Chronic Lymphocytic Leukemia

Joseph M. Flynn, D.O., MPH, FACP
Vice Chair for Quality, Department of Medicine
Co-Director, Division of Hematology
The Ohio State University Comprehensive Cancer Ctr
Arthur G. James Cancer Hospital and
Richard J. Solove Research Institute

Introduction

• One of the most common types of leukemia in the Western Hemisphere
• Estimates of approximately 15,110 patients diagnosed annually
  – More common in males than females
• Over 4,000 deaths related to CLL

The Milwaukee Sentinel
June 14, 1982

Not all leukemias are severe

TO YOUR GOOD HEALTH

The Milwaukee Sentinel
June 14, 1982
### Case
- Pt is a 55 year who presented in consult after found to have elevated white blood cells on new employment physical examination.
- WBC 176,000, hgb 11.5, platelets 111
- Differential with 2% neutrophils, 98% lymphocytes
- Physical examination with multiple cervical nodes, largest measuring 2x2 cm
- Chemistries normal
- FISH without mutation
- IGVH mutated

### Diagnosis
- **IWCLL2008 criteria**
  - Absolute B-cell lymphocyte count of greater than 5000/mL
  - Generally small, mature lymphocytes
  - Large prolymphocytes > 55%
  - Favor B-cell PLL

- **Confirmatory Immunophenotype:**
  - CLL cells co-express antigens, CD5 CD19, CD20, and CD23. Cells generally express restriction of either kappa or lambda immunoglobulin light chains
  - Patient with lymphadenopathy, or splenomegaly and ALC < 5000/mL is consistent with Small Lymphocytic Lymphoma (SLL)
  - Lymphnode biopsy required

### Staging
- There are two accepted staging methods
  - **Binet staging system**
  - **Rai staging system**
    - Lymphocytosis: Rai stage 0
    - Enlarged nodes: Rai stage 1
    - Splenomegaly: Rai stage 2
    - Anemia: Rai stage 3
    - Thrombocytopenia: Rai stage 4
### Staging

- Modified Rai:
  - Lymphocytosis: Low risk
  - Rai stage 1 or 2: Intermediate-risk disease
  - Rai stage 3 or 4: High-risk

### Pretreatment Evaluation

- CT scans: Certain instances
- Pet Scans: Only if considering a Richters transformation
- Cancer Screening: Patients at increased risk of second primary malignancies
- Infectious prophylaxis: Recommended

### Pretreatment Evaluation

- Complete Blood Count and Differential: Required
- Immunophenotype: Required
- Bone marrow biopsy and aspirate:
  - If treatment planned
- Chemistries: Required
- Cytogenetics: Favored

### Monoclonal B-cell Lymphocytosis (MBL)

- Phenotypically consistent with CLL
- Malignant lymphocytes $< 5000$/mL
  - No cytopenias
  - No adenopathy or splenomegaly
- Frequency of MBL ranges from $<1\%$ to over $5\%$, increasing with age
Monoclonal B-cell Lymphocytosis (MBL)

- Incidence increases in family members of patients with CLL
- Estimates of 1-2% per year transform to CLL
  - Similar to MGUS and myeloma

Genetics of CLL

- Prognosis is linked to genetic mutations present
  - No prospective trial has shown treating based on these improves outcome.
- Commonest mutations include:
  - del(13q14): most common
  - Trisomy 12
  - del(11q22.3)
  - del(17p13.1)
  - del(6q22.3)
- P53 mutation occurs in about 5 percent patients
  - del(17p13.1) loci
- IgVH mutational status
- CD38/ZAP-70

CLL Outcome From Diagnosis by Interphase Chromosomal (FISH) Abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% Pts</th>
<th>Median Time to Treatment (mo)</th>
<th>Median Overall Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(17)(p13.1)</td>
<td>7</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>del(11)(q22.3)</td>
<td>18</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>16</td>
<td>33</td>
<td>114</td>
</tr>
<tr>
<td>del(13)(q14)</td>
<td>55</td>
<td>49</td>
<td>133</td>
</tr>
<tr>
<td>None Detected</td>
<td>18</td>
<td>92</td>
<td>111</td>
</tr>
</tbody>
</table>


