of testicular primaries


NED = No evidence of disease
Salvage Chemotherapy - TIP

- Paclitaxel, Ifosfamide, and Cisplatin (TIP)
  - 46 patients previously treated and prior CR
  - Gonadal primaries
- Patients received TIP every 3 weeks x 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>250 mg/m² continuous IV on day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1500 mg/m² IV on days 2-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>25 mg/m² IV on days 2-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>1500 mg/m² IV on days 2-5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- All patients received colony stimulating agents

Salvage Chemotherapy - TIP

- 32 patients (70%) achieved a CR
- 29 patients (63%) achieved a CR at the follow up of 69 months
  - Continue to be NED at 5 years
- 7 of 14 patients with late relapse disease achieved a CR with chemotherapy followed by surgical resection
- Toxicities:
  - 48% admission for neutropenic fever

Other Salvage Chemotherapy

- So why use paclitaxel plus gemcitabine?
  - Single agent paclitaxel results: 11-26%
  - Single agent gemcitabine results: 19-20%
- Review of 32 patients that had progressed after receiving HDC (platinum refractory)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>100 mg/m² IV over 1 hour</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m² IV over 30 minutes days 1, 8, 15 every 28 days</td>
</tr>
</tbody>
</table>

Paclitaxel + Gemcitabine

- 25 received therapy as 3rd line, with 6 patients receiving therapy as 4th line
- Main toxicities: Myelosuppression and neuropathy
- Results:
  - 4 partial remissions (for 2 - 6 months)
  - 6 complete responses
    - 4 of those 6 continued to be NED at 20, 40, 44, and 57 months, respectively

## Other Salvage Chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th># pts</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Oxaliplatin + gemcitabine</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Oxaliplatin + gemcitabine</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Irinotecan + platinum</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Oxaliplatin + irinotecan</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Cisplatin + epirubicin</td>
<td>30</td>
<td>9</td>
</tr>
</tbody>
</table>

RR = Response rate; CR = Complete remission

Other Salvage Chemotherapy

- **Etoposide**
  - Phase II trial in refractory tumors (N = 22)
    - 50 mg/m² orally rounded to nearest 25 mg
      - 3 = Partial response
      - 8 = Stable disease

Other Salvage Chemotherapy

- Maintenance after salvage therapy (N = 34)
  - Median prior regimens = 2
  - 14 received previous stem cell transplant
  - 50 mg/m²/day orally for 21 days
    - Repeat every 28 days x 3 cycles
  - Prior to maintenance therapy:
    - 11 patients achieved PR and 23 patients achieved CR
  - 17 of 23 patients maintained CR with no evidence of recurrence at a median follow-up of 36 months
  - Less toxicities than with continuous administration
  - Neutropenia, mucositis, and neutropenic fever

Supportive Care Issues in GCTs

- Short term toxicities
  - Nausea/vomiting
  - Pain management
  - Febrile neutropenia
  - Testosterone deficiency
Question # 4

Which of the following is a common short-term toxicity associated with testicular cancer chemotherapy?

1. Leukemia
2. Mucositis
3. Pneumonitis
4. Nausea/vomiting
Supportive Care Issues in GCTs

- Nausea/vomiting
  - Highly emetogenic regimens
  - Prophylaxis with 3 drug regimen as per ASCO/NCCN guidelines
    - 5-HT₃ antagonist, dexamethasone, aprepitant
  - Adequate hydration
Supportive Care Issues in GCTs

- Pain Management
  - Initially patients may have increased pain
    - Lower back, abdominal, post-surgical site
  - Pain dramatically ↓’s with chemotherapy
Supportive Care Issues in GCTs

- Testosterone Deficiency
  - No standard treatment/follow-up guidelines
  - Many patients will maintain normal testosterone levels
  - Testosterone levels can be tested when patient experiences symptoms:
    - Loss of libido, fatigue, increased sweating, impotence
    - Check testosterone level early in morning
      - (i.e. 7:00 – 8:00 am)

Supportive Care Issues in GCTs

- **Testosterone Deficiency**
  - Maintain physiologic testosterone range
    - 280-800 ng/dL and monitor every 3 to 4 months
  - Many formulations of testosterone replacement
    - Topical gel, transdermal patches, injections

- **Survey of testicular cancer survivors (n = 83)**
  - 25% of patients experienced hypogonadism
  - Symptoms of androgen deficiency were not associated with testosterone levels
    - Sexual dysfunction, chronic fatigue

Which of the following would be considered a long-term toxicity of testicular cancer treatment?

1. Pain management
2. Nephrotoxicity
3. Neutropenic fever
4. Electrolyte imbalances
Long Term Toxicities

- Sterility
- Neuropathy
- Nephrotoxicity
- Pulmonary toxicity
- Tinnitus
- Vascular toxicities
- Secondary malignancies
- Late relapse

Toxicities that persist >12 months or that are present 12 months after the end of therapy
Long Term Toxicities

- **Sterility**
  - At time of diagnosis 10 - 35% are infertile
  - Reasons induce:
    - Abdominal radiotherapy, RPLND, chemotherapy
  - ↑’s in FSH and LH up to 2 years after therapy
  - ↓’d testosterone leads to worsening sexual function, psychosocial functioning, increased BMI and blood pressure

RPLND = Retroperitoneal lymph node dissection; FSH = follicle stimulating hormone; LH = Luteinizing hormone; BMI = Body mass index
Long Term Toxicities

- Sterility (continued):
  - Likelihood of fathering a child after therapy for testicular cancer
    - Chemotherapy = 71%
    - Chemotherapy + Radiation = 67%
  - Risk factors for azoospermia:
    - Radiation therapy
    - Age > 30 years
    - Chemotherapy duration > 6 months

**SPERM BANKING DISCUSSION!!!!**

Long Term Toxicities

- **Neuropathy**
  - Cisplatin
    - Numbness and tingling
  - Vinblastine
    - “Stocking glove”
  - Can occur in up to 80% of patients
  - Can persist after therapy (up to 50%)

Long Term Toxicities

- Nephrotoxicity: Cisplatin
  - ↓’s in glomerular filtration rate and electrolyte disturbances from tubular dysfunction
  - Damage to proximal tubules: magnesium wasting
  - Can be reversible or irreversible and may last > 12 months
  - Adequate hydration for prevention
  - Risk factors:
    - Total cisplatin dose, other concomitant nephrotoxic agents, pre-existing renal disease

Lon Term Toxicities

- Pulmonary: **BLEOMYCIN**
  - Risk factors:
    - Cigarette smoking, radiation, cumulative bleomycin dose (~ 9% in doses > 300 units)
    - Prior surgery (or intubation), exposure to high concentrations of oxygen
  - Patients may experience:
    - Bronchiolitis obliterans or interstitial pneumonitis
  - Long-term pulmonary function is preserved in most, but the toxicity can persist in others

Long Term Toxicities

- Pulmonary: **BLEOMYCIN**
  - Stop bleomycin therapy!
  - Administer steroids for symptomatic relief
  - Physical assessment prior to each dose of bleomycin should occur to assess changes
  - Pulmonary function tests can be ordered and followed; however do not always predict lung damage

Long Term Toxicities

- **Tinnitus**
  - High frequency hearing loss (4 to 8 MHz)
  - Persistent problems ~ 20% of patients

- **Vascular toxicities**
  - Raynaud’s
    - Bleomycin can cause this
    - Up to 50% of patients experience toxicity
    - Can persist for years after therapy
    - ?? related to cisplatin hypomagnesemia

---

Cardiovascular Complications

- 2 x ↑’s of CV risk compared to general population
- Endothelial cell damage
  - Microalbuminuria
- Indirect effects
  - Can be related to hormonal effects (↓’d testosterone)
- Metabolic syndrome
  - 25 - 40% vs. 3 - 4% in general population

Myocardial infarction
Thromboembolic disease
- Hyperlipidemia
- Hypertension
- Stroke
Metabolic Syndrome
Increased BMI

