A Focus on Chronic Myelogenous Leukemia

An innovative educational initiative developed for pharmacists

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

A knowledge-based CPE activity presented during the ICHP 2010 Annual Meeting

Friday, August 27, 2010
Drury Lane Theater and Conference Center
Oakbrook Terrace, IL
8:00 am – 9:00 am

Planned and conducted by ASHP *Advantage*.
Supported by an educational grant from Novartis Oncology.

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

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ACTIVITY FACULTY

Joseph S. Bubalo, Pharm.D., BCPS, BCOP
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Portland, Oregon

Joseph Bubalo, Pharm.D., BCPS, BCOP, is a board certified pharmacotherapy specialist and Assistant Professor of Medicine, Division of Hematology and Medical Oncology, Oregon Health and Science University (OHSU) in Portland, Oregon. He is also Assistant Professor of Pharmacy, courtesy faculty at Oregon State University School of Pharmacy. Dr. Bubalo is board certified in pharmacotherapy and oncology pharmacy. He is the Clinical Operations Manager at OHSU and is active in patient care and research.

Dr. Bubalo has received multiple research grants including funding for multiple studies investigating ways to improve the control of nausea and vomiting in various patient populations, as well as other topics in supportive care and infectious disease. He continues to look for alternate ways to decrease the adverse symptoms associated with cancer, antineoplastic, and surgical therapies. He has lectured and published on drug treatments and effects in cancer and stem cell transplant patients, and on drug therapy in the management of pain and nausea.

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The faculty and planners report the following relationships:

Joseph S. Bubalo, Pharm.D., BCPS, BCOP

Dr. Bubalo declares that he has served on the advisory board on patient adherence for Novartis.

Ron DeChant, M.S., B.S.Pharm.

Mr. DeChant declares that he has no relationships pertinent to this activity.

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

ACTIVITY OVERVIEW

Chronic myelogenous leukemia (CML) is a hematologic malignancy associated with a chromosomal mutation commonly known as the Philadelphia chromosome. CML accounts for 10-15% of all leukemia in the US, and, with dramatic progress in treatment over the past several years, most people with CML now survive at least six years after diagnosis. The average age at diagnosis is 67, and CML is rarely seen in children.

CML is divided into three phases that predict prognosis and influence treatment decisions. While the definitions for these phases can differ, they are primarily based on the number of immature white blood cells ("blasts") in peripheral blood or bone marrow: chronic phase (fewer than 10% blasts), accelerated phase (more than 10% but fewer that 20% blasts), and blast phase (also called acute phase or blast crisis, more than 20% blasts). Most patients are diagnosed in the chronic phase with mild symptoms, and treatment is very effective. As CML progresses, it does not respond as well to treatment. In the accelerated phase, the leukemia cells generally develop new chromosome changes in addition to the Philadelphia chromosome. In the blast phase, CML acts much like an acute leukemia.

Therapy is guided by multiple factors, including disease phase, mutational analysis, patient characteristics, and potential adverse effects. Imatinib mesylate is the standard for first-line therapy for patients in chronic phase. First approved by the Food and Drug Administration in 2001 as a novel, molecularly targeted, tyrosine kinase inhibitor (TKI), imatinib mesylate is a specific inhibitor of BCR-ABL. Imatinib has demonstrated favorable long-term results over six years of follow-up in clinical trials for response, overall survival, and safety when used as first-line therapy. For patients who develop resistance or intolerance to imatinib, current treatment guidelines recommend the second-generation TKIs dasatinib and nilotinib as second-line therapy for most patients. Nilotinib is 20-50 times more potent than imatinib with high affinity for BCR-ABL. Dasatinib is 300 times more potent than imatinib at BCR-ABL inhibition, and it also inhibits the SRC family tyrosine kinases. Both agents are active against a wide range of mutant clones (except T315I). Responses can be achieved with dasatinib or nilotinib after failure to two prior TKIs (imatinib/nilotinib or imatinib/dasatinib, respectively), but the responses may not be durable except in selected patients.

Preliminary results suggest that the use of second-generation TKIs for first-line therapy induce high rates of response comparable to imatinib. These results will require confirmation in Phase III clinical studies with imatinib as the control arm with study endpoints such as improved survival being evaluated. If nilotinib or dasatinib have superior efficacy results in these trials with comparable toxicity profiles, either drug could replace imatinib as standard front-line therapy. A third generation of TKIs that have activity against T315I mutant BCR-ABL tyrosine kinases are the subject of ongoing clinical trials. The potential effectiveness of different combination therapies is being investigated, as are novel aurora kinase inhibitors, omacetaxine, and HSP90 inhibitors.

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

ACTIVITY DESCRIPTION

Because of dramatic progress in treatment over the past several years, most patients with chronic myelogenous leukemia (CML) are now surviving with disease control beyond six years after diagnosis. The primary drug therapies used to treat CML are commercially available as oral formulations. Knowledge of treatment standards, monitoring methods, dose adjustment strategies, and options for managing toxicities and interactions, require pharmacists to take an active role in the management of patients with CML.

This activity will review the clinical presentation, disease progression, and molecular pathology of CML. Guidelines for the state of the art treatment and monitoring of CML will be presented based on recommendations from the National Comprehensive Cancer Network (NCCN). Drug resistance will be reviewed within the context of the expanding role of second-generation tyrosine kinase inhibitors (TKIs). Recommendations for the management and prevention of toxicities, drug-drug interactions, and drug-food interactions with TKIs will be highlighted. Patient case examples will be discussed to engage participants in the clinical decision-making process.

LEARNING OBJECTIVES

At the conclusion of this knowledge-based CPE activity, participants should be able to

- Describe the epidemiology, molecular biology, clinical presentation, and disease progression of chronic myelogenous leukemia (CML).
- Describe the currently accepted standard treatments and response monitoring parameters for CML.
- Describe the role of second-generation tyrosine kinase inhibitors (TKIs) in imatinib-resistant CML and emerging evidence related to their use.
- Identify options for preventing and managing toxicities, drug-drug interactions, and drug-food interactions related to TKIs.
- Identify areas of emerging research related to therapies for CML.

