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

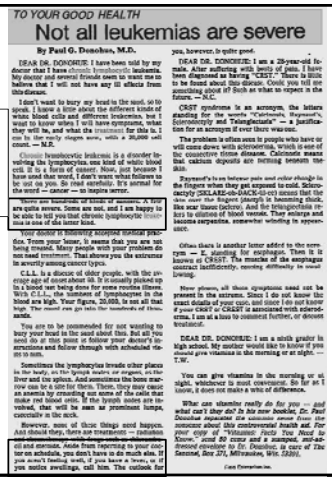
Introduction

- Common in elderly with median age of 72 yrs with general absence of symptoms at time of diagnosis
  - ~30 percent are less than 45 years
- Patients over the age of 70 have poor response to therapy and increased risk to developing toxicity to common agents used in CLL

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



TO YOUR GOOD HEALTH

Not all leukemias are severe

By Paul G. Donohue, M.D.

DEAR DR. DONOHUE: I have been told by my doctor that I have chronic lymphocytic leukemia. My doctor and several friends seem to want me to believe that I will not have any ill effects from this disease.

I don't want to bury my head in the sand, so to speak. I know a little about the different kinds of white blood cells and different leukemias, but I want to know when I will have symptoms, what they will be, and what the treatment for this is. I was in the early stages now, with a 20,000 cell count. — M.S.

Chronic lymphocytic leukemia is a disorder involving the lymphocytes, one kind of white blood cell. It is a form of cancer. Now, just because I have used that word, I don't want what follows to be set up you. So read carefully. It's normal for the word — cancer — to inspire terror.

There are hundreds of kinds of cancers. A few are quite severe. Some are not, and I am happy to be able to tell you that chronic lymphocytic leukemia is one of the latter kind.

Your doctor is following accepted clinical practice. From your letter, it seems that you are not being treated. Many people with your problem do not need treatment. That shows you the extremes in severity among cancer types.

C.L.L. is a disease of older people, with the average age of onset about 60. It is usually picked up in a blood test being done for some routine illness. With C.L.L., the number of lymphocytes in the blood are high. Your figure, 20,000, is not all that high. The count can go into the hundreds of thousands.

You are to be commended for not wanting to bury your head in the sand about this. But all you need to do at this point is follow your doctor's instructions and follow through with scheduled recheck tests.

Sometimes the lymphocytes invade other places in the body, as the lymph nodes or organs, as the liver and the spleen. And sometimes the bone marrow can be a site for them. There, they may cause an anemia by crowding out some of the cells that make red blood cells. If the lymph nodes are involved, that will be seen as prominent lumps, especially in the neck.

However, none of these things need happen. And should they, there are treatments — radiation and steroids. Aside from reporting to your doctor on schedule, you don't have to do much else. If you aren't feeling well, if you have a fever, or if you notice swellings, call him. The outlook for you, however, is quite good.

DEAR DR. DONOHUE: I am a 28-year-old female. After suffering with bouts of pain, I have been diagnosed as having "CRST." There is little to be found about this disease. Could you tell me something about it? Such as what to expect in the future. — N.C.

CRST syndrome is an acronym, the letters standing for the words "Calcinosis, Raynaud's, Sclerodactyly and Telangiectasia" — a justification for an acronym if ever there was one.

The problem is often seen in people who have or will come down with scleroderma, which is one of the connective tissue diseases. Calcinosis means that calcium deposits are forming beneath the skin.

Raynaud's is an intense pain and color change in the fingers when they get exposed to cold. Sclerodactyly (SKLARE-oh-DACK-til-ee) means that the skin over the fingers (sharply) is becoming thick, like scar tissue (sclera). And the telangiectasia refers to dilation of blood vessels. They enlarge and become serpentine, somewhat winding in appearance.

Often there is another letter added to the acronym — E, standing for esophagus. Then it is known as CREST. The muscles of the esophagus contract inefficiently, causing difficulty in swallowing.

