Updates in Leukemia

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Wake Forest University Baptist Medical Center
Overview

• AML Induction
  – Beyond 7+3
  – hidAc and mitoxantrone
  – Gemtuzumab ozogamicin in induction and maintenance
  – Ara-C and amonafide
  – Clofarabine

• Newly Approved Agents in CLL
  – Bendamustine
  – Lenalidomide
  – Ofatumumab
Acute Myelogenous Leukemia
Normal Neutrophil Development
French American British (FAB) Classification of AML

<table>
<thead>
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## WHO (World Health Organization) Classification

### AML with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22), (AML1/ETO)
- AML with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(p13;q22), (CBFβ/MYH11)
- Acute promyelocytic leukemia with t(15;17)(q22;q12), PML/RAR-alpha and variants
- AML with 11q23 (MLL) abnormalities

### AML with multilineage dysplasia
- Following MDS or MDS/MPD
- Without antecedent MDS or MDS/MPD, but with dysplasia in at least 50 percent of cells in two or more myeloid lineages

### AML and myelodysplastic syndromes, therapy related
- Alkylating agent/radiation-related type
- Topoisomerase II inhibitor-related type
- Other

### AML, not otherwise categorized*
- AML, minimally differentiated
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/acute monocytic leukemia
- Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia variants)
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
AML Treatment: Induction Chemotherapy

• Initial treatment for a newly diagnosed patient
• Goal:
  – Recovery of normal hematopoiesis
  – Induce a complete remission
AML Treatment: Consolidation Chemotherapy

- $10^9$ cells are still present even in patients with a “complete remission”
  - “minimal” residual disease
- Additional *consolidation* chemotherapy is needed
- 60-80% of patients with AML can obtain a CR with standard induction chemotherapy (7+3)

AML: Treatment Responses

• However, long term responses (cures) are far less likely

• Depend upon a variety of factors:
  – Age (>60 yo)
  – Cytogenetics
  – Antecedent hematologic disorder
  – AML as a result of prior therapy
  – Comorbidities/performance status
AML: Standard Induction Chemotherapy

- 7+3
- Cytarabine 100-200 mg/m² IVCI on d 1-7
- Daunorubicin 60 mg/m² IV on d 1-3

- 60-80% CR rate

- Common toxicities:
  - Nausea, vomiting, diarrhea
  - Alopecia
  - Cytopenias

AML Induction Variations: High dose ara-C and daunorubicin

- Cytarabine 2 grams/m² IV q 12 hours x 12 doses
  - vs. 200 mg/m² IVCI on d1-7
  - vs. 3 grams/m² IV q 12 hours x 12 doses
    - (DMC terminated this arm due to unacceptable neurotoxicity)
- Daunorubicin 45 mg/m² IVP on d 7-9

- CR rate:
  - 55% in hidAc+dauno
  - 58% in ara-C+dauno

- No benefit in overall survival
- Increased toxicity (fatalities and neurologic toxicities) precluded many patients to receive consolidative therapy

AML Induction Variations: Ara-C + high dose daunorubicin

- Ara-C 100 mg/m² IVCI on d 1-7
- Dauno 90 mg/m² IV on d 1-3
  - vs. 45 mg/m² IV on d 1-3
- CR rates:
  - 71% in ara-C + high dose dauno
  - 57% in ara-C + std dose dauno
- Improvement in OS
- No significant differences in toxicity
  - Hematologic or non-hematologic (cardiac)

AML Induction Variations: Std dose Ara-C and Idarubicin

• Ara-C 25 mg/m² IV bolus followed by 200 mg/m² IVCI on d 1-5
• Idarubicin 12 mg/m² IV on d 1-3
  – vs. daunorubicin 50 mg/m² on d 1-3
• CR rates:
  – 80% with ida + ara
  – 58% with dauno + ara
• Survival not comparable due to discrepancy in transplant status
• Similar toxicity profile

AML Induction Variations: Cytarabine and Mitoxantrone

- Cytarabine 100 mg/m² IVCI on d 1-7
- Mitoxantrone 12 mg/m² IV on d 1-3
  - vs. daunorubicin 45 mg/m² IV on d 1-3

