## Conference Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30 AM</td>
<td>Registration &amp; Exhibits</td>
<td></td>
</tr>
<tr>
<td>8:00 AM</td>
<td>Welcome</td>
<td>M. Yair Levy, MD</td>
</tr>
<tr>
<td>8:15 AM</td>
<td>Non-Cutaneous T-Cell Lymphomas</td>
<td>Estil A. Vance III, MD</td>
</tr>
<tr>
<td>8:45 AM</td>
<td>How I Treat Sickle Cell Disease</td>
<td>Mark Holguin, MD</td>
</tr>
<tr>
<td>9:15 AM</td>
<td>Coffee &amp; Conversation</td>
<td></td>
</tr>
<tr>
<td>9:30 AM</td>
<td>Myeloma: New Strategies, New Therapies</td>
<td>Christopher Maisel, MD</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>Updates in CLL</td>
<td>R. Brian Berryman, MD</td>
</tr>
<tr>
<td>10:30 AM</td>
<td>Approach to Diagnosing &amp; Treating Thrombophilia</td>
<td>Barry Cooper, MD</td>
</tr>
<tr>
<td>11:00 AM</td>
<td>Coffee &amp; Conversation</td>
<td></td>
</tr>
<tr>
<td>11:15 AM</td>
<td>Non-chemotherapeutic Management of Hematologic Malignancies</td>
<td>Christian T. Cable, MD, MHPE</td>
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<tr>
<td>12:15 PM</td>
<td>Lunch</td>
<td></td>
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<tr>
<td>1:00 PM</td>
<td>Current Approach in the Treatment of CML</td>
<td>M. Yair Levy, MD</td>
</tr>
<tr>
<td>1:30 PM</td>
<td>Current Approach in the Treatment &amp; Management of MDS</td>
<td>Micah M. Burch, MD</td>
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<tr>
<td>2:00 PM</td>
<td>Coffee &amp; Conversation</td>
<td></td>
</tr>
<tr>
<td>2:15 PM</td>
<td>AML: What’s New</td>
<td>Edward D. Agura, MD</td>
</tr>
<tr>
<td>2:45 PM</td>
<td>Closing Remarks</td>
<td>Christian T. Cable, MD, MHPE</td>
</tr>
</tbody>
</table>
Course Directors

M. Yair Levy, MD
Medical Director, Hematologic Malignancy Clinical Research
Baylor Charles A. Sammons Cancer Center
Assistant Professor of Internal Medicine, Texas A&M College of Medicine
Dallas, TX

Christian T. Cable, MD, MHPE
Hematology/Oncology Fellowship Director
Scott & White Memorial Hospital
Associate Professor of Medicine
Texas A&M University College of Medicine
Temple, TX

Speakers

Edward D. Agura, MD
Director, Blood and Marrow Transplantation Program
Baylor Charles A. Sammons Cancer Center
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R. Brian Berryman, MD
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Baylor Charles A. Sammons Cancer Center
Dallas, TX

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Dallas, TX

Barry Cooper, MD
Medical Director, Clinical Hematology
Baylor Charles A. Sammons Cancer Center
Dallas, TX
Speakers (continued)

Mark Holguin, MD  
Clinical Oncology  
Scott & White Health System  
Temple, TX

Christopher Maisel, MD  
Texas Oncology  
Baylor Charles A. Sammons Cancer Center  
Dallas, TX

Estil A. Vance III, MD  
Co-Director, CTCL Clinic  
Baylor-Charles A. Sammons Cancer Center  
Medical Director, National Marrow Donor Program Donor Center  
Baylor University Medical Center at Dallas  
Dallas, TX
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Christopher Maisel, MD received honoraria as a member of the speaker’s bureau from Millennium and Onyx.

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- submit completed evaluation form
- submit a completed onsite survey
- submit a completed credit claim form.

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ACKNOWLEDGMENT OF GRANT FUNDING SUPPORT

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Exhibitors

- Bristol-Myers Squibb
- Genentech
- Gilead
- IncyteCARES
- Takeda
- Millennium
- Novartis Oncology
Exhibitors

ARIAD
Blood & Marrow Transplant
Baylor University Medical Center at Dallas
ONYX Pharmaceuticals
Non-Cutaneous T-Cell Lymphomas

Estil A. Vance III, MD
Update on Non-Cutaneous T-cell Lymphoma

Disclosures

• I have served on a Central Adjudication Committee for a Chimerix antimicrobial trial (2012).
• I am on the Celgene speakers bureau.

Goals

• Review current therapies for PTCL.
• Review changes to treatment over the year.
• Look at evolving therapies and research options.
Non-Hodgkin’s Lymphoma

- Follicular (25%)
- Small lymphocytic (7%)
- MALT type marginal zone B cell (7.5%)
- Nodal type marginal zone B cell (< 2%)
- Diffuse large B cell (30%)
- T and NK cell (12%)
- Other subtypes (9%)
- Burkitt (2.5%)
- Mantle cell (8%)
- Follicular (20%)
- Small lymphocytic (7%)
- MALT type marginal zone B cell (7.5%)
- Nodal type marginal zone B cell (< 2%)

**PTCL Subtypes**

**Category**  | **Neoplasm**
---|---
Leukemic  | T-cell prolymphocytic leukemia
          | T-cell large granular lymphocytic leukemia
          | Adult T-cell leukemia/lymphoma (HTLV-1 positive)
          | Aggressive NK-cell leukemia
          | Epstein-Barr virus–positive T-cell lymphoproliferative disorders of childhood
Extranodal  | NKT-cell lymphoma, nasal type
          | Enteropathy-associated T-cell lymphoma
          | Hepatosplenic T-cell lymphoma
Nodal       | Anaplastic large-cell lymphoma (ALK+ or ALK-)
          | Angioimmunoblastic T-cell lymphoma
          | Peripheral T-cell lymphoma, not otherwise specified
Cutaneous   | See later slides

**International T-Cell Lymphoma Project: Frequency of PTCL Subtypes**

- Peripheral T-cell lymphoma (2.5%)
- Angioimmunoblastic (0.9%)
- NKT-cell lymphoma (1.4%)
- Adult T-cell leukemia/lymphoma (1.7%)
- ALCL, ALK+ (25.9%)
- ALCL, ALK- (12.2%)
- Enteropathy-associated T cell (6.6%)
- Primary cutaneous ALCL (6.6%)
- Hepatosplenic T cell (5.5%)
- Subcutaneous panniculitis-like (4.7%)
- Unclassifiable PTCL (9.6%)
- Other disorders (18.5%)
- Unclassifiable PTCL (9.6%)


PTCL: Diagnosis

- ~10% of PTCL cases are incorrectly diagnosed\(^1\)
- Most patients are stage III/IV
- Extranodal involvement common: skin, liver, spleen, bone marrow, peripheral blood
- Diagnosis of PTCL involves immunophenotypic analysis in conjunction with cellular morphology, analysis of lymph node architecture, and molecular genetic assays\(^2,3\)
- Excisional biopsy is usually required; fine needle is not adequate\(^4\)


PTCL Prognosis by Subtype

- OS varies according to subtype and median ranges from 1-3 yrs

Prognostic Indices

- The IPI is useful in ALCI but tends to cluster in intermediate-high and above in other subtypes. It also underestimates poor prognoses associated with enteropathy-type T-cell NHL and NK cell.
- An Italian model showed age>60, LDH, KPS, and marrow involvement to be predictive. Ki67 was later substituted for marrow involvement.
- The ITLP found that age, KPS, and platelet count were predictive.
- All 3 generate similar predictive power.
### Identifying Poor-Risk Patients: Prognostic Indices for PTCL

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>IPI 1</th>
<th>Age-Adjusted IPI 1 (Age ≤ 60 Yrs)</th>
<th>PIT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 60 yrs</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Serum LDH &gt; 1 x normal</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Performance score 2-4</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Extranodal involvement &gt; 1 site</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

#### Number of Risk Factors

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>IPI 1</th>
<th>Age-Adjusted IPI 1 (Age ≤ 60 Yrs)</th>
<th>PIT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Low</td>
<td>Group 1</td>
</tr>
<tr>
<td>1</td>
<td>Low intermediate</td>
<td>High</td>
<td>Group 2</td>
</tr>
<tr>
<td>2</td>
<td>Low intermediate</td>
<td>High intermediate</td>
<td>Group 3</td>
</tr>
<tr>
<td>3</td>
<td>High intermediate</td>
<td>High</td>
<td>Group 4</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>


Outcomes are worse with high IPI in all subgroups.

### Survival by Histologic Subtype Based on the IPI

<table>
<thead>
<tr>
<th>Diagnosis, %</th>
<th>5-Yr OS</th>
<th>5-Yr FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPI 0/1</td>
<td>IPI 4/5</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>Angioimmunoblastic</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>ALCL, ALK+</td>
<td>90</td>
<td>33</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>74</td>
<td>13</td>
</tr>
</tbody>
</table>

Outcomes are worse with high IPI in all subgroups.

