Chronic Myelogenous Leukemia
The Key for Things to Come in Cancer Treatment

Objectives

• Basic understanding of leukemia
• Definition of Chronic Myelogenous Leukemia (CML)
• Signs and symptoms of CML
• Treatment of CML
• Case studies
• Questions

What is Leukemia

Leukemia
• From the Greek word – “white blood”
• A progressive, malignant neoplasm of blood-forming cells, marked by diffuse replacement of bone marrow hematopoietic precursors by neoplastic leukemic cells
• Classified as acute versus chronic
• Differentiated by the predominant proliferating cells; lymphoid vs. myeloid (the latter includes granulocytic, monocytic, erythroid and megakaryocytic lineages)
Percentages of Subtypes of Leukemia

- Acute Lymphoid Leukemia 9%
- Chronic Myeloid Leukemia 10%
- Chronic Lymphoid Leukemia 23%
- Acute Myeloid Leukemia 27%
- Myeloproliferative Diseases 31%

Most common types of leukemia

- **Acute Myelogenous Leukemia (AML)**
  Occurs in both children and adults

- **Acute Lymphocytic Leukemia (ALL)**
  Most common type of Leukemia in children. Also affects adults.

- **Chronic Myelogenous Leukemia (CML)**
  Mainly affects adults

- **Chronic Lymphocytic Leukemia (CLL)**
  Most often in people over age 55
Acute Leukemia

- **ALL**
  - Acute Lymphoblastic Leukemia
    - Lymphoblast (B or T lymphocytes)
    - Develops and progresses rapidly unless treated
    - Can occur at any age but 6 out of 10 cases are in children
  
- **AML**
  - Acute Myeloid Leukemia
    - Bone marrow makes large numbers of abnormal / immature WBCs - BLASTS
    - Derived from the myeloid stem cells
    - Develops and progresses rapidly unless treated
    - Most cases in people over 50

Chronic Leukemia

- **CLL**
  - Chronic Lymphocytic Leukemia
    - Abnormal B lymphocytes
    - Found in large numbers (build-up) because they live too long - cells do not follow the usual life span of a lymphocyte
    - Develops and progresses slowly – over months & years without treatment
    - Most common leukemia in the elderly
    - Most cases occur in patients over the age of 55
  
- **CML**
  - Chronic Myeloid Leukemia
    - Develops due to a mutation in the stem cell
    - Abnormal stem cells multiply and the cells that are made develop into near normal WBCs – granulocytes; including neutrophils, basophils and eosinophils
    - Develops and progresses slowly over months and years without treatment
    - Mainly occurs in adults and becomes more common with increasing age. Average age is 64

What Causes Leukemia?

- Down to the basics
  - Starts from one abnormal cell
    - Vital genes control cell proliferation and also regulate cell death. If these genes are damaged or altered they may result in an abnormal cell being produced
    - When the abnormal cell survives it may multiply “out of control”
  
- Risk Factors
  - Radiation
  - Chemotherapy
  - Genetic disorders
  - Exposure to chemicals
Cells in Chronic Myelogenous Leukemia

CML

• Chronic - Myeloid / Myelogenous / Granulocytic
  – Characterized by increased and unregulated growth of myeloid cells in the bone marrow and accumulation of these cells in the peripheral blood
  – It is a type of myeloproliferative neoplasm
  – There is a characteristic chromosomal translocation

  “PHILADELPHIA CHROMOSOME”

3 Phases:
1. Chronic
2. Accelerated
3. Blast crisis
Chronic Phase in CML

• 85% of patients are in the chronic phase of CML at the time of diagnosis
• Asymptomatic or mild symptoms
  — Many times no symptoms
  — Discovered at yearly physical – elevated WBC on routine CBC
  — Sometimes presents with mild symptoms
  — Enlarged spleen and/or liver – causing upper quadrant pain
  — Loss of appetite and weight due to the enlarged spleen putting pressure on the stomach
  — Mild fever
  — Night sweats – due to elevated basal level metabolism
• In absence of treatment the disease will progress to an accelerated phase