PFS by Interphase Cytogenetics: E2997

Overall Survival is Influenced by IGHV Gene Mutation Status


Indications for Treatment

- Massive or symptomatic lymph nodes: >10 cm
- Massive splenomegaly: >6 cm below the left costal margin
- Progressive lymphocytosis or lymphocyte doubling time of less than 6 months.
- Autoimmune anemia or thrombocytopenia that is poorly responsive to standard treatment

Indications for Treatment

- Constitutional symptoms
  - Unintentional weight loss of 10% or more within the previous 6 months
  - Profound fatigue
  - Fevers for 2 or more weeks
  - Night sweats for more than 1 month
- Cytopenias: Anemia or thrombocytopenia

Drug Discovery for CLL

- Liposomes
- Chlorambucil
- Fludarabine
- Rituximab
- Campath-1H
- Prednisone
- Ofatumumab

- 2000: Fludarabine shown better than Chlorambucil
- 2005: Fludarabine in Comb with Cyclophosphamide
- 2002: Fludarabine in Combination with Rituximab
**Treatment of CLL**

- Chlorambucil therapy standard since 1950’s
  - Response rate of 50%
  - No complete remissions
- Fludarabine standard from late 1990’s
  - Superior ORR (63%)
  - CR (20%)
  - Superior PFS

**Combination Regimens**

- Fludarabine and Rituximab
  - ORR – 84%, CR – 38%
- Pentostatin, Cyclophosphamide, Rituximab
  - ORR – 91%, CR – 41%
- Fludarabine, Cyclophosphamide, Rituximab
  - ORR – 95%, CR – 70%

**Treatment of CLL**

- Fludarabine/Cylophosphamide
  - ORR (74%)
  - CR (25%)
  - Superior PFS as compared to Fludarabine
- Fludarabine/Cyclophosphamide
  - Associated with:
    - Cytopenias
    - Enhanced immune suppression
    - Late risk of secondary leukemia

**Bendamustine + Rituximab in CLL**

- Old Eastern German drug with uncertain mechanism of action but most similar to melphalan in NCI60 cell line screen
- Cytopenias and infections most common
- ORR 59%; with CR in 9%
- 45% response in fludarabine-refractory pts
- 7% response in del(17p13.1) pts (not effective)
- PFS 14 months for pts treated with this (higher in responders)
- Bendamustine + rituximab an active therapy in early-relapsed CLL, must monitor counts closely

Alternative Strategies For CLL

• Immune-based therapy
  « Peptide therapy (antibodies, SMIP)
  « Immune enhancing molecules (lenalidomide)
  « Cytokines (IL-21)
• Targeted small molecule therapy
• Allogeneic Immunotherapy

Antibody Therapy

• Alemtuzumab
  – Humanized anti-CD52 antibody introduced in 1980's for purposes of immune suppression
  – 33% response rate in fludarabine refractory CLL
• Ofatumumab
  – CD20 antibody
  – Recently approved
Alemtuzumab

- Humanized antibody that targets CD52 on majority of lymphocytes, NK cells, monocytes, dendritic cells, and neutrophils
- Effective in fludarabine-refractory CLL with 33% response rate; favorable features of response include
  - Absence of lymph nodes > 5 cm and performance status 0-1
- Toxicities of alemtuzumab have limited use
  - Infusion toxicities (particularly with IV formulation)
  - Opportunistic infections due to immune depletion of T-cells
- Supportive care includes prophylaxis for PCP and VZV infections and CMV monitoring (or prophylaxis)

Antibody Therapy

- Lumiliximab
  - IgG1 macaque-human anti-CD23 monoclonal antibody
  - Phase I single agent study demonstrated good safety profile but only very modest pharmacologic activity

Ofatumumab

- Humanized CD20 antibody with different binding site, improved ADCC, CDC, and direct killing against CLL cells versus rituximab
- Administered as 8 weekly doses followed by 4 monthly doses (dose 1, 300 mg; doses 2–12, 2000 mg); 6 months of therapy
- Overall response rate of 58% for the fludarabine & alemtuzumab refractory and 47% for the bulky LN, fludarabine-refractory pts
- PFS approximately 6 months; OS 14–15 months
- Cytopenias and infections common; 13 (10%) pts had fatal infections within 30 days of Rx
- Better antibody than rituximab, impact will be noted in earlier treated pts

