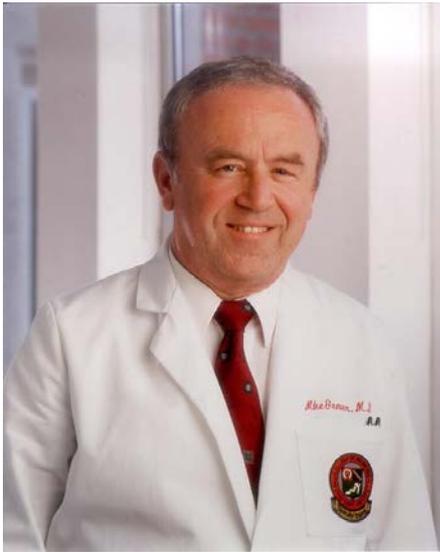




# Living with Hairy Cell Leukemia



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# Introduction to Hairy Cell Leukemia

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# Financial Disclosures

M. Grever served on a data safety monitoring board for Ascerta Inc., as a consultant for Pharmacyclics Inc., and as a consultant for AstraZeneca.

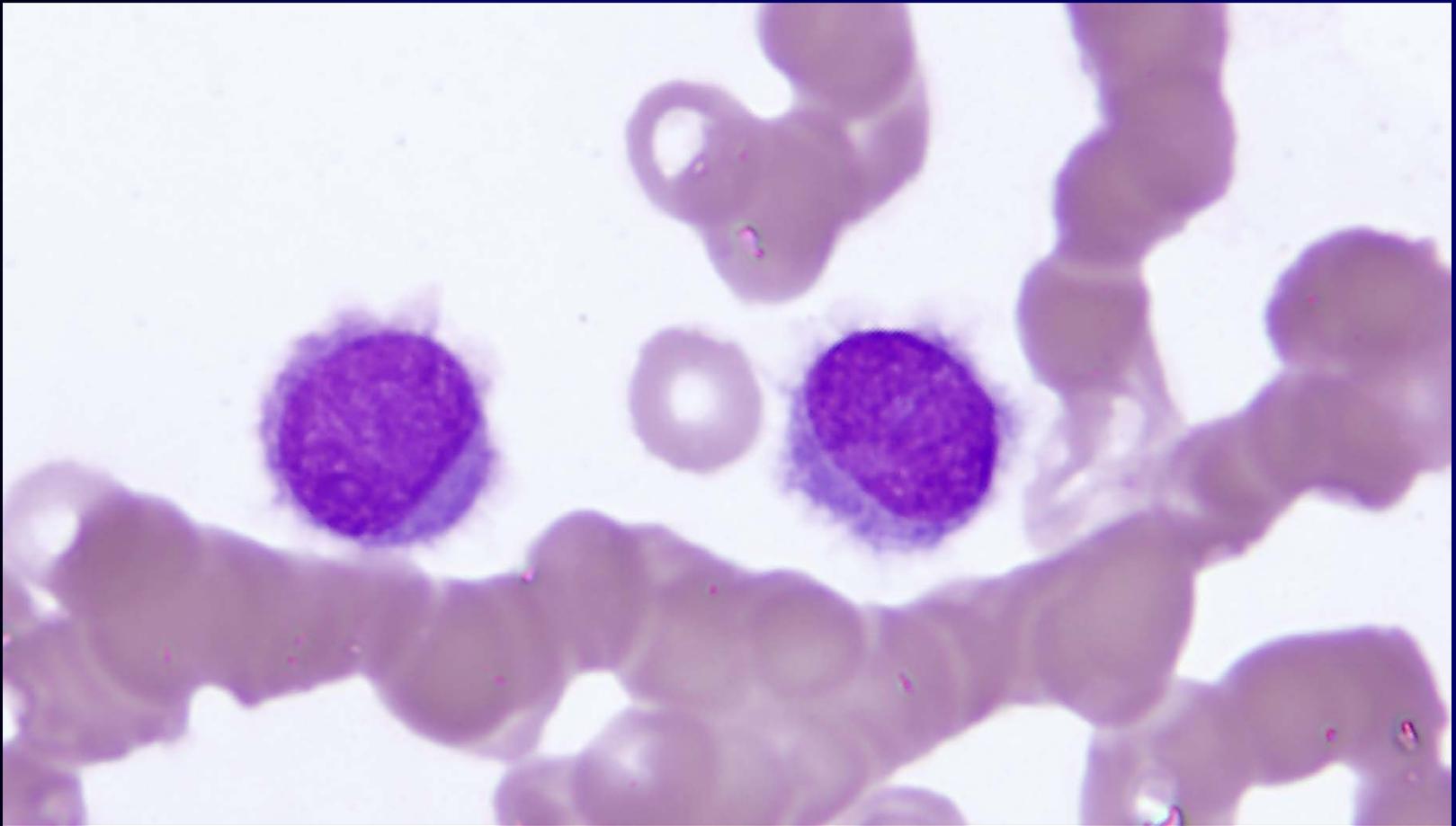
# First Descriptions of Hairy Cell Leukemia