Accelerated Phase in CML

• Criteria for determining if a CML is in the accelerated phase is defined by the World Health Organization (WHO)
• Accelerated Phase if any of the below are present
  — 10-19% myeloblasts in the blood or bone marrow
  — >20% basophils in the blood or bone marrow
  — Platelet count is <100,000 (unrelated to therapy)
  — Platelet count is >1,000,000 (unresponsive to therapy)
  — Cytogenetic evolution – new chromosome abnormalities in addition to Philadelphia chromosome
  — Increased splenomegaly
  — Increased WBC count (unresponsive to therapy)

More on the Accelerated Phase

• This is a significant phase because it signals the disease is progressing and the transformation to a blast crisis is imminent
• Drug treatment is less effective as the disease progresses
  — More serious symptoms in the accelerated phase
    • Bleeding – due to low platelets
    • Petechiae
    • Ecchymosis (nose bleeds)
    • Bone pain
    • Abdominal pain
    • Fatigue
    • Anemia
    • Fever – due to opportunistic type infections
Blast Crisis Phase in CML

- Final phase in CML
- Behaves like an acute leukemia
- Rapid progression and short survival
  - **WHO Criteria** – Blast Crisis if
    - $\geq 20\%$ blasts present in the blood or bone marrow
    - Large clusters of blasts seen in the bone marrow biopsy
  - Symptoms during the blast crisis phase
    - Extreme loss of appetite and weight
    - Fever
    - Bone pain
    - Extreme fatigue
    - Severe anemia
    - Thrombocytopenia – bleeding issues of all types

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Risk Factors in CML

- More common in males than females
- More common in Caucasians than African Americans
- More common in adults over 60 years of age
- Average risk is 1:600 chance
- Higher risk if exposed to ionizing radiation
  - usually peaks 10 years after exposure
  - 50 fold higher incidence of CML in Hiroshima and Nagasaki nuclear bombing survivors
- **No genetic link – not hereditary**

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Making the Diagnosis

- **CBC test**
  - Increased WBC, above 15,000
    - Increase in *eosinophils* and *basophils*
    - Immature granulocytes - metamyelocytes, myelocytes and promyeloctyes present in peripheral blood
  - Bone marrow biopsy
    - Increased myeloid cell production
    - Cytogenetic translocation t(9:22)
      - ABL1 gene on chromosome 9 and BCR gene on chromosome 22 translocate – they switch places
Cancer and Hematology Center Laboratory at LHCP is enjoying the benefit of the Advanced Clinical Parameters on the Sysmex XN-1000.

5 additional reportable parameters:

- Immature Granulocytes (IG)
- Nucleated RBC (NRBC)
- Immature Retic Fraction (IRF)
- Reticulocyte Hemoglobin Equivalent (RET-He)
- Immature Platelet Fraction (IPF)

- Automated IG counts (% and absolute) reported with every automated differential on the XN-1000.
- Measured by fluorescent flow cytometry.
- IG includes metamyelocytes, myelocytes and promyelocytes.
- Our start up comparison studies showed 94% correlation with the manual differential.
New CML Patient with WBC = 110,000 and IG = 27.9%

Immature Granulocytes
Metas, Myelos and Pros
Benefits of IG Parameter @ CHC

- IG provides a more accurate and precise automated count than a manual differential because many thousands of cells are counted by the instrument versus only 100 cells on the traditional manual differential
- We have a substantial number of patients with CML
- At CHC the XN-1000 differential has reduced the number of manual differentials by 75% for this patient population

CML patient with Metas, Myelos and Promyelocytes on the peripheral smear

XN 1000 Automatic Differential on CML patient

IG = 28.9%

(Metas, Myelos and Pros)

Two other things to note: High Basophils (3.7%) and NO Blast flag
Manual Differential on CML patient. Metas, Myelocytes and Promyelocytes IG = 27%