Many persons, all those symptoms need not be present in the extreme. Since I do not know the exact details of your case, and since I do not know if your CRST or CREST is associated with scleroderma, I am at a loss to comment further, or descent treatment.

DEAR DR. DONOHUE: I am a ninth grader in high school. My mother would like to know if you should give vitamins in the morning or at night. — T.W.

You can give vitamins in the morning or at night, whichever is most convenient. So far as I know, it does not make a whit of difference.

What can vitamins really do for you — and what can't they do? In his new booklet, Dr. Paul Donohue separates the nonsense sense from the nonsense about this controversial health aid. For your copy of "Vitamins: Facts You Need to Know," send 50 cents and a stamped, self-addressed envelope to Dr. Donohue, in care of The Sentinel, Box 371, Milwaukee, Wis. 53201.

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

WHAT DO WE DO?

Diagnosis

- 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

Blood. 2008 Jun 15;111(12):5446-56. Epub 2008 Jan 23

Diagnosis

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

Blood. 2008 Jun 15;111(12):5446-56. Epub 2008 Jan 23

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

CLL Outcome From Diagnosis by Interphase Chromosomal (FISH) Abnormalities

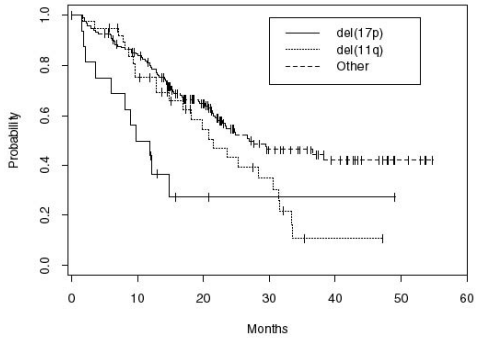
Abnormality	% Pts	Median Time to Treatment (mo)	Median Overall Survival (mo)
del(17)(p13.1)	7	9	32
del (11)(q22.3)	18	13	79
Trisomy 12	16	33	114
del(13)(q14)	55	49	133
None Detected	18	92	111

Döhner H, et al. *N Engl J Med.* 2000;343(26):1910-1916.

Genetics of CLL

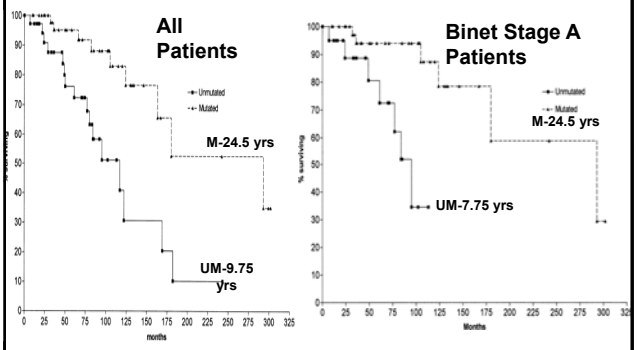
- Prognosis is linked to genetic mutations present
  - No prospective trial has shown treating based on these improves outcome.
- Commonest mutations include:
  - del(13q14): most common
  - Trisomy 12
  - del(11q22.3)
  - del(17p13.1)
  - del(6q22.3)
- P53 mutation occurs in about 5 percent patients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