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To obtain your CPE statement of credit for this live activity, please visit the ASHP Learning Center at http://ce.ashp.org.

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2. Once logged in to the site, click on **"Process Meeting CE."**

3. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The Activity Code for this meeting is **10594.** The **Session Code** was announced at the end of this activity. Click **register** again when prompted. When you receive the "thank you for registering" message, click **continue**. This step will bring you back to your meeting list. Click on the **start** link to the right of the activity title.

4. Enter the session code, which was announced during the activity, and select the number of hours equal to your participation in the activity. Pharmacists should only claim credit for the amount of time they participate in this activity.

5. Click **submit** to receive the attestation page.

6. Confirm your participation and click **submit**. Your transcript page will appear.

7. Select the applicable year from the drop-down menu and locate this activity.

8. Click on **Print Statement of Credit** in the **Status** column.

Activity code: 10594

Session code:

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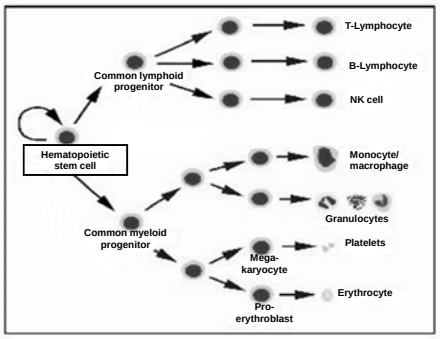
4. Identify options for preventing and managing toxicities, drug-drug interactions, and drug-food interactions related to TKIs.
5. Identify areas of emerging research related to therapies for CML.

Normal Hematopoiesis



From http://bric.postech.ac.kr/trend/issue/2005/images/hematopoietic_1.gif

Epidemiology of Hematologic Malignancies

Estimated new cases for 2009 in the US

- Non-Hodgkin Lymphoma – 65,980
- Multiple Myeloma – 20,580
- Chronic Lymphocytic Leukemia – 15,490
- Acute Myeloid Leukemia – 12,810
- Hodgkin Lymphoma – 8,510
- Acute Lymphocytic Leukemia – 5,760
- Chronic Myelogenous Leukemia – 5,050

Jemal A et al. *CA Cancer J Clin*. 2009; 59:225-49.

CML

- Definition
  - A malignant clonal expansion of hematopoiesis affecting the myeloid lineage
  - The pluripotent (CD34+) stem cell is implicated as the genesis of disease
- Epidemiology
  - 15-20% of all leukemias in adults
  - Slight predominance of males to females (1.3:1)
  - Mean age at diagnosis = 67 years
  - Ionizing radiation is a risk factor

Gordois A, Scuffham P, Warren E et al. Br J Cancer. 2003;89:634-40.

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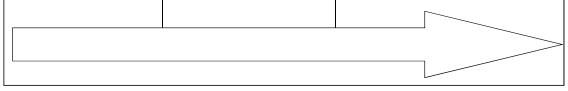
Patient Presentation

- Signs and symptoms
  - Often asymptomatic (20-50%)
  - Splenomegaly (50%)
  - Laboratory findings
    - Anemia (45-60%)
    - Leukocytosis (WBC > 25,000/mm^3)
      - > 100,000/mm^3 → leukostasis (dyspnea, stroke, myocardial infarction)
      - Basophilia, eosinophilia
    - Thrombocytosis (platelets > 600,000/mm^3)
  - Bone marrow aspirate/biopsy
    - Myeloid hyperplasia, hypercellularity
      - Increased megakaryocytes
    - Cytogenetics

CML – Disease Course

Chronic Phase (CP)	Progressive Disease	
	Accelerated Phase (AP)	Blast Crisis (BC)
Median stabilization 3-5 years	Median duration 3-18 months	Median survival 3–6 months



Faderl S et al. *Ann Intern Med*. 1999; 131:207-19.

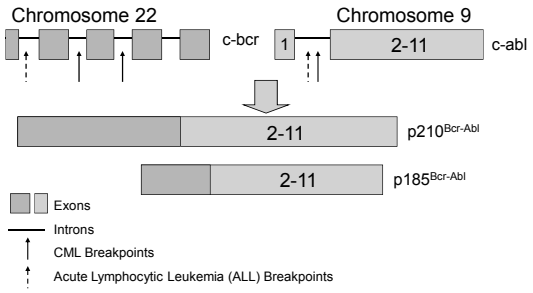
Disease Course

	Chronic Phase	Accelerated Phase	Blast Crisis
Peripheral Blood	Leukocytosis, Basophilia, Eosinophilia, <10% blasts	10-19% blasts, Platelets >1 million/mm^3 or <100,000/mm^3, Basophilia	> 20% blasts
Bone Marrow	Myeloid hyperplasia, Blasts <10%	Evidence of progression, New cytogenetic abnormality	> 20% blasts, Large clusters of blasts
Clinical Findings	Splenomegaly	Splenomegaly	Extramedullary disease

Biology

- Myeloproliferative disorder of unregulated myeloid proliferation
  - Result: excess mature neutrophil production
- Cytogenetics
  - t(9;22) = Philadelphia chromosome
    - Promotes fusion of 2 genes, BCR-ABL
    - Protein $p210^{BCR\text{-}ABL}$ produces unregulated tyrosine kinase activity
      - Promotes continuous cell cycling
      - Inhibits apoptosis
      - Increases mature neutrophil proliferation

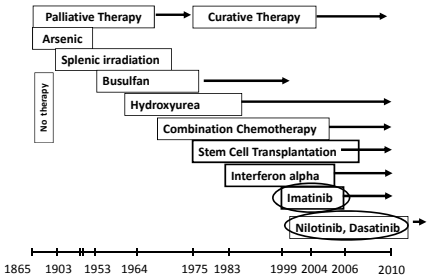
bcr-abl Gene and Fusion Protein Tyrosine Kinases



Melo JV. *Blood.* 1996; 88:2375-84.

