Outline of CML Talk

• Brief Description of Pathophysiology of Chronic Myelogenous Leukemia (CML)
• Brief History of Medical Discovery in CML
• Current Treatment Options for CML
• Side Effect Management
• Future Directions in the Treatment of CML
• Discussion of Cost Issues Associated with the Treatment of CML
• CML Cases
• Question and Answer Period
Chronic Myelogenous Leukemia

• Slow growing cancer of the Granulocytes (type of white blood cell) – a type of Myeloproliferative Neoplasm (MPN)
• Approx 6600 new cases per year in United States (2014)
• Approx 1100 deaths per year in United States (2014)
• Median Age at diagnosis 67 years old (rarely found in children)
CML Blood Smear

CML Blood Smear

CML Blast Crisis

Normal blood smear
Chronic Myelogenous Leukemia

• Possible Symptoms of CML:
  – Night Sweats
  – Enlarged Spleen (Abdominal swelling in the Left Upper Quadrant sometimes with tenderness)
  – Fatigue and/or weakness
  – Bone pains
  – Fevers
  – Frequent Infections
  – Early Satiety and/or Weight loss
Chronic Myelogenous Leukemia

- A single chromosomal translocation may be responsible for the disease (very unusual)
- Translocation of long arm of chromosome 9 and long arm of chromosome 22
- The resultant BCR/ABL gene yields an abnormal protein
- The BCR/ABL encoded protein is permanently “on” leading to inappropriate cell division from hematopoietic stem cells to cancerous granulocytes in the bone marrow
9;22 translocation, BCR-ABL fusion
Hematopoietic Stem Cell Differentiation

- **Blood stem cell**
  - **Myeloid stem cell**
    - Myeloblast
      - Granulocytes (Neutrophil, Eosinophil, Basophil)
      - Platelets
    - Red blood cells
  - White blood cells
    - Granulocytes
    - B lymphocyte
    - T lymphocyte
    - Natural killer cell

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What is the BCR gene?

- BCR (Breakpoint Cluster Region) gene encodes a protein that may be a serine/threonine kinase but is of unknown function.
- The amino-terminus of the BCR protein may confer extra stability and therefore extra long life to BCR/ABL fusion protein.
What is the ABL gene?

- **ABL (Abelson)** is an oncogene (a gene that when over-expressed causes cancer) originally identified in a leukemia virus

- **ABL - tyrosine kinase protein**
  - Involved in the signalling pathway leading to the production of granulocytes from hematopoietic stem cells

- The BCR/ABL tyrosine kinase protein is the target for most directed therapies in CML treatment
ABL function
Inhibition of ABL kinase by Gleevec

CASE COMPREHENSIVE CANCER CENTER
Stages of CML

• **Chronic Phase**
  – <10% blasts (acute leukemia cancer cells)

• **Accelerated Phase**
  – 10-29% blasts and/or resistance to primary therapy

• **Blast Crisis (a type of acute leukemia)**
  – > 30% blasts

• **Sokal Risk Score** (high, intermediate or low risk)
  – Age, spleen size, blast #, platelet count

• **Hasford Risk Score** (high, intermediate or low risk)
  – Age, spleen size, platelet count, blast #, basophil #, eosinophil #
• Peter Nowell MD
  – 1961: Discovered Philadelphia (Ph1) Chromosome abnormality in almost all patients with CML

• Janet Rowley MD (Human geneticist)
  – 1973: Discovered that the Ph1 Chromosome was a translocation of chromosome 9 & chromosome 22

• David Baltimore PhD (Molecular biologist)
  – 1990: Showed that mice expressing BCR/ABL developed CML
Brief History of CML (continued)

• Brian Druker MD
  – **1996**: Demonstrated Imatinib (Gleevec) – an ABL tyrosine kinase inhibitor stopped CML cell growth in the petrie dish.
  – **2001**: Demonstrated safety and efficacy of Imatinib in patients with CML