- CR rates:
  - 63% for ara-C + mito
  - 53% for ara-C + dauno

- Similar survival rates
- Similar toxicity profiles

AML: Treatment: Induction Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR Rate</th>
</tr>
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<tbody>
<tr>
<td>Ara-C + Dauno</td>
<td>60-80%</td>
</tr>
<tr>
<td>Hidac + Dauno</td>
<td>Similar CR rate; too toxic for consolidation</td>
</tr>
<tr>
<td>Ara-C + High dose Dauno</td>
<td>Similar CR rate; duration improved; no increase in toxicity?</td>
</tr>
<tr>
<td>Ara-C + Ida</td>
<td>Similar CR rate; no increase in toxicity</td>
</tr>
<tr>
<td>Ara-C + Mito</td>
<td>CR rate same; no increase in toxicity</td>
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</tbody>
</table>
## AML: Treatment: Induction Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR Rate</th>
<th>Duration</th>
<th>Toxicity</th>
</tr>
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<tr>
<td>Ara-C + Dauno</td>
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High dose Cytarabine and Mitoxantrone is an effective induction therapy for high risk AML

Larson S, et al.
ASH Abstract 1048
December 2009
High dose ara-C and Mitoxantrone

- High risk patients
- >60 yo and at least 2 of the following:
  - Relapsed or refractory disease
  - Poor cytogenetics
  - Therapy-related AML
  - Multiple comorbidities
High dose ara-C and Mitoxantrone

- Retrospective trial
- Cytarabine 2 -3 g/m² over 4 hours on days 1 and 5
- Mitoxantrone 20-30 mg/m² IV over 1 hour immediately after the ara-C
- Lower doses used for patients >60 yo
High dose ara-C and Mitoxantrone

- 78 patients
- Median age 63 (23-85)
  - 56% of patients had poor cytogenetics
  - 37% of patients had intermediate cytogenetics
Table: Best response by diagnosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients (%)</th>
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<th>Induction Death (%)</th>
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<tr>
<td>De novo</td>
<td>18 (23)</td>
<td>9 (50)</td>
<td>1 (5)</td>
<td>7 (39)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>t-MN</td>
<td>24 (31)</td>
<td>13 (54)</td>
<td>1 (4)</td>
<td>6 (25)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Relapsed/ refractory</td>
<td>19 (24)</td>
<td>10 (53)</td>
<td>1 (5)</td>
<td>6 (32)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>AML with myelodysplasia related changes</td>
<td>15 (19)</td>
<td>2 (13)</td>
<td>5 (33)</td>
<td>8 (53)</td>
<td>0 (0)</td>
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<td>Blast Crisis CML</td>
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High dose ara-C and Mitoxantrone

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High dose ara-C and Mitoxantrone

- Overall survival at 1 year was 39%
  - With 40% of patients going on to allogeneic transplant
Preliminary Results of SWOG S0106: An International Intergroup Phase 3 Randomized Trial Comparing the Addition of Gemtuzumab Ozogamicin to Standard Induction Therapy vs. Standard Induction Therapy Followed By a Second Randomization to Post-Consolidation Gemtuzumab Ozogamicin vs. No Additional Therapy for Previously Untreated AML

Petersdorf S, et al.
ASH Abstract 790
December 2009
SWOG S0106

• Randomized phase 3 trial
• 627 patients
  – 18-60 yo
  – Previously untreated AML
• Gemtuzumab ozogamicin
  – Monoclonal antibody to CD-33
  – Conjugated to calicheamicin
    • Binds to DNA, causing double-strand breaks and cell death
  – CD 33 is present on >90% of AML cells
  – CD 33 is NOT present on hematopoietic stem cells or nonhematologic tissue

SWOG S0106

• Arm 1:
  Daunorubicin 45 mg/m² IV on d 1-3 +
  Cytarabine 100 mg/m² IVCI on d1-7 +
  Gemtuzumab Ozogamicin 6 mg/m² IV on d 4