CML Therapy and Use of Imatinib

Historic Development of CML Therapy



Hehlmann R. *Ann Hematol*. 2005; 84:487-97.

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CML - Response Criteria

Hematologic Response	Cytogenetic Response	Molecular Response
Complete Normal peripheral blood count WBC <10,000/mm^3 Platelets < 450,000/mm^3 No immature cells	Complete: 0% Ph+ cells Partial: 1%–34% Ph+ cells Major = CR+PR Minor 35%–95% Ph+ cells	Complete: Negativity for BCR-ABL transcripts by RT-PCR Major: Cytogenetic remission with 3 log or greater reduction in BCR-ABL transcripts by RT-PCR

CR = complete response; PR = partial response;
RT-PCR = reverse transcriptase - polymerase chain reaction

Radich JP. *Blood*. 2009; 114:3376-81.

CML: Overview of Historical vs Modern Perspective

Parameter	Historical Perspective (until 2000)	Modern Perspective (since 2000)
Course	Fatal	Indolent
Prognosis	Poor	Excellent
Median survival, years	3-6	≥ 25*
Frontline treatment	Allogeneic hematopoietic stem cell transplant (HSCT), interferon alfa	Imatinib
Second-line treatment	Not established	Allogeneic HSCT, novel TKIs

*extrapolated from imatinib Kaplan-Meier data.

Faderl S et al. *N Engl J Med*. 1999;131:207-19; Druker BJ et al. *N Engl J Med*. 2001;344:1031-37.

CML – Treatment Goals

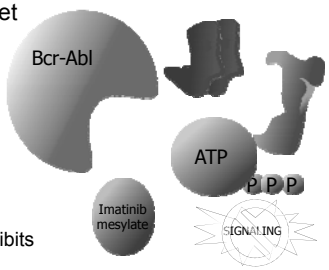
- Maintain chronic phase with sustained hematologic and molecular remission
- Prevent progression to accelerated/blast crisis
- Minimize toxicity of chronic-phase therapy
- Cure:
  - Only proven therapy: allogeneic hematopoietic stem cell transplantation (HSCT)
- Accelerated phase/blast crisis – induce second chronic phase

Imatinib (STI-571)

- Specific inhibitor of enzyme (tyrosine kinase) activated by BCR-ABL
- Dose
  - Chronic phase 400 mg oral daily
  - Accelerated phase/blast crisis 600-800 mg oral daily in divided doses
  - No modifications needed in mild or moderate liver or renal impairment
- Drug interactions
  - CYP3A4 substrate and inhibitor – use caution with potent inhibitors or inducers
  - Food: Take with a full meal and a large glass of water
- Dosage forms: 100 and 400 mg tablets

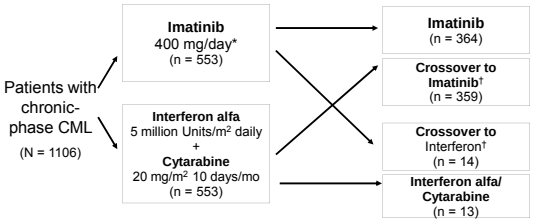
Pharmacodynamics − Imatinib Mesylate

- Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



Savage DG, Antman KH. *N Engl J Med*. 2002;346:683-93.

Imatinib: Phase III IRIS Trial



*Increased stepwise to 400 mg BID allowed if no complete hematologic response (CHR) at 3 months or > 65% Ph+ cells at 12 months.
†Permitted for no CHR at 6 months, no major cytogenetic response (MCyR) at 12 months, loss of response, or treatment intolerance. IRIS – International Randomized Study of Interferon vs STI571.

Hochhaus A et al. *Leukemia* 2009; 23:1054-61; O'Brien S et al. *N Engl J Med* 2003; 348:994-1004.

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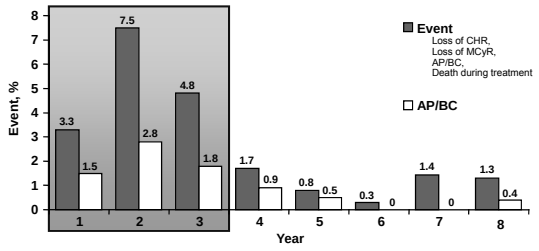
IRIS 8-Year Annual Event Rates



- **Estimated EFS at 8 years = 81%**
  - **1 progression to AP/BC and 2 non-CML related deaths occurred in year 8**
- **Estimated rate of freedom from progression to AP/BC at 8 years = 92%**

Deininger et al. *ASH 2009*;114:Abs # 1126.

8-Year IRIS Follow-Up: Overall Survival (OS) in Imatinib Arm

- Estimated OS is 85%
  - When counting only CML-related deaths, OS = 93%
  - Analysis of all deaths showed 3% of patients died after HSCT and 4% died from non–CML-related causes
- At 5 years, only 38 patients (7%) were lost to follow-up

Deininger et al. *ASH 2009*;114:Abs # 1126.

6-Year Follow-up of Phase III IRIS Trial: Imatinib AEs

Grade 3/4 Imatinib-Related Adverse Events (AEs),%	Years 1-2 (n = 551) (%)	After Year 4 (n = 409) (%)
Neutropenia	14	1
Thrombocytopenia	8	< 1
Anemia	3	< 1
Elevated liver enzymes	5	0
Other drug-related adverse events	14	2

- Severity of hematologic toxicity associated with worse outcomes
  - Patients with grade 3/4 hematologic AEs had more events (loss of CHR or MCyR, AP/BC, and death during treatment) than those with grade 1/2 AEs ($P < .001$)

Hochhaus A et al. *Leukemia.* 2009; 23:1054-61..