Gosselin GR, Hanlon DG, Pease GL. Leukaemic Reticuloendotheliosis. *Can Med Assoc J.* 74(11):886-91, 1956

Bouroncle BA, Wiseman BC, Doan CA. Leukemic Reticuloendotheliosis. *Blood* 13: 609-630, 1958



Dr. Bertha Bouroncle



Typical hairy cells among red blood cells  
(*Dr. Gerard Lozanski, OSU*)

# Clinical Features of Hairy Cell Leukemia

- Remarkable male predominance 4:1
- Median age 55 years
- Symptoms related to fatigue and infection
- Physical exam shows enlarged spleen
- Low blood cell counts (“cytopenias”)
- Diagnosis made by examination of blood and bone marrow
- Flow cytometry is critical for the diagnosis
- Characteristic markers: CD11c, CD25; CD103; CD123

# Manifestations of Hairy Cell Leukemia

- Fatigue and symptoms of anemia
- Easy bruising or bleeding
- Infection
- Herpes zoster (shingles)
- Autoimmune disorders such as vasculitis, rheumatoid-like arthritis, immune thrombocytopenia
- Bone lesions

# Clinical Judgement in Treatment Decisions

- Determine if diagnosis is correct (e.g., classic HCL is different disease than HCL variant).
- While 10% patients with HCL do not require immediate treatment, they require close follow-up.
- Patients with active infection should not receive cladribine, and require special treatment planning
- Need to assess kidney function and history of hepatitis exposure before treatment
- Bone marrow biopsies at initiation and following completion of therapy have value.

# Natural History of HCL Prior to 1984

- Incurable and unresponsive to therapy
- Commonly employed treatments included:
  - Alkylators (minimal responses)
  - Splenectomy (some palliation)
- Median survival of 4.5 years; deaths due to:
  - Infection
  - Cytopenias and bleeding
- Second malignancies in 3-10%



## Treatments

# Historical Approach to HCL Treatment

- Early attempts with chemotherapy unsuccessful; splenectomy became the frontline approach.
- While this temporarily improved blood counts, ultimately patients needed more treatment as disease progressed in the bone marrow.
- In 1984, the use of interferon alpha was successfully introduced, improving blood counts.
- Overall response to interferon challenged need for splenectomy.

# Therapies That Changed the Natural History of a Rare Disease

- 1984 – Quesada reported responses to interferon alpha in 7 patients (3 complete and 4 partial responses). Subsequent studies showed many patients achieve a partial response.
- 1984 – Spiers reported complete response with deoxycoformycin.
- 1986 – Kraut reports 9 of 10 complete responses with low dose deoxycoformycin (pentostatin)
- 1990 – Piro reports 11/12 complete responses with cladribine
- Extensive additional studies with pentostatin and cladribine, alone or in comparison to interferon, and then in combination with rituximab.