Education for the Clinicians
Canned Text Comments for IG

When reporting an elevated IG parameter in a CML patient, a canned text should be used to let the clinician know what a high IG % and absolute mean

Canned text
IG parameter reflects the combination of Metas, Myelos and Promyelocytes

Typical CBC Findings from a Patient with CML

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<th>Component</th>
<th>Value</th>
<th>Abnormality</th>
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<td>HbC</td>
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<td>HtC</td>
<td>39.9 %</td>
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<td>MCV</td>
<td>91.7 fL</td>
<td>Low HbC</td>
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<td>MCH</td>
<td>29.2 g/dL</td>
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<td>MCHC</td>
<td>34.4 g/dL</td>
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<td>Platelet</td>
<td>32.0 x 10^9</td>
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<tr>
<td>Lymph</td>
<td>6.1 x 10^9</td>
<td>Low Lymph</td>
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<td>Mono</td>
<td>5.9 x 10^9</td>
<td>Low Mono</td>
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<td>EOS</td>
<td>4.1 x 10^9</td>
<td>Low EOS</td>
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<tr>
<td>BAS</td>
<td>9.2 x 10^9</td>
<td>Low BAS</td>
</tr>
<tr>
<td>Immature Gran %</td>
<td>12.7</td>
<td>High IGs</td>
</tr>
</tbody>
</table>

IG parameter reflects the combination of Metas, Myelos and Promyelocytes
Typical Findings on the Bone Marrow Slide

So, What Causes CML?

? ? ? ?

Cause of CML

- The BCR-ABL1 fusion protein is the cause of CML
How to identify and measure the presence of the Philadelphia Chromosome

Conventional Cytogenetics t(9:22)(q34;q11.2)

FISH – fluorescent in-situ hybridization
BCR/ABL-1 Translocation

rt PCR - reverse transcription Polymerase Chain Reaction

Based on Size and Charge

The Significance of the 9;22 Translocation

- CML is the 1st cancer to be linked to a clear genetic abnormality - the 9;22 translocation
- Translocation called the Philadelphia Chromosome because it was first discovered and described in 1960 by two scientists from Philadelphia

Dr. Peter Nowell
Dr. David Hungerford

BCR/ABL1 – it’s a bit complicated

The ABL gene on chromosome 9 is fused to the BCR (Breakpoint Cluster Region) gene on chromosome 22
The “fusion” gene generates a protein of p210 or p185 weight
ABL carries a domain that can add phosphate groups to tyrosine residues (a tyrosine kinase)
Therefore: The BCR/ABL1 fusion gene product is a tyrosine kinase Tyrosine kinase activity is responsible for the activation of signal transduction pathways which leads to abnormal bone marrow proliferation
Let’s Learn about Tyrosine Kinases

- Tyrosine kinases are important mediators of the signaling cascade
- Tyrosine kinases play key roles in diverse biological processes in response to external and internal stimuli
- Tyrosine kinases help control
  - Cell growth
  - Cell differentiation
  - Cell metabolism
  - Cell apoptosis (cell death)

Let’s Learn about Tyrosine Kinases

- Tyrosine kinases are a family of enzymes which catalyze phosphorylation of select tyrosine residues in target proteins using ATP
- Though their activity is tightly regulated in normal cells, they may acquire transforming functions due to mutations, which may lead to malignancy

Breaking the BCR-ABL1 Process Down

- Fused BCR-ABL1 protein interacts with interleukin 3 beta receptor subunit
- The BCR-ABL1 transcript is continuously active
  - It does not require activation by messaging proteins
- BCR-ABL1 activates a cascade of proteins that control cell cycle thus speeding up cell division
- Also, BCR-ABL1 protein inhibits DNA repair causing genomic instability
  - DNA becomes more susceptible to developing other genetic abnormalities
- BCR-ABL1 is found in all myeloid lineages and in some lymphoid and endothelial cells
Now Let’s Learn About ABL

Some genes control when our cells grow and divide

• Certain genes that promote cell growth and division are called Oncogenes

  ABL is an Oncogene

• Others that slow down cell division or cause cells to die at the right time are called tumor suppressor genes

More About ABL

• Cancers can be caused by changes in DNA (mutations) that turn on oncogenes or turn off tumor suppressor genes

• The swapping of DNA between the ABL (an oncogene) and the BCR creates a dangerous situation

  It makes a tyrosine kinase/oncogene causing cells to reproduce out of control
Philadelphia Chromosome Negative CML?