Lenalidomide

- Thalidomide derivative with novel properties that afford several novel anti-leukemia effects
- Clinical trials have demonstrated activity in patients with myelodysplastic syndrome and multiple myeloma

**Lenalidomide**

- **Mechanisms of action**
  - Down-modulation of cytokines including TNF-α, and IL-6 that influence the microenvironment
  - Inhibition of VEGF and other pro-angiogenesis mediating cytokines
  - Enhancement of innate immune system activation that leads to synergy when combined with antibody therapies

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**Flavopiridol (Alvocidib)**

- Synthetic flavone
- Inhibits cyclin-dependent kinases
- Reduces RNA polymerase II phosphorylation
- Down-regulates Mcl-1
- Induces p53-independent apoptosis (4-hr LC50 = 1.15 mM)

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**Dinaciclib (SCH72765)**

- Cyclin Dependent Kinase Inhibitor
- Selected versus other pre-clinical candidates based upon in vivo therapeutic index (10) in ovarian xenograft model whereas other known CDK inhibitors had very low therapeutic index (<1-2)
- Broad inhibitor of CDK1, CDK2, CDK5, CDK9 (1-5 nM) > CDK4, CDK7 (100 nM) >> GSKβ (800 nM)

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**The Future is Now**
CLL Cell Viability after Treatment with Dinaciclib

![Graph showing cell viability](image)

**SCH 727965**

2 hr exposure, 24 hr analysis

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**Partial Response by Mutation**

![Graph showing mutation response](image)

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**Frequency of Grades 3 and 4 Treatment Related Adverse Events in ≥10% Subjects**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>n=39 (%)</th>
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</thead>
<tbody>
<tr>
<td>Subjects Reporting Any Adverse Event</td>
<td>36 (92)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29 (74)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (26)</td>
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<tr>
<td>Aspartate Aminotransferase Increased</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Lymphocyte Count Decreased</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Tumor Lysis Syndrome</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Alanine Aminotransferase Increased</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>

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**Dramatic Activity in CLL**

Pt 1: 71 year, relapsed CLL, previous response to flavopiridol in 2007 with progressive disease after 8 months off therapy.

The patient was refractory to other biologic therapies.

In September 2009, started Dinaciclib (SCH727965).

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**Post cycle 7: 8.8 x 5.4 cm**

**Pre treatment: 17 x 9.2 cm**

**Post cycle 3: 12.2 x 6.5 cm**
**CAL-101/GS-1101**

- Selective orally available PI3K-δ inhibitor at doses tested
- Initial phase I dosing done in healthy volunteers with favorable human PK
- Target inhibition shown in vivo at 50-100 nM concentrations
- Pre-clinical activity in CLL based upon target specificity with no NK or T-cell toxicity

Herman S et al: Blood 2010

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**Results of PCI32765 in CLL**

- Response to therapy remarkable
  - De novo disease 85% with node/spleen response; 67% PR or CR based upon lymphocytosis (with continued improvement)
  - Relapsed disease: 89% with node response
  - 48% PR based upon continued lymphocytosis (with continued improvement)
- Response and remissions observed independent of high risk genomic features
- Only 3 pts off therapy due to PD!
- 81% of refractory patients on Rx at 12 months
- Toxicity profile modest (loose stools, dyspepsia, rash) with minimal myelosuppression

Byrd et al: ASCO 2011

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**PCI-32765: A Potent Btk Inhibitor**

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent irreversible Btk inhibition with IC₅₀ = 0.5 nM
- Inhibits BCR signaling and active in spontaneous canine model of lymphoma
- Orally available
- Once daily dosing results in 24-hr sustained target inhibition


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**CLL Pt 1 With Baseline Lymphocytosis**