• **2001**: FDA Approval of Gleevec for CML
Treatments for Chronic Phase CML

- **Tyrosine Kinase Inhibitors** (year of FDA approval)
  - Imatinib (Gleevec) 2001
  - Dasatinib (Sprycel) 2006
  - Nilotinib (Tasigna) 2007
  - Bosutinib (Bosulif) 2012
  - Ponatinib (Iclusig) 2012

- **Protein Translation Inhibitor**
  - Omacetaxine (Synribo) 2012

- Interferon alpha
- Hydroxyurea
- Allogeneic Stem Cell Transplant
Treatment for Acute Phase CML

- Tyrosine Kinase Inhibitors
- Hydroxyurea
- High dose Cytarabine
- Busulfan
- Interferon alpha
- Omacetaxine
- Allogeneic Stem Cell Transplant
- Clinical Trial when available
Treatment for Blast Crisis CML

- Tyrosine Kinase Inhibitor
- Acute Leukemia Induction Chemotherapy
- Allogeneic Stem Cell Transplant
- Clinical Trial when available
Imatinib (Gleevec)

- Must take one 400 mg tablet daily lifelong (not a cure)
- High cost (400 mg tablets of Gleevec cost $6980 for just 30 tablets)
- Imatinib going generic soon?
- Relatively few side effects
- High efficacy
  - 89% of patients alive at 7 years after initiation of imatinib compared to 68% of patients alive at 5 years prior to the FDA approval of imatinib
Side Effects of Imatinib and Management of Side Effects

• Drop in blood counts
  – Adjust dose

• Elevation in liver enzymes
  – Adjust dose

• Fluid retention/peri-orbital edema
  – Diuretics, heart echo, adjust dose, surgery

• Nausea
  – Take with meals and large glass of water, anti-nausea meds

• Muscle cramps
  – Calcium supplementation, tonic water

• Rash
  – Topical or systemic steroids, adjust dose

• Diarrhea – anti-diarrhea meds, adjust dose
Dasatinib (Sprycel)

• One 100 mg Tab dose daily
• Expensive (30 tabs cost $10,572)
• May be more efficacious than Imatinib
• No survival benefit over Imatinib
• More side effects, more interactions with other medications than Imatinib
Side Effect Management in Dasatanib

• **Drop in Blood Counts**
  – Adjust dose

• **Pulmonary Arterial Hypertension**
  – Stop Dasatanib

• **Pleural & Pericardial Effusions, Fluid Retention**
  – Diuretics, steroids, dose reduction

• **Fluid Retention**
  – Diuretics

• **Nausea**
  – Take with meal and large glass of H2O, anti-emetics

• **Rash** — topical or systemic steroids, adjust dose.
Nilotinib (Tasigna)

- One 300 mg tablet twice a day
- Expensive (approx $10,000 per month)
- Possible cardiac toxicity and Arterial blood clots
- May be more efficacious than Imatinib
- No demonstrated survival advantage over Imatinib
- More side effects and medication interactions than Imatinib
Management of Nilotinib Side Effects

• Blood Count Drops
  – Adjust dose

• QTc prolongation (can cause fatal heart arrhythmias)
  – Adjust dose or stop, check potassium and magnesium

• Elevated liver and/or pancreatic enzymes
  – Adjust dose or stop

• Blood sugar changes
  – Treat with anti-hyperglycemic meds

• Peripheral Arterial Occlusive Disease
  – Stop Medicine – consider alternative therapies in patients with h/o PAOD and CAD

• Rash – topical or systemic steroids.
Bosutinib (Bosulif)

- Treatment for CML resistant to other TKI’s or patient intolerance to other TKI’s
- One 500 mg tablet daily
- Expensive (approx $8000 per month)
- More side effects than Imatinib
Management of Bosutinib Side Effects

- **Drop in Blood Counts**
  - Adjust dose

- **Elevated Liver Enzymes**
  - Adjust dose, stop med

- **Diarrhea**
  - Anti-diarrhea meds, adjust dose, stop med

- **Fluid Retention**
  - diuretics

- **Nausea**
  - Take with a meal and/or large glass of H2O, anti-emetics

- **Rash**
  - Topical or systemic steroids, adjust dose
Ponatinib (Iclusig)