- In the past, patients that had the rest of the signs and symptoms of CML but did not have the BCR-ABL1 translocation were classified as Philadelphia Chromosome negative CML.
- The WHO updated diagnostic criteria for CML in 2008 such that patients must have the BCR-ABL1 translocation to be classified as CML.
- The so-called "Philadelphia Chromosome negative" cases are now grouped as a form of myeloproliferative/myelodysplastic neoplasm.

Treatment of CML

- Curative
  - Bone marrow transplant
  - Allogeneic stem cell transplant
    - Risk verses benefit
- Palliative
  - Tyrosine kinase inhibitors
  - Myelosuppressive therapy
    - Hydroxyurea – helps to quickly decrease the number of WBCs
      - Many times used in conjunction with tyrosine kinase inhibitors at 1st
  - Splenectomy

Tyrosine-kinase inhibitors

- Drugs that specifically target BCR-ABL protein
- First of this class of drugs was imatinibmesylate
  - Gleevec
    - FDA approved in 2001
    - Inhibited progression of CML in 75% of compliant patients
    - Allowed re-growth of normal bone marrow stem cell population
      - Stable, maturing WBC line able to be re-established
    - Small amount of persistent BCR-ABL still present in patients undergoing treatment, thus imatinib needs to be given to the patient indefinitely.
How Gleevec Works

Although the 9;22 translocation still occurs, the imatinib (Gleevec) “locks” it up so it is unable to receive the phosphate resulting in a blocked signal for cell proliferation & survival.

Additional Tyrosine Kinase Inhibitors

- Dasatinib and Nilotinib
  - Blocks several further oncogenic proteins and has more potent inhibition of BCR-ABL
  - Drugs were first FDA approved to treat patient with CML who were either resistant to or intolerant of imatinib
  - Both of these drugs have now been approved as first line therapy in place of imatinib because of greater inhibition

- Radotinib
  - FDA approved in 2015
  - Used in chronic phase CML when patient is resistant or intolerant of imatinib
**BCR-ABL Mutations**

- Drug resistance is common after prolonged use of Gleevec and the other tyrosine kinase inhibitor drugs due to additional mutations occurring
- Most common BCR-ABL mutation is known as T315I
- Other treatment options have been developed to combat the T315I mutation
- Ponatinib – FDA approved in 2013 is used for treatment of patients with resistant CML
- Efficacy of this drug is against the T315I as well as all other known mutations of the oncoprotein

**BCR / ABL Monitoring by Molecular Testing**

- The degree to which the bulk of the disease is reduced is an important prognostic indicator
- Poor primary response or relapse after initial response both suggest the need to change therapy
- Molecular monitoring provides a deeper assessment of the response as well as a means to detect relapse earlier than other methods

**Prognosis of CML**

Factors that affect the overall prognosis of CML

- **Age** at onset of the disease
- **Phase** of CML at time of diagnosis
- Number of **blasts** in the blood and bone marrow at time of diagnosis
- Size of the **spleen** at the time of diagnosis
- Patient’s general **overall health**
Good News for CML

• Before tyrosine kinase inhibitors the median survival time for a patient with CML was 3-5 years
• Now, <1% of CML patients who are compliant with their tyrosine kinase inhibitor treatment die of leukemia progression