Pretreatment  
Fifth month of treatment

Lymph node/Spleen PR with lymphocytosis
Other Active Targeted Therapies

- GA101—Type II CD20 antibody in phase III trial in elderly, untreated CLL-20% single agent response in relapsed CLL
- TRU-016—CD37 SMIP (antibody like molecule) in randomized phase II study (BT vs B) with 40% single agent response in previously treated CLL
- ABT263—bcl-2 antagonist in randomized phase II study (R vs R + ABT263) with 30% single agent response in previously treated CLL

Conclusions

- Not everyone needs chemotherapy
- Combination therapies standard in most patients with CLL
- Elderly patients, less is more
- Novel Therapeutic advances in CLL are available now
- Targeted non-cytoxic therapies offer effective, minimally toxic alternatives

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- IGVH mutated

WHAT DO WE DO?

The OSU CLL Team:

Clinical Faculty
John C. Byrd, MD Amy Johnson PhD
Michael Grever MD David Lucas PhD
Kristie Blum MD Raj Mutthusamy DVM, PhD
Leslie Andritsos MD Rosa Lapalombella PhD
Jeff Jones MD
Jennifer Woyach MD
Samantha Jaglowski MD
Gerard Lozanski MD (Pathology)
Nyla Heerema PhD (Cytogenetics)
Delilah Deam RN
Beth Wiley BS
Cheryl Keaufuer RN, BS
Weihong Chase RNP
Margaret Lucas PA
Gretchen McNalley RNP, PhD
Mollie Moran RNP
Sharon Waymer LPN

Technicians
Carolyn Cheney BS
Melanie Davis PhD
Ryan Edwards BS
Frank Frissora BS
Virginia Guetti DVM, PhD
Amber Gordon BS
Josh Hessler BS
Julita Jendrajewska BS
Arleta Lozanski BS
Courtney Prince BS
Asha Ramanunni MD, MS
Ellen Sass BS
Lisa Smith MS
Matthew Stefanovski
Will Towner BS
Amy Wagner BS
Katie Williams BS

http://cll.osu.edu/
Chronic Myeloid Leukemia in 2012

Rebecca B. Klisovic, MD
Assistant Professor of Internal Medicine
Division of Hematology
The Ohio State University Comprehensive Cancer Ctr
Arthur G. James Cancer Hospital and
Richard J. Solove Research Institute

Objectives

• Presentation and diagnosis of chronic myeloid leukemia (CML)
• Treatment options for CML
• Management of patients receiving tyrosine kinase inhibitors

CASE: Diagnosis

• RJ is a 58 year old male who had a CBC drawn as part of an annual physical exam
• No complaints except mild fatigue which he attributed to “old age”
• Physical exam unremarkable except for palpable spleen tip
• CBC reveals WBC 109K, Hgb 13.6, platelets 602K

Comparative Peripheral Blood Smear

Nórmal  Chronic Phase CML

Courtesy of John K. Choi, MD, PhD, University of Pennsylvania.
**DDx: Neutrophilic leukocytosis**

- Chronic myeloid leukemia (CML)
- Leukemoid reaction – history of infection, etc.
- Juvenile myelomonocytic leukemia – childhood disorder
- Chronic myelomonocytic leukemia – monocytosis, dysplasia
- Bcr-Abl negative CML
- Chronic eosinophilic leukemia – significant eosinophilia
- Chronic neutrophilic leukemia – mature granulocytes without immature precursors
- Other MPNs (PV, ET, MF)

**Clinical Presentation of Chronic Phase CML**

- Asymptomatic in ~50% of cases
- Common symptoms
  - Fatigue
  - Weight loss/anorexia
  - Abdominal fullness
- Common signs
  - Palpable splenomegaly

**Epidemiology: CML**

- About 15-20% of all leukemias in adults
- Annual incidence of 1-2 cases per 100,000 with slight male predominance
- About 4800 new diagnoses in the US each year
- As of November 2007, about 25,000 people living with CML
- With success of new agents, anticipate that more than 250,000 CML patients by 2040
- Only known risk factor: exposure to radiation