PFS by Interphase Cytogenetics: E2997



Grever MR, et al: J Clin Oncol 2007

Overall Survival is Influenced by *IGHV* Gene Mutation Status



Hamblin TJ, et al. *Blood* 94:1848, 1999

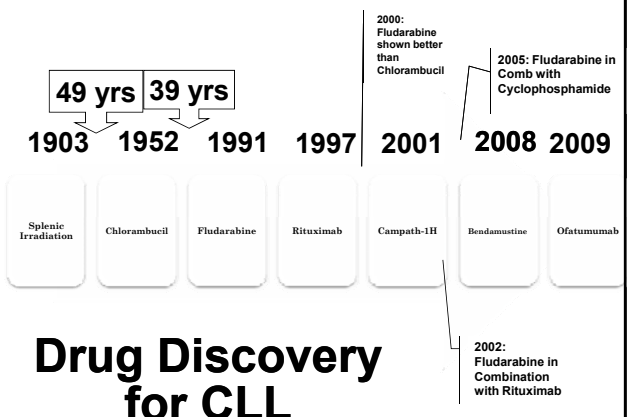
Indications for Treatment

- 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



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

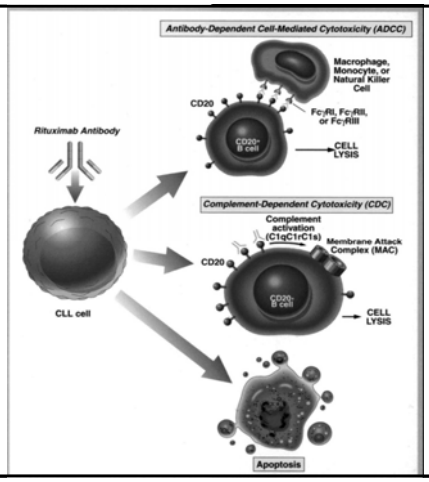
Bendamustine + Rituximab in CLL

- 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

Fischer K, et al. *J Clin Oncol* 29:3559-66, 2011

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 Therapies

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

Coiffier B, et al: *Blood* 111:1094, 2008
Wierda WG, et al: *J Clin Oncol* 28:1749, 2010

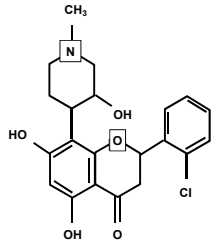
Lenalidomide

- 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-angioangiogenesis mediating cytokines
  - « Enhancement of innate immune system activation that leads to synergy when combined with antibody therapies

Flavopiridol (Alvocidib)



- Synthetic flavone
- Inhibits cyclin-dependent kinases
- Reduces RNA polymerase II phosphorylation
- Down-regulates Mcl-1
- Induces p53-independent apoptosis (4-hr LC_{50} = 1.15 mM)

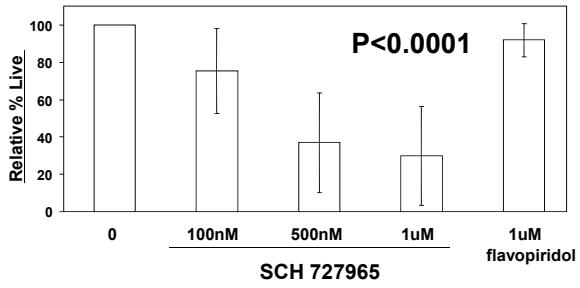
Konig et al, Blood 90: 4307, 1997
Parker et al, Blood 91: 458, 1998
Byrd et al, Blood 92: 3804, 1998
Kitada et al, Blood 96: 393, 2000
Chen et al, Blood 106: 2513, 2005

The Future is Now

Dinaciclib (SCH72765)

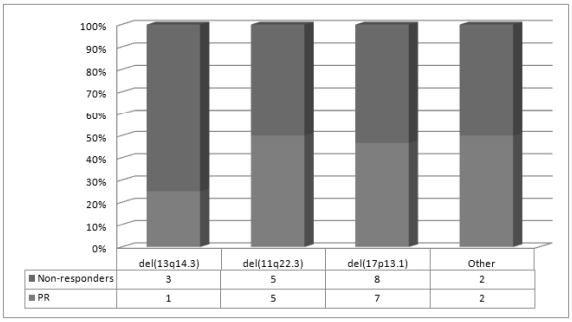
- Cyclin Dependent Kinase Inhibitor
- Selected versus other pre-clinical candidates based upon in vivo therapeutic index (10) in ovarian xenograft model whereas other known CDK inhibitors had very low therapeutic index (<1-2)
- Broad inhibitor of CDK1, CDK2, CDK5, CDK9 (1-5ηM) > CDK4, CDK7 (100 ηM)>>GSKβ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

