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HAIRY CELL LEUKEMIA FOUNDATION

HCL Webinar Update-2024

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No conflicts of interest to disclose

Goals of today presentation

- *Acknowledge that the attendees of this talk are a very diverse group*:
  - Patient/family member/friend, etc.
  - Duration of having been diagnosed with HCL may vary from a week to > 20 years
  - Your care is provided in a variety of public/private health care systems
  - Your understanding and learning of HCL could be minimal vs. being up to date on the latest research publication
- Provide an overview of HCL diagnosis and treatment that hopefully will be understandable to all.
- With limited time will defer ?'s re: HCL variant to Q/A

History of hairy cell leukemia

- **1923: Ewald first described this as leukemic reticuloendotheliosis**
- **1958: Gosselin**
- **1958: classic description of 26 patients by Dr. Bertha Bouroncle**
- **1966: Shrek and Donnelly "hair like projections" on phase contrast microscopy**
- **1971: TRAP stain (Yam, Li, and Lam)**
- **1983: B-cell disorder (Korsemeyer)**

splenectomy

- **1984: α recombinant interferon**
- **1986: pentostatin**
- **1989: 2-CDA**
- **1998: Rituximab**
- **2008: WHO Classic HCL and HCL variant (HCLv)**
- **2011: BRAF V600E mutation; 2012: vemurafenib**
- **2013: MEK Kinase and BTK pathway inhibitors**

Hairy cell leukemia-Dx

- +/- 2% of adult leukemia
- 4:1 male to female
  - Median age approx. 55
- Presentation:
  - Pancytopenia (low blood counts)
    - Anemia, Low WBC, Low platelets

    Only about 15% with increased WBC

    Monocytopenia

  --Enlarged spleen

  --May have associated bone pain

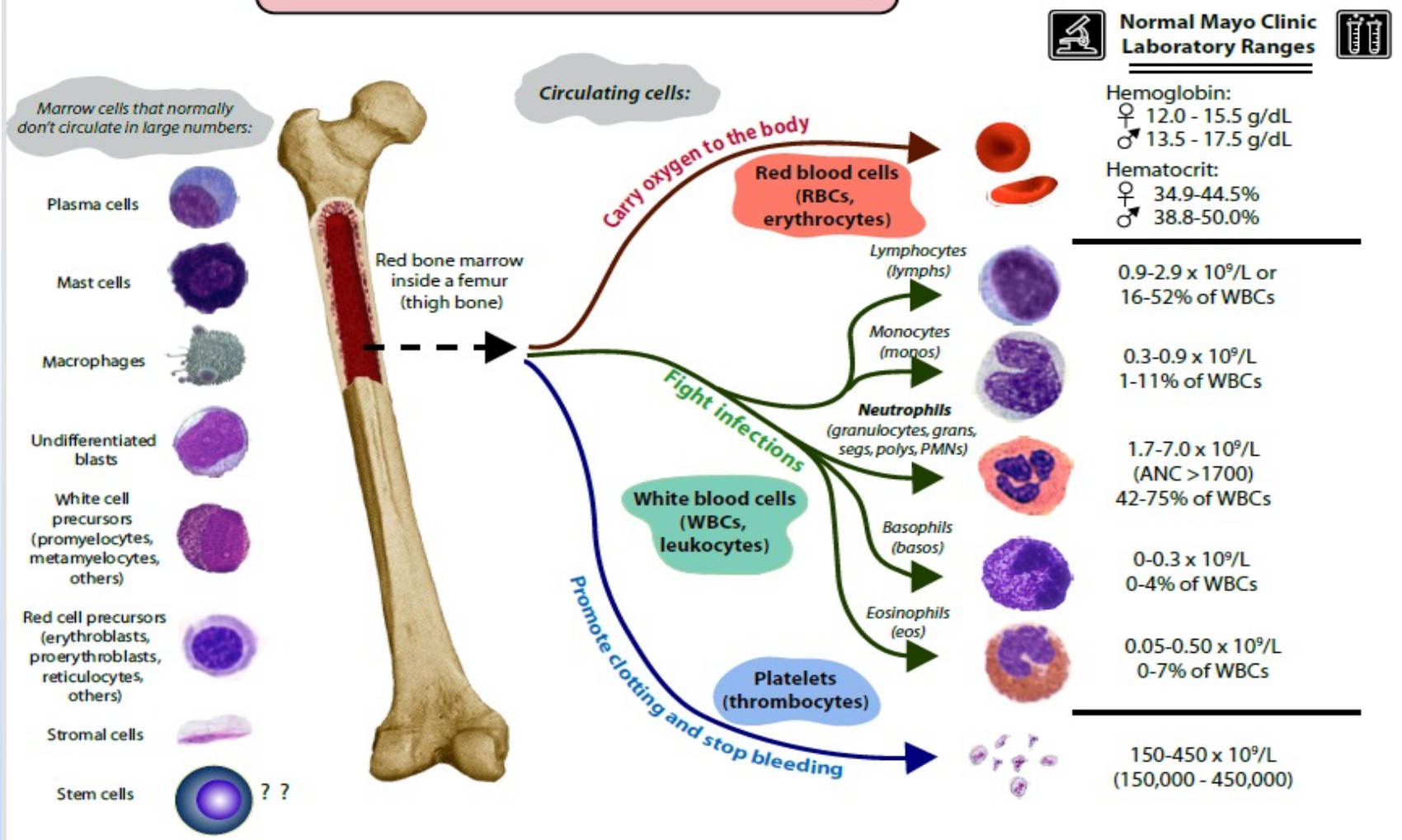
  --May present with associated infection