**Typical Laboratory Parameters by Phase of CML**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic</th>
<th>Accelerated</th>
<th>Blast</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>≥20 x 10^9/L</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Blasts</td>
<td>1%–15%</td>
<td>≥15%</td>
<td>≥30%</td>
</tr>
<tr>
<td>Basophils</td>
<td>↑ or normal</td>
<td>↑ ≥20%</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>↑ or normal</td>
<td>↓ or ↑</td>
<td>↓</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Myeloid hyperplasia</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Ph+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bcr-Abl</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

WBC = white blood cell; Ph+ = Ph chromosome–positive.
**Diagnosis of CML**

- History and physical
- CBC (including manual differential)
- Demonstration of Ph chromosome
- Bone marrow aspirate and biopsy strongly recommended
  - Cytogenetics: to detect chromosomal abnormalities not detectable by PB FISH
  - Clarification of disease phase

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**The Ph Chromosome and the bcr-abl Gene**

- t(9;22) translocation
- bcr-abl gene structure

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**Cytogenetic Abnormality of CML: the Ph Chromosome**

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**Molecular Methods for Detecting bcr-abl**

- FISH
- Interphase
- Metaphase

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Courtesy of Charles L. Sawyers, MD, UCLA.
**Options for Monitoring Cytogenetic Response in CML**

<table>
<thead>
<tr>
<th>Test</th>
<th>Target</th>
<th>Tissue</th>
<th>Sensitivity (%)*</th>
<th>Use</th>
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</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Ph</td>
<td>BM</td>
<td>1-10</td>
<td>• Confirm diagnosis of CML</td>
</tr>
<tr>
<td></td>
<td>chromosome</td>
<td></td>
<td></td>
<td>• Evaluate cytogenetic abnormalities other than Ph chromosome (e.g., clonal evolution)</td>
</tr>
<tr>
<td>FISH</td>
<td>juxtaposition of bcr and abl</td>
<td>PB/BM</td>
<td>0.5-5</td>
<td>• Confirm diagnosis of CML</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Routine monitoring of cytogenetic response in clinically stable patients</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>bcr-abl mRNA</td>
<td>PB/BM</td>
<td>0.0001-0.001</td>
<td>• Routine measurement of MRD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Determine the breakpoints of the fusion genes</td>
</tr>
</tbody>
</table>

*Number of leukemic cells detectable per 100 cells.

BM = bone marrow; FISH = fluorescence in situ hybridization; PB = peripheral blood; MRD = minimal residual disease; RT-PCR = reverse transcriptase polymerase chain reaction.


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**Frontline Therapy**

- Tyrosine kinase inhibitors (TKIs) now mainstay of therapy for CML
- Imatinib approved in 2001 for treatment of CP CML
- Second generation TKI therapy versus imatinib as first line therapy
  - Dasatinib 18 month follow up
    - Shah N et al., Abstract #206
    - Kantarjian H et al., NEJM 2010; 362:2260-70
  - Nilotinib 18 month follow up
    - Hughes T et al., Abstract #207
    - Saglio G et al., NEJM 2010; 362:2251-9

Dasatinib and nilotinib FDA approved in 2010 for frontline therapy of CP CML

---

**Cytogenetic Responses**

<table>
<thead>
<tr>
<th>Complete: No Ph+ metaphases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major: 0-35% Ph+ metaphases</td>
</tr>
<tr>
<td>Partial: 1-34% Ph+ metaphases</td>
</tr>
<tr>
<td>Minor: 35-90% Ph+ metaphases</td>
</tr>
</tbody>
</table>

**Frontline TKI: % Complete Cytogenetic Response (CCyR)**

<table>
<thead>
<tr>
<th>DASISION TRIAL*</th>
<th>ENESTnd TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASATINIB</td>
<td>IMATINIB</td>
</tr>
<tr>
<td>No. patients</td>
<td>259</td>
</tr>
<tr>
<td>6 months</td>
<td>73</td>
</tr>
<tr>
<td>12 months</td>
<td>77</td>
</tr>
<tr>
<td>18 months</td>
<td>78</td>
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</tbody>
</table>

CCyR: absence of Ph-positive metaphases in at least 20 metaphase cells in BM

*Primary endpoint: CCyR at 12 months
### Frontline TKI: % Complete Cytogenetic Response (CCyR)