Cardiovascular Risk- 20 year follow-up

- 990 men in 20 year follow-up study
- 4 treatment groups
  - Surgery (n = 206)
  - Radiotherapy alone (n = 386)
  - Chemotherapy alone (n = 264)
  - Radiotherapy + chemotherapy (n = 34)
    - Anti-hypertensive use was highest:
      - Chemotherapy alone arm

## Cardiovascular Risk - 20 year follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary Artery Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>2.1</td>
<td>0.78 - 5.5</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2.6</td>
<td>0.96 - 6.9</td>
</tr>
<tr>
<td>RT + Chemotherapy</td>
<td>5.3</td>
<td>1.5 - 18.5</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (BEP)</td>
<td>3.1</td>
<td>1.2 - 7.7</td>
</tr>
<tr>
<td>RT + Chemotherapy</td>
<td>4.8</td>
<td>1.6 - 13.9</td>
</tr>
</tbody>
</table>

Radiation therapy; HR = Hazard ratio, CI = Confidence Interval.
Secondary Malignancies

- Cancer registry of 28,843 testicular cancer patients demonstrated increased risk:
  - Observed to expected ratio:
    - 1.43 (CI, 1.36-1.51)
  - Risk’s with chemotherapy or radiation

<table>
<thead>
<tr>
<th>Secondary Malignancies Associated After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular (contralateral)</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Bladder</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
</tr>
</tbody>
</table>

Secondary Malignancies

- Leukemia
  - Etoposide
    - Doses > 2 grams/m², total dose, schedule
  - Relative risk within 10 years: 3 - 7%
- Retrospective review of 113 pts after HDC
  - Risk of leukemia ↑’d by 2.6% with etoposide
- NCI Cancer Therapy Evaluation Program
  - 6 year rate of leukemia: 0.7 - 3.2% after etoposide therapy

Secondary Malignancies: ASCO 2010

- Horwich A. 2010;28:15s:4538
  - 2,703 patients: Infradiaphragmatic radiotherapy
  - Primary outcome: # of secondary cancers
    - 18 year follow-up demonstrated increased rates of:
      - Stomach, pancreas, and bladder cancers

- Lewinshtein C. 2010;28:15s:4537
  - Retrospective: SEER database (1973-2006)

<table>
<thead>
<tr>
<th>Total patients = 20,300</th>
<th>Leukemia/Lymphoma</th>
<th>Bladder Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n)</td>
<td>139</td>
<td>99</td>
</tr>
<tr>
<td>Radiotherapy (n)</td>
<td>76</td>
<td>56</td>
</tr>
</tbody>
</table>
Late Relapse

- One of the most challenging dilemmas
- Defined as recurring 2 years or later after successful treatment
- Very rare: 1 - 3%
- Predominate site of relapse:
  - Retroperitoneum and chest
- Surgery is mainstay of therapy
  - Often refractory to chemotherapy

Late Relapse

- **Seminomas**
  - Those on surveillance are cured by radiation therapy, cisplatin based chemotherapy, or surgery

- **Non-seminomas**
  - Surgery is considered the mainstay in patients that have already received chemotherapy
What to do when there is no drug?

- Everyone is dealing with national shortages
- All drugs affected
- What do you do?
  - Delay treatment?
    - Not an option
  - Transplant?
    - High dose etoposide (if you can get it)
  - Bring out the old regimens!!
Other Chemotherapy Options

- Good risk patients (PVB)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>20 mg/m² IV on days 1-5</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>0.20 mg/kg IV days 1, 2</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>30 units IV on day 2</td>
</tr>
</tbody>
</table>

- Poor risk disease (VeIP)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage and Administration</th>
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<td>Vinblastine</td>
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</tr>
<tr>
<td>Cisplatin</td>
<td>20 mg/m² IV on days 1-5</td>
</tr>
</tbody>
</table>
Conclusions

- Testicular cancer is a very curable disease
- If a patient recurs, cure is still an option
- HDC followed by stem cell transplant is an option for 2\textsuperscript{nd} line therapy and offers cure
- Salvage regimens such as VeIP, TIP, paclitaxel + gemcitabine have been used
- An understanding of short-term and long-term toxicities is important
Germ Cell Tumors (GCT): Beyond BEP

Kellie L. Jones, Pharm.D., BCOP
Clinical Associate Professor
Purdue University College of Pharmacy
Salt Lake City, UT
Chronic Lymphocytic Leukemia: Treatment Update

Ashley Morris Engemann, Pharm.D., BCOP
Clinical Associate
Duke University Medical Center
Ashley Morris Engemann has received consulting fees from Genzyme and Sanofi Aventis
Learning Objectives

- Compare and contrast initial treatment strategies for symptomatic or advanced stage chronic lymphocytic leukemia (CLL).
- Differentiate treatment options for management of relapsed or refractory CLL.
- Justify the role of allogeneic stem cell transplantation in selected patients with CLL.
Epidemiology and Natural History

- 15,000 new cases in US annually
- 4,400 deaths in US annually
- Median age at diagnosis 65-70 years
- May initially be asymptomatic (25%)
- Symptoms increase with disease progression
- Incurable with conventional chemotherapy

Prognostic Factors

- **Favorable**
  - Early stage or low risk
  - Immunoglobulin Variable Region (IgV\(_H\))
    - > 2% mutation
  - Del(13q) as sole abnormality; median survival 133 months

- **Unfavorable**
  - Advanced stage or high risk
  - CD38 (if >= 30%)
  - Zeta-associated protein 70 (ZAP 70) (if >= 20%)
  - Del(11q); median survival 79 months
  - Del(17p); median survival 32 months

First-Line Therapy
1. Initiation of treatment is recommended for which of the following patients with CLL?
   A. All patients regardless of stage
   B. All patients with high risk features regardless of stage
   C. Only patients with significant disease-related symptoms
   D. Patients with Rai Stage III or IV disease only
Active Surveillance

- Recommended for
  * Rai Stage 0 (low risk)
  * Rai Stage I-II (intermediate risk)

- Early treatment in asymptomatic patients
  * May improve progression-free survival
  * Has no impact on overall survival

- Remains an active area of research
  * Primary focus on high-risk disease

Indications for Treatment

- Significant disease-related symptoms
  - Night sweats
  - Fatigue
  - Weight loss
  - Fever without infection
- Progressive bulky disease
- Lymphocyte doubling time <= 6 months

Indications for Treatment (continued)

- Progressive anemia or thrombocytopenia
- Threatened end-organ function
- Absolute lymphocyte count >200,000-300,000 x 10^9/L or symptoms related to leukostasis
- Eligible for clinical trial

2. At your institution, what is the preferred first-line regimen for standard-risk CLL patients less than 70 years of age?

A. Fludarabine, cyclophosphamide, rituximab (FCR)
B. Bendamustine, rituximab (BR)
C. Pentostatin, cyclophosphamide, rituximab (PCR)
D. Alemtuzumab
E. Other
### First-Line Treatment: Chlorambucil versus Fludarabine

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Fludarabine</th>
<th>Chlorambucil</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rai 2000 (C9011)</td>
<td>ORR</td>
<td>63%</td>
<td>37%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n=509</td>
<td>CR</td>
<td>20%</td>
<td>4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(F=170/C=181)</td>
<td>PFS</td>
<td>20 months</td>
<td>14 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Last f/u 1999</td>
<td>OS</td>
<td>66 months</td>
<td>56 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rai 2009 (C9011)</td>
<td>OS</td>
<td>63 months</td>
<td>59 months</td>
<td>0.04</td>
</tr>
<tr>
<td>N=509</td>
<td>Alive at 4 yrs</td>
<td>60%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Last f/u 2009</td>
<td>Alive at 6 yrs</td>
<td>43%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alive at 8 yrs</td>
<td>31%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

Fludarabine 25 mg/m² IV daily x 5 days q28d  
Chlorambucil 40 mg/m² PO once q28d

# First-Line Treatment: Chlorambucil versus Fludarabine

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Fludarabine</th>
<th>Chlorambucil</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catovsky 2007</td>
<td>ORR</td>
<td>80%</td>
<td>72%</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>15%</td>
<td>7%</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>PFS</td>
<td>20 months</td>
<td>23 months</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>5-yr OS</td>
<td>52%</td>
<td>59%</td>
<td>0.2</td>
</tr>
<tr>
<td>N=777</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eichhorst 2009</td>
<td>ORR</td>
<td>72%</td>
<td>51%</td>
<td>0.003</td>
</tr>
<tr>
<td>n=193</td>
<td>CR</td>
<td>7%</td>
<td>0%</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>PFS</td>
<td>19 months</td>
<td>18 months</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>46 months</td>
<td>64 months</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Eichhorst: Fludarabine 25 mg/m² IV daily x 5 days q28d or chlorambucil 0.4 mg/kg PO once q14d (to max. 0.8 mg/kg as tolerated)
Catovsky: Fludarabine 25 mg/m² IV (or 40 mg/m² PO) daily x 5 days q28d or chlorambucil 10 mg/m² daily x 7 days q28d

First-Line Treatment: Chlorambucil versus Fludarabine

- Fludarabine has shown improvement in PFS compared to chlorambucil, but this has not been demonstrated in all studies.