  Pneumonia

  Atypical TB

  --However, may be diagnosed solely on the finding of abnormal blood counts

Human Blood and Bone Marrow



Synonyms are in parentheses. Normal laboratory values may differ in other laboratories, hospitals and clinics, even within the Mayo Health System. In some circumstances it may be normal to see a small proportion of bands, myelocytes, or metamyelocytes in the blood (all neutrophil precursors.)

by DP Steensma 2005, for the Mayo Clinic Division of Hematology

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Case

- Previously healthy 48 y.o. male presented to the emergency room with cough and fever.
- CXR showed Left lower lobe pneumonia.
- He was admitted and started on "empiric" antibiotics.

Pancytopenia

- Initial CBC
  - Hgb- 7.8 (nl 13.5-16)
  - Platelets – 109,000 (nl 135K-400K)
  - WBC- 0.7 (nl 3.5-10.5)
- Differential
  - Neutrophils 29% (***Neutropenia***)
  - Lymphs 64%
  - Monocytes 2%
- Antibiotics/steroids/ oxygen started
- Sputum culture: Legionella
- Over about a week his pneumonia improved. However even after recovery his low blood counts persisted.
- Hgb 10.8/ WBC 1.8/plts 75,000

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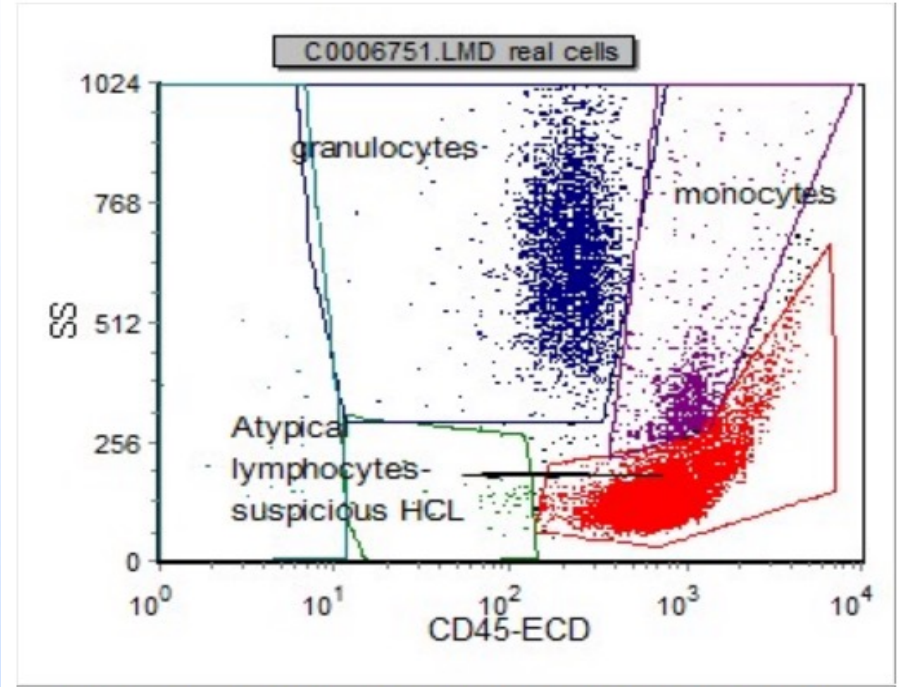
Hematology consulted by medical team