CLL Cell Viability after Treatment with Dinaciclib



2 hr exposure, 24 hr analysis

Partial Response by Mutation



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

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

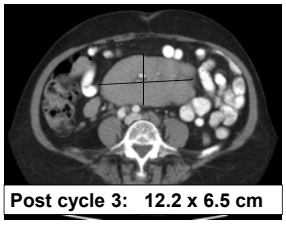
Dramatic Activity in CLL

Pt 1: 71 year, relapsed CLL, previous response to flavopiridol in 2007

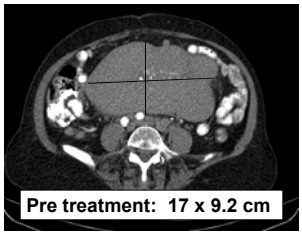
with progressive disease after 8 months off therapy.

The patient was refractory to other biologic therapies.

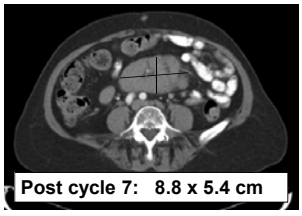
In September 2009, started Dinaciclib (SCH727965).



Post cycle 3: 12.2 x 6.5 cm



Pre treatment: 17 x 9.2 cm



Post cycle 7: 8.8 x 5.4 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 ηM concentrations
- Pre-clinical activity in CLL based upon target specificity with no NK or T-cell toxicity

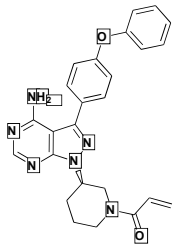
Herman S et al: Blood 2010
Lanutti B, et al: Blood 2011

Results of PCI32765 in CLL

- Response to therapy remarkable
  - De novo disease 86% 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

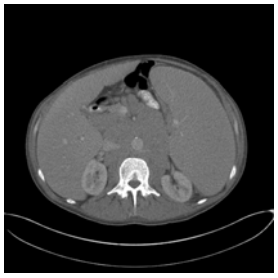
PCI-32765: A Potent Btk Inhibitor



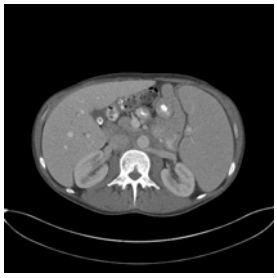
- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent irreversible Btk inhibition with IC_{50} = 0.5 nM
- Inhibits BCR signaling and active in spontaneous canine model of lymphoma
- Orally available
- Once daily dosing results in 24-hr sustained target inhibition

Honigberg LA et al: Proc Natl Acad Sci U S A.107:13075-80, 2010

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

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

WHAT DO WE DO?

The OSU CLL Team:

Clinical

John C. Byrd, MD
Michael Grever MD
Kristie Blum MD
Leslie Andritsos MD
Jeff Jones MD
Jennifer Woyach MD
Samantha Jaglowski MD
Gerard Lozanski MD (Pathology)
Nyla Heerema PhD (Cytogenetics)
Deidre Deam RN
Beth Wiley BS
Cheryl Kefauver RN, BS
Weihong Chase RNP
Margaret Lucas PA
Gretchen McNalley RNP, PhD
Mollie Moran RNP
Sharon Waymer LPN

Laboratory

Faculty
Amy Johnson PhD
David Lucas PhD
Raj Muthusamy DVM, PhD
Rosa Lapalombella PhD

Technicians
Carolyn Cheney BS
Melanie Davis PhD
Ryan Edwards BS
Frank Frissora MS
Virginia Goettl DVM, PhD
Amber Gordon BS
Josh Hessler BS
Julita Jendrzejewska BS
Arletta Lozanski BS
Courtney Prince BS
Asha Ramanunni MD, MS
Ellen Sass BS
Lisa Smith MS
Matthew Stefanovski
Will Towns 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