<table>
<thead>
<tr>
<th>Trial</th>
<th>DASATINIB</th>
<th>IMATINIB</th>
<th>NILOTINIB 300</th>
<th>NILOTINIB 400</th>
<th>IMATINIB</th>
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</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>259</td>
<td>260</td>
<td>282</td>
<td>281</td>
<td>283</td>
</tr>
<tr>
<td>6 months</td>
<td>73</td>
<td>59</td>
<td>67</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>12 months</td>
<td>77</td>
<td>66</td>
<td>80</td>
<td>78</td>
<td>65</td>
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<tr>
<td>18 months</td>
<td>78</td>
<td>70</td>
<td>85</td>
<td>82</td>
<td>74</td>
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</tbody>
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CCyR: absence of Ph-positive metaphases in at least 20 metaphase cells in BM

*Primary endpoint: CCyR at 12 months

### Frontline TKI: % Major molecular response (MMR)

<table>
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<tr>
<th>Trial</th>
<th>DASATINIB</th>
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<tbody>
<tr>
<td>No. patients</td>
<td>259</td>
<td>260</td>
<td>282</td>
<td>281</td>
<td>283</td>
</tr>
<tr>
<td>3 months</td>
<td>8</td>
<td>0.4</td>
<td>9</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>6 months</td>
<td>27</td>
<td>8</td>
<td>33</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>9 months</td>
<td>39</td>
<td>18</td>
<td>43</td>
<td>38</td>
<td>18</td>
</tr>
<tr>
<td>12 months</td>
<td>46</td>
<td>28</td>
<td>44</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>18 months</td>
<td>57</td>
<td>41</td>
<td>66</td>
<td>62</td>
<td>40</td>
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</tbody>
</table>

MMR: BCR-ABL transcript level ≤0.1% in PB on international scale (IS)

*Primary endpoint: MMR at 12 months
Frontline TKI: % Major molecular response (MMR)

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MMR: BCR-ABL transcript level ≤0.1% in PB on international scale (IS)

*Primary endpoint: MMR at 12 months

Frontline TKI: Other Outcomes

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<thead>
<tr>
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<th>ENESTnd TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DASATINIB</td>
<td>IM</td>
</tr>
<tr>
<td>No. patients</td>
<td>259</td>
<td>260</td>
</tr>
<tr>
<td>Treatment failure, No. (%)</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>AP/BP, No. (%)</td>
<td>(2.3)</td>
<td>(4.3)</td>
</tr>
<tr>
<td>D/C due to AEs, No. (%)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Death, any cause at 24 mo, No. (%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CML-related death at 24 mo, No.</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Managing TKI Toxicities

- GI upset (imatinib, dasatinib): largest, “fattiest” meal with large glass of water
- Muscle cramps: calcium supplements, tonic water
- Rash: topical or systemic steroids, consider dose reduction, interruption or discontinuation
- Elevated LFTs: Hold for Grade 2 and dose reduce at recovery; Grade 3 or 4, consider alternative therapy
- Pleural/pericardial effusions: systemic steroids, dose interruptions

TOXICITY PROFILES

<table>
<thead>
<tr>
<th></th>
<th>GR 3/4 HEME (%)</th>
<th>NON-HEME (%)</th>
</tr>
</thead>
</table>

QTc >500 msec
- Nilotinib trial: 1 patient on imatinib, no patients on nilotinib
- Dasatinib trial: 1 patient on imatinib, 1 patient on dasatinib
IRIS Long Term Follow Up

- No new safety issues in later years
  - Expected rates of cardiovascular disease, second malignancies, and infections
- Progression to AP/BC in 3% of patients who initially achieved CCyR (only 1 patient w/ PD in years 6 and 7)
- Time taken to achieve CCyR did NOT correlate with progression to AP/BC


What is the best strategy for frontline therapy?