# Pentostatin Studies in HCL

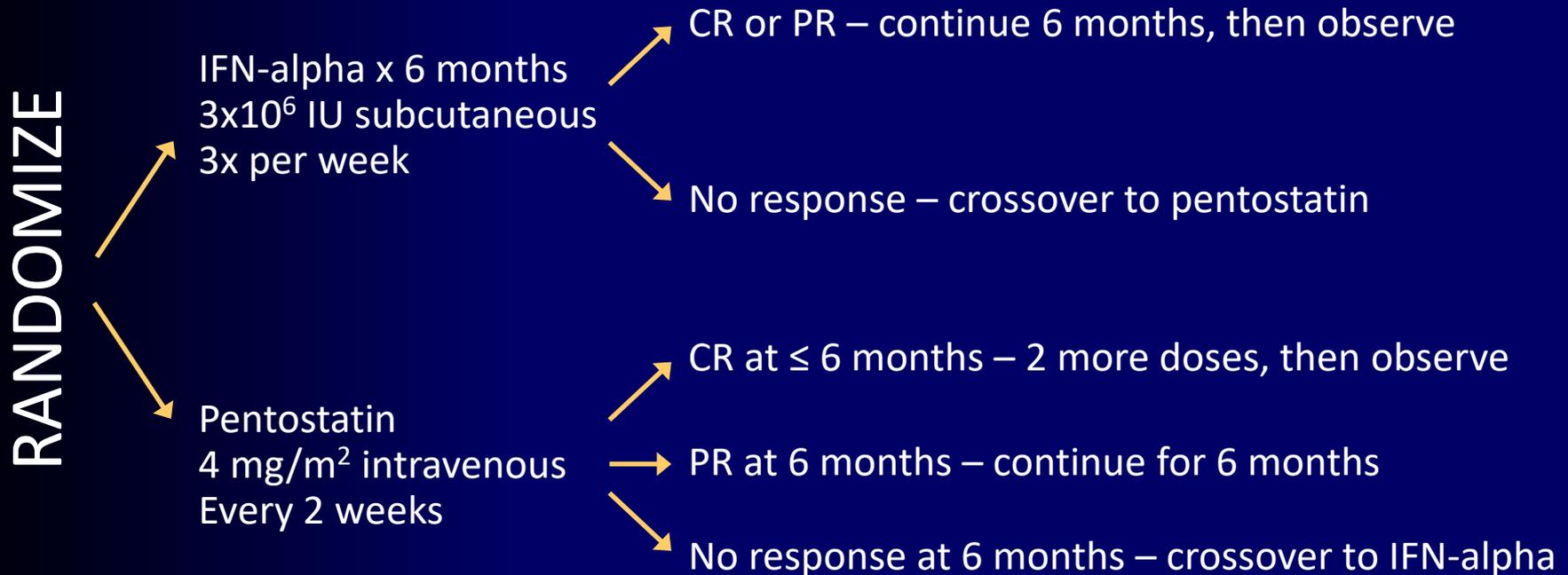
<u>STUDY</u>	<u>DOSE (i.v.)</u>	<u>Complete Response %</u>
SPIERS (ECOG)	5 mg/m <sup>2</sup> for 2 days every 2 weeks	59
JOHNSTON (NCIC)	4 mg/m <sup>2</sup> per week for 3 weeks, repeat every 8 weeks	89
HO (EORTC)*	4 mg/m <sup>2</sup> per week for 3 weeks, then every 2 weeks X 3	33
GREM (NCI)	4 mg/m <sup>2</sup> every 2 weeks (variable schedule of drug administration)	56
KRAUT	4 mg/m <sup>2</sup> every 2 weeks	87

\*RESTRICT TO INF FAILURES

# Cladribine in Hairy Cell Leukemia

- Piro: 11/12 patients achieve complete remission with 7 day continuous IV infusion (*NEJM*, 1990)
- Tallman: 80% patients achieve complete remission with 7 day continuous IV infusion. Several additional patients achieved CR with more therapy. (*Blood*, 1992)
- Juliusson: 81% patients achieve complete remission with subcutaneous dose for 7 days (*JCO*, 1995)

# HCL Intergroup Study (Grever *et al.* *JCO*, 1995)



CR = complete remission

PR = partial remission

# HCL Intergroup Study (Grever *et al.* JCO, 1995)

Therapy	Initial Pentostatin	Crossover to Pentostatin	Initial IFN-alpha
Evaluatable Patients	154	86	159
Complete Remission (%)	76	66	11

# Long-Term Results: Pentostatin in HCL (Flinn *et al.*, *Blood*, 2000)

- 241 patients evaluable for long-term follow-up
- Median duration of follow-up 9.3 years
- Projected 10-year overall survival 81%
- Relapse-free survival estimate 67%