Breakthrough in Cancer Treatment

• Because of Drs Nowell and Hungerford’s discovery back in 1960 we now know that if we can define the point of the abnormality in a cancer, we can treat the cancer with a targeted therapy
• Targeted therapy blocks the growth and spread of cancer by preventing cancer cells from dividing or by destroying them directly

• While standard chemotherapy affects all cells in the body, targeted therapy directs the drugs or other specially created substances to attack cancer cells
• The goal of targeted therapy is to interfere with specific molecules involved in tumor growth to block the growth and spread of the disease
• Because targeted therapy specifically seeks out cancer cells, it can avoid harming healthy cells
• Plus, targeted therapy may have fewer side effects than standard chemotherapy
Case Studies in CML

This is the beginning of the story but let's see how it can end

Case Number 1

• This is a 56 year old married man with two children in relatively good health working in a high pressure sales position
• His employer requires a yearly physical (or he has to pay a higher out of pocket insurance premium)
• Routine appointment with his PCP - he presents with no complaints or issues
• Physical exam and routine lab work was done
  CBC, CMP, Lipid Profile and Urinalysis

The Results

• On Physical Exam
  – Physician notes enlarged spleen
  – Patient states a bit more fatigued than usual but blames it on his high stress job and work / life balance
• The Lab Results
  – CBC shows critical high WBC and low Hgb
    • WBC = 78,000
    • Hgb = 10.9
• Patient referred to CHC for a Hematology Consultation
Patient is referred for a Hematology Consultation due to his high WBC & low Hgb

- Labs drawn and run include:
  - CBC
  - CMP
  - BCR/ABL
  - JAK2

CBC Results
- High WBC
- Low Hgb
- High IGs
- High Eos
- High Baso

Manual Differential Results
- (Matches Autodiff)
- 13% IGs
Results:
Results are NEGATIVE for JAK2 V617F mutation.

Notes:
Results of JAK2 testing are NEGATIVE, indicating the V617F (1849G>T) mutation is NOT DETECTED in the JAK2 gene.

BCR/ABL by FISH

Treatment
Patient is started on Imatinib (Gleevec) 600mg/day
Patient returns in 3 weeks for repeat CBC
WBC drops to 31.4
Hgb goes up to 11.3
IGs drop to 2%
Eosinophils and Basophils also drop
Fast Forward 6 years

Patient continues Gleevec but reduced dose of 400mg/dl

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<td>BASO%</td>
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<td>Neutrophile RBC %</td>
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<tr>
<td>Immature Granulocytes</td>
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Blood count shows complete hematologic remission

BCR/ABL shows Major Molecular Remission

Patient rates Quality of Life as a 10

Case Number 2

• 50 year old married man with 4 children
• Reports to ER with chest pain
• History of psoriasis – not on any treatment
• Smoker – 1 ½ packs a day for over 30 years
• Symptoms include: S.O.B., dizziness, blurred vision and lightheadedness

Workup: Chest X‐ray – normal
Troponin – negative X2
D‐Dimer - negative
CBC - WBC = 65,000, Plt = 119,000

Ches pain ruled as musculoskeletal but patient referred to CHC due to increase WBC and decreased platelet count

Hematology Consultation
• Labs drawn and run include:
  CBC
  CMP
  BCR/ABL
  JAK2
  Flow Cytometry
CBC Results

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<th>RBC</th>
<th>HGB</th>
<th>HCT</th>
<th>MCV</th>
<th>MCH</th>
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<td>High Eosinophils</td>
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Under the Microscope

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<td>Increased Basophils</td>
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<td>Metamyelocytes</td>
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<td>Myelocytes</td>
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The Rest of the Results

- CMP: Normal
- Flow Cytometry: No diagnostic flow cytometric abnormality detected. Most of the cells (81%) have flow cytometric characteristics of mature granulocytes. Rare immature myeloid cells (<1%)
- BCR/ABL: Positive for t(9;22) BCR/ABL1 dual gene fusion 89.75% - 359 out of 400 cells are positive for Philadelphia chromosome
- JAK2 V617F Quant PCR: Negative <1.0
- Confirms diagnosis of Chronic Myelogenous Leukemia
**Treatment**