HCL surface molecular markers ("QR code"

Hairy cells are larger than normal and positive for CD19, CD20, CD22, CD11c, CD25, CD103, and FMC7. Hairy cell leukemia-variant (HCL-V), does not show CD25 (also called the Interleukin-2 receptor, alpha). Also BRAF+



Note the red lymphocyte population and the variation in size (higher SSC) requiring further investigation.

HCL:BRAF + in nearly 100%

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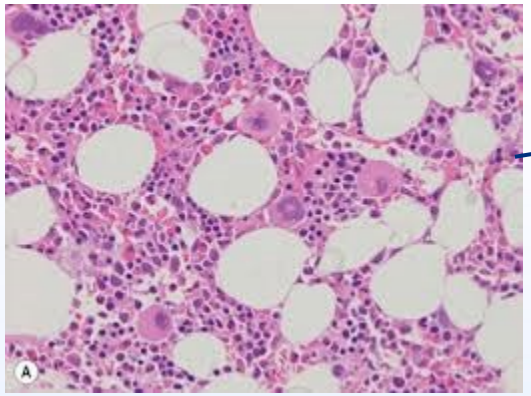
Noted by Hematology

- Mild splenomegaly, noted on CT chest
- Peripheral smear
  - Leukoerythroblastic smear (sign of a crowded bone marrow)
    - Nucleated RBC and myelocyte
    - Monocytopenia
    - Hairy cells seen
- Peripheral blood flow cytometry:
  - Involved by a B-cell lymphoproliferative disorder, kappa light chain-restricted. The immunophenotypic features, including the bright expression of CD19, CD20, and CD200, and the coexpression of CD11c/CD22 and CD103 are most consistent with hairy cell leukemia.
- Bone marrow biopsy was performed