# Long-term Follow-up (Else *et al.*, *BJH*, 2009)

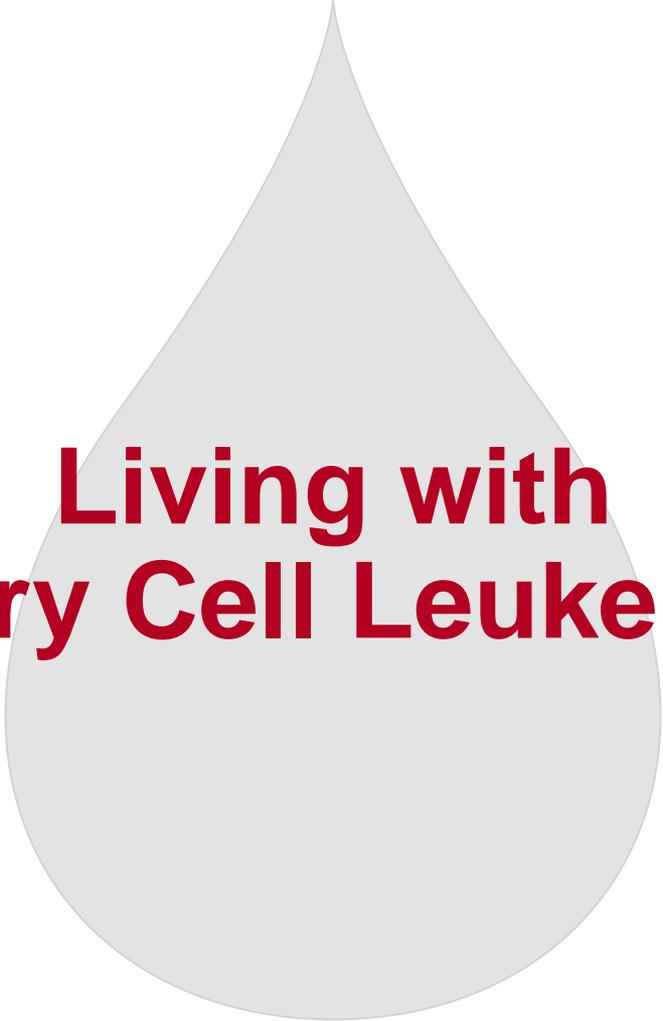
- 233 HCL patients (188 treated with pentostatin and 45 with cladribine) were followed for median 16 years
- These agents were essentially interchangeable; equal in efficacy.
- Patients achieving complete remission had longer relapse-free survival (RFS).
- CR rates initial therapy 80% first remission; 69% with second remission; and 50% with third remission.
- Remission durations progressively shorter with each relapse and re-treatment (RFS were 16, 11, and 6.5 years, respectively).
- Majority of patients have normal life expectancy

# Considerations in Clinical Decisions

- Attempt to control active infection before starting leukemia-directed therapy if possible
- Important to improve absolute granulocyte count in patients with active infection
- Cladribine not initially utilized in treatment of HCL patients with infections, but is used most often in non-infected patients.
- Lower hemoglobin, lower platelet count, older age, and large spleen associated with lower complete remission rate.

# When to Initiate Therapy

- Confirm correct diagnosis & assessment of bone marrow compromise
- Progressive decrease in blood counts, with absolute neutrophil count (ANC)  $<1,000$ , platelet count  $<100,000$ , or hemoglobin  $<11$
- Symptoms associated with bone marrow failure or from an enlarged spleen



# Living with Hairy Cell Leukemia

# Long-Term Consequences of Therapy for HCL

- Prolonged immunosuppression with reduced CD4 and CD8 T-cells
- Most common long-term infection is shingles
- Careful assessment of risk for secondary malignancies reveals either a slight increase in lymphoid malignancies or no increase related to treatment.
- Bone marrow toxicity can result from excessive therapy