- Patient is started on standard therapy of 400mg/day of Gleevec
- Weekly CBCs are run
- WBC drops from 92.8 down to 7.6 in six weeks
- Platelets increase to normal at 240,000

### Blood Count

<table>
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<th>Result</th>
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<td>MDU %</td>
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**Return visit in 6 weeks to see physician**

- Patient feels awful:
  - fatigue, achy, itching red eyes, diarrhea, rash, severe back pain and nausea
- CBC results are normal
  - Excellent hematologic response
    - But
  - Side effects of Gleevec are difficult to tolerate
  - Quality of Life per patient is at a 2 out of 10
- Gleevec is held and patient to return in 3 weeks for labs and evaluation

**3 Week Return Visit – Treatment Held**

**Disease Progression**

Patient is put back on Gleevec but dose reduced

Due to continued side-effects patient switched to Sprycel (Dasatinib) and many of his issues were resolved
Case Number 3

- 83 year old widowed man with a history of Rheumatoid Arthritis referred to CHC for evaluation of leukocytosis and thrombocytosis
- Patient had been taking Methotrexate for ten years for treatment of his arthritis but was recently weaned off as his RA was doing well
- Patient reports overall high quality of life with no complaints
- Differential diagnosis is myelofibrosis versus a myeloproliferative disorder
- Lab tests performed include: CBC, CMP, JAK2 and FISH for BCR/ABL

Test Results and Treatment Plan

- JAK2: Negative
- CMP: Normal
- FISH BCR/ABL: Positive - 376 out of 400 cells positive for t(9:22) BCR/ABL1 dual gene fusion (93.5%)
- Due to high WBC he is first cytoreduced with hydrea at 1000mg twice daily. Once WBC dropped to 50,000 he was started on Sprycel (Dasatinib) at 100 mg/day
- He tolerates the treatment well with no side-effects and he has a complete hematologic response
- He has most likely had CML for some time but due to the long term use of Methotrexate for his RA it most likely suppressed his WBC and platelet counts hiding his disease
CBC results after being on treatment for 6 months

WBC and Platelet counts return to normal

CML with Complete Hematologic Response

Let’s Quick Review the Last 3 Cases

• So far, 3 men
• Ages 56, 50 and 83
• All cases discovered “by accident”
• All had positive BCR/ABL t(9;22) translocation
• All had a complete hematologic response with Imatinib or other tyrosine kinase inhibitor
• Pretty much follows what we have learned today

Case Number 4- It’s Complicated

• A 34 year old, white, single male reports to urgent care for extreme shoulder and abdominal pain
• On physical exam, patient found to have massive splenomegaly. Blood work showed a marked leukocytosis with a WBC of 308,000
• Patient was transferred to the hospital and a bone marrow biopsy was performed including flow cytometry, cytogenetics and FISH
• BCR/ABL1 was positive at 96%(382 out of 400 cells positive)
• Diagnosis of Chronic Myelogenous Leukemia (CML)
Treatment

- Patient was started on hydroxyurea (1000mg twice daily) to lower his WBC but after two weeks – no response
- Gleevec at 400mg/day was added along with an increase in the hydroxyurea to 1500mg 2X/day
- Bi-weekly CBCs were done and WBC began to decrease
- Follow up visit with CHC Hematologist
- WBC normal at 8.1
- Hydroxyurea discontinued
- Patient to remain on Gleevec at 400mg/day
- Patient to have weekly CBCs and monthly BCR/ABL by PCR