- No differences exist in overall survival between the two; trend toward worse survival with fludarabine in one study.

- Chlorambucil remains a good option for elderly patients or those unlikely to tolerate a purine analog.
First-Line Treatment:
Cladribine

- Randomized 229 subjects
  - Cladribine 0.12 mg/kg/day IV over 2 hours and prednisone 30 mg/m²/day x 5 days OR
  - Chlorambucil 12 mg/m²/day PO and prednisone 30 mg/m²/day x 7 days

- Responses significantly better with cladribine plus prednisone
  - ORR 87% vs. 57% (p=0.001)
  - CR 47% vs. 12% (p=0.001)
  - PFS better with cladribine; no difference OS

**First-Line Treatment:**

**Rituximab**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose and Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Brien 2001</td>
<td>Dose 1: 375 mg/m²</td>
<td>Most toxicity occurred with first infusion (grade 1 and 2); 12% with hypoxia, dyspnea, hypotension; PR 36% (CLL); response increased with dose</td>
</tr>
<tr>
<td>(n=50)</td>
<td>Dose 2+: range 500-2250 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

# First-Line Treatment: Rituximab

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose and Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hainsworth 2003</td>
<td>375 mg/m² weekly x 4; If response or stable disease, repeat course every 6 months for total of 4 courses</td>
<td>ORR 58% (CR 9%) 1st course; PFS 18.6 months (20 month follow-up); PFS 1-year 62%; PFS 2-years 49%</td>
</tr>
<tr>
<td>n=44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del Poeta 2008</td>
<td>Treated with fludarabine x 6 cycles, then rituximab 375 mg/m² x 4 weekly doses; if MRD+ (28 patients) monthly rituximab 375 mg/m² x 4 months, then 150 mg/m² x 12 months</td>
<td>Initial therapy (fludarabine plus rituximab x 4 doses) CR 81% and PR 13%; longer response duration in 28 patients with MRD given rituximab (87% vs. 32% at 5 years; p=0.001) versus no consolidation</td>
</tr>
<tr>
<td>n=75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# First-Line Treatment: Chlorambucil versus Alemtuzumab

## CAM307 Study

<table>
<thead>
<tr>
<th></th>
<th>Alemtuzumab</th>
<th>Chlorambucil</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>149</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>14.6 months</td>
<td>11.7 months</td>
<td>0.0001</td>
</tr>
<tr>
<td>ORR</td>
<td>83%</td>
<td>55%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR</td>
<td>24%</td>
<td>2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>84%</td>
<td>84%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Median follow-up 24.6 months
Alemtuzumab 30 mg IV 3x/week up to 12 weeks
Chlorambucil 40 mg/m² every 28 days up to 12 months

First-Line Treatment: Consolidation with Alemtuzumab

- Several studies have addressed the role of alemtuzumab for consolidation following remission induction
  - German CLL Study Group
    - PFS significantly prolonged in patients randomized to alemtuzumab following treatment with fludarabine +/- cyclophosphamide
  - CALGB 10101
    - Alemtuzumab given following fludarabine plus rituximab
      - With 36 month follow-up, PFS was 36 months, 2-yr PFS 72%, 2-yr OS 86%
  - Severe infectious toxicity occurred in both studies

First-Line Treatment: Alemtuzumab

- Not recommended for routine consolidation due to infectious toxicity
- Reasonable single-agent option in patients unlikely to tolerate aggressive alkylator-based regimens
- Not highly effective in patients with bulky disease
- Efficacy demonstrated in patients with del(17p) because its mechanism is not dependent on p53
- Commonly administered subcutaneously rather than intravenously
- Prophylaxis recommended against HSV and Pneumocystis; monitor for CMV reactivation and consider valganciclovir prophylaxis
First-Line Treatment:
Chlorambucil versus Bendamustine

- Phase III randomized study comparing chlorambucil and bendamustine in 319 patients with previously untreated advanced CLL
  - Bendamustine 100 mg/m² IV daily on Days 1 and 2
  - Chlorambucil 0.8 mg/kg orally on Days 1 and 15
  - Repeated every 28 days for maximum 6 cycles

# First-Line Treatment: Chlorambucil versus Bendamustine

<table>
<thead>
<tr>
<th></th>
<th>Bendamustine (n=162)</th>
<th>Chlorambucil (n=157)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>68%</td>
<td>31%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR</td>
<td>31%</td>
<td>2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PFS (ITT)</td>
<td>21.2 months</td>
<td>8.8 months</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gr 3/4 heme toxicity</td>
<td>40%</td>
<td>19%</td>
<td>-</td>
</tr>
</tbody>
</table>

No difference overall survival; patients achieving CR had longer OS than patients not in CR (median not reached vs. 76.2 months; p=0.002); QOL same in both treatment groups

First-Line Treatment: Bendamustine and Rituximab

- German CLL Study Group
  - 117 patients with previously untreated CLL
- Treatment regimen (28-day cycles)
  - Bendamustine 90 mg/m² IV daily x 2 days
  - Rituximab 375 mg/m² IV once Cycle 1, then 500 mg/m² IV once Cycles 2-6
- Median follow-up 15.4 months
- ORR 90.9%
- CR 32.7%
- Median PFS not reached

First-Line Treatment: Combinations with Purine Analogs

- Several studies demonstrated benefit of combination therapy with fludarabine
  - Fludarabine plus cyclophosphamide versus fludarabine alone
  - Fludarabine plus concurrent rituximab versus fludarabine plus sequential rituximab
  - Fludarabine, cyclophosphamide, plus rituximab

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

<table>
<thead>
<tr>
<th>FCR Regimen</th>
<th>Fludarabine</th>
<th>25 mg/m²</th>
<th>daily x 3 days</th>
<th>Days 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>250 mg/m²</td>
<td>daily x 3 days</td>
<td>Days 1-3</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>once</td>
<td>Cycle 1, Day 0</td>
</tr>
<tr>
<td></td>
<td>500 mg/m²</td>
<td>once</td>
<td>Cycles 2-6, Day 1</td>
<td></td>
</tr>
</tbody>
</table>

Repeated cycles every 28 days for 6 cycles; treatment discontinued after 3 cycles if no PR or CR

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

- German CLL Study Group (CLL8)
  - 817 patients with advanced, symptomatic CLL randomized to FCR or fludarabine and cyclophosphamide (FC)
- Primary endpoint progression-free survival
- Median age 61 years (30-81); 30% >= 65 years); relatively physically fit
- No prophylaxis with CSFs or antivirals; PCP prophylaxis if neutropenic > 7 days

# First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

<table>
<thead>
<tr>
<th></th>
<th>FC (%)</th>
<th>FCR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All n=817</strong></td>
<td>CR</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td><strong>Del(17p) n=51</strong></td>
<td>CR</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td><strong>Del(11q) n=142</strong></td>
<td>CR</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td><strong>IgV_H unmutated n=390</strong></td>
<td>CR</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>76</td>
<td>91</td>
</tr>
</tbody>
</table>

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

Progression-Free Survival in All Patients

- Median PFS for FCR: 51.8 mo.
- Median PFS for FC: 32.8 mo.
- PFS at 3 yrs.:
  - FCR: 65%
  - FC: 45%