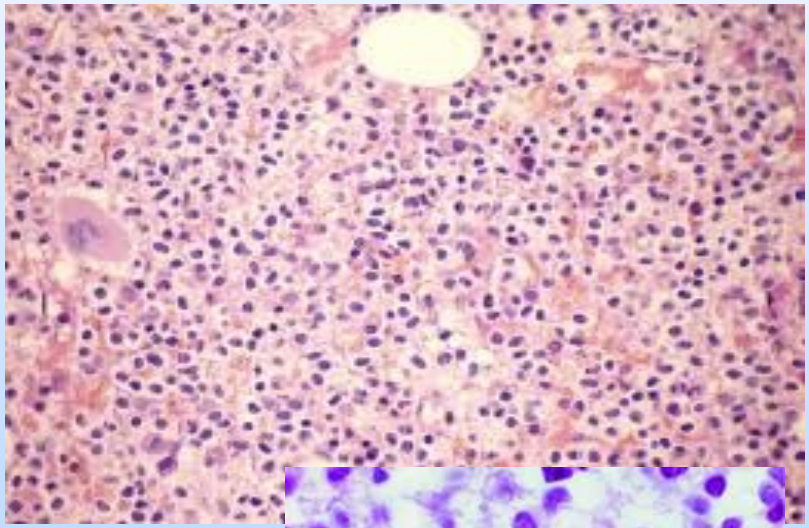
Result: Hairy cell leukemia

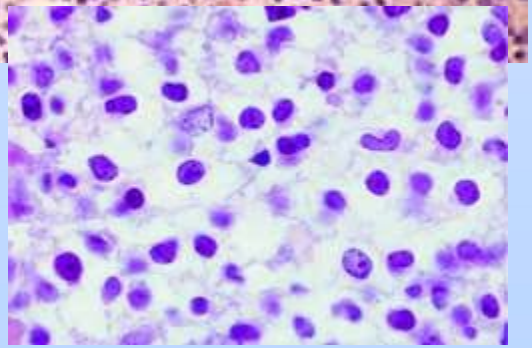


normal bone marrow bx

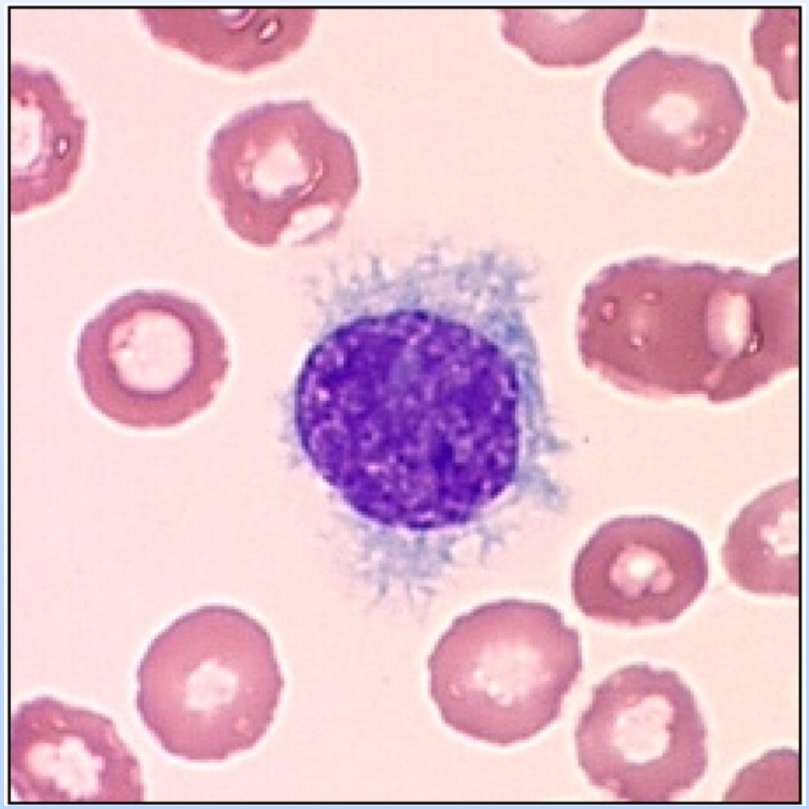
Bone marrow (HCL)

- Aspirate: dry tap





Peripheral smear (HCL)

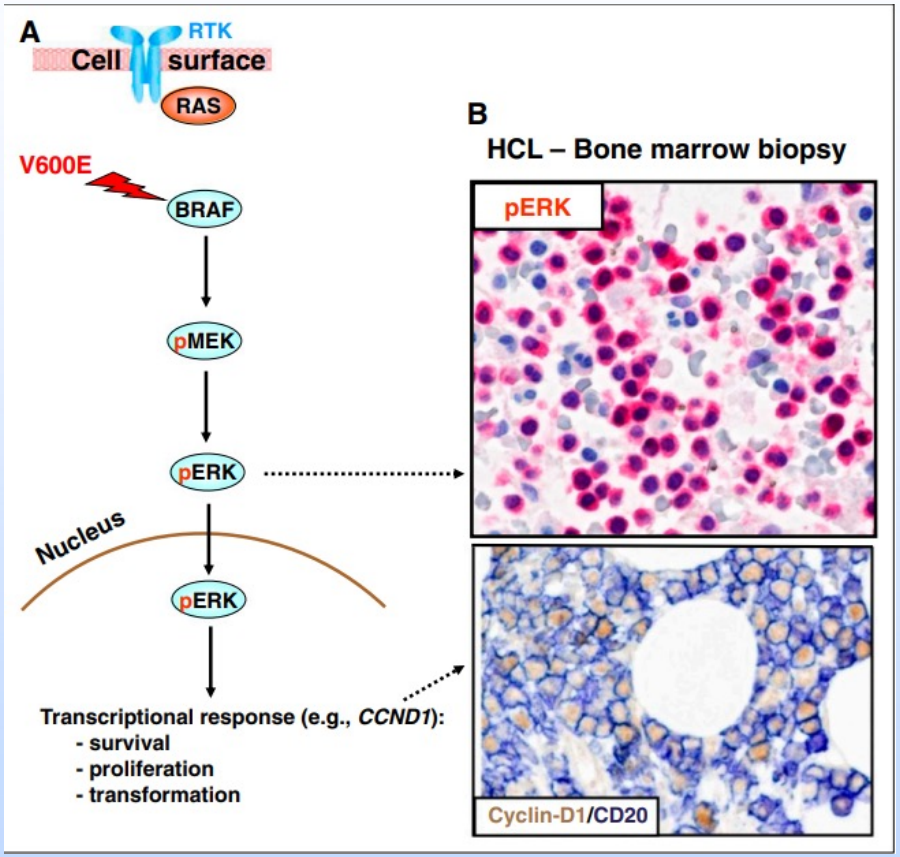


What are these projections in hairy cells?