### Importance of Stratifying Patients by Prognostic Score: OS

[Graph showing survival by IPI for PTCL-U and Prognostic Index for PTCL-U (N = 322)]
Problems in Characterizing Peripheral T-Cell Lymphomas

- Difficulty in establishing clonality
- Variable immunological patterns
- Cytogenetics only occasionally characteristic
- Few characteristic oncogenes

Distinct Gene Signatures for Different Core Groups of PTCL and NKCL

PTCL GEP: Conclusions to Date

- AITL, ALCL, ATLL, and NKCL have robust, reproducible signatures
- PTCL-U seems to have 3 or 4 subgroups and is not yet clearly defined
- 20% of patients with PTCL-U (9/44) redefined as AITL by gene profiling
Current Treatment of PTCL

- Guidelines are generalized and recommend clinical trial at all stages[1,2]
- Current (old) approach using CHOP-like regimens has largely not been successful
- Finally . . . not all subsets are treated the same
  - NK/T cell, EATL have distinct treatment algorithms
- Not enough molecular data are available yet on the biology of these diseases to inform treatment choices, especially for relapsed patients

Guidelines for PTCL Subtypes: PTCL-NOS; ALCL, ALK-; AITL; and EATL

- All Stages
  - clinical trial (preferred) or 6 cycles multi-agent chemotherapy ± locoregional radiotherapy (30-40 Gy)
    - CR: clinical trial, HDT with stem cell rescue, or observation
    - PR, no response, or progression: clinical trial or second-line therapy; transplantation if eligible/responsive disease (CR or PR)
  - At completion of induction, complete all positive studies. If PET-CT+, rebiopsy before changing therapy.

Treatment Guidelines for PTCL: Still CHOP Based

**First-line Therapy**
- Clinical trial (preferred)
- ALCL, ALK+ history
- CHOEP-21
- CHOP-P2
- Other histologies (ALCL, ALK-, PTCL-NOS, AITL, EATL) regimens that can be used include:
  - CHOEP
  - CHOEP-14
  - CHOP-21
  - CHOP followed by ICE
  - CHOP followed by ICE, alternating with intermediate-dose methotrexate (Newcastle regimen). Studied only in EATL
  - DA-EPOCH
  - HyperCVAD, alternating with high-dose methotrexate and cytarabine

**First-line Consolidation**
All patients should be considered for high-dose therapy and stem cell rescue. ALCL, ALK+ is a subtype with good prognosis and does not need consolidative transplant if in remission.
OS in Anaplastic Large Cell Lymphoma, All Ages

<table>
<thead>
<tr>
<th>ALK Population, n</th>
<th>Censored</th>
<th>Failed</th>
<th>Total</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK negative</td>
<td>38</td>
<td>33</td>
<td>71</td>
<td>4.48</td>
</tr>
<tr>
<td>ALK positive</td>
<td>54</td>
<td>23</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing OS in ALCL, ALK negative vs. ALK positive]

ALCL Associated with Breast Implants

- Most are stage I (49/59), confined to fibrous capsule.
- Optimal therapy is still debated.
- Removal of the implant and capsule is recommended.
- Poorer outcome with evidence of disease beyond stage I or if grossly evident tumor mass.
- Role of chemotherapy debated for early disease.

Meta-analysis of Anthracycline-Based Therapy in PTCL: Need for Better Therapy

- Data from 31 studies (n = 2815)
- Efficacy for PTCL excluding ALK+ ALCL
  - CR: 50.1% (95% CI: 44.9-55.3)
  - 5-yr DS: 36.6% (95% CI: 31.5-42.0)

![Graph showing OS in PTCL, anthracycline as part of initial treatment]

International T-cell Lymphoma Project

- [Reference to studies and guidelines]
Etoposide in Initial Treatment of PTCL: GHGLSG

- 343 pts (289 with ALCL, PTCL-NOS, AITL)
- Treatment with 6-8 cycles of CHOP or CHOEP
  - Nonrandomized
  - Various doses/schedules
- Median follow-up: 43.8 mos
- CHOP-21 remained "standard" for older pts (> 60 yrs)


German High-Grade Lymphoma Study Group: T-Cell Lymphoma Cohort Analysis

- 320 patients with mature nodal or extranodal T-cell or NK-cell lymphoma treated on 7 phase II or III studies (1993-2007)
  - ALK positive: 78 patients (24.4%)
  - ALK negative: 113 patients (35.3%)
  - Treated with CHOP ± etoposide: 100%
- Patients younger than 60 yrs of age with normal LDH
  - Addition of etoposide to CHOP improved 3-yr EFS: 75% vs 51% with CHOP alone (P = .003)


Etoposide in Initial Treatment of PTCL (GHGLSG): EFS

- CHOP-21 vs CHOEP-21
  - Pts (18-60 yrs)
  - EFS (%)

No Etoposide (n = 41)
- Etoposide (n = 103)
- P = .004

P vs 1010 20 30 40 50 60 70 80 90100

Time (mos)
Guidelines for Extranodal NK/T-Cell Lymphoma

- If stage I and NO risk factors, Clinical trial, RT alone, concurrent chemoradiotherapy or sequential chemo-radiotherapy.
- If Stage II or stage I with any risk factor, Concurrent or sequential chemoradiotherapy.
- If nasal stage IV or extranasal I,II, or IV, clinical trial, concurrent chemoradiotherapy, or chemotherapy chemotherapy
- Risk factors include age>60, B sx, PS>2, high LDH, regional nodal involvement, local tumor invasion (bone or skin), high Ki67 or EBV>6x10^7 copies/mL

Suggested treatment regimens

- Combination chemotherapy (L-asparaginase based)
  - Dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide (SMILE)
  - L-asparaginase, methotrexate, dexamethasone (AspaMetDex)
- Concurrent chemoradiotherapy (CCRT)
  - 50 Gy RT + 3 courses dexamethasone, etoposide, ifosfamide, carboplatin (DeVIC)
  - 40 to 52.8 Gy RT + cisplatin followed by 3 cycles etoposide, ifosfamide, cisplatin, dexamethasone (VIPD)
- Sequential is SMILE or VIPD followed by 45-50.4 Gy
- Radiotherapy alone: ≥ 50 Gy

Suggested treatment regimens post induction

- If nasal/stage I without risk factors
  - CR=> Observe
  - PR=> Consider HSCT (allogeneic preferred)
  - Refractory=> Supportive care vs Salvage; if responds, consider HSCT (allogeneic preferred)
- If nasal/stage II,IV or extranasal I,II, or IV
  - CR or PR=> Consider HSCT (allogeneic preferred)
  - Refractory=> Supportive care or salvage chemotherapy
Enteropathy-Associated T-cell Lymphoma

• Doxorubicin based chemotherapy at least initially.
• Critical role of nutritional support
• Gluten-free diet in Celiac associated dz.
• EBMT data showing 4 yr OS and DFS of 59% and 54%, likely best in CR1 (66% vs 36%, p=0.06)

Subcutaneous Panniculitis-like T-cell Lymphoma

• αβ vs γδ.
• αβ is associated with OS 82% at 5yrs and relatively low rates of HPS (17%, though HPS carries a poor px 46% with vs 91%).
• γδ is associated with a 5yr OS of 11% and is now classified as cutaneous T-cell lymphoma.
• Anthracycline-based rx remains standard perhaps in combination with XRT or surgery.