P<0.0001

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

Overall Survival

3 yr. OS
FCR 87%
FC 83%
P=0.012

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

Incidence of Grade 3 and 4 Adverse Events

First-Line Treatment: FCR versus BR

- FCR strongly encouraged in guidelines for younger patients without co-morbidities
- Current trial ongoing to compare FCR to BR in first-line setting
  - German CLL 10 Protocol
  - Non-inferiority design
First-Line Treatment: Pentostatin, Cyclophosphamide, and Rituximab

- Pentostatin 2 mg/m² Day 1
- Cyclophosphamide 600 mg/m² Day 1
- Rituximab 375 mg/m² Day 1
  - First cycle 100 mg/m² Day 1, 375 mg/m² Day 3, and 375 mg/m² Day 5

- 65 patients
  - ORR 91%
    - CR 41%
    - Nodular PR 22%
    - PR 28%

First-Line Treatment:
HDMP and Rituximab

- High-dose methylprednisolone (HDMP)
  - 1 g/m² IV daily x 3 days with rituximab
  - Repeated every 28 days x 3 cycles

- 28 patients
  - ORR 96%
  - CR 32%
  - Median follow-up 3 years
    - PFS 30.3 months

- Option in patients with limited myeloid reserve, those with del(17p), immune cytopenias

Selection of First-Line Regimen

- Patient factors
  - Age
  - Co-morbidities

- Disease factors
  - Presence of poor prognostic factors
    - Del(17p)
      - Chemotherapy or chemoimmunotherapy recommended in younger patients
      - Older patients may respond well to alemtuzumab
    - Del(11q)
      - Alkylator-based therapy recommended
### First Line Therapy

<table>
<thead>
<tr>
<th>Frail patient or co-morbidities</th>
<th>Age &gt;=70 or younger with co-morbidities</th>
<th>Age &lt; 70 or older with no co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil +/- Pred</td>
<td>Chlorambucil +/- Pred</td>
<td>FCR</td>
</tr>
<tr>
<td>Rituximab</td>
<td>BR</td>
<td>FR</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Cyclophosphamide, Pred +/- R</td>
<td>PCR</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td></td>
<td>BR</td>
</tr>
<tr>
<td>Rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F +/- R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cladribine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B=bendamustine; R=rituximab; F=fludarabine; C=cyclophosphamide; P=pentostatin

Summary Slide
First Line Therapy

<table>
<thead>
<tr>
<th>del(17p)</th>
<th>del(11q) and age (\geq 70) or younger with co-morbidities</th>
<th>del(11q) and age &lt; 70 or older with no co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR</td>
<td>Chlorambucil +/- Pred</td>
<td>FCR</td>
</tr>
<tr>
<td>FR</td>
<td>BR</td>
<td>BR</td>
</tr>
<tr>
<td>HDMP + R</td>
<td>Cyclophosphamide, Pred +/- R</td>
<td>PCR</td>
</tr>
<tr>
<td>Alemtuzumab +/- R</td>
<td>Reduced-dose FCR</td>
<td></td>
</tr>
<tr>
<td>BR</td>
<td>Alemtuzumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td></td>
</tr>
</tbody>
</table>

F=fludarabine; C=cyclophosphamide; R=rituximab; HDMP=high-dose methylprednisolone; B=bendamustine; P=pentostatin

Treatment of Relapsed or Refractory CLL
3. At your institution, what is the preferred regimen for patients less than 70 years of age with standard-risk relapsed CLL?
A. Fludarabine, cyclophosphamide, rituximab
B. Bendamustine, rituximab
C. Alemtuzumab
D. Rituximab
E. Ofatumumab
F. Other
Relapsed/Refractory CLL: FCR

Previously-treated CLL
- Binet stage A 10%
- Binet stage B 59%
- Binet stage C 31%

Primary endpoint
- PFS

Stratification
- Prior therapy
  - Alkylator-refractory
  - Alkylator-sensitive
  - Fludarabine exposed
- Time from diagnosis

Relapsed/Refractory CLL: FCR
REACH Study

- One prior line of therapy
  - Not alkylator or purine combination
  - If prior fludarabine, NOT refractory (response < 6 months); few had prior fludarabine exposure)
  - No prior rituximab
- Tumor lysis syndrome prophylaxis
- PCP and HSV prophylaxis
- CSFs allowed
Relapsed/Refractory CLL: FCR

Progression-Free Survival by Independent Review Panel

Median PFS
FCR 27 months
FC 21.9 months
P=0.0218
(median f/u 25 months)

Relapsed/Refractory CLL: FCR

Overall Survival

Relapsed/Refractory CLL: Bendamustine and Rituximab

- 81 patients (62 evaluable for response)
- Median number of 2 prior regimens
- Treatment
  - Bendamustine 70 mg/m² Days 1 and 2
  - Rituximab 375 mg/m² Day 1, Cycle 1
  - Rituximab 500 mg/m² Day 1, Cycles 2-6
  - Repeated every 28 days up to 6 cycles
- ORR 77.4%
- CR 14.5%
- PR 62.9%

Relapsed/Refractory CLL: Alemtuzumab

- Several phase II studies have demonstrated efficacy of single agent alemtuzumab in the salvage setting
  - Fludarabine-refractory patients
    - ORR 33%; CR 2% (IV alemtuzumab)
    - ORR 34%; CR 4% (SC alemtuzumab)
  - Patients with p53 mutations or del(17p)
    - ORR 39-50%
- Current studies in combination with rituximab or fludarabine

Ofatumumab

- Anti-CD20 monoclonal antibody
- Binds to a different epitope of CD20 than rituximab
- Improved complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity compared to rituximab
- Approved for the treatment of CLL resistant to both fludarabine and alemtuzumab

Relapsed/Refractory CLL: Ofatumumab

- 206 patients with fludarabine- and alemtuzumab-refractory CLL (final analysis)
- Eight weekly doses of ofatumumab followed by 4 monthly doses
  - 300 mg x 1 dose, then 2000 mg x 11 doses
    - 89% completed 8 infusions
    - 50% completed 12 infusions
- Response evaluated over 24-week period

## Relapsed/Refractory CLL: Ofatumumab

<table>
<thead>
<tr>
<th></th>
<th>FA-Ref</th>
<th>BF-Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of prior therapies</td>
<td>5 (1-14)</td>
<td>4 (1-16)</td>
</tr>
<tr>
<td>Rai Stage III-IV at screening (%)</td>
<td>61</td>
<td>70</td>
</tr>
<tr>
<td>Prior rituximab-containing regimen (%)</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>Overall response rate (ORR) (%)</td>
<td>51</td>
<td>44</td>
</tr>
<tr>
<td>Complete response (CR) (%)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Partial response (PR) (%)</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>Median response duration (months)</td>
<td>5.7</td>
<td>6</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>14.2</td>
<td>17.4</td>
</tr>
</tbody>
</table>

FA-Ref (fludarabine- and alemtuzumab-refractory); BF-Ref (fludarabine-refractory with bulky (> 5 cm) lymphadenopathy); PFS (progression-free survival)

Relapsed/Refractory CLL: Ofatumumab

Progression-Free Survival and Overall Survival

Relapsed/Refractory CLL: Ofatumumab

Overall Survival FA-Ref Group

Overall Survival BF-Ref Group

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose and Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrd 2001</td>
<td>Day 1: 100 mg</td>
<td>ORR 45%</td>
</tr>
<tr>
<td>(n=33)</td>
<td>Day 3: 250 mg/m² or 375 mg/m², then 3x/week x 4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Relapsed/Refractory CLL: HDMP and Rituximab

- **Regimen**
  - Methylprednisolone 1 g/m² IV daily x 5 days
  - Rituximab 375 mg/m² IV weekly x 4 weeks

- **Twenty-seven patients (Bowen)**
  - Nine with del(17p) and six with del(11q)
  - ORR 78%; CR 22% after one cycle
  - Infectious complications 29% during first cycle
  - 3-year survival 41%

- **Fourteen fludarabine-refractory patients (Castro)**
  - ZAP-70 positive 79%
  - ORR 93%; CR 36% after 3 cycles
  - Median time to progression 15 months

