Welcome and Introductions

Living with Chronic Myeloid Leukemia

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Living with Chronic Myeloid Leukemia (CML)

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CML - Background

CML - Clinical Features

• Approximately 6,000 new US cases per year

• The typical age at presentation is 53 years

• We cannot identify convincing risk factors for most patients

• The disease is clinically divided into two phases
  ▪ Chronic phase
  ▪ Advanced phase
    • Accelerated phase
    • Blast crisis phase
CML – Chronic Phase

• Approximately 40 percent of patients are without symptoms (fatigue and night sweats can occur)

• 85 percent of newly diagnosed CML patients are in the chronic phase

• Prior to 2000, the chronic phase typically would last approximately 4-6 years before becoming highly aggressive
  ▪ After 2000 – it is not clear how long the chronic phase will last, but it is certainly greater than 10 years and may be long enough to allow most patients to live a normal lifespan

• Interventions can lead to durable responses in chronic phase

CML - Blast Crisis Phase

• Failure of normal blood cell development

• Responds poorly to medical intervention even today
  ▪ bleeding, infections, anemia common

• Typical survival approximately 6-9 months
  ▪ Bone marrow transplantation can help cure this phase
First Hint at the Cause of CML: The Philadelphia Chromosome

46,XX,t(9;22)(q34;q11.2)

Philadelphia chromosome

BCR-ABL fusion gene (activated tyrosine kinase)

CML

The Philadelphia (Ph) Chromosome Leads to CML

BCR

chr 22

ABL

chr 9

Philadelphia chromosome

BCR-ABL fusion gene (activated tyrosine kinase)

CML

Forrest et al, 2008; Bakshi et al, 2008; Image courtesy of Larry Beauregard, Jr., PhD.
**Chronic Phase CML - Goals of Therapy**

- **Prevention of disease transformation to blast phase**
  - Chronic phase CML is not immediately life-threatening, so if blast phase can be prevented indefinitely, patients will be “functionally” cured
  - Will almost certainly require lifelong therapy
    - Chronically administered therapies should ideally be well-tolerated and minimally intrusive to everyday life
- **True disease cure - enabling patients to be off all therapies**
  - Allogeneic stem cell transplantation (~70% cure rate)
    - ~20% risk of short-term death (1-2 years)
    - ~50-60% risk of chronic graft vs host disease
      - “trading one disease for another”
  - Interferon-alpha
    - Low, but real, likelihood of effecting deep and durable molecular remissions (more than 20 years)
    - Difficult for many patients to tolerate
      - Long-acting preparations may be better tolerated
        - Signs of activity in CML as well as related conditions such as polycythemia vera

**FDA Approval, May 2001**
Imatinib - Conclusions

- Imatinib 400 mg daily was widely adopted as standard frontline treatment for chronic phase CML in 2001
- The observed overall survival with imatinib (85% after eight years) exceeds that of all previous CML therapies
  - 7% patients died due to CML after eight years of follow-up
- 82% of patients treated with imatinib achieved a complete cytogenetic response, which is associated with longer survival
  - However, only ~55% of all imatinib treated patients were still on the drug after eight years, and nearly all of these were in complete cytogenetic response
- Loss of response is uncommon, and if it occurs, usually does so within the first 3-4 years
- There have been no new concerning side effects observed with long term follow-up
  - Many patients experience bothersome side effects

IMATINIB RESISTANCE

Can disease monitoring identify patients at risk for doing poorly?
BCR-ABL Level Following 3 Months of Imatinib Predicts Overall Survival (PCR)

- BCR-ABL/ABL $\leq 9.84\%$
  - 8-yr OS: 93.3%
- BCR-ABL/ABL $> 9.84\%$
  - 8-yr OS: 56.9%