Enteropathy-Associated T-Cell Lymphoma: The Newcastle Regimen

• Newcastle regimen: CHOP x 1, followed by IVE (ifosfamide, etoposide, epirubicin, methotrexate), followed by ASCT

<table>
<thead>
<tr>
<th></th>
<th>5-Yr PFS, %</th>
<th>5-Yr OS, %</th>
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<tbody>
<tr>
<td>Chemo*</td>
<td>Newcastle</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>52</td>
</tr>
<tr>
<td>Conventional chemotherapy</td>
<td>22</td>
<td>52</td>
</tr>
</tbody>
</table>

*Anthracycline-based
OS in PTCL by Response at Time of Stem Cell Transplantation

- Retrospective analysis of 82 patients with PTCL who received high-dose therapy
- Transplantation in chemoresponsive patients produced superior 3-yr OS
  - Chemoresponsive: 58%
  - Chemoresistant: 36%
  - \( P = .007 \)


**OS by Status at Transplantation**

<table>
<thead>
<tr>
<th>CR1 (n = 31)</th>
<th>CR2/PR/SD (n = 19)</th>
<th>PD (n = 14)</th>
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<tbody>
<tr>
<td>0-2 yrs</td>
<td>20</td>
<td>20</td>
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<tr>
<td>2-4 yrs</td>
<td>40</td>
<td>40</td>
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<tr>
<td>4-6 yrs</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>6-8 yrs</td>
<td>80</td>
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Autologous SCT in First Remission: Prospective Data

<table>
<thead>
<tr>
<th>Study Author (Yr)</th>
<th>n</th>
<th>Regimen</th>
<th>Transplanted, %</th>
<th>Outcomes, %</th>
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<tbody>
<tr>
<td>Corradini (2006)</td>
<td>62</td>
<td>Mitoxantrone/ melphalan or BEAM</td>
<td>73</td>
<td>12-yr EFS: 30 12-yr OS: 34</td>
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<tr>
<td>Rodriguez (2007)</td>
<td>26</td>
<td>MegaCHOP ± IFE</td>
<td>73</td>
<td>3-yr PFS: 56 3-yr OS: 84</td>
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<tr>
<td>Mercadal (2008)</td>
<td>41</td>
<td>High-dose CHOP/ESHAP</td>
<td>41</td>
<td>4-yr PFS: 30 4-yr OS: 39</td>
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<tr>
<td>Reimer (2009)</td>
<td>83</td>
<td>dexamBEAM or ESHAP ± TBI</td>
<td>66</td>
<td>3-yr PFS: 36 3-yr OS: 48</td>
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<tr>
<td>d’Amore (2011)</td>
<td>160</td>
<td>CHDEP-14 x 6 ± BEAM/BEAC</td>
<td>71</td>
<td>5-yr OS: 51 5-yr PFS: 44</td>
</tr>
</tbody>
</table>

**Activity of Single Agents in PTCL**

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Pts</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>Duration, mo</th>
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<tbody>
<tr>
<td>O’Connor[1]</td>
<td>Pralatrexate</td>
<td>109</td>
<td>29</td>
<td>11</td>
<td>PFS: 3.5</td>
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<tr>
<td>Czuczman[4]</td>
<td>Nelarabine</td>
<td>19</td>
<td>10.5</td>
<td>0</td>
<td>EFS: 1.2</td>
</tr>
<tr>
<td>Enblad[5]</td>
<td>Alemtuzumab</td>
<td>14</td>
<td>36</td>
<td>21.4</td>
<td>2, 6, 12*</td>
</tr>
<tr>
<td>Dearden[6]</td>
<td>Pentostatin (ATLL)</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Zinzani[7]</td>
<td>Gemcitabine</td>
<td>20</td>
<td>55</td>
<td>30</td>
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<tr>
<td>Pollianne[8]</td>
<td>Vitaxin</td>
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<td>25</td>
<td>10</td>
<td>9</td>
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<tr>
<td>Friedberg[9]</td>
<td>Alisertib</td>
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<td>Not reported</td>
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<td>Damaj[10]</td>
<td>Bendamustine</td>
<td>38</td>
<td>47</td>
<td>29</td>
<td>5</td>
</tr>
</tbody>
</table>

*Pts achieving CR.

**Novel Therapies for PTCL**

**Pralatrexate**

- Pralatrexate is a new class of antifolate
  - Inhibitor of dihydrofolate reductase
  - Preclinical enhanced activity with gemcitabine
  - Primary AEs noted in phase I study: stomatitis, thrombocytopenia (DLT)
  - ORR: 54%, including 8 CR/CRu of 26 evaluated pts with PTCL

**PROPEL: Phase II Study of Pralatrexate in Relapsed/Refractory PTCL**

- Pivotal international study to evaluate pralatrexate with vitamin B12 and folate in relapsed/refractory PTCL
- Primary endpoint: ORR
  - September 2009: FDA approved use of pralatrexate in relapsed/refractory PTCL
  - Pts, N 115
  - Median age, yrs 58
  - Median number of previous therapies 3
  - Previous treatment, %
    - CHOP 70%
    - ASCT 16%
  - ORR, % 29
  - CR, % 10
  - Grade 3/4 toxicities, %
    - Thrombocytopenia 33
    - Mucositis 24
Romidepsin (Depsipptide) in Relapsed T-cell Lymphoma

<table>
<thead>
<tr>
<th>Response</th>
<th>CTCL Registration (N = 96)</th>
<th>PTCL Registration (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>CR/CRu, %</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>PR, %</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Duration of response, mos</td>
<td>15.0</td>
<td>16.6</td>
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</tbody>
</table>

June 2011: FDA approved use of romidepsin in patients with PTCL who received at least 1 previous therapy.

Romidepsin: Responses by PTCL Subgroup

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Response, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL, unspecified or not classified</td>
<td>20/69 (29)</td>
</tr>
<tr>
<td>ATLL</td>
<td>8/27 (30)</td>
</tr>
<tr>
<td>ALCL, ALK−</td>
<td>5/21 (24)</td>
</tr>
<tr>
<td>Other subgroups</td>
<td>0/13 (0)</td>
</tr>
</tbody>
</table>

Belinostat

- Pan-HDAC inhibitor (inhibits all 3 types of Zn-dependent histone deacetylators).
- BELIEF Trial: 129 relapsed or refractory PTCL (no prior HDACi, >100 days from auto to relapse).
  - 1,000 mg/m2 IV daily, days 1-5 of a 21 day regimen
  - ORR 26% (CR 11%, PR 15%).
  - By type, ORR PTCLNOS-23%, NKT-50%, ATLL-45%, and Alk-neg ALCL 15%. 2 cases each EATL, Alk+ALCL, and HSTCL without response.
  - Stratified by baseline platelet count (<100K), PFS 1.8 vs 1.3 mos and OS 9.2 vs 4.3 mos.
  - Primarily GI sx/constitutional, thrombocytopenia and neutropenia.

On July 3, 2014, the U. S. Food and Drug Administration granted accelerated approval to belinostat (BELEODAQ, Spectrum Pharmaceuticals, Inc.) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).
Brentuximab Vedotin in Rel/Ref sALCL: Responses

- Clinical responses to brentuximab vedotin appear durable
- Low CR rates associated with a few baseline factors
  - Bone-marrow involvement: 14% vs 63% no involvement
  - ALK− disease: 55% vs 69% ALK+
  - Failure to respond to previous therapy: 38% vs 63% with previous response
  - 1 previous therapy: 25% vs 64% with > 1 previous therapy
  - No previous ASCT: 53% vs 73% with previous ASCT

### Outcome

| Brentuximab vedotin (n = 58) |  
|-----------------------------|---
| ORR, % (95% CI)             | 86 (74.6-93.9)  
| Median duration of response, mos (95% CI) | 12.6 (5.7-NE)  
| CR, % (95% CI)              | 57 (43.2-69.8)  
| Median duration of CR, mos (95% CI) | 13.2 (10.8-NE) 


Brentuximab Vedotin in Rel/Ref sALCL: Other Results

- Median PFS: 14.3 mos with brentuximab vedotin vs 5.9 mos on last previous therapy
  - HR: 0.48; P = .001
  - PFS not related to ALK status
- Median OS not yet reached
  - Estimated 1-yr OS: 70%
- Median follow-up from first dose: 14.7 mos

- AEs
  - Most grade 1-2
  - Few cases of grade 4 neutropenia and fatigue
  - Peripheral neuropathy in 53% of pts
    - Median time to onset was 13.3 wks
    - Resolved or improved in 81% of cases
    - Managed through dose delays, reductions to 1.2 mg/kg

Evolving Therapies for PTCL

Crizotinib

- ALK+ ALC is characterized by the NPM1-ALK fusion in most cases leading to ALK overexpression.
- Crizotinib is a small molecule TKI (ALK domain) with known activity in EML4-ALK fusion NSCLC.
- ASH 2013- 14 ALK1+ ALC and one DLBCL (advanced, resistant) treated with ORR 60%. 4/15 gr 4 SAE’s (abd pain, increased CPK, lymphopenia, and one MOF).
- Monitor for bradycardia, hepatic dysfunction, QT prolongation, and interstitial lung disease.

Approval Only in ALK+ NSCLC. Use in ALC Currently Off Label.

Lenalidomide

- 3 phase II trials in patients with refractory/relapsed PTCL
- ORR from 22% to 30%
- Trend towards better in AITL
Mogamulizumab

- Targeted against CCR4 expressed in ATLL and some PTCL.
- 50% ORR in relapsed ATLL with OS 13.7 mos.
- Neutropenia and thrombocytopenia in 35%. IRAE 22% (gr2).