# Remaining Questions

- When should anti-CD20 antibody (e.g. rituximab) be added to treatment? Sequential vs. concurrent? Optimal dose, duration?
- How important is minimal residual disease? What is the health-related cost of eradication of residual leukemia?
- When should a patient be referred for investigational agents?
- What order of investigational agents should be pursued?
- What new combination of agents is effective and well-tolerated?
- What therapy is best for the variants of HCL?
- Many other clinical management questions (importance of infection prophylaxis, pregnancy and disease management, etc.)
- Needed: A long-term quality of life study

# Living with Hairy Cell Leukemia

- Approximately 10% of patients may not require immediate treatment, but need close follow-up
- Most patients will require treatment.
- About 40% will relapse over time and require re-treatment.
- Living with a rare chronic disease can produce anxiety and depression
- Challenges with medical insurance, life insurance, and employment related to diagnosis of a chronic leukemia.
- Difficulty identifying medical team with experience in a rare disease

# Successes and Challenges

- Pentostatin and cladribine have changed the natural history of hairy cell leukemia
- Patients may live as long as they would have without this disease, but multiple relapses may require re-treatment
- Drug resistance can still occur
- Novel therapeutic agents and combinations are needed
- Managing infection and other complications of disease require close attention

# Experimental Approaches to Relapsed HCL

- BRAF inhibitors for classic HCL with BRAF mutation (e.g. vemurafenib)
- Immunotoxin conjugates (e.g. HA22)
- BTK inhibitors (e.g. ibrutinib)
- New targeted agents under investigation (e.g. MEK inhibitors)
- Strategic combinations:
  - pentostatin or cladribine with monoclonal antibody
  - novel agents + monoclonal antibody
  - combinations of novel agents that may be effective in resistant disease

(Tiaci E et al., Targeting mutant BRAF in relapsed or refractory hairy cell leukemia, *NEJM* 373 (18): 1733-47, 2015)  
(Dietrich S, et al: BRAF inhibition in hairy cell leukemia with low dose vemurafenib, *Blood* 127 (23): 2847-55, 2016)

# Hairy Cell Leukemia Foundation

Sharing knowledge across the globe

[www.hairycellleukemia.org](http://www.hairycellleukemia.org)



## Upcoming Patient Seminar

Our next Patient Seminar will be held in Heidelberg, Germany on May 21, 2016. Join us to learn more about the latest advancements in the diagnosis and treatment of hairy cell leukemia and to interact with investigators from around the world.

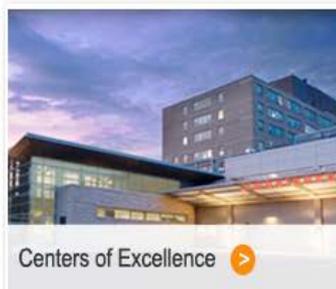
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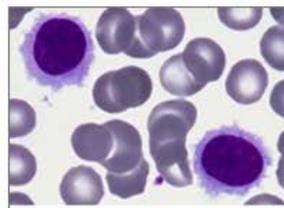


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## Supporting Research and Patient Education



The Hairy Cell Leukemia Foundation is dedicated to improving outcomes for patients by advancing research into the causes and treatment of hairy cell leukemia, as well as by providing educational resources and comfort to all those affected by hairy cell leukemia. The Foundation is a 501(c)(3) organization created and led by hairy cell leukemia survivors.



## Question & Answer Session



## Closing Comments



# The Leukemia & Lymphoma Society Offers:

- **Information Resource Center:** Information Specialists, who are master's level oncology professionals, are available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.

➤ EMAIL: [infocenter@LLS.org](mailto:infocenter@LLS.org)

➤ TOLL-FREE PHONE: 1-800-955-4572

- **Free Education Booklets:**

➤ [www.LLS.org/booklets](http://www.LLS.org/booklets)

- **Free Telephone/Web Programs:**

➤ [www.LLS.org/programs](http://www.LLS.org/programs)

- **Live, weekly Online Chats:**

➤ [www.LLS.org/chat](http://www.LLS.org/chat)





# The Leukemia & Lymphoma Society Offers:

- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)
- **LLS Podcast, *The Bloodline with LLS*:** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.LLS.org/thebloodline](http://www.LLS.org/thebloodline)
- **Education Video:** Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)
- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)
- **What to ask:** Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)





**THANK  
YOU FOR  
PARTICIPATING!**

**We have one goal:  
A world without  
blood cancers**