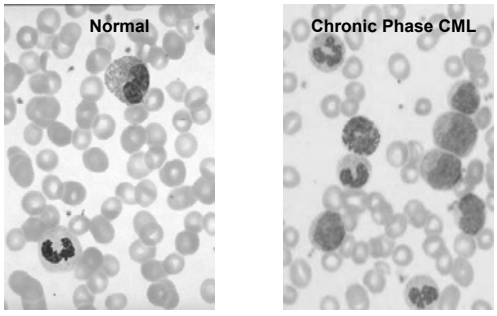
CASE: Diagnosis

- 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

Objectives

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

Comparative Peripheral Blood Smear



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
- Common laboratory findings
  - Abnormal differential
  - Leukocytosis
  - Thrombocytosis
  - Anemia
  - Basophilia

Faderl et al. *Ann Intern Med*. 1999;131:207.
Goldman. *Curr Opin Hematol*. 1997;4:277.

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

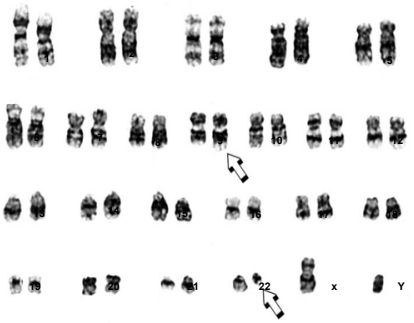
Parameter	Phase of CML: Chronic	Accelerated	Blast Crisis
WBC count	≥20 x 10^9/L	—	—
Blasts	1%–15%	≥15%	≥30%
Basophils	↑	≥20%	—
Platelets	↑ or normal	↓ or ↑	↓
Bone marrow	Myeloid hyperplasia		
Cytogenetics	Ph+	→	
Bcr-Abl	+	→ + →	+

WBC = white blood cell; Ph+ = Ph chromosome–positive.

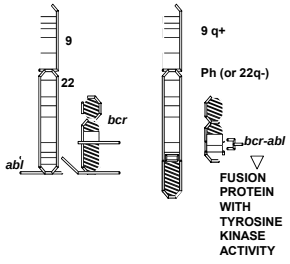
Diagnosis of CML

- 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

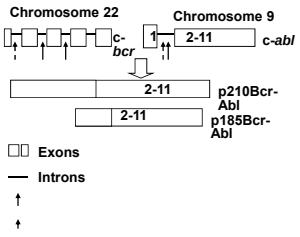
Cytogenetic Abnormality of CML: the Ph Chromosome



The Ph Chromosome and the *bcr-abl* Gene

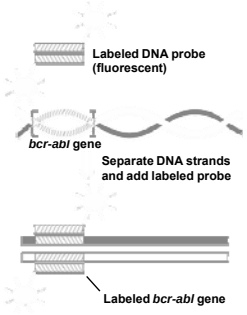


t(9;22) translocation



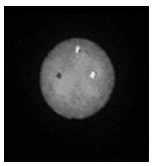
bcr-abl gene structure

Molecular Methods for Detecting *bcr-abl*

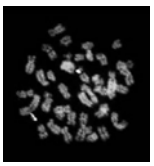


- FISH

Interphase



Metaphase



Courtesy of Charles L. Sawyers, MD, UCLA.
Wang et al. *Genes Chromosomes Cancer*. 2001;32:97

Options for Monitoring Cytogenetic Response in CML

Test	Target	Tissue	Sensitivity (%)*	Use
Cytogenetics	Ph chromosome	BM	1-10	■ Confirm diagnosis of CML ■ Evaluate karyotypic abnormalities other than Ph chromosome (ie, clonal evolution)
FISH	Juxtaposition of *bcr* and *abl*	PB/BM	0.5-5	■ Confirm diagnosis of CML ■ Routine monitoring of cytogenetic response in clinically stable patients ■ Routine measurement of MRD
RT-PCR	*bcr-abl* mRNA	PB/BM	0.0001-0.001	■ Routine measurement of MRD ■ Determine the breakpoints of the fusion genes

*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.