Imatinib Monitoring

- After initiation of 400 mg PO daily
  - 3 months – assess hematologic remission
  - 6, 12, 18 months – bone marrow cytogenetics
- If not in complete remission
  - Assess patient adherence
  - Consider mutational analysis
- If partial remission, consider increase to 400 mg PO BID

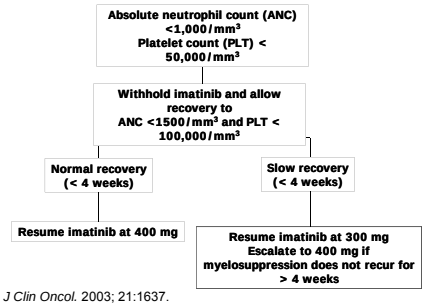
Imatinib Adherence

- Claims data from 878 imatinib-treated patients from US health plan
  - 69% CML, 8% gastrointestinal stromal tumor (GIST), 23% other diagnoses
- Adherence defined as medication possession ratio (MPR)
  - MPR=Total days imatinib supply/365
- Mean MPR = 76%
  - Improved with age until 50
  - Decreased as number of medications increased
  - Lower in women than in men
  - Lower in patients with more cancer complications

Darkow T et al. *Pharmacoeconomics* 2007; 25:481-496.

Imatinib – Hematologic Monitoring Parameters

Chronic Phase CML – 400 mg PO daily



Deininger M. *J Clin Oncol.* 2003; 21:1637.

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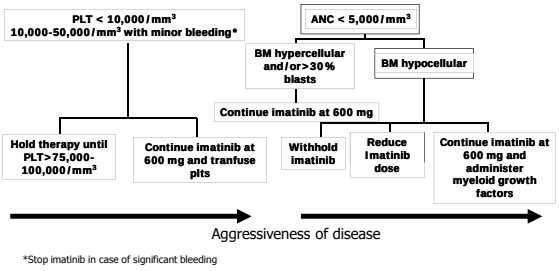
Imatinib – Hematologic Monitoring Parameters

Advanced CML – 600 mg PO daily



Deininger M. *J Clin Oncol*. 2003; 21:1637.

Imatinib – Monitoring Parameters

- Cardiomyopathy
- GI toxicity
  - Abrogate nausea/vomiting (N/V) by taking with food
- Edema
  - >50% patients, often periorbital edema
  - Increased risk for
    - Females, age >65, cardiac/renal disease
    - Start with 300 mg and titrate
  - Manage with diuretics
  - Stop drug and restart at a lower dose of imatinib for severe edema

Deininger M, *J Clin Oncol.* 2003; 21:1637.

Definitions of Imatinib Resistance and Intolerance

Imatinib Resistance in CP CML

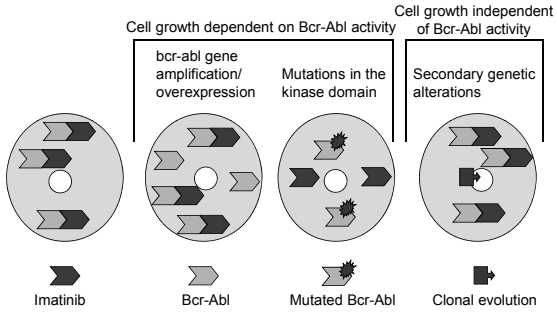
Primary
- Rare (< 5%)
- No CHR at 3 months or
- No CCyR at 6 months or
- No MCyR at 1 year

Acquired
- Loss of CHR or CCyR
- Mutations
  - T315I

Imatinib Intolerance

- Inability to continue therapy despite optimal management of side effects

Potential Mechanisms of Resistance to Imatinib



von Bubnoff et al. *Leukemia.* 2003; 17:829.

Treatment Options for Refractory CML Patients

- Dose escalation of imatinib
- Second-generation TKI
  - Dasatinib
  - Nilotinib
- Allogeneic HSCT
- Donor lymphocyte infusion (relapse post-HSCT)
- Investigational therapy

Patient Case #1

- HS is a 59 yo male in excellent health and presents for his annual employment physical exam.
- The only medication he takes is hydrochlorothiazide 50mg PO daily for essential hypertension.
- Labs: WBC of 84,000/mm^3; platelets were 197,000/mm^3, hemoglobin 14.1g/dL. Chemistries are normal.
- He is referred for a clinic visit with a hematologist.

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Patient Case #1

- The patient is diagnosed with CML based on findings from the peripheral smear, bone marrow biopsy, and cytogenetics - t(9;22).

Which of the following is the best option to lower the WBC count?

A. Allogeneic HSCT
B. Busulfan
C. Chlorambucil
D. Hydroxyurea

Which of the following is the best initial treatment for newly diagnosed CML?

A. Imatinib
B. Busulfan
C. Chlorambucil
D. Hydroxyurea

Patient Case #1 (continued)

- The patient is treated with imatinib and achieved a CCyR and MMR at 7 and 12 months respectively, and continues in chronic phase at 28 months without any significant toxicity.
- When the patient comes back to his hematologist for routine follow-up he finds that his CML has progressed to accelerated phase.

Which of the following is the optimal treatment option for this patient with resistant disease?

A. Continue imatinib at present dose
B. Busulfan
C. Hydroxyurea
D. Second generation TKIs

TKI Activity vs. BCR-ABL Point Mutations

TK Point Mutations	Imatinib	Dasatinib	Nilotinib
WT BCR-ABL	S	S	S
M224V	I	S	S
G250E	I	S	S
Q252H	I	I	I
Y253H	R	S	I
Y253F	R	S	I
E255K	R	I	I
E255V	R	I	I
V299L	S	I	NA
F311L	S	S	S
T315I	R	R	R

S = Highly Sensitive I = Intermediate Sensitivity R = Resistance

Quintas-Cardama A. *Blood* 2009; 113:1619.