Selection of Regimens in Patients with Relapsed/Refractory CLL

- Patient factors
  - Age
  - Co-morbidities

- Disease factors
  - Duration of prior remission
  - Presence of poor prognostic factors
  - Repeat FISH before each subsequent therapy to further guide treatment
    - New cytogenetic abnormalities often acquired as disease progresses
## Summary Slide

### Relapsed/Refractory Treatment

<table>
<thead>
<tr>
<th>Frail patient or co-morbidities (without del(11q) or del(17p))</th>
<th>Age &gt;=70 &amp; short response (without del(17p))</th>
<th>Age &lt; 70 or older with no co-morbidities &amp; short response (without del(17p))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil +/- Pred</td>
<td>Reduced-dose FCR</td>
<td>FCR</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Reduced-dose PCR</td>
<td>PCR</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>B +/- R</td>
<td>BR</td>
</tr>
<tr>
<td>HDMP + R</td>
<td>Fludarabine + alemtuzumab</td>
<td></td>
</tr>
<tr>
<td>Chlorambucil +/- Pred</td>
<td>CHOP-R</td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>HyperCVAD-R</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab +/- R</td>
<td>Dose-adjusted EPOCH-R</td>
<td></td>
</tr>
<tr>
<td>Dose-dense rituximab</td>
<td>OFAR</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

F=fludarabine; C=cyclophosphamide; R=rituximab; P=pentostatin; B=bendamustine; HDMP=high-dose methylprednisolone; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; HyperCVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine; EPOCH=etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide; OFAR=oxaliplatin, fludarabine, cytarabine, rituximab; Short response= < 2 years; Long response = > 3 years

### Summary Slide

**Relapsed/Refractory Treatment**

<table>
<thead>
<tr>
<th>del(17p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP-R</td>
</tr>
<tr>
<td>CFAR</td>
</tr>
<tr>
<td>HyperCVAD-R</td>
</tr>
<tr>
<td>OFAR</td>
</tr>
<tr>
<td>Ofatumumab</td>
</tr>
<tr>
<td>Alemtuzumab +/- rituximab</td>
</tr>
<tr>
<td>High-dose dexamethasone +/- rituximab</td>
</tr>
<tr>
<td>Bendamustine +/- rituximab</td>
</tr>
</tbody>
</table>

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; R = rituximab; CFAR = cyclophosphamide, fludarabine, alemtuzumab, rituximab; HyperCVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab

Hematopoietic Stem Cell Transplantation
4. For patients in whom hematopoietic stem cell transplantation (HSCT) is indicated, which of the following is preferred?

A. Autologous HSCT
B. Ablative allogeneic HSCT
C. Nonmyeloablative allogeneic HSCT
D. Donor lymphocyte infusion
Autologous and Allogeneic Stem Cell Transplantation

- Retrospective analysis of 162 patients with CLL at Dana Farber (1989-99)
- Matched sibling allogeneic HSCT (n=25) and autologous HSCT (n=137)
- Ablative conditioning with total body irradiation and cyclophosphamide
- No difference in overall survival with median follow-up of 6.5 years
- High rate of treatment-related complications
- Low relapse rate in allogeneic group at 2 years with evidence of graft-versus-leukemia

Allogeneic Stem Cell Transplant

- Retrospective evaluation of the Center for International Blood and Marrow Transplant Research
- 38 CLL patients underwent myeloablative conditioning followed by matched unrelated donor transplant
  - Chemotherapy-refractory 55%; prior fludarabine in 89%
  - CR 58%; PR 17%
  - Grade 2-4 acute GVHD 45%; chronic 85% at 5 years
  - 5-year OS 33%; treatment-related mortality 38%

### Allogeneic Stem Cell Transplant

- Reduced intensity (German CLL3X) conditioning with fludarabine- and cyclophosphamide-based regimen (n=90)
- Median follow-up 46 months
  - 4-year non-relapse mortality 23%
  - 4-year event-free survival 42%
  - Overall survival 65%
  - 27 (52%) of 52 patients with monitoring available for minimal residual disease (MRD) were alive and MRD negative at 12 months
  - Uncontrolled disease at transplant and T-cell depletion with alemtuzumab were poor prognostic factors

Allogeneic Stem Cell Transplant

- 50 patients (1996-2006)
  - 21 reduced-intensity conditioning (RIC)
  - 29 full-intensity conditioning (FIC)
- 5-year OS
  - RIC 63% versus FIC 18% (p=0.006)
- Transplant-related mortality at Day 100
  - RIC 14% versus FIC 27% (p=0.005)
- Relapse rate 15%

Allogeneic Stem Cell Transplant: Reduced Intensity Conditioning

- 82 patients with fludarabine-refractory CLL
  - Conditioning regimen 2 Gy total-body irradiation (TBI) +/- fludarabine
  - Related (n=52) or unrelated donors (n=30)
- CR 55% and PR 15%
- 5-year incidence
  - Non-relapse mortality 23%
  - Progression/relapse 38%
  - Overall survival 50%
  - PFS 39%

European Group for Blood and Marrow Transplantation (EBMT) reported on 44 patients with del(17p)

- Matched related donor (n=24) or matched unrelated donor (n=20)
- 5 myeloablative; 39 reduced intensity
- 53% in remission at HSCT
- 3-year OS 44%; PFS 37%
- Grade 2-4 acute GVHD 43%; extensive chronic GVHD 53%
- No late relapses in 9 patients after 4+ years

Indications for Allogeneic HSCT: NCCN Guidelines

- Without del(11q) or del(17p)
  - Consider after short response to salvage therapy
- With del(17p)
  - Consider if achieve CR or PR to first-line therapy
- With del(11q)
  - Consider if achieve PR to first-line therapy
  - If CR, observe and retreat with non-transplant modality at disease progression

Indications for Allogeneic HSCT: EBMT Transplant Consensus

- Option for younger patients with one of the following poor-risk features:
  - Non-response or early relapsed (within 12 months) after purine analogs
  - Relapse within 24 months after response with purine-analog-based combination therapy or autologous transplantation
  - Patients with p53 abnormalities (del(17p)) requiring treatment

Conclusions

- FCR has become the standard for first-line treatment of CLL in patients able to tolerate this therapy.
- FCR is the treatment of choice for most patients in the second-line setting.
- It is not clear which regimen patients should receive for salvage if they receive FCR in the first-line setting.
- Many other treatment options are available for patients unable to tolerate highly intensive regimens.
- Greater support is now available for reduced-intensity allogeneic stem cell transplantation in selected patients with CLL that have a suitable donor.
Chronic Lymphocytic Leukemia: Treatment Update

Ashley Morris Engemann, PharmD, BCOP
Clinical Associate
Duke University Medical Center
March 2011
Updates in the Treatment of Metastatic Breast Cancer

Michael J. Berger, Pharm.D., BCOP
Specialty Practice Pharmacist,
The James Comprehensive Breast Center,
The James Cancer Hospital and Solove Research Institute at The Ohio State University
Faculty Disclosure

- Michael Berger has no areas of conflict to disclose.
Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- Compare and contrast targeted therapies for the treatment of HER2(+) MBC
- Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability
- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile
MBC - Background

- 5-10% breast cancer patients initially present with MBC
- Heterogeneous behavior
- Median survival \( \approx \) 3 years
- Goals of therapy
  - Palliation, quality of life, prolong survival
- < 5% patients live 5 years
  - Curable subset?