• Arm 2:
  Daunorubicin 60 mg/m² IV on d 1-3 +
  Cytarabine 100 mg/m² IVCI on d 1-7
SWOG S0106

• If CR was obtained, both arms completed consolidation chemotherapy
  – Ara-C 3 g/m² IV q 12 hours on d 1, 3, 5 q 28 days

• If CR was still present, patients were randomized again:
  – Gemtuzumab Ozogamicin 5 mg/m² IV q 28 days x 3 doses
  – vs. observation
SWOG S0106

- CR rates were similar:
  - 66% ara-C + dauno + gemtuzumab
  - 69% ara-C + dauno

- Overall response rates similar:
  - 74% CR + CRi for both groups

- Relapse free survival was similar as well

- Fatal adverse events possibly related to treatment during induction were higher in the group that got gemtuzumab:
  - 5.8% vs. 0.8%
  - 1 death due to sinusoidal obstruction syndrome
• In terms of post-consolidation randomization:
  • 150 patients randomized to maintenance with gemtuzumab or observation:
    – 36 patients who received gemtuzumab relapsed
    – 25 patients who received observation relapsed
  • No evidence of improved disease free survival whatsoever
SWOG S0106

• Gemtuzumab in induction
• Maintenance therapy
  – Is the fact that gemtuzumab is the maintenance regimen important?
SWOG S0106

- Gemtuzumab in induction
- Maintenance therapy
  - Is the fact that gemtuzumab is the maintenance regimen important?
  - Yes
    - Resistance to gemtuzumab ozogamicin is associated with P glycoprotein expression
      - Pgp is a cell surface molecule that actively transports drugs out of a cell
      - Gene for Pgp is *MDR-1* (multidrug resistance gene)

A Phase II Study of Maintenance Therapy with Decitabine Following Standard Induction and Cytogenetic Risk-Adapted Intensification in Previously Untreated Patients with AML < 60 Years

CALGB 10503
• Inclusion criteria:
  – Ages > 15 and < 60 yo
  – No prior azacitadine or decitabine
  – No prior treatment for leukemia or MDS
  • Except: leukopheresis, hydrea for leukostasis symptoms, one dose of cranial XRT for CNS leukostasis, growth factor support
Amonafide in Combination with Cytarabine is Equally Effective in Older and Younger Patients with Secondary AML: Final Data from the Phase 2 Study

Erba, HP et al.
ASH Abstract 1047
December, 2009
Ara-C and Amonafide

• Amonafide
  – Topoisomerase II inhibitor
  – Intercalates between DNA bases and inhibits topo II
  – May have activity in cells that overexpress Pgp

• Up to 70% of patients with secondary AML will have overexpression of Pgp

Ara-C and Amonafide

- 88 patients
  - Median age 62.5 (23-87 yo)
  - 51% had received prior leukemogenic therapy
  - 49% had a prior MDS documented
  - 48% had poor cytogenetics
  - 41% had intermediate cytogenetics
Ara-C and Amonafide

- Amonafide 600 mg/m² IV on d1-5
- Cytarabine 200 mg/m² IVCI on d 1-7

- Overall response rate: 42%
  - 39% CR, 3% CRi
- Median overall survival of entire population was 200 days; for responders 435 days

- For comparison:
  - Patients with poor cytogenetics had only a 32% CR rate in de novo AML

A Phase 3 Open-Label Randomized Study of Amonafide in Combination with Cytarabine Compared to Daunorubicin in Combination with Cytarabine in Patients with Secondary AML

CCCWFU 22307
CCCWFU 22307

• Randomization arm 1:
  – Amonafide 600 mg/m² IV over 4 hours on d 1-5
  – Cytarabine 200 mg/m² IVCI on d 1-7

• Randomization arm 2:
  – Daunorubicin 45 mg/m² IV over 30 minutes on days 1-3
  – Cytarabine 200 mg/m² IVCI on d 1-7