Wang et al. *Genes Chromosomes Cancer*. 2001;32:97.

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

Complete: No Ph+ metaphases
Major: 0-35% Ph+ metaphases
Partial: 1-34% Ph+ metaphases
Minor: 35-90% Ph+ metaphases

Frontline TKI: % Complete Cytogenetic Response (CCyR)

	DASISION TRIAL*		ENESTnd TRIAL		
	DASATINIB	IMATINIB	NILOTINIB 300	NILOTINIB 400	IMATINIB
No. patients	259	260	282	281	283
6 months	73	59	67	63	45
12 months	77	66	80	78	65
18 months	78	70	85	82	74

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)

	DASISION TRIAL*		ENESTnd TRIAL		
	DASATINIB	IMATINIB	NILOTINIB 300	NILOTINIB 400	IMATINIB
No. patients	259	260	282	281	283
6 months	73	59	67	63	45
12 months	77	66	80	78	65
18 months	78	70	85	82	74

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)

	DASISION TRIAL		ENESTnd TRIAL*		
	DASATINIB	IMATINIB	NILOTINIB 300	NILOTINIB 400	IMATINIB
No. patients	259	260	282	281	283
3 months	8	0.4	9	5	1
6 months	27	8	33	30	12
9 months	39	18	43	38	18
12 months	46	28	44	43	22
18 months	57	41	66	62	40

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

***Primary endpoint: MMR at 12 months**

Frontline TKI: % Complete Cytogenetic Response (CCyR)

	DASISION TRIAL*		ENESTnd TRIAL		
	DASATINIB	IMATINIB	NILOTINIB 300	NILOTINIB 400	IMATINIB
No. patients	259	260	282	281	283
6 months	73	59	67	63	45
12 months	77	66	80	78	65
18 months	78	70	85	82	74

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)

	DASISION TRIAL		ENESTnd TRIAL*		
	DASATINIB	IMATINIB	NILOTINIB 300	NILOTINIB 400	IMATINIB
No. patients	259	260	282	281	283
3 months	8	0.4	9	5	1
6 months	27	8	33	30	12
9 months	39	18	43	38	18
12 months	46	28	44	43	22
18 months	57	41	66	62	40

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)

	DASISION TRIAL		ENESTnd TRIAL*		
	DASATINIB	IMATINIB	NILOTINIB 300	NILOTINIB 400	IMATINIB
No. patients	259	260	282	281	283
3 months	8	0.4	9	5	1
6 months	27	8	33	30	12
9 months	39	18	43	38	18
12 months	46	28	44	43	22
18 months	57	41	66	62	40

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

***Primary endpoint: MMR at 12 months**

TOXICITY PROFILES

	GR 3/4 HEME (%)	NON-HEME(%)
Imatinib	Anemia (5-7) **Neutropenia (20)** Thrombocytopenia (9-10)	**Fluid retention/edema (39-42)** **Nausea (20-21)** **Diarrhea (17-21)** Rash (11-17) **Elevated amylase (18)**
Dasatinib	Anemia (10) **Neutropenia (21)** **Thrombocytopenia (19)**	Fluid retention/edema (19) Pleural effusion (10, no grade 3/4) Nausea (8) **Diarrhea (17)** Rash (11) Elevated amylase (Not listed)
Nilotinib	Anemia (3) Neutropenia (10-12) Thrombocytopenia (10-12)	Fluid retention/edema (7-8) **Nausea (11-19)** Diarrhea (6-8) **Rash (31-36)** **Elevated amylase (12-15)**

QTc >500 msec
- **Nilotinib trial: 1 patient on imatinib, no patients on nilotinib**
- **Dasatinib trial: 1 patient on imatinib, 1 patient on dasatinib**