$P < .001$


Chromosome Response After 12-18 Months of Imatinib Predicts Outcome

- CCyR with $\geq 3$ log reduction
  - n=139 100%
  - Estimated rate at 60 months
  - $P = .11$
- CCyR with $< 3$ log reduction
  - n=54 98%
  - $P < .001$
- No CCyR
  - n=88 87%


CCyR = complete cytogenetic response
CML – Monitoring Recommendations

• At diagnosis, bone marrow biopsy with chromosome analysis, FISH for BCR-ABL and a quantitative BCR-ABL PCR test should be performed

• PCR testing should be done every three months following initiation of treatment

• Treatment milestone 1: BCR-ABL level of ≤10% on the International Scale after 3-6 months of treatment

• Treatment milestone 2: BCR-ABL level of ≤0.1% or a complete cytogenetic response after 12-18 months of treatment
  ▪ Lack of milestone achievement should prompt change of treatment

• Analysis for drug-resistant mutations in any patient with loss of response to treatment (assuming he/she is reliably taking the medication)

CURRENT TREATMENT OPTIONS
Treatment of Imatinib Resistance or Intolerance

- Imatinib resistance is commonly caused by drug-resistant mutations in BCR-ABL, the target of imatinib
  - Dasatinib and nilotinib retain activity against most imatinib-resistant mutations, and were approved by the FDA for patients with imatinib resistance or intolerance in 2006 and 2007, respectively
  - Bosutinib also retains activity against most imatinib-resistant mutations, and was approved by the FDA for patients with imatinib resistance or intolerance in 2012
- The T315I mutation is resistant to all four of these drugs, but sensitive to ponatinib, which was FDA-approved in 2012
  - Ponatinib is associated with a concerning rate of thrombotic events, and should only be used if all other TKI options have failed

Non-TKI Treatment of Imatinib Resistance or Intolerance

- Allogeneic stem cell transplantation can be curative, but is generally reserved for chronic phase patients with a history of prior advanced phase CML, resistance or intolerance to the approved TKIs, or the T315I mutation
- Omacetaxine was approved by the US FDA in 2012 as an injectable protein synthesis inhibitor that is active in a minority of cases that are resistant or intolerant to two or more previous TKIs
  - Low blood counts and hyperglycemia can occur
  - Responses do not appear to be highly durable
- Interferon is known to be highly and durably active in a minority of newly diagnosed CML cases, and is believed to be safe for use during pregnancy
  - Flu-like side effects are common
CML – Frontline Treatment for Chronic Phase CML Patients

• In 2010, the US FDA approved nilotinib and dasatinib for the treatment of newly diagnosed chronic phase CML patients based upon cytogenetic and molecular response rates that are superior to imatinib
  ▪ Many (but not all) patients tolerate these newer drugs better than imatinib

• The recommended starting dose of these medications is:
  ▪ Nilotinib 300 mg twice daily on an empty stomach
    • If side effects develop, 150 mg twice daily may be an option
  ▪ Dasatinib 100 mg once daily with or without food
    • If side effects develop, 20, 40, 50, 60, 70 or 80 mg once daily may be an option

Nilotinib and Dasatinib: Some Distinguishing Features

<table>
<thead>
<tr>
<th>Nilotinib</th>
<th>Dasatinib</th>
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<tr>
<td>Taken twice daily on an empty stomach</td>
<td>Taken once daily, with or without food</td>
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<tr>
<td>Risk of hyperglycemia</td>
<td>Risk of pleural effusion</td>
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<tr>
<td>Risk of pancreatitis</td>
<td>Risk of bleeding</td>
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<tr>
<td>Need to periodically monitor ECG (baseline, after one week, monthly thereafter due to FDA Black Box warning for QT prolongation and sudden death)</td>
<td>After-market evidence of pulmonary arterial hypertension</td>
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<td>After-market evidence of peripheral arterial occlusive disease and ischemic heart disease</td>
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Noteworthy Side Effects of the Approved TKIs for CML

- **Imatinib**
  - Edema/fluid retention
  - Muscle pain
  - Low phosphate level
  - GI effects (diarrhea, nausea)