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Treatment – Accelerated Phase

Allogeneic HSCT	Administration of induction chemotherapy prior to allogeneic HSCT to achieve second chronic phase is controversial
Imatinib mesylate: 400 mg/d (n = 77) and 600 mg/d (n = 158)	CHR achieved in 29% patients on 400 mg/day and 41% patients on 600 mg/day (overall 37%) Return to chronic phase in 26% with 400 mg/day and 17% with 600 mg/day (overall 20%); MCyR in 18% patients on 400 mg/day and 30% on 600 mg/day (26% overall). CCR overall in 18% (higher in 600 mg/day group)[1]

Talpaz M. *Blood*. 2002; 99:1928.

Treatment – Blast Crisis

Induction chemotherapy: **Etoposide (100 mg/m²/day) IV** **Carboplatin (150 mg/m²/day) CIV** **Cytarabine (500 mg/m²) IV q12h; all agents given on days 1–3 and 8–10** **(Other salvage - AML salvage therapies are reasonable)**	Lymphoid blast crisis more responsive to chemotherapy than myeloid; VAC regimen had overall CR rate in 58% in 31 patients with median survival of 7 mo; Consider allogeneic HSCT if second chronic phase achieved; many opt for palliative care[1]
Imatinib 400 mg/day (n = 37) 600 mg/day **(n = 223)**	CHR overall in 4%; return to chronic phase in 19% overall (22% previously untreated, 15% treated) MCR, 13.5% overall; CCR, 5% overall[2]

IV = intravenous; CIV = ; AML = acute myelogenous leukemia; VAC = etoposide, intermediate-dose cytarabine, and carboplatin.

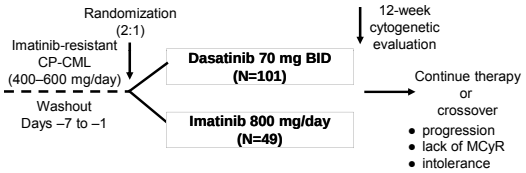
Amadori S. *Leukemia*. 1996; 10:766; Sawyers CL. *Blood*. 2002; 99:3530-39.

Second Generation

Tyrosine Kinase Inhibitors

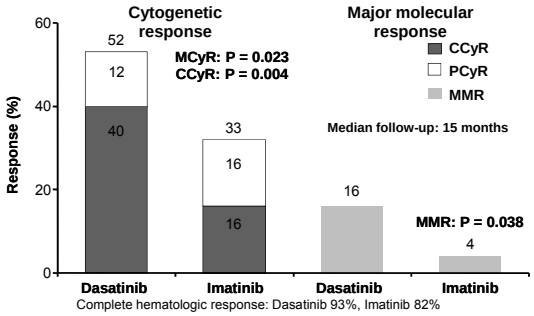
Study Design: Dasatinib vs High-Dose Imatinib

- International, randomized, open label, phase II



Kantarjian H et al. *Blood*. 2007; 109:5143.

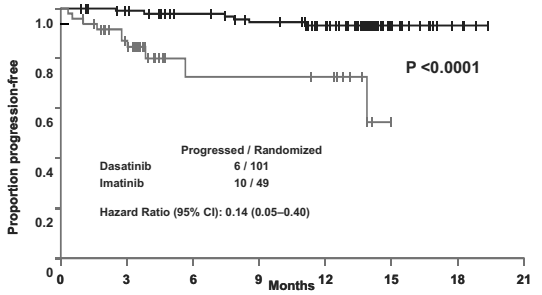
Response Rates: Dasatinib vs High-dose Imatinib



Complete hematologic response: Dasatinib 93%, Imatinib 82%

Kantarjian H et al. *Blood*. 2007; 109:5143.

Progression-free Survival: Dasatinib vs High-dose Imatinib

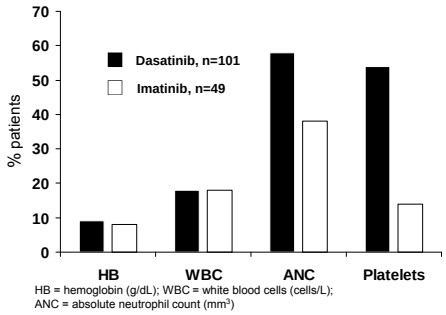


Progression was defined as confirmed AP / BP, loss of CHR / MCyR, or increasing WBC count (doubling from the nadir to >20,000 on ≥2 assessments 2 weeks apart)

Kantarjian H et al. *Blood*. 2007; 109:5143.

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Hematologic Toxicity Dasatinib vs High-dose Imatinib



HB = hemoglobin (g/dL); WBC = white blood cells (cells/L); ANC = absolute neutrophil count (mm^3)

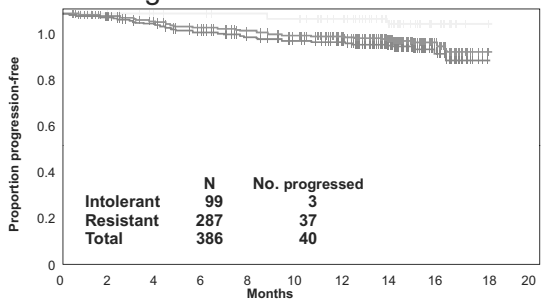
Kantarjian H et al. *Blood.* 2007; 109:5143.

Dasatinib Phase II Trials in Imatinib-Refractory Patients

Parameter	Chronic Phase[1]	Accelerated Phase[2]	Blast Crisis[3]
Hematologic Response	91%	63%	35%
Complete Cytogenetic Response	49%	24%	32%
Major Cytogenetic Response	59%	34%	39%

Hochhaus A. *Leukemia* 2008; 22:1200; Guilhot F. *Blood* 2007; 109:4143; Cortes J. *Leukemia* 2008; 22:2167.

Dasatinib 70 mg BID in CP-CML Progression-Free Survival



Progression was defined as confirmed AP / BP, loss of CHR / MCyR, or increasing WBC count

Hochhaus A. *Leukemia.* 2008; 22:1200.