<table>
<thead>
<tr>
<th>Lymphoma subtypes</th>
<th>N</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>CR</th>
<th>ORR (95% CI)</th>
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<tbody>
<tr>
<td>PTCL</td>
<td>29</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>10</td>
<td>54% (18-54)</td>
</tr>
<tr>
<td>PTCL-AOS</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>7</td>
<td>46%</td>
</tr>
<tr>
<td>ATLL</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>50%</td>
</tr>
<tr>
<td>A.L.L. AOS-1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>CTCL</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>33% (9-78)</td>
</tr>
<tr>
<td>MF</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>29%</td>
</tr>
<tr>
<td>C-ALCL</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>5</td>
<td>8</td>
<td>18</td>
<td>11</td>
<td>55% (20-83)</td>
</tr>
</tbody>
</table>

CHOP-Bortezomib in T-cell Lymphomas

- 46 pts with PTCL
  - NOS-16, eNK/T-10, CTCL-5
- Stage IV: 69.6%
- IPI (high/high intermediate): 54%
- ORR: 76%
- CR: 65%
- Most common grade 3/4 toxicities were thrombocytopenia and febrile neutropenia

Gemcitabine+Bortezomib

- 32 patients with refractory/relapsed DLBCL and PTCL (16 each)
- Bortezomib 1.6 mg/m2 + Gemcitabine 800 mg/m2 days 1,15 of a 28 day cycle
- Initial 1, 8 q 21 not tolerated
- ORR 36% (CR 27%)
- 6 patients ITT on modified schedule with ORR 50% (CR30%)
- Poor activity in DLBCL (ORR 10%)
Tipifarnib in T-Cell NHL

- Farnesyl transferase needed for prenylation of proteins enhancing malignant cell growth
- Tipifarnib: farnesyl transferase inhibitor
- Dose 300 mg orally BID on Days 1-21 of 28-day cycle
- T-cell NHL: n = 12/93
  - ORR 50%: equal numbers of CR and PR
- Median TTP: 3.6 mos
- Grade 3/4 toxicities: fatigue (10%), neutropenia (37%), anemia (11%), thrombocytopenia (32%)


Alisertib in Aggressive B-cell and T-cell NHL: Response

- ORR: 32% (95% CI: 18-48) in overall population and responses observed in all histologic disease subtypes

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Pts (N = 41)</th>
<th>ORR by Histology, %</th>
<th>Pts</th>
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<tbody>
<tr>
<td>ORR</td>
<td>32</td>
<td>B-cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DLBCL</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCL</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transformed FL</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burkitt’s lymphoma</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-cell</td>
<td>57</td>
</tr>
<tr>
<td>CR</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>39</td>
<td></td>
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</tr>
<tr>
<td>PD</td>
<td>20</td>
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ORR by Histology,*

<table>
<thead>
<tr>
<th>Pts</th>
</tr>
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<tbody>
<tr>
<td>B-cell</td>
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</tr>
<tr>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>T-cell</td>
</tr>
</tbody>
</table>

*ORR: PR + CR.

Richard Fisher MD, MD Clinical Care Options

PTCL: Selected ASCO 2014

- Romidepsin by line of therapy: Responses to romidepsin were similar for patients with 1, 2 or \(\geq 3\) (ORR 24/23/31%) with CR 13/16/17%, PFS 5.4/3.1/3.8 mos, OS 18.2/9.4/9.2 mos, discontinuation rates 16/14/25%), N=130.
- PTCL outcome after CR following standard therapy.
  Analyzed 109 pts from 1980 to 1/2014. 109 patients achieved CR post CHOP-like regimen. 5 yr OS Alk-ALCL, AITL, and PTCL NOS were 69%, 67% and 46% with PFS of 62%, 50% and 30%. Salvage with HDASCT was 20% beyond first CR (2/10 surviving).

Foss 8563, Lavoie 8555.
PTCL: Selected ASCO 2014 (2)

- **SWOG 1108 - Alisertib in relapsed PTCL**: Of 37 evaluable patients, 2 CR and 7 PR (ORR 24%). Average prior lines rx 3.
- **Role of Radiologic surveillance**: Of 341 pts in the database, 145 achieved CR of whom 64 relapsed. Most patients had sx, signs, or LDH heralding relapse. No obvious benefit to surveillance.
- **CHOP+Alemtuzumab**: Dose finding study. CHOP+alemtuzumab 10 mg weekly achieved similar results to 60 mg on day 1. Of 20 patients ORR was 65% (6 PR and 7 CR). 10 pts had CMV viremia requiring valganciclovir. 2 fungal pneumonias and one fatal TB reactivation.

---

Allogeneic Transplant in PTCL

- **Treatment-related mortality**: ~ 15% to 20% for full myeloablative allogeneic transplant in aggressive NHL
- **Reduced intensity conditioning and allogeneic transplant**
  - 17 pts with relapsed (n = 15) or refractory (n = 2) PTCL
    - 3-yr EFS rate: 64%
    - 2-yr nonrelapsed mortality: 6%
    - Responses seen after donor lymphocyte infusion
  - Update: 26 pts
    - 5-yr OS rate: 51%
    - 5-yr PFS rate: 61%
    - 3-yr transplant-related mortality rate: 13%
- **Conclusion**: Some evidence of graft vs lymphoma effect in PTCL – remains restricted to younger pts

---

Reduced-Intensity Allogeneic BMT in Relapsed PTCL: Retrospective Data

- 52 patients; 12 had DLI for relapse
- Chemosensitive patients (n = 39) did better
- Patients who had ≥ 2 previous regimens (n = 13) had inferior outcomes
CONCLUSIONS and QUESTIONS
How I Treat Sickle Cell Disease

Mark Holguin, MD
Sickle Cell Disease

• Autosomal recessive disease
  – Dr. Linus Pauling in 1948 demonstrated abnormal hemoglobin protein was at the root of this disease
  – 1956 Dr. Vernon Ingram and J.A. Hunt sequenced sickle and normal hemoglobin beta chain and showed sickle hemoglobin substituted valine for glutamic acid at the 6th position

Pathophysiology

• Sickle Hemoglobin will polymerize when deoxygenated
  – Polymerized hemoglobin is gel-like, distorting the red cell
  – These “sickled” red cells are unable to pass through smaller vessels
  – Sickling results in hemolysis and tissue ischemia
Various Hemoglobins and Electrophoresis

- Homozygous Hgb S/S
- Heterozygous Hgb S/A
  - Sickle cell trait
- Hemoglobin F
  - Normally present in the first 6 months of life. Hgb F is non-permissive for sickling. Persistence of Hgb F ameliorates the clinical manifestations of sickle cell disease
- Hemoglobin C
  - Permissive for sickling. Hemoglobin SC disease is similar to sickle cell disease
- Sickle beta thalassemia
  - One beta globin gene affected by thalassemia resulting in lower Hgb A
  - Clinical effect depends on Hgb F and Hgb A

Hemoglobin Electrophoresis

Clinical Manifestations: Pain

- Severity and frequency vary considerably among sickle cell patients
- According to Platt et al. 1991, approximately 5% of sickle cell patients account for more than one third of hospital admissions.
  - Over half of patients require hospitalization less than once a year.
  - Approximately 10% of patients require hospitalization more than 3 times a year.
Clinical manifestations: Pain

• The pain of sickle cell crisis can be excruciating
  – Worse than childbirth, kidney stone, etc.
• Sickle cell patients are reliable reporters of pain severity
  – No reliable objective indicators of pain
  – Pain should be believed and treated appropriately

Clinical Manifestations: Infection

• Patients with sickle cell disease infarct their spleens to a fibrous nubbin by the time they are 1 or 2
• This functional asplenia results in an inability to create antibodies effectively
• Sickle cell patients have an immune deficit and don’t deal with sepsis well.
  – Fever in a sickle cell patient should be taken seriously. Patients can become seriously ill quickly.

Clinical Manifestations: Hemolysis

• A chronic hemolytic anemia is seen in patients with sickle cell disease which leads to several problems
  – Chronic anemia, elevated bilirubin, retic
  – Expanded marrow cavity
  – Need for folate supplementation
  – Gallbladder disease
Clinical Manifestations: Eye

• Ischemic events occurring in the retina can result in a proliferative retinopathy, similar to that seen in diabetes.
  – Risk of bleeding
  – Risk of retinal detachment
• The proliferative retinopathy can be treated with laser
• Need for yearly eye exam

Clinical Manifestation: Bone

• Bone is frequently infarcted with sickle cell episodes
  – H shaped vertebra
  – Avascular necrosis of hips, knees, shoulders
  – Fat embolism
Clinical Manifestation: Renal

- The renal medulla is one of the most hypoxic areas in the body
  - Microscopic hematuria
  - Papillary necrosis
- Note that sickle cell patients have an increased GFR and will normally have reduced serum creatinine.
  - Creatinine greater than 1 signifies renal problems in sickle cell patients

Clinical Manifestation: Pulmonary

- Acute Chest Syndrome is the most common cause of death and hospital admission for sickle cell disease
  - Defined as fever, hypoxia and pulmonary infiltrate
  - Studies suggest this can be caused by infection (broad spectrum of agents), fat embolism and infarction.
  - ~50% of patients develop acute chest after admission