• Inclusion criteria:
  – Known and documented exposure to specific leukemogenic therapy of a specified nature for a non-myeloid condition
  – OR: documented MDS for at least 3 months prior to study entry (bone marrow biopsy to be centrally reviewed)
  – 18 yo or older
  – ECOG ≤ 2
  – Adequate cardiac, hepatic, and renal function
Single Agent Clofarabine Produces Durable Remissions in Patients with Acute Myelogenous Leukemia Who are ≥70, Have Intermediate or Unfavorable cytogenetics, Antecedent Hematological Disorders, or 2 or More Unfavorable Prognostic Factors

Erba HP, et al.
ASH Abstracts 2083
December, 2009
Clofarabine

- Purine analog
- Mechanisms of action:
  - Inhibits ribonucleotide reductase
  - Inhibits DNA polymerase
  - Induces apoptosis

Clofarabine

• Clofarabine 30 mg/m² IV on d 1-5
  – Reinduction or consolidation, 20 mg/m² IV on d 1-5

• 112 high risk patients:
  – >60 yo with at least one additional unfavorable prognostic factor:
  • Age > 70 yo
  • Antecedent hematologic disorder
  • ECOG 2
  • Intermediate or poor cytogenetics
Clofarabine

- 78% of patients had 2+ unfavorable factors
  - Overall response rate of 51%
  - Disease free survival of 26 weeks
  - Overall survival of 37 weeks
- 36% of patients had 3+ unfavorable factors
  - Overall response rate of 38%
  - Overall survival of 37 weeks

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Patients ≥ 70 (n=69)</th>
<th>Patients w/AHD (n=41)</th>
<th>Patients w/ Intermediate Cytogenetics (n=46)</th>
<th>Patients w/ Unfavorable Cytogenetics (n=62)</th>
</tr>
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<tbody>
<tr>
<td>ORR</td>
<td>39%</td>
<td>51%</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>CR</td>
<td>33%</td>
<td>39%</td>
<td>48%</td>
<td>32%</td>
</tr>
<tr>
<td>Median DoR</td>
<td>65 weeks (17, NE)</td>
<td>≥37 weeks* (37, NE)</td>
<td>65 weeks (65, NE)</td>
<td>41 (28, NE)</td>
</tr>
<tr>
<td>Estimated median DFS</td>
<td>51 weeks (17, NE)</td>
<td>51 weeks (26, NE)</td>
<td>65 weeks (17, NE)</td>
<td>34 weeks (23,51)</td>
</tr>
<tr>
<td>Estimated median OS</td>
<td>31 weeks (17, 55)</td>
<td>50 weeks (30, NE)</td>
<td>53 weeks (33, NE)</td>
<td>31 weeks (19, 48)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>13%</td>
<td>7%</td>
<td>11%</td>
<td>10%</td>
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WFUBMC Clofarabine Trials

- **CCCWFU 22109**: A Phase I Open-Label Study of Continuous Infusion Clofarabine in Adult Patients with Refractory or Relapsed AML

- **CCCWFU 22110**: A Phase II Study Evaluating Mechanisms of Resistance Following Treatment with Clofarabine and Daunorubicin in Newly Diagnosed AML Patients > 60 yo

- **CCCWFU 29307**: A Phase IIa Open-Label Dose Confirmation Study of Oral Clofarabine in Previously Untreated Adult Patients with MDS

- Ready for accrual in the next 1-2 months
CLL
Chronic Lymphocytic Leukemia
Chronic Lymphocytic Leukemia

• Leuko-: white; -emia: in blood
• Ann Arbor Staging System does not apply
• Many patients diagnosed incidentally and are asymptomatic from their disease
• 10,000 new diagnoses each year in US
• Only 4600 deaths per year in US
• Median age 72 years
Lymphoma: Concepts

Lymphoma

SLL

CLL

Leukemia
Normal B Cell Development

• Primary follicles
  – Naïve B cells

• Secondary follicles
  – B cells that are proliferating after encountering an antigen
  – Naïve B cells in secondary follicles get pushed to periphery and form the mantle zone
  – Have germinal centers
    • Dark zone: centroblasts
    • Light zone: centrocytes
    • Tingible body macrophages: destroy B cells with “wrong” antibodies
CLL: Pathophysiology