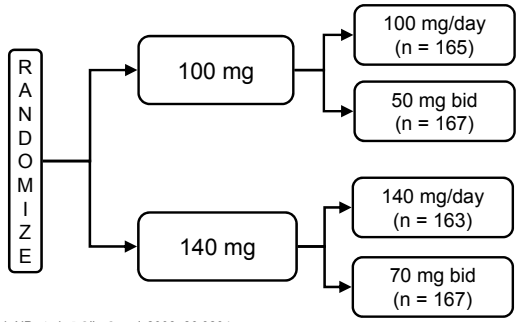
Clinical Trials of Dasatinib in CML-CP: Selected Non-Hematologic Adverse Events (all grades)

	START-C	START-R
Diarrhea	32%	26%
Superficial edema	20%	13%
Pleural effusions	17%	11%
Increase serum transaminases	54%	N.A.

*Monitor for drug-drug interactions via CYP3A4.

Hochhaus A. *Leukemia.* 2008; 22:1200; Guilhot F. *Blood.* 2007; 109:4143; Cortes J. *Leukemia.* 2008; 22:2167.

Dasatinib: Dose and Schedule Optimization in CP-CML



Shah NP et al. *J Clin Oncol.* 2008; 26:3204.

Dasatinib: Dose and Schedule Optimization in CP-CML

- Hematologic and cytogenetic response (CHR, MCyR, CCyR) similar among all arms
- Progression-free survival significantly favors 100 mg/day vs 70 mg bid (P = 0.032)
- Safety: Significantly superior toxicity and tolerability profile with 100 mg/day compared to other arms:
  - Cardiac toxicity (P = 0.032)
  - Thrombocytopenia (P = 0.004)
  - Dose interruption (P = 0 .047)
  - Dose reduction (P < 0.001)
  - Dose escalation (P = 0.037)
- Dasatinib 100 mg PO daily is the optimal dose for CP-CML

Shah NP et al. *J Clin Oncol.* 2008; 26:3204.

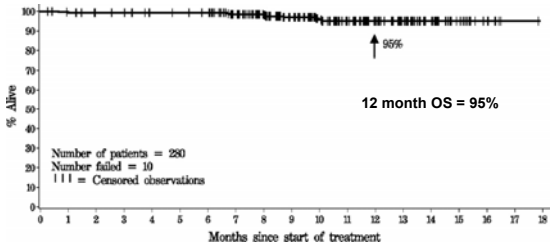
Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Nilotinib Phase II Trials in Imatinib Refractory Patients

	Chronic Phase N=280	Accelerated Phase N=119
Hematologic Response	**74%**	**47%**
Major Cytogenetic Response	**48%**	**29%**
Complete Cytogenetic Response	**31%**	**19%**

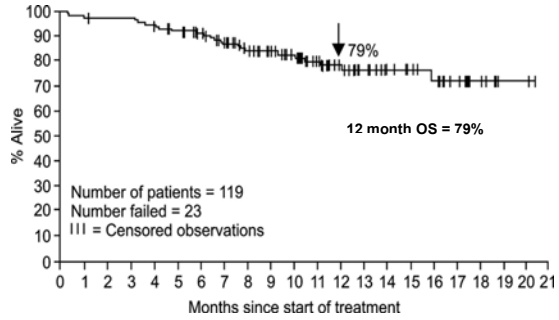
Kantarjian H. *Blood* . 2007; 110:3540; Coutre P. *Blood.* 2008; 111:1834.

OS in CML-CP Treated with Nilotinib



Kantarjian H. *Blood*. 2007;110:3540.

OS in CML-AP Treated with Nilotinib



Coutre P. *Blood*. 2008; 111:1834.

Select Nilotinib Toxicities

Toxicity	Overall	Grade III/IV
Neutropenia		**29%**
Thrombocytopenia		**29%**
Anemia		**13%**
Rash	**28%**	**3%**
Nausea	**24%**	**1%**
Pruritis	**24%**	**1%**
Fatigue	**19%**	**1%**
Headache	**11%**	**1%**
Constipation	**12%**	**0%**
Diarrhea	**11%**	**2%**
QT prolongation	**1%**	

Kantarjian H. *Blood* . 2007; 110:3540; Coutre P. *Blood.* 2008; 111:1834.

Patient Case #2

- A 72 yo patient was enrolled in the original IRIS trial and had a 6 year period of progression-free survival on imatinib 400 mg PO daily.
- She subsequently progressed to AP CML and was started on dasatinib 140 mg PO daily with an initial CCyR at 6 months. At that time, she presented with a pleural effusion.

What is the best option for maintaining long-term disease control for this patient while minimizing toxicity?

A. Switch back to imatinib at 400 mg PO daily
B. Switch back to imatinib but increase dose to 600 mg PO daily
C. Start nilotinib 400 mg PO BID
D. Allogeneic stem cell transplant

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Which of the following clinical concerns are important when considering appropriateness of allogeneic stem cell transplant for this patient?

A. Patient age
B. Donor availability
C. Patient comorbidities
D. All of the above

TKI Comparison - Summary

	Imatinib	Dasatinib	Nilotinib
Chronic phase dose	400 mg PO daily	100 mg PO daily	400 mg PO BID
Food effect	With food (improved tolerability)	With or without food (avoid acid reducers)	Empty stomach (safety)
Fold potency against BCR-ABL	1	300	25
Metabolism	CYP3A4 substrate/ inhibitor	CYP3A4 substrate	CYP3A4 substrate/ inhibitor (also 2C8, 2C9, 2D6)

DeRemer DL et al. *Clin Ther*. 2008; 30:1956-1975.