- Non-retractable cell surface projections and cytoskeleton-mediated functional defects are the distinguishing features of HCL.
- These are attributed to over-expression of beta-actin and leukocyte-specific transcript 1 (LST1), an f-actin-binding leukocyte-specific phosphoprotein.

Myoshi, *Leuk Res 2001*, 252:57-67

Biology of hairy cell leukemia



- Cladribine/Pentostatin: interfere with DNA synthesis and repair
- Targeted treatment options:
  - BRAF inhibitor
  - MEK inhibitor
  - CD20 monoclonal antibody (cell surface membrane)

Tiacci; *Blood, 2016*; 128(15):1918-1927

Evaluation and indications to treat

Table 1. Initial work-up for patient suspected of hairy cell leukemia

Recommendations	Specific procedures and considerations
Diagnosis and initial evaluation	
Complete blood count	
Peripheral blood smear review	Use Wright's stain, perform white blood cell differential, and identify leukemic cells.
Immunophenotypic analysis by flow cytometry	Check for positivity for CD19, CD20, CD11c, CD25, CD103, CD123, CD200, and immunoglobulin light chain restriction of the circulating mononuclear cells for confirmation of diagnosis.
Bone marrow aspiration and trephine biopsy	Use hematoxylin and eosin stain, reticulin stain, and immunohistochemistry for CD20, and annexin-1, DBA.44, and VE1 (for $BRAF^{V600E}$); identify $BRAF^{V600E}$ mutation by allele-specific polymerase chain reaction, sequence analysis, or immunohistochemical stain to confirm diagnosis and extent of bone marrow involvement.
Complete history and physical examination	Include assessment of renal function for patients in whom nucleoside analog therapy is planned.
Optional imaging studies	Perform chest x-ray to assess for infection; use computed tomography or ultrasound scan of abdomen to evaluate organomegaly, and lymphadenopathy. These procedures should be considered for patients in a clinical trial or those with associated symptoms referable to these systems.
Serology for hepatitis if planning on using an anti-CD20 monoclonal antibody	
Differential diagnosis	Consider hairy cell leukemia; hairy cell leukemia variant; splenic marginal zone lymphoma; splenic diffuse red pulp small B-cell lymphoma (outlines for specific immunophenotypic profiles of differential entities[33-36]).
Indications for treatment	
Hematologic parameters consistent with initiating treatment	Include at least one of the following: hemoglobin <11 g/dL, platelet count <100 000/μL, or absolute neutrophil count <1000/μL.
Clinical features or symptoms for which therapy may be considered	Include symptomatic organomegaly, progressive lymphocytosis, or lymphadenopathy, unexplained weight loss (>10% within prior 6 months, excessive fatigue (National Cancer Institute Common Terminology Criteria for Adverse Events grade >2).