Pagani O et al. JNCI. 2010; 102(7):1-8
Factors which influence treatment initiation and continuation:

- Estrogen / Progesterone receptor (ER/PR) status
- HER2 status
- Duration of relapse-free interval
- Location and extent of metastases
- Previous treatment
- Patient symptoms, performance status

Sequential single agent vs. combination

Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- Compare and contrast targeted therapies for the treatment of HER2(+) MBC
- Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability
- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile
Phase III Trial of Paclitaxel ± Bevacizumab in First-line MBC (E2100)

MBC
• Previously untreated locally recurrent or MBC, HER2(−)

Primary endpoint
• PFS in months (mo) by independent review facility (IRF)

Stratification
• Disease-free interval
• Adjuvant therapy
• ER+, ER−, unknown
• Number of metastatic sites

Paclitaxel 90 mg/m² days 1, 8, 15 q 28 days (n=326)
Treat until disease progression, no crossover permitted

Paclitaxel 90 mg/m² days 1, 8, 15 q 28 days + Bevacizumab 10 mg/kg days 1, 15 q 28 days (n=347)

Miller KD et al. NEJM. 2007; 357(26):2666-76
Phase III Trial of Paclitaxel ± Bevacizumab in First-line MBC (E2100)

Kaplan-Meier estimate of PFS:

No significant difference in OS

Reprinted with permission from the NEJM. Miller KD et al. NEJM. 2007; 357(26):2666-76
## Chemotherapy ± Bevacizumab in First-line MBC: Study Designs

<table>
<thead>
<tr>
<th></th>
<th>E2100¹</th>
<th>AVADO²</th>
<th>RIBBON-1³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo (Pl)</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Controlled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Paclitaxel (P)</td>
<td>Docetaxel (D)</td>
<td>Capecitabine (C), Taxanes (T), Anthracyclines (A)</td>
</tr>
<tr>
<td><strong>Bevacizumab (B)</strong></td>
<td>10 mg/kg Q2 weeks</td>
<td>15 mg/kg Q3 weeks</td>
<td>15 mg/kg Q3 weeks</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>PFS</td>
<td>PFS</td>
<td>PFS</td>
</tr>
</tbody>
</table>

1. Miller KD et al. NEJM. 2007; 357(26):2666-76  
# Chemotherapy ± Bevacizumab in First-line MBC: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>E2100&lt;sup&gt;1&lt;/sup&gt;</th>
<th>AVADO&lt;sup&gt;2&lt;/sup&gt;</th>
<th>RIBBON-1&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>P</td>
<td>D + Pl</td>
<td>C + Pl</td>
</tr>
<tr>
<td>P</td>
<td>5.9</td>
<td>8.2</td>
<td>5.7</td>
</tr>
<tr>
<td>P + B</td>
<td>11.8</td>
<td>10.1</td>
<td>8.6</td>
</tr>
<tr>
<td>PFS, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.60</td>
<td>0.77</td>
<td>0.69</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td>p = 0.006</td>
<td>p = 0.0002</td>
<td>p &lt; 0.0001</td>
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<tr>
<td>OS, mo</td>
<td>25.2</td>
<td>31.9</td>
<td>21.2</td>
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<td></td>
<td>26.7</td>
<td>30.2</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>23.8</td>
<td>29</td>
<td>23.8</td>
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<tr>
<td></td>
<td>25.2</td>
<td>30.2</td>
<td>25.2</td>
</tr>
</tbody>
</table>

1. Miller KD et al. NEJM. 2007; 357(26):2666-76  
# Chemotherapy ± Bevacizumab in First-line MBC: Safety

<table>
<thead>
<tr>
<th>Selected grade ≥ 3 Adverse Events (AEs), %</th>
<th>Chemotherapy + Bevacizumab (n = 1679)</th>
<th>Chemotherapy (n = 982)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>7.1</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>9.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>1.2</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>6.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>2.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Treatment related death</td>
<td>2.1</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Which of the following statements regarding the use of bevacizumab in the treatment of MBC is most accurate and compelling?

1. Significant PFS advantage in combination with 2nd line chemotherapy
2. Significant OS advantage in combination with 1st line chemotherapy
3. Significant ORR advantage in combination with capecitabine 1st or 2nd line
4. Significant PFS advantage in combination with 1st line chemotherapy
Role of Bevacizumab in MBC - Summary

- Significant advantage in PFS (primary endpoint) when bevacizumab added to chemotherapy for 1st line MBC
  - Combination with weekly paclitaxel appears most efficacious
- No OS advantage
- No new safety concerns
- July 2010 – ODAC\(^1\) ruling
- December 2010 – FDA\(^2\) initiated process to withdraw prior accelerated approval
- FDA Label remains unchanged
- Future

\(^1\)Oncologic Drugs Advisory Committee  \(^2\)Food and Drug Administration
Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- **Compare and contrast targeted therapies for the treatment of HER2(+) MBC**
- Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability
- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile
## Chemotherapy ± Trastuzumab: First Line Treatment of HER2(+)-MBC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median TTP, mo</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel or Doxorubicin + Cyclophosphamide (AC)(^1)</td>
<td>4.6</td>
<td>20.3</td>
</tr>
<tr>
<td>Paclitaxel or AC + Trastuzumab(^1)</td>
<td>7.4</td>
<td>25.1</td>
</tr>
<tr>
<td>Docetaxel(^2)</td>
<td>6.1</td>
<td>22.7</td>
</tr>
<tr>
<td>Docetaxel + Trastuzumab(^2)</td>
<td>11.7</td>
<td>31.2</td>
</tr>
<tr>
<td>Paclitaxel + Trastuzumab(^3)</td>
<td>7.1</td>
<td>32.2</td>
</tr>
<tr>
<td>Paclitaxel + Carboplatin + Trastuzumab(^3)</td>
<td>10.7</td>
<td>35.7</td>
</tr>
<tr>
<td>Vinorelbine + Trastuzumab(^4)</td>
<td>15.3</td>
<td>38.8</td>
</tr>
<tr>
<td>Docetaxel + Trastuzumab(^4)</td>
<td>12.4</td>
<td>35.7</td>
</tr>
</tbody>
</table>

---

Chemotherapy ± Trastuzumab: Second Line Treatment of HER2(+) MBC - “Trastuzumab Beyond Progression Trial”

**MBC**
- HER2(+), progressive, locally advanced breast cancer (LABC) or MBC
- Previous trastuzumab
- Trastuzumab-free interval < 6 weeks
- Left ventricular ejection fraction (LVEF) ≥ 50%

**Primary endpoint**
- TTP

**Stratification**
- Previous treatment
- Participating center

---

R A N D O M I Z E 1:1

- **Trastuzumab**
  - 6 mg/kg q 21 days
  - +
  - Capecitabine 1250 mg/m²
  - BID × 14 days
  - q 21 days (n=78)

- **Treat until unacceptable toxicity or disease progression**

- Capecitabine 1250 mg/m²
  - BID × 14 days
  - q 21 days (n=78)

---

Chemotherapy ± Trastuzumab: Second Line Treatment of HER2(+) MBC - “Trastuzumab Beyond Progression Trial”

Kaplan-Meier estimate of TTP:

Significant difference in TTP: 8.2 vs 5.6 mo

No significant difference in OS

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Chemotherapy ± Lapatinib: Second Line Treatment of HER2(+) MBC

**MBC**
- Progressive, HER2(+) LABC or MBC
- Previous treatment with anthracycline, taxane and trastuzumab
- Normal left ventricular ejection fraction (LVEF)

**Primary endpoint**
- TTP by IRF

**Stratification**
- Disease stage
- Presence or absence of visceral disease

Randomize 1:1

- Lapatinib 1250 mg daily + Capecitabine 1250 mg/m² BID × 14 days q 21 days (n=163)

- Capecitabine 1250 mg/m² BID × 14 days q 21 days (n=161)

Geyer et al. NEJM. 2006; 355(26):2733-43
Chemotherapy ± Lapatinib: Second Line Treatment of HER2(+) MBC

Kaplan-Meier estimate of TTP:

Reprinted with permission from the *NEJM*. Geyer et al. *NEJM*. 2006; 355(26):2733-43

No significant difference in OS
## Chemotherapy ± Lapatinib: Second Line Treatment of HER2(+) MBC

<table>
<thead>
<tr>
<th>Selected any grade AEs, %</th>
<th>Capecitabine + Lapatinib</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Geyer et al. NEJM. 2006; 355(26):2733-43
Phase III Trial of Lapatinib ± Trastuzumab in HER2(+) MBC

MBC
- HER2(+) MBC
- Previous progression on trastuzumab
- Heavily pretreated, including anthracycline and taxane in adjuvant or metastatic setting

Primary endpoint
- PFS

Stratification
- Visceral disease
- Hormone receptor status

Lapatinib 1500 mg daily (n = 148)