Chronic Myeloid Leukemia
Role of Hematopoietic Stem Cell Transplant (HSCT)

- Cure
  - Allogeneic stem cell transplant
    - Considerable toxicity
    - Lack of donor
- Maintain disease in chronic phase
  - Evolving role of TKIs post-HSCT

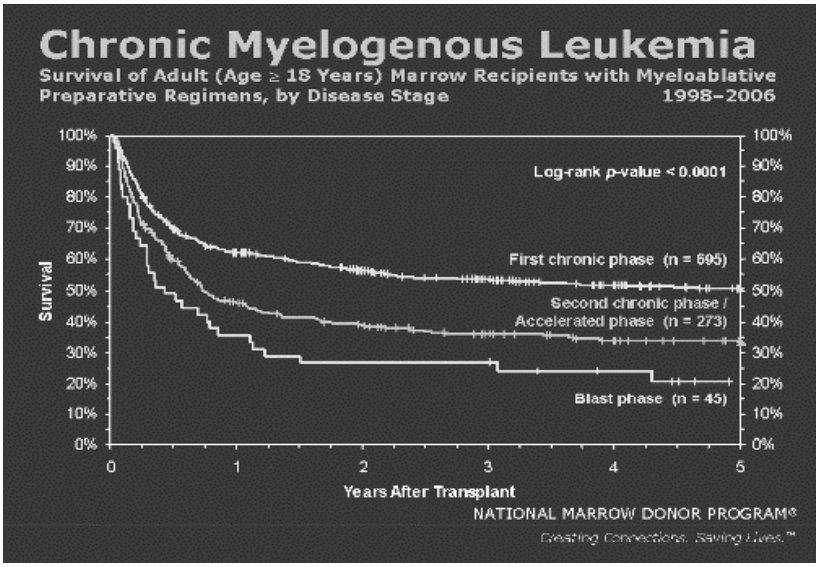
CML-CP – HSCT Outcomes

Treatment	Overall Survival	Notes
Allogeneic HSCT	Matched sibling donor = 50%–70% long-term DFS	Proven curative therapy; mortality up to 30%; relapse rate = 15%–20%; presence of GVHD decreases relapse rate; outcome improved if early BMT[1]
Unrelated donor allogeneic HSCT	40%– 50% long-term DFS for early transplant	Curative option, early mortality up to 50%; risk of GVHD and infection increased; younger patients fare better[2]

DFS = disease-free survival; GVHD = graft-versus-host disease; OS = overall survival; BMT = bone marrow transplant.

Clift RA. *Blood*. 1994; 84:4368; Kernan NA. *New Engl J Med*. 1993; 328:593; Koizner B. *Cancer*. 2002; 95:2339.

Historical Data for HSCT in CML

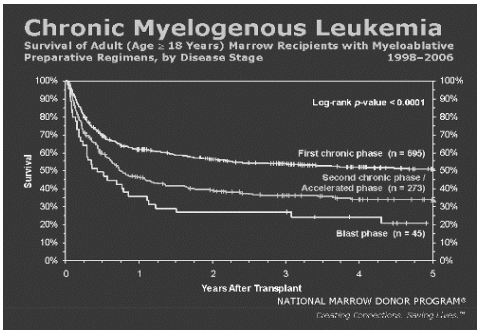


National Marrow Donor Program (NMDP) overview slide presentation.

Available at: http://www.marrow.org/PHYSICIAN/Outcomes_Data/index.html#transplant

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Historical Data for HSCT in CML



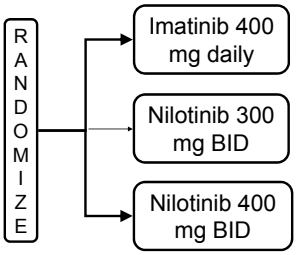
National Marrow Donor Program (NMDP) overview slide presentation.
Available at: http://www.marrow.org/PHYSICIAN/Outcomes_Data/index.html#transplant

Long-term Complications Post-HSCT

Disease	Transplant N = 248	Sibling Controls N = 317
Eye	49%	14%
Oral health	26%	13%
Endocrine	25%	11%
Bone/joint	13%	3%
Cardiopulmonary	33%	26%
GI	17%	9%
Neurosensory	40%	20%
Neuromotor	21%	6%

Baker KS et al. *Blood*. 2004; 104:1898-906.

Phase III Front-line Data for Nilotinib



N = 846 patients with newly diagnosed Ph positive CML randomized 1:1:1

Stratification:
Sokal score

Primary endpoint:
MMR at 12 months
All patients 12 months minimum treatment

Median follow-up:
14 months

Saglio G et al. *N Engl J Med* 2010 Published on line June 5.

Efficacy Results

Parameter	Nilotinib 300 mg BID	Nilotinib 400 mg BID	Imatinib 400 mg daily
MMR at 12 months	44% (P<.0001)	43% (P<.0001)	22%
CCyR at 12 months	80% (P<.0001)	78% (P=.0005)	65%
Progression to AP/BC	<1% (P=.0095)	<1% (P=.0037)	4%

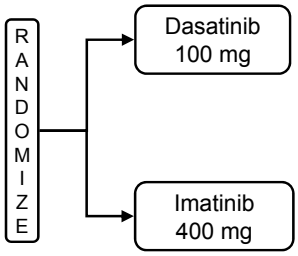
Saglio G et al. *N Engl J Med* 2010 *Published on-line June 5 , 2010.*

Grade III/IV Toxicity Results

Parameter	Nilotinib 300mg PO BID	Nilotinib 400mg PO BID	Imatinib 400mg PO daily
Neutropenia	12%	10%	20%
Thrombocytopenia	10%	12%	9%
Anemia	3%	3%	5%
Rash	1%	3%	1%
↑ Total Bili	4%	8%	1%
↑ ALT	4%	9%	2%
↑AST	1%	3%	1%
↑ Lipase	6%	6%	3%
↓ Phosphate	5%	5%	3%

Saglio G et al. N Engl J Med 2010 Published on line June 5. 2010.