- **Withdrawn** from market for a period of time due to **Vascular Occlusion** in 27% of patients.
- One **45 mg tablet** once daily
- Indicated for **CML resistance** with **T315I** mutation or failure/intolerance of all other TKI’s
- **Expensive** ($9850 per month)
- Lots of **Potential Side Effects**
Ponatinib Side Effect Management

- **Signs of heart attacks, strokes, DVT**  
  - stop med, treat event
- **Drop in Blood Counts**  
  - Adjust dose, growth factors
- **Liver and pancreatic dysfunction**  
  - Adjust dose or stop med
- **Bleeding**  
  - Stop med, treat hemorrhage
- **Cardiac Arrhythmias**  
  - Stop med, treat arrhythmia
- **Fluid Retention** – diuretics, dose interruption/reduction/cessation
- **Hypertension** - Medically treat hypertension
- **Rash** – Topical or systemic steroids, dose adjustment/cessation
Omacetaxine (Synribo)

• Given only to Pt’s with Intolerance to or Progression on TKI’s
• Subcutaneous injection twice daily 14 days on 14 days off until hematologic response and then maintenance injections twice daily 7 days on and 21 days off.
• Not a cure
• Less efficacious than TKI’s
• Few side effects
Monitoring for Response with Therapy

- Blood Counts (CBC’s)
- Spleen measurements
- FISH for peripheral blood \(9;22\) translocation
- PCR for peripheral blood \(bcr/abl\) transcript
- Bone Marrow Biopsy
- Mutational Analysis of \(bcr/abl\) transcript if inadequate response or if relapse or progression of disease
Timing of Follow Up Tests for Chronic Phase CML

• Bone Marrow Biopsy at Diagnosis
• FISH for 9;22 to confirm diagnosis
• Quantitative PCR of bcr/abl at diagnosis and every 3 months for 2 years after no evidence of detectable transcript.
• Mutational Analysis of bcr/abl transcript if 1 log increase in bcr/abl transcript or relapse from undetectable to detectable transcript or progression into accelerated phase or blast crisis.
Treatments for CML on the Horizon

- **Farnesyl Transferase Inhibitors**
  - Lonafarnib and Tipifarnib
- **T315I mutation agents**
- **Histone Deacetylase Inhibitors**
  - Panobinostat
- **Proteosome Inhibitors**
  - Bortezomib
TKI Cessation in “Cured” CML patients?

• Clinical trials of TKI cessation are ongoing
• Preliminary data suggest that a subgroup (approx 40%) of PCR - BCR/ABL negative patients can stay in remission for a prolonged period of time.
• Studies ongoing to pre-identify those patients who:
  – Stay in remission after TKI cessation
  – Whether these patients are truly “cured”
Cost Issues and CML Treatment

• High monthly cost of life-long treatment
  – $6,000 to $14,000 per month lifelong cost to healthcare system

• Patient Position
  – Affordable
  – Effective Therapy
  – Minimal Side Effects
Pharmaceutical Company Position

- Patients and doctors requesting new medications
- High cost of drug development (approximately $1 billion dollars to develop 1 new cancer therapy medication)
- Rare diseases need financial incentive to develop new drugs
- Most new medications developed in United States
- High costs balanced by generous patient assistance programs
Health Care/Insurance System Position

• Increasing Costs of Lifelong Medications May Bankrupt System
• No legal ability to regulate or negotiate medication costs
• Increasing costs of meds increase cost of insurance premiums
Physician Position

• Balance
  – New medications need to be developed by pharmaceutical companies
  – No bankruptcy of health care system
  – Medications readily available to patients
  – Medications affordable to patients that need them
Physician and Consumer Questions

• Why did cost of Gleevec rise?
  • $2200 per month in 2001
  • $7000 per month in 2015
  • $14 per month to manufacture (Andrew Hill – Univ of Liverpool)
  • Theoretically recouped development investment by end of 2004