Expert pathology review

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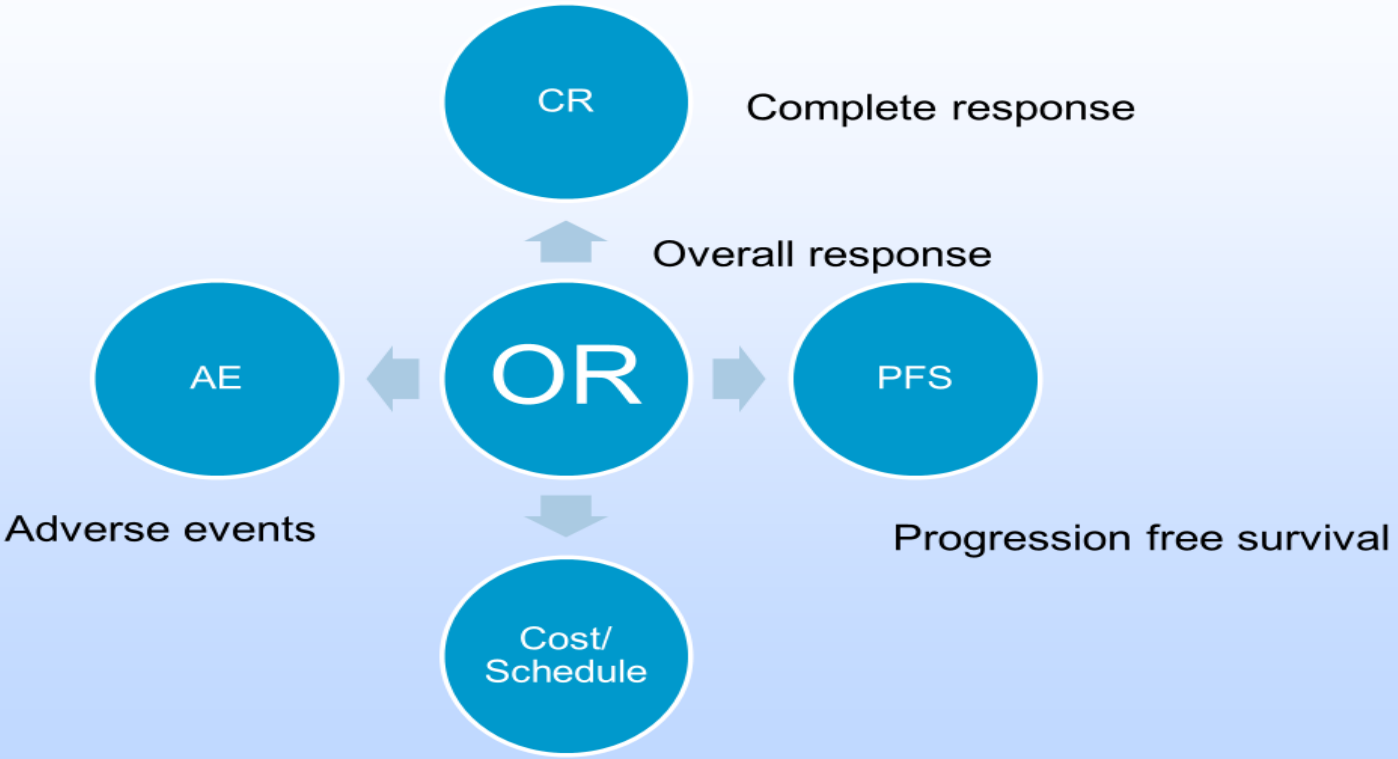
Grever, Blood (2017) 129 (5): 553–560

Median= point at which 50% have met the endpoint
Mean= Average of all meeting the endpoint

Selecting Therapy



MRD (minimal residual disease) assessed at varying levels of sensitivity (1:10,000, 1:100,000 or even 1:1,000,000 need to interpret carefully with your specialist

Purine nucleoside analog treatment in frontline HCL

- Cladribine monotherapy:
  - 5.6 mg/m^2/day given as a 2-h IV infusion for 5 consecutive days*
- Pentostatin monotherapy:
  - 4 mg/m^2, IV, every 2 weeks until maximum response (no more than 6 months)
- No head-to-head comparative studies between cladribine and pentostatin in hairy cell leukemia
- Both cladribine and pentostatin achieve a CR rate of 72-95% and an ORR of 70-100%
- Median PFS ranges from 8-12 years; with overall survival at >10 years of 80-95%, regardless of the purine nucleoside analog used

Grever; *J Clin Oncol* 13:974-982

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*Several different schedules and routes of administration for cladribine can be used; shown is our preferred regimen

Italy..330 patients treated with frontline 2-CDA (cladribine)

Following treatment of HCL with 2CDA, 80% of patients are estimated to be alive 15 years after diagnosis.