- Centroblasts are where the B cells normally undergo somatic hypermutation in their V genes
  - More mature

- A sequence that differs from germline by 2% or more is considered mutated

- If CLL cells have 2% or more mutations in their IgVH sequence, this is associated with a more indolent course of disease

CLL: Pathophysiology

• IgV<sub>H</sub> somatic mutations
  – Indolent
  – Median OS 25 years
• Unmutated IgV<sub>H</sub> genes
  – More aggressive
  – Median OS 8 years
• Replaces prior notion that CLL cells are stuck in G<sub>0</sub>
• ~50% of patients with CLL will have unmutated IgVH

CLL: Pathophysiology

- **CD 38:**
  - expressed when B cells are activated to allow for interaction with other cells
  - amplifies signaling of B cell receptors and inhibits apoptosis through the Src pathway
  - >30% expression is considered unfavorable

- **ZAP-70 (zeta chain associated protein 70):**
  - serves a similar function on normal T cells
  - aberrantly expressed on CLL cells
  - exact cutoff unclear
  - lab reproducibility is poor

CLL: Prognostic Factors

- **Favorable:**
  - <2% mutation in IgVH
  - <30% CD38 expression
  - ZAP-70 expression

- **Cytogenetics…..**

CLL: Cytogenetics

- Not diagnostic
- Abnormalities detected in over 80% of CLL patients

**TABLE 1. INCIDENCE OF CHROMOSOMAL ABNORMALITIES IN 325 PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.**

<table>
<thead>
<tr>
<th>Aberration</th>
<th>No. of Patients (%)</th>
</tr>
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<tbody>
<tr>
<td>13q deletion</td>
<td>178 (55)</td>
</tr>
<tr>
<td>11q deletion</td>
<td>58 (18)</td>
</tr>
<tr>
<td>12q trisomy</td>
<td>53 (16)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>23 (7)</td>
</tr>
<tr>
<td>6q deletion</td>
<td>21 (6)</td>
</tr>
<tr>
<td>8q trisomy</td>
<td>16 (5)</td>
</tr>
<tr>
<td>t(14q32)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>3q trisomy</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Clonal abnormalities</td>
<td>268 (82)</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>57 (18)</td>
</tr>
</tbody>
</table>

*One hundred seventy-five patients had one aberration, 67 had two aberrations, and 26 had more than two aberrations.*

CLL: Prognostic Factors

- **Favorable:**
  - <2% mutation in IgVH
  - <30% CD38 expression
  - ZAP-70 expression

- **Cytogenetics**

CLL: Prognostic Factors

- Favorable:
  - <2% mutation in IgVH
  - <30% CD38 expression
  - ZAP-70 expression
  - del 13q

CLL: Diagnosis

- (+) CD5, CD19, CD23
- (+/-) CD20 (weak expression)
- (+/-) surface immunoglobulin
- Light chain restriction
- (-) for cyclin D1 and CD10
- Do not need a bone marrow for diagnosis
**CLL: Criteria for Diagnosis**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NCI-WG 1996*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB Lymphocytes</td>
<td>&gt; 5 x 10⁹/L</td>
</tr>
<tr>
<td>Morphology</td>
<td>Not specified</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>1. &gt; 1 B cell marker (CD19, CD20, or CD23) and CD5; absence of other pan-T cell markers</td>
</tr>
<tr>
<td></td>
<td>2. Monoclonal expression of K or λ chain</td>
</tr>
<tr>
<td></td>
<td>3. Low-density surface Ig</td>
</tr>
<tr>
<td>Atypical cells (prolymphocytes)</td>
<td>&lt;55% and/or 15 x 10⁹/L</td>
</tr>
<tr>
<td>Duration of lymphocytosis</td>
<td>&gt;4 weeks</td>
</tr>
<tr>
<td>Bone marrow lymphocytes</td>
<td>&gt;30%</td>
</tr>
</tbody>
</table>