Acute Chest syndrome

- Treatment
  - Broad spectrum antibiotics to include atypical organisms
  - Hydration
  - Pain management
  - Incentive spirometry
  - Transfusion (simple vs exchange)
  - Oxygen (>80% of patients requiring mechanical ventilation recovered)
Acute Chest Syndrome

Clinical Manifestation:
Cardiovascular

- Cardiomegaly is routine
- LVH on EKG and echocardiogram
- Pulmonary hypertension
  - Article in NEJM suggests that 30% of patients with sickle cell disease may have pulmonary hypertension. Diagnose with doppler echocardiogram
  - Treatment?
- Risk of thrombosis is high
  - Consider prophylactic therapy on admission

Clinical Manifestation:
Neurovascular

- Approximately 10% of sickle cell patients will experience stroke by age 12. Risk of stroke predicted by transcranial doppler.
  - STOP I trial demonstrated that regular exchange transfusions monthly to reduce sickle hemoglobin to 30% effective in reducing stroke
  - STOP II trial demonstrated that even if transcranial doppler normalizes, patient remains at risk and treatment must continue
  - SWITCH trial compared hydroxyurea and iron chelation to standard transfusion therapy. Trial was stopped early with increased number of stroke in hydroxyurea arm.
Clinical Manifestation:
Psychosocial

- Not an organ system, but a significant problem area for patients with sickle cell disease
  - Frequent, unpredictable episodes of pain
  - Limits career choices
  - Limits ability to have any job
- Challenge to find resources just to get by
  - Hard to focus on vaccinations, hydrea when you have no place to live

Treatment: Antibiotic

- 1992 study from NEJM demonstrated that prophylactic antibiotic therapy was effective in preventing infections, reducing hospitalizations for children under 5.
  - PenVK 250 mg BID
- Repeat study on adults failed to show a benefit

Treatment: Hydroxyurea

- The Multicenter Study of Hydroxyurea in Sickle Cell Disease (NEJM 1995) randomized adult sickle cell patients having more than 3 hospitalizations for pain crisis/year to use of hydroxyurea or supportive care.
  - Use of hydroxyurea was associated with decrease pain episodes, hospitalizations
**Transfusion**

- Exchange transfusion which decrease sickle hgb to 30% will prevent stroke, ameliorate acute chest syndrome
- Routine transfusions are not helpful in pain crises
- Preop transfusion to Hgb of 10 are helpful in preventing sickle cell complications in the perioperative period.

**Iron chelation**

- Transfusion and hemolysis lead to iron overload
- Desferal
- Exjade

**Vaccination**

- Sickle cell disease causes an immune defect
- Vaccinations recommended
  - Value not proven
  - Influenza, pneumococcal, meningococcal, Haemophilus, Hepatitis B
**Treatment: Bone marrow transplant**

- A potentially curative procedure
- To date, approximately 200 sickle cell patients have been transplanted worldwide, almost all pediatric.
  - 90% cure rate with subsequent freedom from sickle cell complications
  - Requires an HLA compatible sibling
  - Only for patients with severe life-threatening complications like stroke, acute chest syndrome.
- Recently, reports of nonmyeloablative HLA matched sibling bone marrow transplant for adults (18 to 65)
  - Almost 90% engraftment with mixed chimerism
  - Able to taper immunosuppressives with persistent engraftment
  - Small numbers but low toxicity and reversal of sickle cell complications

**Pain Crisis Management**

- When confronted with a sickle cell patient in the ER or clinic having a pain episode, what do you do?
- History
  - Type of pain, typical?
  - What do they usually take?
  - What have they done so far?
- Physical
  - Check temp and oxygen saturation
  - Neurologic exam

**Pain Crisis**

- Hospital Admission Guaranteed
  - Fever
  - Nausea, vomiting, unable to take po meds
  - Neurologic symptoms, signs
  - Chest pain, shortness of breath, hypoxia
- If any of these are present, admit to the hospital, do not pass Go…
Pain Crisis

• If the patient is having a pain crisis and nothing else, you can try to treat as an outpatient
  – Morphine 5mg IV Q 15 min til you get on top of the pain
  – Check with the patient regarding the meds that work for them
• If this works, patient can continue with oral pain meds as outpatient
• If this doesn’t work, admit for pain management

Pain Crisis

• If you have to admit a sickle cell patient for pain management:
  – Find out what they were taking as an outpatient and make sure they get at least that much medicine
  – In adults, PCA dosing can be very helpful
  – Ask about emergency cards which may explain typical dosing strategies for that patient
  – Remember, the patient is the best judge of their pain
  – Venous access is frequently a problem. Write orders for both IV and IM/PO approaches

Admission Orders

• There is a set of admission orders for sickle cell pain crisis on the intranet
  – Physician Work Center
  – Include reminders for routine meds, suggestions on pain regimens, routine labs
Emergency Card

• We have developed an emergency card for our patients
  – Name, phone number
  – Routine meds
  – Suggested outpatient regimen
  – Successful inpatient regimen
  – My name and beeper number

Ya Gotta Believe

• The most difficult part of caring for sickle cell patients is believing the patient’s report of pain.
  – Virtually all sickle cell patients have stories to tell in which pain has been ignored or inappropriately treated
  – Ample documentation that sickle cell patients can be believed
  – Lack of objective findings to corroborate pain description is a problem
Myeloma: New Strategies, New Therapies
Christopher Maisel, MD
**Myeloma 2014: New Strategies and Therapies**

Christopher Maisel, M.D.

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**Disclosures**

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td>Research Support</td>
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<td>Major stockholder</td>
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<td>Bortezomib, carfilzomib, lenalidomide, pomalidomide</td>
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**Topics**

- Epidemiology and Molecular Risk-Stratification
- Induction therapy in 2014
- Length of therapy/maintenance
- Role of ASCT
- Relapsed disease
- Novel agents
Myeloma Epidemiology

- Myeloma 2013 estimates in USA*
- 22,350 new cases
- 10,710 deaths
- Patients diagnosed between 1998-2008 had overall survival of 44.8 months**

*ACS facts and figures
**Kumar et al Blood 2008;111

Myeloma Risk-Stratification: International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>β2-microglobulin &lt; 3.5 mg/L and Albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td>II</td>
<td>Neither I nor III</td>
</tr>
<tr>
<td>III</td>
<td>β2-microglobulin ≥ 5.5 mg/L</td>
</tr>
</tbody>
</table>

Greipp, San Miguel, Durie et al JCO 2005;23

Overall survival of MM patients stratified by Cytogenetic Abnormality

P<0.001

- Poor
- Intermediate
- Good


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### Risk-Stratification of Myeloma

<table>
<thead>
<tr>
<th></th>
<th>Standard Risk</th>
<th>High Risk</th>
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<tbody>
<tr>
<td>β-2 microglobulin</td>
<td></td>
<td>≥ 5.5</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Hyperdiploidy, t(11;14), t(6;14)</td>
<td>t(4;14), del13q, t(14;16), del17p</td>
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<tr>
<td>Plasma Cell Leukemia</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Gene Expression Profile</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

All Myeloma patients should be risk-stratified at diagnosis

Risk-stratification should influence therapy

Table adapted from Avet-Loiseau H Hematology 2010;2010

---

### What is the Optimal Induction Regimen in 2014?

---

### EVOLUTION: A Multicenter, Phase 2 Trial of Induction Regimens in Myeloma

*Kumar et al Blood 2012;119*

- Comparison of 4 induction regimens in upfront MM
- CyBorD, CyBorD (mod), RVD, and VDCR
- Pts received up to 8 cycles of induction
- All arms then received bortezomib (V) maintenance (unless going to ASCT)
EVOLUTION: Study Methods
Kumar et al Blood 2012;119

- Patients received up to 8 cycles of induction, then bortezomib maintenance (unless going on to ASCT)
- Allowed to go off-study for ASCT after 4 cycles
- 122/140 patients evaluable after 4 cycles
- 59/140 patients (42%) underwent ASCT

EVOLUTION: Results

<table>
<thead>
<tr>
<th></th>
<th>RVD</th>
<th>CyBorD</th>
<th>CyBorD-mod</th>
<th>VDCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR or better after 4 cycles</td>
<td>32</td>
<td>13</td>
<td>41</td>
<td>33 %</td>
</tr>
<tr>
<td>Overall RR after 4 cycles</td>
<td>71</td>
<td>63</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>VGPR or better after all therapy</td>
<td>51</td>
<td>41</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>Overall RR after all therapy</td>
<td>85</td>
<td>75</td>
<td>100</td>
<td>88</td>
</tr>
</tbody>
</table>