<table>
<thead>
<tr>
<th>Imatinib 400 mg daily</th>
<th>Second generation TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longest track record of safety &amp; durability</td>
<td></td>
</tr>
<tr>
<td>Highly effective salvage therapy</td>
<td></td>
</tr>
<tr>
<td>No evidence of improved survival with MMR or CMR (yet?)</td>
<td></td>
</tr>
<tr>
<td>Cost issues not insignificant</td>
<td></td>
</tr>
</tbody>
</table>

AGENT | ANNUAL COST|
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib 400 mg daily</td>
<td>$66,500</td>
</tr>
<tr>
<td>Dasatinib 100 mg daily</td>
<td>$102,000</td>
</tr>
<tr>
<td>Nilotinib 300 mg BID</td>
<td>$118,000</td>
</tr>
</tbody>
</table>

**“Cash cost”: Walgreens 01/10/11**
What is the best strategy for frontline therapy?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Annual Cost</th>
</tr>
</thead>
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<tr>
<td>Imatinib 400 mg daily</td>
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**“Cash cost”: Walgreens 01/10/11**

Case: Monitoring

- RJ is started on nilotinib therapy
- He tolerates it well, and denies missing doses
- Repeat BM assessment at 12 months demonstrated resolution of CML with normal karyotype (CCyR)
- How should he be monitored in the future?

Monitoring Response: After CCyR

- FISH can be used to complement traditional karyotype until less than 5-10%
- After confirming CCyR in BM with cytogenetics, monitor with quantitative PCR bcr-abl from peripheral blood every 3-6 months in clinically stable patient
- Therapy changes should not be based on changes in transcript levels, but rising transcript levels should lead to further evaluation (i.e. BM with karyotype, etc.)
CASE: New symptom

- RJ has now been on CML therapy for 18 months, and has met all expected benchmarks
- He sees his internist for increasing heartburn and is diagnosed with GERD
- What should his internist keep in mind when treating this problem?

QTc Prolongation

- Prolongation of QTc is likely class effect
- Cautious use of agents which are associated with prolonged QTc; EKG monitoring if clinically necessary
- Amiodarone, citalopram, clarithromycin, moxifloxacin, methadone, sotalol
- WEBSITE: www.qtdrugs.org/

TKIs Drug Interactions

- PPI/H2 blockers: decrease drug levels of TKIs
- Acetaminophen: limit to 2000 mg/day or less
- Grapefruit juice: increases drug concentrations, should be avoided
- Warfarin: TKIs may cause an increase in INR; LMWH as alternative
- Caution with other agents that may prolong QTc

CASE: Poor response

- SS is a 25 year old female who has failed to achieve a meaningful cytogenetic response to all three commercially available TKIs.
- What alternatives are available?
### CML and Transplant

- With success of TKIs in this disease, the number of patients needing allogeneic transplant is decreasing.
- Reserved for patients who are intolerant or refractory to all TKIs.

### CML and Pregnancy

- Increased risk of birth defects with TKI exposure especially in 1st trimester.
- Counseling with women about risks.
- No apparent risk for men on TKIs who father children.
- For patients wishing to become pregnant:
  - Recommend not becoming pregnant, particularly if within first few years of therapy.
  - Discontinuation of TKI at least 2 weeks before attempting to conceive.
  - Use of interferon during pregnancy for count control.
  - Probably OK for re-initiation of TKI in 2nd-3rd trimester if needed.

### CASE: “I want a baby”

- MB is a 21 year old female with 2 year history of CML treated with imatinib.
- She approaches you about having a baby.
- How do you counsel her?

### THE FUTURE IN CML

- Additional TKIs underdevelopment with improved activity for patients refractory to currently available TKIs.
- Combination therapy studies: Interferon + TKI.
- Do patients need lifelong therapy?
### STIM Study

- **Stop Imatinib Study**: CMR required at least 5 molecular timepoints in preceding 2 years
- 100 patients with median follow up of 17 months
- Approximately 60% relapsed, usually within 6 months
- All relapsed patients responded to rechallenge with TKI


### CONCLUSIONS

- The emergence of tyrosine kinase inhibitors has revolutionized the treat of CML
- Given the success, the number of patients with CML is expected to increase significantly in the coming years
- Drug interactions exist with TKIs and may have significant clinical outcomes
- Allogeneic transplant remains an effective therapy, but is reserved for TKI failures