- **Ponatinib**
  - Pancreatitis
  - Hypertension
  - Skin toxicity
  - Thrombotic events

- **Nilotinib**
  - Pancreatitis
  - Hyperglycemia
  - EKG changes
  - Cardiovascular events
  - Rash

- **Common Effects**
  - Low blood counts
  - Liver toxicity
  - Fatigue
  - Electrolyte Changes

- **Dasatinib**
  - Pleural effusions
  - Bleeding risk
  - Pulmonary arterial hypertension

- **Bosutinib**
  - Diarrhea
  - Nausea/vomiting
  - Rash

DISCUSSING QUALITY OF LIFE ISSUES WITH YOUR HEALTHCARE TEAM
Treatment-related Side Effects

• Many people living with CML suffer bothersome side effects of their TKI treatment
• Given that indefinite treatment is currently recommended, maximizing quality of life is particularly important
• It can be difficult to be certain sometimes whether particular symptoms are related to CML treatment or another cause
  ▪ A 2-week break from TKI therapy can be useful in assessing whether symptoms are related to CML treatment
    • Depending upon the symptom, supportive treatments may be beneficial. Alternatively, reducing the dose appropriately or switching to an alternate treatment may help
  ▪ Having multiple options is great news for patients!!!
    • In most instances, it is possible to find a drug that is both sufficiently active and well-tolerated

EMERGING TREATMENT OPTIONS
ABL001

- ABL001 binds to BCR-ABL in a region distinct from that bound by the five approved TKIs, and is designed to force BCR-ABL into an inactive conformation
  - Currently undergoing phase I clinical trial evaluation and showing some signs of activity
  - Likely will be combined with nilotinib in the future in an effort to suppress even more drug-resistant mutations and hopefully further improve treatment outcomes and be more safe than ponatinib

Treatment Discontinuation?

- A substantial proportion of patients have very deep remissions to the point where even PCR, the most sensitive test available, can no longer detect any CML
  - Hundreds of people with sustained (>1-2 years) undetectable levels of BCR-ABL have enrolled in trials examining the impact of treatment discontinuation
  - Approximately 50% of patients in this setting remain in deep molecular remissions for 5+ years
  - At the present time, treatment discontinuation should only be undertaken in the setting of a clinical trial, where patients can be carefully monitored
Summary

• There are three approved TKIs for newly diagnosed chronic phase CML patients that are active and in most cases, reasonably well-tolerated.
• Two additional TKIs are approved for patients with resistance to at least one TKI:
  • Stem cell transplantation, interferon and omacetaxine are less commonly used treatments.
• Careful monitoring of disease burden is essential for maximizing treatment outcomes.
• Discussing quality of life issues with your healthcare team is very important. The first goal of treatment is to achieve a deep remission. Once that is accomplished, minimizing side effects and maximizing quality of life/productivity assume greater importance. If indicated, TKI dose reduction can be attempted under medical supervision, or an alternate TKI treatment can be administered.
• New treatments currently being developed promise to further improve treatment outcomes, and continued participation of CML patients in clinical trials is necessary to facilitate further progress.

Question & Answer Session

The speaker’s slides are available for download at www.LLS.org/programs
Resources to make informed treatment decisions

The Leukemia & Lymphoma Society (LLS) offers:

• Live, weekly Online Chats that provide a friendly forum to share experiences and chat with others about anything from the initial phase of diagnosis to treatment and survivorship. Each chat is moderated by an oncology social worker and is password protected.
  ➢ WEBSITE: www.LLS.org/chat

• Free publications are available ranging from disease specific information to health insurance options and resources to help patients and their families cope with the financial aspects of cancer.
  ➢ WEBSITE: www.LLS.org/publications

• For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.
  ➢ TOLL-FREE PHONE: (800) 955-4572
  ➢ EMAIL: infocenter@LLS.org