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Non-compliance

- Patient is non-compliant in getting his weekly blood test, in keeping his follow-up appointments with his physician and with taking his Gleevec. (Patient states he lost his job so he had no insurance and couldn’t afford to buy the drug)
- Patient finally presents for his appointment 7 months later
- Again, patient has massive splenomegaly and leukocytosis; 
  \[ WBC = 172,000 \text{ and } 80\% \text{ circulating blasts} \]
- Bone marrow biopsy performed
- Results of bone marrow, flow cytometry & cytogenetics
  \[ T \text{ Lymphoblastic Blast phase Leukemia} \]
Lymphoblasts under the microscope

**Treatment**
- Patient to have an immediate hospital admission to start treatment for his acute lymphoblastic leukemia
- Patient declines to go to the hospital at this time. He states he is the sole caregiver for his 11 year old son. Patient waits until son starts back to school 3 weeks later before being admitted
- Patient has a 2 month hospital stay
- Treated with 3 cycles of hyperCVAD chemotherapy (cyclophosphamide, vincristine and Adriamycin)
- During his 2 month stay patient has many complications including bacterial pneumonia and sepsis
- Patient attains remission status for his ALL
- WBC = 7.3 at discharge

**Follow-up**
- Patient is recommended for bone marrow transplant but due to his continued non-compliance he is not accepted for transplant
- Patient’s rt-BCR/ABL levels rise
- Patient’s medication is switched from Gleevec to Sprycel (dasatinib)
- But, again, the patient is non-compliant both with his new medication and with keeping his doctor appointments
- Patient calls the office after a year of not showing up for his appointments. Patient states he is having some abdominal pain and increased fatigue
- Patient comes into the office for a physician appointment and blood work
The Results

**COMPLETE BLOOD COUNT W/DIFF and PT/INR**

<table>
<thead>
<tr>
<th>WBC</th>
<th>HGB</th>
<th>HCT</th>
<th>MCHC</th>
<th>MCV</th>
<th>PLT</th>
<th>PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.53</td>
<td>9.9</td>
<td>30.7</td>
<td>32.2</td>
<td>114</td>
<td>2233</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**WBC** high at 114,000 with an **IG** of 36%

**Platelets** extremely high at over 2 million

**BCR/ABL** is up over 1

No hematologic or molecular response

Patient states he lost his disability and disability insurance and is unable to afford medication

Patient is put on an assistance program and able to resume taking Sprycel

Patient is scheduled for weekly CBCs and a monthly follow-up appointment with his physician

One Month Later

**COMPLETE BLOOD COUNT W/DIFF and PT/INR**

<table>
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**Patient shows improved compliance**

He continues to take Sprycel and have weekly lab work done

**Patient has both good hematologic and molecular response**

Bad Habits are Hard to Break

- Patient **does not return** for lab work or office visit **for 6 months**
- When he does come in, WBC high at 31.9 with 75% circulating blasts – bone marrow biopsy with flow, cytogenetics and FISH
- Results show Acute Myelogenous Leukemia with components of T Lymphoblastic Leukemia giving the patient the diagnosis of **Mixed Lineage Leukemia**
- Recommend that patient have an immediate hospital admission and to begin intense chemotherapy
- Patient declines again stating he is in the middle of moving into a different apartment and he is not available for hospitalization for several weeks
- Patient is finally admitted 2 months later and treated with FLAG chemotherapy (Fludarabine, high dose cytarabine plus G-CSF)
**A Rough Ride**

- Patient remains in hospital for 4 months
- Treatment with FLAG gets his leukemia in remission but he presents with many complications
  - Febrile neutropenia
  - Gingival ulcer with exposure of cortical bone requiring tooth extraction
  - Pancreatitis
  - Thrombocytopenia requiring numerous platelet transfusions
  - Fungal infection in his lungs
  - Extreme weight loss, down to 117 pounds

**The Rest of the Story... to be continued**

Patient has been much more compliant in taking his medication, seeing his physician and getting his labs done as scheduled

Hematologic response is good

Molecular response is at the best point so far

**Sometimes patients do everything right and outcomes are bad**

**Sometimes patients do everything wrong and they still come out all right**
Don't do that. You have no idea what it could lead to.

Sorry, I just thought I would try something different.