A 40 YEAR PERSPECTIVE OF MYELOPROLIFERATIVE DISEASES

Presented by:
Robert J. Jacobson, M.D., F.A.C.P., F.R.C.P (C)
Palm Beach Cancer Institute
Consulting Professor Duke University Medical Center
Affiliate Professor Florida Atlantic University
1960’s

- Medical School and Residency Training
- Anatomic and pathologic descriptions of Myeloproliferative Diseases
- CML, Polycythemia Vera, Agnogenic Myeloid Metaplasia, Primary Thrombocytosis
- Philadelphia Chromosome described in 1960 in patients with CML
1970’s

- Clonality of the MPD described by Fialkow and colleagues using isoenzymes and genetic markers.
- MPD arise in pluripotent hematopoietic stem cells.
- Myelofibrosis a reactive process not malignant.
- Bone marrow transplantation introduced as modality of treatment.
1980’s

- Polycythemia Vera Study Group reported on diagnostic criteria, natural history, complications and treatment of P.Vera
- Thrombosis and bleeding complications and role of phlebotomy in keeping hemoglobin in normal range reported.
- Leukemic transformation in patients treated with phlebotomy alone (2%) vs. P₃₂ (7%) vs. Chlorambucil (9%)
1990’s

- Treatment with Hydroxyurea vs. Aneugrelide© for elevated platelet counts

- Role of Alpha- Interferon in MPD especially for patients with splenomegaly

- Splenomegaly and radiation to spleen performed in selected patients
### 2000’s to current period

- Imatinib (Gleevec) targeted therapy for CML developed and approved

- JAK 2 mutation, V617F mutation and dysregulated JAK2 kinase activity found in 65-97% of patients with P.Vera, Essential Thrombocytopenia 23-57%, and Chronic Idiopathic Myelofibrosis 35-50%
CML – Philadelphia Chromosome
BCR/ABL
Chronic Myelogenous Leukemia

- CML associated with and diagnosed by presence of t (9;22) and the BCR-ABL fusion gene (Philadelphia chromosome)
- Originates from abnormal pluripotent hematopoietic stem cell
- Annual incidence 1.3/1,000,000 population and median age of onset is 55 years
- First and most successful cancer treated to date with targeted drug therapy, the tyrosine kinase inhibitor Imatinib and now 2nd generation inhibitors, Dasatinib and Nilotinib.
Imatinib

Gleevec: HOW IT WORKS

CML Enzyme → ATP → Cancer Protein → CML

Gleevec blocks the CML Enzyme, preventing the formation of Cancer Protein and CML.
Ruxolitinib (JAKAFI)

- Approved by FDA in November 2011 for treatment of intermediate and high risk myelofibrosis, including primary myelofibrosis, post-P Vera myelofibrosis, and post-essential thrombocytopenia myelofibrosis.

- In clinical trials goal was to reduce spleen size by at least 35%

- Starting dose 20mg twice daily, for kidney and liver impairment dose reduced to 10 mg twice a day

- Side effects: thrombocytopenia, anemia and neutropenia
CONCLUSION

- Over 40 years original descriptions of the diseases are now elucidated at a molecular level.
- Specific therapy developed to target defective genes and proteins
- Future holds much promise for the treatment of patients with these diseases as we begin to unravel the molecular pathways involved.
- Cost of new targeted drugs are enormous, spread over the number of years patients may need them.