Optional crossover to trastuzumab arm if progressive disease after 4 wks (n = 77)

Trastuzumab
4 mg/kg loading dose then 2 mg/kg q 7 days +
Lapatinib 1000 mg daily (n=148)

Phase III Trial of Lapatinib ± Trastuzumab in HER2(+) MBC

Kaplan-Meier estimate of PFS:

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib</th>
<th>Lapatinib + trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>145</td>
<td>146</td>
</tr>
<tr>
<td>Progressed or died, n</td>
<td>128</td>
<td>127</td>
</tr>
<tr>
<td>Median, weeks</td>
<td>8.1</td>
<td>12.0</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.73 (0.57 to 0.93)</td>
<td>.008</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>.008</td>
</tr>
</tbody>
</table>

No significant difference in OS

Targeted Therapy + Endocrine Therapy in Chemo Naive HER2(+) MBC

- **Anastrozole vs. Anastrozole + Trastuzumab**¹
  - Postmenopausal, HER2(+) , ER+, MBC
  - Primary endpoint – PFS
  - PFS - 5.6 mo (combination) vs. 3.8 mo anastrozole, HR 0.62, p = 0.006

- **Letrozole vs. Letrozole + Lapatinib**²
  - Postmenopausal, HER2(+) , ER+, MBC
  - Primary endpoint: PFS in Her2(+) group
  - PFS – 8.2 mo (combination) vs. 3 mo letrozole, HR 0.71, p = 0.019

Lapatinib Monotherapy in HER2(+) CNS Disease

Crosses the blood brain barrier (BBB)
- Subset of capecitabine + lapatinib vs. capecitabine\(^1\)
- Pilot study\(^2\), n=39
  - Progressive brain metastases, prior trastuzumab, at least one measurable brain lesion
  - ORR 2.6%, median TTP 3 mo
- Phase II trial\(^3\), n=242
  - Brain mets developed while on previous trastuzumab
  - Completed cranial radiation
  - ORR 6%, median PFS 2.4 mo

JW is an 65 yo female with HER2+ MBC to her bones and liver. She has received Docetaxel + Trastuzumab for over 6 months but restaging scans reveal progressive systemic disease as well as new lesions in her brain. Her ECOG is 0. Following radiation therapy, what chemotherapy is most appropriate for JW?

1. Gemcitabine + Cisplatin + Trastuzumab
2. Capecitabine + Trastuzumab
3. Capecitabine + Lapatinib
4. Trastuzumab + Lapatinib
“Targeted Therapy” Options for HER2(+) MBC - Summary

- Trastuzumab - significant ↑ PFS and OS in first line when combined with chemotherapy
- Trastuzumab - may continue post-progression, combine with different chemotherapy
- Lapatinib - significant ↑ in PFS in second line when combined with capecitabine in trastuzumab refractory patients
- Trastuzumab + Lapatinib - well tolerated, may be used in salvage setting for heavily pretreated patients
- Trastuzumab or Lapatinib - may be combined with endocrine therapy in the first line treatment of appropriately selected HER2+, ER+ patients
Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- Compare and contrast targeted therapies for the treatment of HER2(+) MBC
- Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability
- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile
Options for Anthracycline & Taxane Refractory MBC

- More patients exposed to both anthracyclines and taxanes in neo/adjuvant setting
- Definition for “resistant” or “refractory” disease as inclusion criteria in clinical trials may vary
  - Progressive disease during treatment
  - Recurrence within 6 months of neo/adjuvant therapy
  - Recurrence within 6-12 months of last dose in metastatic setting
  - Not defined
# Gemcitabine Monotherapy Following Anthracyclines and Taxanes

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Phase</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rha</td>
<td>38</td>
<td>II</td>
<td>4.5</td>
<td>11</td>
<td>20%</td>
</tr>
<tr>
<td>Smorenburg</td>
<td>23</td>
<td>II</td>
<td>1.9 (TTP)</td>
<td>7.8</td>
<td>0%</td>
</tr>
<tr>
<td>Modi</td>
<td>18</td>
<td>II</td>
<td>NR</td>
<td>9.5</td>
<td>17%</td>
</tr>
<tr>
<td>Suzuki</td>
<td>56</td>
<td>II</td>
<td>3</td>
<td>17.8</td>
<td>8.1%</td>
</tr>
<tr>
<td>Spielmann*</td>
<td>47</td>
<td>II</td>
<td>NR</td>
<td>NR</td>
<td>29%</td>
</tr>
</tbody>
</table>

*Prior therapy included only an anthracycline

## Vinorelbine Monotherapy Following Anthracyclines and Taxanes

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Phase</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelek</td>
<td>40</td>
<td>II</td>
<td>6 (TTP)</td>
<td>6</td>
<td>25%</td>
</tr>
<tr>
<td>Livingston*</td>
<td>40</td>
<td>II</td>
<td>3.3 (TTP)</td>
<td>8.3</td>
<td>25%</td>
</tr>
<tr>
<td>Martin</td>
<td>126</td>
<td>III</td>
<td>4</td>
<td>16.4</td>
<td>26%</td>
</tr>
<tr>
<td>Degardin†</td>
<td>100</td>
<td>II</td>
<td>3 (TTF)</td>
<td>23.5</td>
<td>16%</td>
</tr>
<tr>
<td>Terzoli*†</td>
<td>80</td>
<td>II</td>
<td>9 (TTP)</td>
<td>19</td>
<td>52.5%</td>
</tr>
</tbody>
</table>

* *Required GCSF support*  
† *Prior therapy included only an anthracycline*

References:
## Capecitabine Monotherapy Following Anthracyclines and Taxanes

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Phase</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum</td>
<td>135</td>
<td>II</td>
<td>3.1 (TTP)</td>
<td>12.6</td>
<td>20%</td>
</tr>
<tr>
<td>Venturini</td>
<td>631</td>
<td>III</td>
<td>6.6 (TTP)</td>
<td>10</td>
<td>34.7%</td>
</tr>
<tr>
<td>Miller</td>
<td>230</td>
<td>III</td>
<td>4.2</td>
<td>14.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Thomas</td>
<td>377</td>
<td>III</td>
<td>4.2</td>
<td>11.1</td>
<td>14%</td>
</tr>
<tr>
<td>Reichardt</td>
<td>136</td>
<td>II</td>
<td>3.5 (TTP)</td>
<td>10.1</td>
<td>15%</td>
</tr>
<tr>
<td>Fumoleau</td>
<td>126</td>
<td>II</td>
<td>4.9 (TTP)</td>
<td>15.2</td>
<td>28%</td>
</tr>
</tbody>
</table>

Venturini M et al. Oncology. 2007;72(1-2):51-7
## Phase III Trials of Capecitabine ± Ixabepilone in Patients Previously Treated With an Anthracycline and Taxane

<table>
<thead>
<tr>
<th>Previous Chemo</th>
<th>Anthracycline &amp; Taxane “Resistant” ¹</th>
<th>Anthracycline &amp; Taxane “Pretreated” ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 total</td>
<td></td>
<td>≤ 2 total</td>
</tr>
<tr>
<td>Placebo Controlled</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>n</td>
<td>752</td>
<td>1221</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Capecitabine (C) 2000 mg/m² daily × 14 days ± Ixabepilone (I) 40 mg/m² Q3 weeks</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>PFS</td>
<td>OS</td>
</tr>
</tbody>
</table>

### Phase III Trials of Capecitabine ± Ixabepilone: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Anthracycline &amp; Taxane “Resistant” $^{1,3}$</th>
<th>Anthracycline &amp; Taxane “Pretreated” $^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>C + I</td>
<td>C + I</td>
</tr>
<tr>
<td>PFS, mo</td>
<td>5.8</td>
<td>6.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.75, $p = 0.0003$</td>
<td>0.79, $p = 0.005$</td>
</tr>
<tr>
<td>OS, mo</td>
<td>12.9</td>
<td>16.4</td>
</tr>
<tr>
<td>HR</td>
<td>0.9, $p = 0.19$</td>
<td>0.9, $p = 0.1162$</td>
</tr>
<tr>
<td>ORR</td>
<td>35%</td>
<td>43%</td>
</tr>
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</table>