Phase III Dasatinib Front-line



N = 519 patients with newly diagnosed Ph positive CML randomized 1:1

Stratification:
Hasford risk score

Primary endpoint:
CCyR at 12 months
All patients 12 months minimum treatment

Mimimum follow-up:
12 months

Kantarjian HM et al. *N Engl J Med*. 2010; *Published June 5, 2010.*

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Efficacy Results

Parameter	Dasatinib (n=259)	Imatinib (n=260)
CCyR at 12 months	77%*	66%
MMR at 12 months	46%**	28%

•*P=0.007
•** P <0.0001

Kantarjian HM et al. *N Engl J Med.* 2010; *Published June 5, 2010.*

Grade III/IV Toxicity Results

Parameter	Dasatinib 100mg PO daily	Imatinib 400mg PO daily
Neutropenia	21%	20%
Thrombocytopenia	19%	10%
Anemia	10%	7%
Fluid Retention	1%	1%
Pleural Effusion*	0%	0%
Diarrhea	<1%	1%
Musculoskeletal Pain	0%	1%
Myalgia	0%	0%
Rash	0%	1%

* Grade I or II pleural effusions reported in 10% of dasatinib patients

Kantarjian HM et al. *N Engl J Med.* 2010; *Published June 5, 2010.*

Remaining Questions in CML Treatment

- Is 400 mg/day the right initial dose of imatinib?
- Dasatinib or nilotinib following imatinib?
  - Long-term survival data still ongoing
- When to offer allogeneic transplant?
- Role of dasatinib/nilotinib in **initial** disease management is evolving
- How crowded can this market become?
  - Bosutinib
- Treatment for T315I mutations
  - Omacetaxine
  - AP24534

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R E F E R E N C E S *(continued)*

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SELF–ASSESSMENT QUESTIONS

1. The only proven curative therapy for chronic myelogenous leukemia (CML) is:
   a. Allogeneic stem cell transplant.
   b. Autologous stem cell transplant.
   c. Hydroxyurea.
   d. Imatinib.

2. A notable finding of the six year follow-up from the IRIS trial for CML was:
   a. Most patients treated in the imatinib arm crossed over to treatment with interferon alfa and cytarabine because of significant toxicity caused by imatinib.
   b. Toxicity with imatinib over the five years was cumulative and led to a significant drop out rate in the study.
   c. Most patients treated with imatinib did not achieve a cytogenic or molecular response over the course of treatment.
   d. Imatinib maintained chronic phase in excess of 90% of patients with minimal toxicity over the study period.

3. Reasonable second-line treatment for CML following imatinib failure includes all the following EXCEPT:
   a. Allogeneic stem cell transplant.
   b. Hydroxyurea.
   c. Dasatinib.
   d. Nilotinib.

4. Which BCR-ABL kinase mutation is truly resistant to all kinase inhibitors developed so far?
   a. M224V.
   b. E255K.
   c. F359V.
   d. T315I.

Answers

1. a
2. d
3. b
4. d

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Activity Evaluation Form

August 27, 2010 **Joseph S. Bubalo, Pharm.D., BCPS, BCOP** ***Oakbrook Terrace, IL***

ASHP Advantage appreciates your participation in this educational activity and values your feedback. Please complete this brief evaluation form to assist us in improving the quality of future educational activities.

1 = strongly disagree 2 = disagree 3 = neither agree nor disagree 4 = agree 5 = strongly agree

Evaluation of Educational Objectives

After attending this knowledge-based CPE activity, I am able to	**Strongly Disagree**				**Strongly Agree**
1. Describe the epidemiology, molecular biology, clinical presentation, and disease progression of chronic myelogenous leukemia (CML).	1	2	3	4	5
2. Describe the currently accepted standard treatments and response monitoring parameters for CML.	1	2	3	4	5
3. Describe the role of second-generation tyrosine kinase inhibitors (TKIs) in imatinib-resistant CML and emerging evidence related to their use.	1	2	3	4	5
4. Identify options for preventing and managing toxicities, drug-drug interactions, and drug-food interactions related to TKIs.	1	2	3	4	5
5. Identify areas of emerging research related to therapies for CML.	1	2	3	4	5

Evaluation Content

	Strongly Disagree				**Strongly Agree**
1. The content presented was relevant to the target audience……..	1	2	3	4	5
2. I will be able to apply the knowledge skills I learned ……..	1	2	3	4	5
3. The activity fulfilled my education needs ……..	1	2	3	4	5
4. The activity enhanced my ability to apply learning objectives to my practice …….	1	2	3	4	5

5. Based on my previous knowledge and experience, the content level of the activity for attending audience was:
☐ Too basic ☐ Appropriate ☐ Too Complex

Faculty/Instructional Materials

	Strongly Disagree				**Strongly Agree**
6. The teaching methods were effective…….	1	2	3	4	5
7. The instructional materials were effective …….	1	2	3	4	5

Continue on next page ⟶

Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy

Faculty/Instructional Materials *(continued)*

8. Please indicate the extent to which you agree or disagree with the following statement: "Faculty statements and therapeutic recommendations in this activity were based on supported evidence or professional opinion and did **NOT** evidence commercial bias."

   ☐ Strongly Disagree ☐ Disagree ☐ Agree ☐ Strongly Agree

9. If you answered **strongly disagree or disagree** to question 8, what commercial bias did you perceive in this activity?
   _____

10. What did you find to be the most helpful aspect of this activity?
    _____
    _____

11. What was the least helpful aspect of this activity?
    _____
    _____

12. List ONE (and no more than three) changes that you intend to make in your practice as a result of this activity.
    _____
    _____

13. How confident are you that you will be able to apply these changes in your practice?
    a. Very confident
    b. Somewhat confident
    c. Not confident

14. Please indicate any barriers you perceive to implementing these changes.
    a. Cost
    b. Lack of experience
    c. Lack of resources
    d. Lack of administrative support
    e. Other, please specify:_____
       _____

15. What question(s) do you still have about this topic?
    _____

16. Based on your educational needs, list any topics you would like to see addressed in future educational activities.
    _____

17. Other comments or suggested improvements:
    _____
    _____

18. Using the following scale, in the table below rate presentation skills, content knowledge, degree of balance, objectivity, and scientific rigor of faculty:

1 = very poor 2 = poor 3 = average 4 = above average 5 = excellent

	Presentation Skills	Knowledge of Content	Degree of Balance, Objectivity, & Scientific Rigor
Joseph S. Bubalo, Pharm.D., BCPS, BCOP	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5