EVOLUTION: Results

<table>
<thead>
<tr>
<th></th>
<th>RVD</th>
<th>CyBorD</th>
<th>CyBorD-mod</th>
<th>VDCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS – 1 year</td>
<td>83</td>
<td>93</td>
<td>100</td>
<td>86 %</td>
</tr>
<tr>
<td>PFS – 1 year for pts going to ASCT</td>
<td>100</td>
<td>88</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>PFS – 1 year for pts, excluding ASCT*</td>
<td>68</td>
<td>97</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>1-yr OS estimate for all pts</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>92</td>
</tr>
</tbody>
</table>
EVOLUTION: Conclusions

• Grade 3 AE’s most common in 4-drug arm, especially hematologic toxicities
• 4 drug arm did not improve PFS over 3 drug regimens
• Trend to worse outcome with 4 drugs
• All 3 drug regimens had similar outcome

Are 3 Drug Induction Regimens Superior to 2 Drug Regimens?
2 Drug Regimen Response Rates

- Lenalidomide + dexamethasone: 
  ≥ VGPR 40%
- Bortezomib + dexamethasone:  
  ≥ VGPR 38%

Rajkumar et al, ASCO 2008, Abstract 8504
Harousseau et al ASH 2006, JCO 2008;28

Bortezomib-containing Regimen
Remains Effective in High-Risk Myeloma
Harousseau et al ASH 2006, JCO 2008;28

<table>
<thead>
<tr>
<th></th>
<th>BTZ + Dex</th>
<th>VAD</th>
</tr>
</thead>
</table>
| ORR (≥ PR, all patients) | 78.5      | 62.8| P < .05
| ≥ VGPR (all patients) | 37.7%     | 15.1%|
| ≥ VGPR- Del 13     | 46.5%     | 14.6%|
| ≥ VGPR- t(4;14) or del17p | 40.0%     | 17.2%|

Progression- Free Survival 36 months 30 months P = .06

Carfilzomib, Revlimid, and Dexamethasone (CRd) in Frontline
Myeloma Therapy
Jakubowiak et al Blood 2012;120

- Phase I/II Study, 53 patients
- Median age 59
- CFZ given on D 1, 2, 8, 9, 15, 16 of 28 day cycle
- Len 25 mg D1-21, Dex 40 mg weekly
- Median 12 cycles of therapy
sCR = 42%  
  ≥ VGPR = 81%  
  ≥ PR = 98%
Conclusions About Induction Therapy

• A regimen with lenalidomide or bortezomib is considered standard
• Triplet therapy should be strongly considered for patients who are ASCT candidates or have high-risk disease
• Elderly patients can be treated effectively with acceptable toxicity

Summary Schema: Initial Therapy of Myeloma

Patients eligible for ASCT
• ASCT candidates typically receive 4-6 cycles of induction, to hopefully achieve ≥ PR
• Then proceed to stem cell collection, followed by ASCT with Mel200
• Consider post-ASCT maintenance

Patients not eligible for ASCT
• Non-Transplant candidates receive therapy to maximal response, hopefully ≥ PR
• Role for maintenance?

Role of Autologous Stem Cell Transplant and Maintenance Therapy
Role of Autologous Stem Cell Transplant and Maintenance Therapy in Myeloma
Boccadoro et al, ASCO 2013;8509
Palumbo et al, NEJM 2014;371

- 402 MM patients, ASCT eligible, median age 58
- All patients received Len-dex (Rd) for 4 cycles
- Randomized to ASCT x 2, or MPR consolidation
- Second randomization: + Lenalidomide maintenance
- Median f/u of 51 months

PFS and OS: ASCT and Maintenance
Boccadoro et al, ASCO 2013, Palumbo et al, NEJM 2014

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>MPR</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PFS</td>
<td>38 months</td>
<td>24 months</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>OS @ 48 months</td>
<td>82%</td>
<td>65%</td>
<td>0.02</td>
</tr>
<tr>
<td>Len maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>42 months</td>
<td>22 months</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>OS @ 36 months</td>
<td>88%</td>
<td>79%</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Len maintenance improved PFS whether pts were in CR or not after ASCT
Len maintenance did not improve PFS in pts with t(4;14), t(14;16), or del17p
**ASCT and Lenalidomide Maintenance: Conclusions**

- ASCT followed by maintenance lenalidomide improves PFS and possibly OS
- Maintenance lenalidomide improves PFS but not OS
- ASCT and Len maintenance are most beneficial for patients with standard-risk MM
- Remains controversial as to how much these therapies benefit high-risk MM patients
- This study compared ASCT to one targeted therapy, not to combination (RVD, etc).

**Continuous Therapy vs Fixed-duration Therapy**

- Two phase III trials comparing induction + maintenance (CT) to induction only (FDT) in non-transplant candidates
- Trial 1: Len + dex + melphalan + Len maintenance
- Trial 2: BTZ + dex + melphalan + BTZ maintenance
- 452 pts received CT
- 461 pts received FDT (no maintenance)
- Median follow up 52 months

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>FDT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS-1</td>
<td>35 mos</td>
<td>24 mos</td>
<td>0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>NR</td>
<td>70 mos</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

**Double-Refractory Patients**

- Carfilzomib
- Pomalidomide
- Investigational Agents
Carfilzomib

- Epoxyketone 20S proteasome inhibitor
- In phase 2 trial of patients with refractory MM (including refractory to Len and BTZ), ORR 23% with single-agent CFZ*
- Minimal neuropathy
- Approved in relapsed Myeloma: at least 2 prior lines of Rx, including BTZ and IMiD

*Siegel et al, Blood 2012;120

CRd in Relapsed MM
Wang et al, ASCO 2013

- 88 pts with relapsed MM, phase 1b/2 study
- 1-3 prior therapies
- 77% prior BTZ, 18% refractory
- 70% prior LEN, 35% refractory
- ORR 69%, VGPR 38%
- Median 8.5 cycles

Pomalidomide

- IMiD with similar chemical structure to lenalidomide
- Approved based upon phase 2 data
- 113 pts: prior tx with both Len and BTZ, ORR 30%
- ORR 28% in double-refractory group

Vij, Richardson, et al JCO 2012;30
Pomalidomide in RR Myeloma
San Miguel, Weisel et al, ASCO 2013: 8510

- Phase 3 study of RR myeloma patients: Pom + dex vs high-dose dex
- 455 patients, median 5 prior lines of therapy
- 74 % of patients refractory to both BTZ and Len
- Patients received either:
  Pom 4 mg D 1-21 + dex 40 mg weekly or
dex 40 mg D 1-4, 9-12, 17-20 (28 day cycle)

<table>
<thead>
<tr>
<th></th>
<th>Pomalidomide + dex</th>
<th>Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>31 %</td>
<td>10 %</td>
</tr>
<tr>
<td>VGPR + CR</td>
<td>6 %</td>
<td>1 %</td>
</tr>
<tr>
<td>PFS</td>
<td>4 months</td>
<td>1.9 months</td>
</tr>
<tr>
<td>OS</td>
<td>12.7 months</td>
<td>8.1 months*</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>7 %</td>
<td>6 %</td>
</tr>
<tr>
<td>&gt;grade 3 neutropenia</td>
<td>42 %</td>
<td>15 %</td>
</tr>
</tbody>
</table>

P<.001 for all
*OS benefit maintained despite 29 % crossover

New Agents

- Daratumumab
- SAR650984
- Panabinostat
- Elotuzumab
**Daratumumab**

- Human IgG1k monoclonal antibody
- Broad spectrum mechanism of action including CDC, ADCC, ADCP, apoptosis induction and inhibition of enzymatic activity
- In development for relapsed multiple myeloma as a single-agent and potential combination

**Daratumumab Trials**

- Phase 2 trial of Daratumumab open at Texas Oncology-Baylor Sammons
- Dose is 16 mg/kg IV
- Relapsed Myeloma: dara + pom + dex
- Upfront Myeloma: dara + BTZ + dex

Lokhorst et al, ASCO 2013;Abc 8512
**SAR650984**
Martin et al ASCO 2014;8512

- Humanized mAb to CD38
- Phase Ib study of RRMM patients
- SAR combined with Len + Dex
- 100% of evaluated pts had prior Len, median 6 prior lines of therapy
- ORR 58%

---

**Panabinostat**

- Oral pan-deacetylase inhibitor
- Synergistic with bortezomib
- Panorama trial*; phase 3 trial of 768 patients with prior BTZ
- 1-3 prior lines of therapy, not refractory to BTZ. Median 1 prior line of therapy

<table>
<thead>
<tr>
<th></th>
<th>Pan + BTZ/Dex</th>
<th>BTZ/Dex</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>12.0 months</td>
<td>8.1 months</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Richardson et al, ASCO 2014;8510

---

**Elotuzumab**

- Humanized, anti CS1 Monoclonal Antibody
- CS1 is a cell surface protein highly expressed in MM which mediates adhesion to stromal cells
- Elotuzumab enhances MM cell death via NK cell ADCC
- Most active in combination with other agents
### Phase I/II Study of Elotuzumab Combined with Lenalidomide and Dexamethasone
Lonial et al, ASCO 2013