### Phase III Trial of Capecitabine ± Ixabepilone: Safety

<table>
<thead>
<tr>
<th>Selected grade ≥ 3 AEs, %</th>
<th>Capecitabine + Ixabepilone</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>68</td>
<td>11</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Phase II Trial of Ixabepilone in Anthracycline, Taxane and Capecitabine Refractory Patients

- MBC or LABC
- Resistance: disease progression while receiving therapy for MBC or recurrence within 6 months of neo/adjuvant
- n = 113
- Primary end point - ORR by IRF
  - ORR – 11.5%
- Secondary endpoint – PFS
  - 3.1 mo

Eribulin Mesylate (Halaven™)

- Novel microtubule inhibitor
  - Prevents spindle formation
- Synthetic analogue of halichondrin B (sea sponge)
- Given as IV bolus (2-5 min), days 1 and 8 q 21 days
  - Incompatible with dextrose
  - Dose reduce in mild/moderate hepatic dysfunction
  - Dose reduce for CrCl < 50 mL/minute
- Negligible CYP3A4 activity
  - excreted unchanged in feces
  - no active metabolites
Phase III Trial of Eribulin vs Treatment of Physician’s Choice (EMBRACE)

MBC
- Heavily pretreated (median 4 regimens), at least 2 for MBC
- Previous anthracycline and taxane-based chemo

Primary endpoint
- OS by IRF

Stratification
- Geographic region
- Previous capecitabine treatment
- HER2 status

Eribulin 1.4 mg/m²
days 1, 8 q 21 days
(n=508)

Treatment of Physician’s Choice (TPC)
Any monotherapy approved for cancer treatment - 97% received chemo
(n = 254)

### Phase III Trial of Eribulin vs TPC: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Eribulin</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, mo</td>
<td>13.1</td>
<td>10.7</td>
</tr>
<tr>
<td>HR</td>
<td>0.81, p = 0.041</td>
<td></td>
</tr>
<tr>
<td>PFS, mo</td>
<td>3.7</td>
<td>2.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.85, p = 0.14</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>12%</td>
<td>5%</td>
</tr>
</tbody>
</table>

# Phase III Trial of Eribulin vs TPC: Safety

<table>
<thead>
<tr>
<th>Selected grade ≥ 3 AEs, %</th>
<th>Eribulin</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>45</td>
<td>21.1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Asthenia / fatigue</td>
<td>8.8</td>
<td>10.1</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>8.2</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.6</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Phase II Trial of Paclitaxel-albumin bound in Taxane Refractory MBC

- MBC - disease progression while receiving taxane-based treatment for MBC (or within 12 months of adjuvant treatment)
- > 50% of patients received adjuvant anthracyclines
- 100 mg/m² (n=106) or 125 mg/m² (n=75) given on days 1, 8, 15 q 28 days
- Primary endpoint – ORR
  - 14.1% and 16% respectively
- Secondary endpoint – PFS
  - 3 mo and 3.5 mo respectively

CD is a 54 yo female who received FEC x 4 cycles followed by weekly paclitaxel x 12 cycles as neoadjuvant treatment of her locally advanced, HER2(−) breast cancer. Six months after surgery and radiation, CD is diagnosed with metastatic disease in her chest wall. Which of the following monotherapy treatment options would be most appropriate for CD?

1. Capecitabine
2. Ixabepilone
3. Paclitaxel-albumin bound
4. Vinorelbine
Chemotherapy Options for Anthracycline and Taxane Refractory MBC - Summary

- Phase III data exists:
  - Capecitabine
  - Capecitabine + Ixabepilone
  - Vinorelbine
  - Eribulin
- Combination therapy may ↑ ORR and ↑ PFS
- Expected toxicity (cost?) influence treatment choice
- No head-to-head monotherapy comparisons
- Anthracycline, taxane and capecitabine refractory
  - Ixabepilone
  - Eribulin
Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- Compare and contrast targeted therapies for the treatment of HER2(+) MBC
- Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability
- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile
“PARP” Inhibitors

- Key mechanisms of DNA repair:
  - BRCA1 / BRCA2 pathway
    - homologous recombination (HR) of double strands
  - PARP1 - poly (ADP-Ribose) polymerase 1
    - base excision repair (BER) of single strand breaks

- PARPs:
  - Large family of multifunctional enzymes
  - Most abundant is PARP1

- Characteristics of triple negative breast cancer (TNBC)
  - Shares common features of hereditary BRCA1
  - PARP1 up-regulated

- Analogy of table with 4 legs

- Agents: olaparib, veliparib, iniparib
Mechanisms of DNA Repair

DNA Damage = Single-strand breaks

- X-rays
- Chemotherapy
- Oxygen radicals
- Spontaneous reactions

A: Normal cell
   - BER
   - HR
   - DNA repair
   - Cell lives

B: BRCA mutation
   - BER
   - HR
   - DNA repair
   - Cell lives

C: PARP deficient
   - BER
   - HR
   - DNA repair
   - Cell lives

D: BRCA mutation + PARP deficient
   - BER
   - HR
   - DNA repair
   - Cell death
Randomized Phase II Trial of Gem/Carbo ± Iniparib in Triple-Negative MBC

MBC
- ≤ 2 previous chemotherapies for MBC
- No prior gemcitabine, platinum agent, or PARP inhibitor

Primary endpoint
- Clinical benefit rate (CBR)

Stratification
- NR

Randomize

Iniparib 5.6 mg/kg IV, Days 1, 4, 8, 11 + Gemcitabine 1000 mg/m² + Carboplatin AUC = 2, Days 1, 8 q 21 days (n = 61)

Crossover to experimental arm allowed at progression

Gemcitabine 1000 mg/m² + Carboplatin AUC = 2, Days 1, 8 q 21 days (n = 62)

### Phase II Trial of Gem/Carbo ± Iniparib in Triple-Negative MBC: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Iniparib + Gem/Carbo</th>
<th>Gem/Carbo</th>
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</thead>
<tbody>
<tr>
<td><strong>CBR</strong></td>
<td>56%</td>
<td>34%</td>
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<tr>
<td><strong>p value</strong></td>
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<td>0.01</td>
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<tr>
<td><strong>OS, mo</strong></td>
<td>12.3</td>
<td>7.7</td>
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<tr>
<td><strong>HR</strong></td>
<td>0.57, p = 0.01</td>
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<tr>
<td><strong>PFS, mo</strong></td>
<td>5.9</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.59, p = 0.01</td>
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</table>

### Phase II Trial of Gem/Carbo ± Iniparib in Triple-Negative MBC: Safety

<table>
<thead>
<tr>
<th>Selected grade ≥ 3 AEs, %</th>
<th>Iniparib + Gem/Carbo</th>
<th>Gem/Carbo</th>
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</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>19</td>
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<tr>
<td>Diarrhea</td>
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<td>2</td>
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<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Anemia</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>Febrile neutropenia²</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Trastuzumab-DM1 - “T-DM1”

- Trastuzumab linked to “DM1” – derivative of antimicrotubule inhibitor maytansanine
- Phase I\(^1\), n = 24
  - Progressed on prior trastuzumab
  - 3.6 mg/kg IV q 21 days - MTD
  - Grade 4 thrombocytopenia - DLT
- Phase II\(^2\), n = 112
  - Single arm, previous targeted therapy for MBC with disease progression (RECIST) within 60 days of last treatment
  - ORR – 25.9%, PFS – 4.6 mo
  - Grade 3 or worse AE: hypokalemia (8.9%), thrombocytopenia (8%), fatigue (4.5%)

MK is a 44 yo female with a PMH of triple negative breast cancer for which she received adjuvant anthracycline and taxane-based regimens. Following diagnosis of MBC, MK received capecitabine + bevacizumab for MBC. Her disease has now progressed. Which of the following treatment options has exhibited minimal toxicity and a possible survival advantage in the treatment of triple negative MBC?

1. Eribulin
2. Trastuzumab-DM1
3. Ixabepilone
4. PARP1 inhibitor + chemotherapy
Thank You

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