* Updated in 2008

<table>
<thead>
<tr>
<th>Risk</th>
<th>Rai Stage</th>
<th>Location</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>Lymphocytosis only</td>
<td>&gt; 10 years</td>
</tr>
<tr>
<td>Intermediate</td>
<td>I</td>
<td>Lymphocytosis, Lymphadenopathy</td>
<td>&gt; 8 years</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Lymphocytosis, Splenomegaly</td>
<td>~ 5 years</td>
</tr>
<tr>
<td>High</td>
<td>III</td>
<td>Lymphocytosis, Hb &lt; 11.0 due to progression of CLL in the marrow</td>
<td>8-12 months</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Lymphocytosis, Plts &lt; 100K due to progression of CLL in the marrow</td>
<td>8-12 months</td>
</tr>
</tbody>
</table>
CLL: Indications for Treatment

- Significant B symptoms
- Recurrent infections
- Symptomatic lymphadenopathy
- Symptomatic splenomegaly
- “Symptomatic” bone marrow involvement
  - Stage III or IV disease
- Note that the absolute white cell count is NOT an indication to treat!
  - Doubling time of < 6 months
  - Increase of > 50% over 2 months

Phase III study of asymptomatic patients with untreated CLL randomized to early intervention vs. observation with later treatment in the high risk CLL population

CALGB 10501
CALGB 10501

• Upon enrollment, patients were assessed for their IgVH mutational status

• If they were $\geq 98\%$ IgVH unmutated (high risk)
  – Randomized to immediate treatment with FR
  – vs. observation

• Currently closed to accrual
CLL: Treatment

- Purine analog-based
- FCR x 6 cycles
  - Fludarabine 25 mg/m² IV days 1-3
  - Cyclophosphamide 250 mg/m² days 1-3
  - Rituximab 375 mg/m² with cycle 1; 500 mg/m² in cycles 2-6
- Repeat bone marrow three months after last cycle
- 95% ORR, 70% CR
- Median TTP:
  - 80 months for CR
  - 80 months for nPR
  - 27 months for PR
- Presented 5 year follow up data at ASCO 2006 and this was durable

Keating MJ et al. JCO 2005
Tam CS et al. JCO abstr 2007

FDA Approved 2/18/10
CLL: FCR Treatment

- **Prophylaxis:**
  - **Tumor lysis:**
    - Allopurinol 300 mg daily
    - Hold rituximab with first cycle; split dose if WCC still >20K
  - **Infection:**
    - TMP-SMX DS one tablet bid q M, W, F
    - Acyclovir 400 mg bid
    - Antibacterials if became neutropenic
    - Growth factors if needed
  - **Anti-emetic**
- **FCR Downsides:**
  - Cytopenias persist for up to a year after completion of treatment
  - Multi-day regimen
  - Can be tough on patients
  - Fludarabine is associated with an autoimmune hemolytic anemia

Keating MJ et al. JCO 2005
Tam CS et al. JCO abstr 2007
CLL: PCR Treatment

- Pentostatin
  - Purine analog
  - Pentostatin 2 mg/m² vs 4 mg/m² on day 1
  - Cyclophosphamide 600 mg/m² on day 1
  - Rituximab 375 mg/m² on day 1
- Supportive meds:
  - 1500 cc NS on day of treatment
  - Anti-emetic
  - Tumor lysis prophylaxis
  - Infectious prophylaxis

- Front line data:
  - ORR 95%
  - CR 70%
  - 69% of patients were treatment failure free at 4 years
- Much better tolerated – better choice for older patients
- Treatment completed in one day
- Far less risk for AIHA
- No prolonged cytopenias

Kay NE et al Blood 2007
CLL: Treatment

- Alemtuzumab (Campath)
  - Anti-CD52 monoclonal antibody
  - FDA approved for front line use on 9/17/07
  - Compared to chlorambucil with similar OS rates
    - Allowed for crossover
- CMV reactivation
  - Ganciclovir is more effective than acyclovir

CLL: Treatment

• Chlorambucil
  – Alkylator
  – Oral
  – Increases risk of secondary AML
  – ORR ~40%
  – CR 2%
  – Is the “standard arm” for many randomized controlled trials in CLL.