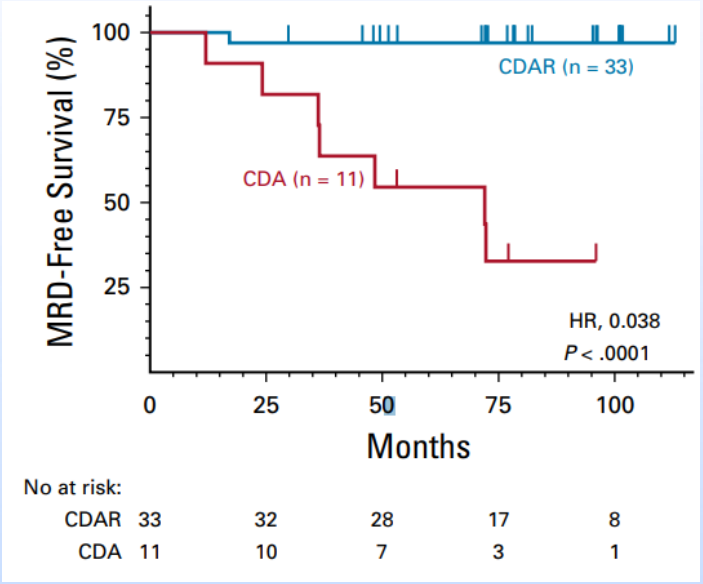
Pagano
Blood Cancer Journal (2022) 12:109 ; https://doi.org/10.1038/s41408-022-00702-9

Pentostatin

- Equal efficacy to cladridine
- Can also be combined with rituximab
- Different sequence of administration
- Minor differences in side effects

Cladribine and rituximab in frontline HCL

- Randomized phase 2 study of cladribine plus concurrent rituximab (starting cycle 1 day 1, 375 mg/m^2 for 8 weekly courses vs. delayed rituximab (same schedule starting after 6 months, if blood MRD was detected)
- At 6 months:
  - CR rates were comparable between cladribine + rituximab vs. cladribine alone (100% vs. 88%, P=0.11)
  - MRD-free CR rates were significantly higher with cladribine + rituximab vs. cladribine alone (97% vs. 32%, P<0.0001)
  - MRD-free survival was significantly longer with cladribine + concurrent rituximab vs. cladribine + delayed rituximab (not reached vs. 6 years, P=0.0001)
  - *Long term PFS and OS data comparing these two approaches not available yet*



Chihara; *J Clin Oncol, 2020;* 38:1527-1538

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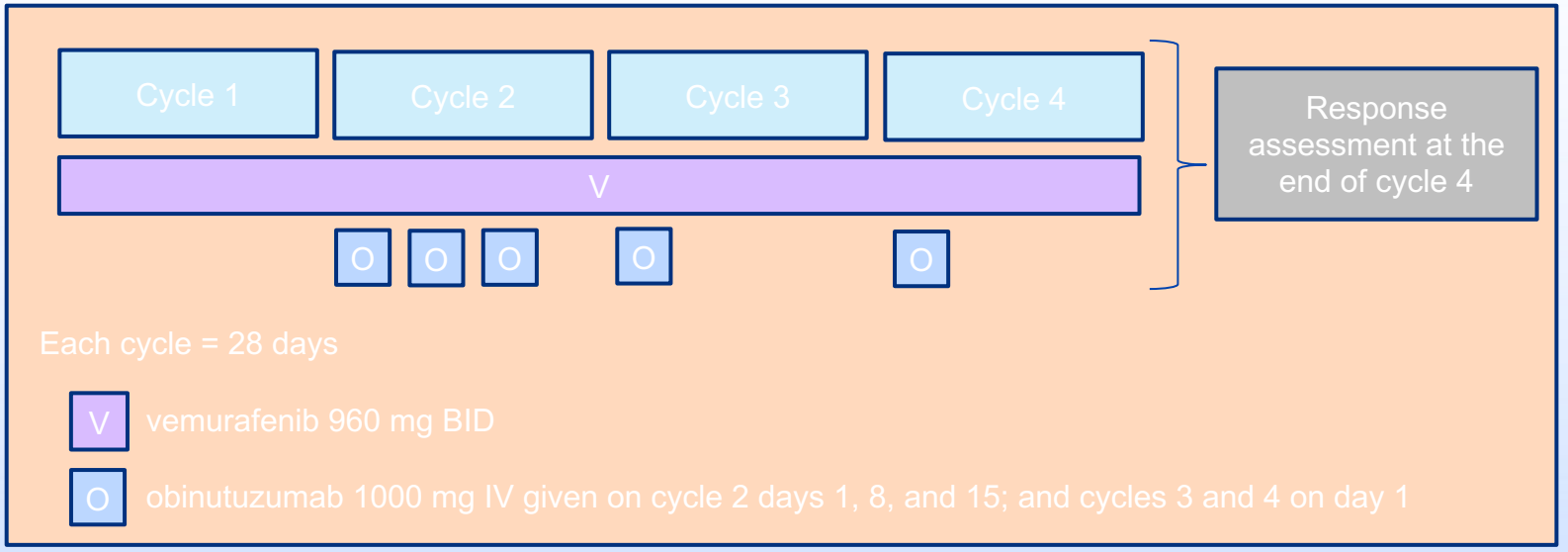
Vemurafenib and obinutuzumab in frontline HCL