Frontline TKI: Other Outcomes

	DASISION TRIAL		ENESTnd TRIAL		
	DAS	IM	NIL 300	NIL 400	IM
No. patients	259	260	282	281	283
Treatment failure, No. (%)	6 (2.3)	11 (4.3)	4 (1.4)	4 (1.4)	16 (7.1)
AP/BP, No. (%)	6 (2.3)	9 (3.5)	2 (0.7)	1 (0.4)	12 (4.2)
D/C due to AEs, No. (%)	15 (6)	10 (4)	7 (2.5)	12 (4.3)	9 (3.2)
Death, any cause at 24 mo, No. (%)	NR	NR	9 (3.2)	6 (2.1)	11 (3.9)
CML-related death at 24 mo, No.	NR	NR	5	3	10

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**

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/BP

O'Brien S, Guilhot F, Goldman J, et al. Abstract #186. Blood Nov 2008; 112: 76

What is the best strategy for frontline therapy?

Imatinib 400 mg daily	Second generation TKI
•Longest track record of safety & durability	
•Highly effective salvage therapy	
•No evidence of improved survival with MMR or CMR (yet?)	
•Cost issues not insignificant	

What is the best strategy for frontline therapy?

Imatinib 400 mg daily	Second generation TKI

What is the best strategy for frontline therapy?

Imatinib 400 mg daily	Second generation TKI
•Longest track record of safety & durability	
•Highly effective salvage therapy	
•No evidence of improved survival with MMR or CMR (yet?)	
•Cost issues not insignificant	

AGENT	ANNUAL COST*
Imatinib 400 mg daily	$66,500
Dasatinib 100 mg daily	$102,000
Nilotinib 300 mg BID	$118,000

*"Cash cost": Walgreens 01/10/11

What is the best strategy for frontline therapy?

Imatinib 400 mg daily

- Longest track record of safety & durability
- Highly effective salvage therapy
- No evidence of improved survival with MMR or CMR (yet?)
- Cost issues not insignificant

AGENT	ANNUAL COST*
Imatinib 400 mg daily	$66,500
Dasatinib 100 mg daily	$102,000
Nilotinib 300 mg BID	$118,000

*"Cash cost": Walgreens 01/10/11

Second generation TKI

- No clear superior second generation agent
- Lower risk of suboptimal response and progression
- Improved tolerance
- If "quicker" MMR translates to more frequent and durable CMR in the future, greater potential for discontinuation of therapy (?)

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?

What is the best strategy for frontline therapy?

Imatinib 400 mg daily

- Longest track record of safety & durability
- Highly effective salvage therapy
- No evidence of improved survival with MMR or CMR (yet?)
- Cost issues not insignificant

AGENT	ANNUAL COST*
Imatinib 400 mg daily	$66,500
Dasatinib 100 mg daily	$102,000
Nilotinib 300 mg BID	$118,000

*"Cash cost": Walgreens 01/10/11

Second generation TKI

- No clear superior second generation agent
- Lower risk of suboptimal response and progression
- Improved tolerance
- If "quicker" MMR translates to more frequent and durable CMR in the future, greater potential for discontinuation of therapy (?)

PATIENT EDUCATION
CAREFUL MONITORING STRATEGY

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

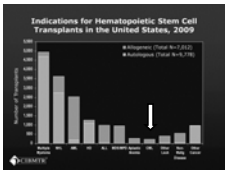
- PPI/H2 blockers: decrease drug levels of TKIs
- Acetaminophen: limit to 2000 mg/day or less
- Grapefruit juice: increases drug concentrations, should be avoided
- Warfarin: TKIs may cause an increase in INR; LMWH as alternative
- Caution with other agents that may prolong QTc

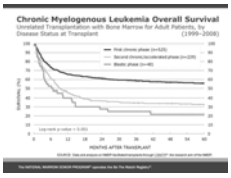
CASE: Poor response

- SS is a 25 year old female who has failed to achieve a meaningful cytogenetic response to all three commerically 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

Mahon F, et al. Lancet Oncol 2010: 1029-35

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