CLL: Treatment

• Bendamustine
  – Combination purine analog/alkylating agent
  – FDA approved for single agent use in CLL on 3/20/08
  – Randomized controlled trial:
    • 301 untreated, symptomatic patients with CLL
    • Bendamustine 100 mg/m2 IV on days 1, 2 q 28 days x 6 cycles
    • Chlorambucil 0.8 mg/kg/day po on days 1 and 15 q 28 days x 6 cycles
    • ORR 59% for bendamustine; 26% for chlorambucil
    • CR 8% for bendamustine; >1% for chlorambucil
    • Median PFS for bendamustine 18 months; 6 months for chlorambucil

Knauf WU, et al JCO 2009
Bendamustine Combined with Rituximab in First-Line Therapy of Advanced CLL: A Multicenter Phase II Trial of the German CLL Study Group

Fisher K et al.
ASH Abstract 205
December, 2009
Bendamustine and Rituximab

- Bendamustine 90 mg/m² IV on d 1,2
- Rituximab 375 mg/m² on day 1 of first cycle
  - 500 mg/m² with subsequent cycles
- 28 day cycles; maximum of 6
Bendamustine and Rituximab

- 114 patients, previously untreated
- Overall response rate 90.9%
  - CR rate 32.7%
  - After 18 months, 75.8% of patients were still in remission
    - Median PFS was not reached
  - With 17p-, ORR 42.9%
  - Unmutated IgVH ORR 88.9%
Lenalidomide

- Similar to thalidomide
- Immunomodulator
  - Inhibits secretion of pro-inflammatory cytokines (TNF-alpha)
- Anti-angiogenic
- “Anti-neoplastic”
- CLL cells produce and express cell surface receptors for pro-survival cytokines
  - TNF-alpha
  - VEGF
- Creates an autocrine loop that leads to prolonged survival

Kay NE Leuk Res 2004
Kay NE et al, Leukemia 2002
Lenalidomide in CLL

- Phase II non-randomized study
- 45 patients with relapsed or refractory CLL
  - 51% were refractory to fludarabine
- Lenalidomide 25 mg po days 1-21 of a 28 day cycle
- Rituximab was added upon disease progression
- ORR 47%; 9% CR

CC-5013-CCL-001 (CCCWFU 27106)

- Phase 2/3 parallel group study
- Comparing 2 dose regimens of lenalidomide in relapsed or refractory CLL patients
  - 10 mg po qd x 28 days q 28 days
  - 25 mg po qd x 21 days q 28 days

- Plan was to enroll 310 patients
- After 18 patients enrolled
  - Marked activity noted (decreased ALC)
  - Temporary suspension:
    - 4 cases of tumor lysis syndrome
    - 2 associated with renal failure and tumor flare reaction
    - 2 fatalities
Lenalidomide

• Redesigned to phase I study only
  – ie: determine maximum tolerated dose level

• Separate protocol generated for phase 2:
  – After MTD in CLL patients is identified,
  – Evaluate cyclic vs. continuous dosing in a gentle stepwise dose escalation

  – CC-5013-CCL-009…. 
CC-5013-CLL-009 (CCCWFU 27109)

• Relapsed or refractory CLL
• Randomized to 3 different arms:
  – 5 mg po qd x 28 days → 10 mg → 15 mg → 20 mg → 25 mg (or highest dose tolerated)
  – 10 mg po qd x 28 days → 15 mg → 20 mg → 25 mg (or highest dose tolerated)
  – 15 mg po qd x 28 days → 20 mg → 25 mg (or highest dose tolerated)
CC-5013-CLL-009 (CCCWFU 27109)

• Inclusion criteria:
  - \( \geq 18 \) yo
  - Relapsed or refractory to 1 to 3 regimens
    • At least one must be a purine analog
  - Meet criteria for needing treatment
CC-5013-CLL-002 (CCCWFU 27209)

- Phase 3 randomized controlled trial evaluating lenalidomide as *maintenance* therapy after second line chemotherapy
- Lenalidomide 2.5 mg po qd x 28 days (vs. placebo) → 5 mg po qd x 28 days x 5 cycles → 10 mg po qd x 28 days
CC-5013-CLL-002 (CCCWFU 27209)