- Pts with relapsed MM, 1-3 prior therapies (phase 2 cohort, n=73 patients)
- Pts could have received BTZ or thal, but no prior lenalidomide
- ORR 84 % (92 % in 10 mg/kg, 76 % in 10 mg/kg)
- At 20.8 mos, median PFS not-reached in 10 mg/kg cohort
- Most common AE's hematologic: neutropenia, anemia, thrombocytopenia
- Phase 3 trial open at TxO-Baylor Sammons
- Len/dex + Elotuzumab as induction therapy for patients who are not ASCT candidates

### Conclusions

- New therapies/combinations are extending survival in Myeloma
- How to employ these therapies most effectively remains a question to be answered
- We can still do better

### The End
Updates in CLL

R. Brian Berryman, MD
Please respect our presenters and remain seated until the conclusion of each presentation.
Please respect our presenters and remain seated until the conclusion of each presentation.
Approach to Diagnosing & Treating Thrombophilia

Barry Cooper, MD
Objectives

• Role of new oral anticoagulants in treatment of acute and chronic venous thrombosis.
• Reversal of newer anticoagulant effects.
• Duration of anticoagulation in unprovoked thrombosis.
• Management of anticoagulation in cancer patients.
Dabigatran vs Warfarin in Treatment of Acute Venous Thromboembolism (VTE) (Recover Study Group)

1. 2500 patients given parenteral anticoagulant (median of nine days).
2. Patients randomized to dabigatran 150 mg po BID or warfarin. Eligible patients had creatinine clearance > 30 ml/min.
3. No difference in recurrent thrombosis with similar safety profile.
4. 5% of patients had cancer, with 3.1% recurrence in dabigatran group and 5.3% in warfarin group.


Risk of VTE or Death in Patients Treated with Dabigatran or Warfarin.

Risks of Major Bleeding and any Bleeding in Patients Treated with Dabigatran or Warfarin.
Oral Rivaroxaban for Symptomatic Venous Thrombosis
(Einstein Investigators)

- 3500 patients randomized to rivaroxaban (15 mg po BID X 3 wks, then 20 mg po daily) vs enoxaparin/coumadin.
- Creatinine clearance >30 ml/min.
- Recurrent venous thrombosis was 2.1% for rivaroxaban vs 3.0% for enoxaparin/coumadin treatment (p<0.001).
- Bleeding events were 8.1% in both groups.
- 6% of patients had cancer, with 3.4% recurrent thrombosis in rivaroxaban vs 3.0% in enoxaparin/coumadin-treated group.
Kaplan-Meier Cumulative Event Rates for Continued Treatment Study

Kaplan-Meier Cumulative Event Rates for Recurrent VTE in Pulmonary Embolism Trial

Kaplan-Meier Cumulative Event Rates for Major Bleeding in Pulmonary Embolism Trial
Oral Apixaban for Treatment of Thromboembolism  
(Amplify Investigators)

1. 5395 patients randomized to treatment with apixaban 10 mg po BID for 1 wk, then 5 mg po BID for 6 months vs enoxaparin/coumadin
2. Creatinine clearance > 25 ml/min
3. 2.5% of patients in each group had cancer
4. Recurrent venous thromboembolism was 2.3% in patients treated with apixaban vs 2.7% in the enoxaparin/coumadin group.
5. Major bleeding occurred in 0.6% of patients treated with apixaban vs 1.8% for those treated with enoxaparin/coumadin (69% reduction, p<0.001).

Kaplan-Meier Curves for First Event of Recurrent VTE or VTE-related Death

Kaplan-Meier Curves for First Episode of Major Bleeding
Drug Interactions with >50% Change in Exposure to Dabigatran or Rivaroxaban

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interacting Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-gp inhibition</td>
<td>Ketoconazole</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>~50%</td>
</tr>
<tr>
<td></td>
<td>Amiodrone</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>53</td>
</tr>
<tr>
<td>P-gp induction</td>
<td>Rifampicin</td>
<td>~67</td>
</tr>
<tr>
<td></td>
<td>St John's Wort</td>
<td>NO</td>
</tr>
<tr>
<td>CYP3A4 inhibition</td>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>St John's Wort</td>
<td>NO</td>
</tr>
</tbody>
</table>
| ND, not determined; *Contraindicated; Variable depending on formulation of verapamil

Comparative Properties of Thrombin and Factor Xa Inhibitors in Late Development

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran etoxilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>&gt;80%</td>
<td>&gt;50%</td>
<td>&lt;6%</td>
</tr>
<tr>
<td>T(max)</td>
<td>2.5-4 h</td>
<td>3 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>5-9 h healthy, 9-13 h</td>
<td>8-15 h</td>
<td>14-17 h</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Administration</td>
<td>Once or twice daily</td>
<td>Twice daily</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Metabolism and elimination</td>
<td>CYP3A4: 66% renal, 33% fecal</td>
<td>CYP3A4: 25% renal, 75% fecal</td>
<td>80% renal, 20% fecal</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reversal of Factor Xa and Thrombin Inhibitors

1. No decreased clotting factors so fresh frozen plasma ineffective.
2. Four-factor PCC most effective option for factor Xa inhibitors (rivaroxaban/apixaban) with presence of activated II, VII, IX, and X. Less effective with thrombin inhibitors (dabigatran).
3. Recombinant VIIa an option but not likely effective.
4. Plasma-derived Factor Xa modified without catalytic activity in clinical trials as antidote for Xa inhibitors.
5. The antibody fragment (aDabi-Fab) has 350-fold more affinity for dabigatran than thrombin. It does not bind thrombin substrates and has no activity in coagulation tests (Blood, 121:3554-62, 2013).
Plasmin cleaves the polymerized fibrin strand at multiple sites and releases fibrin degradation products, including D-Dimer.

D-Dimer Testing to Determine Duration of Anticoagulation (Prolong Study)

1. Unprovoked DVT in 608 patients
2. Patients with AT-III deficiency, APLA syndrome, or malignancy were excluded.
3. Minimum of three months anticoagulation with warfarin.
4. 37% of patients had positive D-Dimer one month after anti-coagulation stopped.
5. 15% of D-Dimer positive patients had recurrence over 1.4 years compared to 6.2% in D-Dimer negative group.
Cumulative Incidence of and Hazard Ratios for Main Outcomes


D-Dimer to Guide Duration of Anticoagulation in Venous Thromboembolism

1. DVT in 1010 patients treated for 3 – 12 months with warfarin.
2. 52% of patients had negative D-Dimer off treatment for two years.
3. 482 patients had elevated D-Dimer and 109 refused resumption of anticoagulation.
4. 8.8% patient year risk of DVT off anticoagulation compared to 0.7% in treated population.

Prevalence of first-time-ever D-dimer result above the predefined cut-off levels in the investigated study population at the serial measurement days after VKA withdrawal.

Palareti G et al. Blood 2014;124:196-203
Kaplan-Meier cumulative event rates for the primary efficacy outcome in patients with negative vs positive D-dimer results

Cumulative incidence of first VTE recurrence among Olmsted County, Minnesota, residents with incident DVT or PE, 1966-2000, and followed-up through December 31, 2005, by active cancer status.

Multiple Mechanisms in Trousseau's Syndrome

Approach to Diagnosing & Treating Thrombophilia
Barry Cooper, MD
**Trial of Apixaban for Prevention of Thromboembolism in Cancer Patients**

1. 120 patients randomized to placebo, 5, 10, or 20 mg of apixaban daily for 12 weeks.
2. Three of thirty patients in placebo group had DVT and none in apixaban group.
3. Three of ninety patients receiving apixaban had bleeding.


---

**Criteria for use of New Oral Anticoagulants in Cancer Patients**

1. No major bleeding past two months
2. Absence of intracranial or visceral tumor at high risk of bleeding
3. Platelets >50,000 /μL and no anticipated decrease from chemotherapy
4. Normal PT, PTT, and Fibrinogen
5. No significant hepatic impairment
6. Creatinine clearance > 30 ml/min
7. No concurrent drugs with strong effects on CYP3A4 and/or P-glycoprotein

Short and Connors. Oncologist 2014;19:82
Non-chemotherapeutic Management of Hematologic Malignancies

Christian T. Cable, MD, MHPE
Hematologic Malignancies
-molecular (r)evolution-

Christian T. Cable, MD, MHPE
September 27, 2014

Objectives

• I want to tell a story . . .
  – three centuries
  – physicians, scientists & the humanity they serve
  – prophecy & perseverance
  – progress & hope
  – simple & sophisticated tools
  – wisdom & stewardship
pre-19th century

Ramayana & Arsenic

1673
The ratio of pigmented to colorless corpuscles was reversed.

- Leukämie
- Post-mortem dx
- CML? CLL?