• Why is Imatinib not yet available as a generic?
  – Newest release date of generic Imatinib July 2016
  – Imatinib (the chemical structure) initially due to be off patent January 2013
  – Final patent expiration of beta crystal of Imatinib 2019
Case #1: 34 yo male with symptoms of weight loss and abdominal discomfort

- CBC: WBC 250,000, hemoglobin 9.5, platelet 104,000, enlarged spleen on physical exam.
- FISH positive for BCR/ABL
- Bone marrow biopsy showed chronic phase CML, BCR/ABL PCR showed 73% transcripts
- Hydrea started until wbc < 70,000 and then Imatinib (Gleevec) 400 mg daily
- After 3 months wbc 4.5, hemoglobin 14.5, platelets 165,000, BCR/ABL PCR 9% transcripts
- After 6 months normal CBC, BCR/ABL PCR – undetectable
- 7 years later, undetectable BCR/ABL. Side effects of muscle cramping from Gleevec.
Case #2: 76 yo female with abdominal discomfort and night sweats

- CBC with diff showed wbc 135,000, hemoglobin 12, platelets 104,000, elevated neutrophils and basophils
- Physical Exam showed splenomegaly with spleen 5 cm below left rib cage
- BCR/ABL FISH was positive
- Bone marrow aspirate and biopsy consistent with chronic phase chronic myelogenous leukemia.
- BCR/ABL PCR showed 78% transcripts.
- Hydroxyurea started and then switched to Imatinib (Gleevec) 400 mg daily once wbc < 70,000.
- After 3 months of Gleevec, WBC 35,000, hemoglobin 9.5, platelets 70,000 and BCR/ABL PCR 53%
Case #2 continued

- Gleevec stopped
- CBC recovered to wbc 50,000, hemoglobin 10.5, platelet 115,000
- Dasatanib (Sprycel) 100 mg started
- Patient developed side effects of fluid retention, nausea, diarrhea, and rash
- CBC after 1 month showed wbc 500, hemoglobin 7.9, platelets 15,000, BCR/ABL PCR 35% and Sprycel stopped
- After 3 months CBC recovered to WBC 17,000, hemoglobin 10.2, platelets 105,000
Nilotinib (Tasigna) started at 300 mg twice daily

After one month CBC showed WBC 2,500, hemoglobin 9.5 and platelets 35,000 and nilotinib stopped. Pt otherwise without symptoms, splenomegaly resolved.

After 6 weeks CBC recovered to WBC 11,000, hemoglobin 10.9, platelets 115,000.

Nilotinib restarted at 200 mg twice daily

After 3 months WBC 4,900, hemoglobin 12.0, platelets 85,000, BCR/ABL PCR 15%

After 2 years on Nilotinib 200 mg twice daily BCR/ABL PCR 1%
Case #3: 61 year male presented with malaise and fatigue

- CBC showed wbc 96,000, hb 11, plt 114,000
- Started on Gleevec 400 mg daily
- Pt on and off Gleevec for 7 years with BCR/ABL transcript level rising or falling
- Always had detectable BCR/ABL transcript
- Off Gleevec and lost to follow up for over 1 year until patient hospitalized for fever and weight loss.
- CBC showed wbc 140,000 with 25% blasts
Case #3 continued

- Started on Dasatinib and given acute leukemia chemotherapy (Daunarubicin and Cytarabine)
- Allogeneic transplant after patient in remission
- Recovering slowly from transplant with significant graft versus host disease
Case #4: Healthy 44 year old with elevated WBC at PCP office

- CBC showed 53,000 wbc, elevated eosinophils, neutrophils and basophils.
- Bone marrow biopsy showed chronic phase CML, FISH positive for 9;22 translocation and PCR for BCR/ABL was 43%
- Gleevec started and normal wbc, undetectable BCR/ABL transcript.
- Side effects of fluid retention and peri-orbital edema.
- Diuretics started, plastic surgery on eyelids
- Symptom-free in continued remission x 7 years
Questions?

CML can develop from either of these cells.

Stem cell

Myeloid stem cell

Myeloid blast

Monocyte

Granulocyte