• Inclusion criteria:
  – 18 yo or older
  – Must have been treated with a purine analog-containing regimen in the first and/or second line treatment
  – Must have a minimum response of PR after completion of their second line therapy prior to randomization
  – Last cycle of second line treatment must have been completed between 8 and 16 weeks prior to randomization
  – ECOG 0-2
Combination Therapy with Lenalidomide and Rituximab in Patients with Relapsed CLL

Ferrajoli A, et al.
ASH Abstract 206
December, 2009
Lenalidomide

• Rituximab 375 mg/m² IV on days 1, 8, 15, and 22 of cycle 1
  – Then once every 4 weeks during cycles 3-12
• Lenalidomide 10 mg/day starting on day 9 of cycle 1
  – continued daily for 12 28-day cycles
Lenalidomide

- 60 patients accrued
- 37 patients have received at least 6 cycles for evaluation
- ORR 68%
  - No CRs
Ofatumumab

- Fully human monoclonal antibody to CD20
  - Results in cell lysis, through CDC and ADCC
- Binds to a different epitope (small loop) than rituximab
- Slower off-rate; more stable binding
  - In vitro studies show that rituximab-resistant cells will still lyse with ofatumumab

Ofatumumab

- Phase I/II study was performed in 33 patients with relapsed or refractory CLL
- Dose escalation performed; MTD not reached
  - A: 100 mg then 500 mg IV qwk x 4 total doses
    - 3 patients
  - B: 300 mg then 1000 mg IV qwk x 4 total doses
    - 3 patients
  - C: 500 mg then 2000 mg IV qwk x 4 total doses
    - 27 patients

Ofatumumab

- Adverse events:
  - Infusional reactions
  - Cytopenias
  - Infection

- FDA approved 10/28/09

Ofatumumab Combined with Fludarabine and Cyclophosphamide Shows High Activity in Patients with Previously Untreated CLL: Results from a Randomized Multicenter International Two-Dose Parallel Group, Phase II Trial

Wierda WG, et al.
ASH Abstract 207
December, 2009
Ofatumumab

- 61 untreated patients with CLL
- Ofatumumab 500 mg or 1000 mg +
- Fludarabine 25 mg/m² IV on d 1-3 +
- Cyclophosphamide 250 mg/m² IV on d 1-3
- 28 day cycles x 6
Ofatumumab

- Mean PFS has not been reached – 8 months follow up to date

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=31)</th>
<th>Group B (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ofatumumab 500 mg</td>
<td>Ofatumumab 1000 mg</td>
</tr>
<tr>
<td>Age, years</td>
<td>56 (38-73)</td>
<td>56 (38-72)</td>
</tr>
<tr>
<td>Serum β₂-microglobulin, mg/L</td>
<td>3.96 (1.79-11.50)</td>
<td>3.97 (2.13-10.70)</td>
</tr>
<tr>
<td>ALC, ×10⁹/L</td>
<td>95.4 (3.5-302)</td>
<td>77.4 (8.4-307)</td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rai Stage III/IV*</td>
<td>12 (39)</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Binet Stage C*</td>
<td>8 (26)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Unmutated IGHV</td>
<td>16 (52)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Genomic abnormalities by FISH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17p del</td>
<td>2 (6)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>11q del</td>
<td>7 (23)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>4 (13)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>No abnormality</td>
<td>5 (16)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>13q del (sole abnormality)</td>
<td>12 (39)</td>
<td>13 (43)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (52)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>1-2</td>
<td>15 (48)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Response rates (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response, %</td>
<td>32 (17, 51)</td>
<td>50 (31, 69)</td>
</tr>
<tr>
<td>Overall response, %</td>
<td>77 (59, 90)</td>
<td>73 (54, 88)</td>
</tr>
</tbody>
</table>

*At the time of screening.
CLL: Concepts

- Cytotoxic therapy vs immunologic therapy
  - Antibodies alone be sufficient?