"The existence of true pus, formed universally within the vascular system, independent of any local purulent collection from which it could be derived."

- Leucocythemia
- Post-mortem dx
How I think about leukemia . . .

<table>
<thead>
<tr>
<th></th>
<th>ACUTE</th>
<th>CHRONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>LYMPHOID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
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<td>CLL</td>
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<td>CLL</td>
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<tr>
<td>MYELOID</td>
<td></td>
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<tr>
<td>AML</td>
<td></td>
<td>CML</td>
</tr>
<tr>
<td>CML</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

My favorite cell
Diagnostic & medicinal chemistry

Objectives

• three centuries
• physicians, scientists & humanity they serve
• prophecy & perseverance
• progress & hope
• simple & sophisticated tools
• wisdom & stewardship

• Thousands of dyes catalogued: screening
• They interacted with living matter - - could they treat disease?
• Immunology, Hematology, Infectious Disease . . .
Objectives

• three centuries
• physicians, scientists & humanity they serve
• prophecy & perseverance
• progress & hope
• simple & sophisticated tools
• wisdom & stewardship

magische Kugel

• Compound 606
• Arsenamine
• Salvarsen - - 1910
• Primary treatment for syphilis until PCN in the 1940s

The War(s) to end all Wars . . .
Father of all chemotherapy

Descendants

- cyclophosphamide
- chlorambucil
- bendamustine
- ifosfamide

Non-chemotherapeutic Management of Hematologic Malignancies
Christian T. Cable, MD, MHPE
Objectives

- three centuries
- physicians, scientists & humanity they serve
- prophecy & perseverance
- progress & hope
- simple & sophisticated tools
- wisdom & stewardship

Col. Ogden Bruton

- Chief of Pediatrics
- Walter Reed Army Hospital
- Observation and a new piece of laboratory equipment
1952

AGAMMAGLOBULINEMIA

By Col. Ocean C. Beutler, M.C., U.S.A.
Washington, D.C.

The complete absence of gamma globulins in human serum, as determined by electrophoretic analysis, does not appear to have as yet been reported in the literature. Fourteen cases of hypogammaglobulinemia in children who had "demonstrated complete absence of gamma globulins and were singularly free from infections," Schick reported a similar complication case without nephropathy with a review of the literature in which the total protein was low, the gamma globulins function low, and ektacytosis present. The latter findings in nephropathy are well known. Kunitz reported a case in which there was a "prostration" of globulin globulin in hypogammaglobulinemia due to malnutrition. The present author had the opportunity of following a patient without nephropathy, with normal nutrition, with complete absence of the gamma globulins fraction and normal total serum protein through several years of many infections, including two episodes of cerebral spasm in which serum protein was measured by blood cultures 10 times. This case, which it was found, could be controlled by supplying gamma globulin as a concentrated immune human serum globulin, appears to be unique.

Bruton's cell
In 1966, Glick et al. (1) described the role of the bursa of Fabricius, a lymphoid organ, in the development of humoral immunity in the chicken. With the subsequent definition of the presumed role of the mammalian thymus in the development of T-cells (2-5), the chickens served as the interest of many investigations because it has both a thymus as well as a bursa. A functional differentiation of the chickens immune system based on differences in thymic and bursal influences was initially suggested by Wynn et al. (6-11). Although experimental support for this hypothesis was forthcoming from several laboratories (12-17), conflicting data was obtained in some of the studies of surgically and hormonally hormone-treated and hormone-treated animals. Partially confirmed were the data of the functional separation of the morphologic basis for the development of the immune system in the bursa of Fabrisicus and function of the thymus and mammalian lymphoid systems.
### Back to CML . . .


### 1960


### Further Progress

<table>
<thead>
<tr>
<th>CLL</th>
<th>CML</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1993: BTK named in Bruton’s honor, on X chromosome, mutations causing agammaglobulinemia</td>
<td>- 1973: t(9;22)</td>
</tr>
<tr>
<td></td>
<td>- 1982: ABL on 9</td>
</tr>
<tr>
<td></td>
<td>- 1984: BCR on 22</td>
</tr>
<tr>
<td></td>
<td>- 1985: BCR/ABL fusion gene with constitutively active kinase function</td>
</tr>
</tbody>
</table>
History Repeats?

Compound 606: Salvarsan

• STI-571: Imatinib

Different actors

• Erlich
• Druker
magische Kugel

Objectives

• three centuries
• physicians, scientists & humanity they serve
• prophecy & perseverance
• progress & hope
• simple & sophisticated tools
• wisdom & stewardship

Next Gen Sequencing
2014

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

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FDA News Release

FDA expands approved use of Imbruvica for chronic lymphocytic leukemia

New clinical data supports traditional approval for CLL

For Immediate Release

July 28, 2014

The U.S. Food and Drug Administration today expanded the approved use of Imbruvica (ibrutinib) to treat patients with chronic lymphocytic leukemia (CLL) who carry a deletion in chromosome 17 (17p-deletion), which is associated with poor response to standard treatment for CLL. Imbruvica received a breakthrough therapy designation for this use.
FDA News Release

FDA approves Zydelig for three types of blood cancers

For Immediate Release July 23, 2014

The U.S. Food and Drug Administration today approved Zydelig (idelalisib) to treat patients with three types of blood cancers.

Zydelig is being granted traditional approval to treat patients whose chronic lymphocytic leukemia (CLL) has returned (relapsed). Used in combination with Rituxan (rituximab), Zydelig is to be used in patients for whom Rituxan alone would be considered appropriate therapy due to other existing medical conditions (co-morbidities). Zydelig is the fifth new drug with breakthrough therapy designation to be approved by the FDA and the third drug with this designation approved to treat CLL.

Human Genome Harvest: 2013

- trametinib
- Ra 223
- pomalidomide
- afatinib
- dabrafenib
- sorafenib (thyroid)
- crizotinib
- erlotinib (1st line)
- trastuzumab-emtansine
- pertuzumab
- obinutuzumab
- nab-paclitaxel (pancreatic)
- ibrutinib (MCL)
- ponatinib (suspended)
- lenalidomide (MCL)

Human Genome Harvest: 2014

- ceritinib
- ibrutinib (CLL)
- trametinib + dabrafenib
- ponatinib (reinstated)
- idelalisib
- siltuximab
- ramucirumab
- ofatumumab
Objectives

• three centuries
• physicians, scientists & humanity they serve
• prophecy & perseverance
• progress & hope
• simple & sophisticated tools
• wisdom & stewardship
Non-chemotherapeutic Management of Hematologic Malignancies

Christian T. Cable, MD, MHPE

Cost Consciousness in Patient Care — What Is Medical Education’s Responsibility?

Holly Cooke, M.D.

It is old news that the cost of medical care in the United States is unsustainable, yet we seem unable to grapple with the issue effectively. As everyone knows, the health care reform debate has highlighted the need for disciplined cost management in providing care, and the debate over whether managed care can be part of the solution. However, the evidence for the effectiveness of managed care is anecdotal and not well-supported by scientific data. The fact that managed care programs can be implemented in a variety of ways without meaningful measurement of outcomes has led to the conclusion that managed care is effective. However, well-designed randomized, controlled trials are needed to determine whether managed care is effective.

Blood Forum

The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts

Experts in Chronic Myeloid Leukemia

As a group of more than 100 experts in chronic myeloid leukemia (CML), we draw attention to the high prices of cancer drugs, with particular focus on the prices of approved tyrosine kinase inhibitors for the treatment of CML. The editor addresses the multiple facets related to these high drug prices and their impact on patient care. We endorse a call for the need to decrease the cost of cancer drugs while remaining acutely aware of the need for innovation.

IN THE SUPREME COURT OF INDIA

CIVIL APPEAL NO. 2785 OF 2013

NOVARTIS AG VERSUS

UNION OF INDIA & OTHERS

APPELLANTS

VERSUS

CIVIL APPEAL NO. 2786 OF 2013

NACCO PHARMA LTD. VERSUS

UNION OF INDIA & OTHERS

APPELLANTS

VERSUS

Respondents
Objectives

• I wanted to tell a story . . .
  – three centuries
  – physicians, scientists & the humanity they serve
  – prophecy & perseverance
  – progress & hope
  – simple & sophisticated tools
  – wisdom & stewardship

Thank you! ccable@sw.org
Current Approach in the Treatment of CML

M. Yair Levy, MD
Please respect our presenters and remain seated until the conclusion of each presentation.
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Current Approach in the Treatment & Management of MDS

Micah M. Burch, MD
Please respect our presenters and remain seated until the conclusion of each presentation.
Please respect our presenters and remain seated until the conclusion of each presentation.
AML: What’s New
Edward D. Agura, MD
Please respect our presenters and remain seated until the conclusion of each presentation.
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