- 30 patients enrolled
- Median age = 54 years; 27 men
- 3 patients stopped treatment due to AE (verrucous hyperplasia, pneumonia and rash)
- 26/27 (96%) achieved CR; uMRD in 96%
- Grade 3 rash: 46%; grade 3 arthralgia: 11%
- No relapses after median follow-up of 17 mos

Park; *ASH Abstracts*; 2021

Relapsed HCL

- Most patients with classic hairy cell leukemia will achieve an excellent response to initial cladribine based treatment:
  - If no response, re-assess the original diagnosis
  - Hairy cell leukemia variant?
- Retreatment with purine nucleoside analog:
  - May switch to alternate treatment (pentostatin -> cladribine and vice versa)
  - CR rates are lower (45-75%), and duration of response is also lower (3-7 years)
- Rituximab alone:
  - ORR of 26-80%
  - 36-month PFS: 58%
- Retreatment with cladribine and rituximab:
  - CR rates (80-100%) and duration of response (5-year FFS: 100%) better than single-agent cladribine used in the relapsed setting

Thompson, *Brit J of Haem*; 2017,177,543–556

Targeted agents for relapse

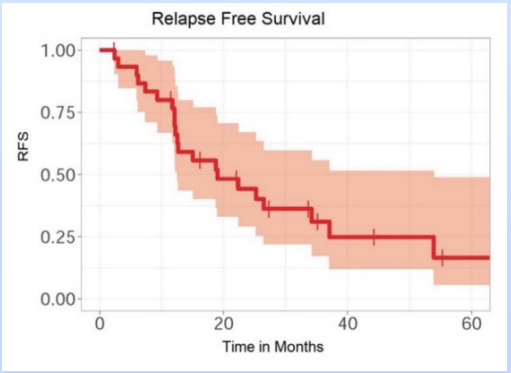
- Vemurafenib (off label)
  - 99%+ HCL BRAF +
  - 96% response rate
  - 35% CR
  - BUT: relapse free survival was 9 months
- Vemurafinib + Rituximab
  - CR 87%/PFS 78% @37 months
- Vemurafinib/Obinutuzumab
  - 96% CR/@ 16.7 months all remaining in remission
- Ibrutinib
  - Clinical trial(Rogers 2021) Overall response rate 54%-often delayed. PFS @ 36 months 73%
- Moxetumumab
  - Immunotoxin that binds to CD22
  - 71% RR/CR 41%
  - Median PFS not met for MRD neg
  - FDA approved
  - Tox: CLS/HUS

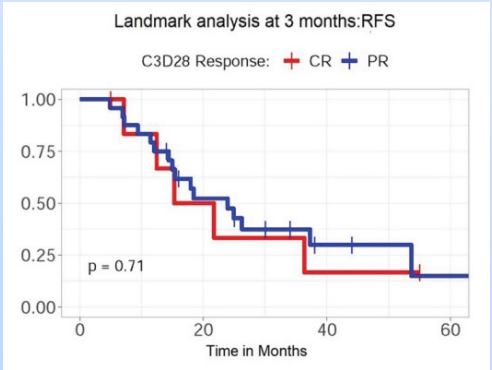
Practical management points

- Supportive care after cladribine:
  - Pegylated filgrastim on day 6, particularly in older individuals (>60-65 years)
  - Anti-pneumocystis (with sulfamethoxazole-trimethoprim) and antiviral (with acyclovir) prophylaxis for at least 3-6 months
- Treatment of a HCL patient with an infection:
  - Prefer the use of vemurafenib monotherapy (due to significant risk of worsening neutropenia with purine nucleoside analog based treatment)
- Assessment of response:
  - Purine nucleoside analog based treatment: repeat marrow 5-6 months after completion of treatment
  - BRAF inhibitors: 2-4 weeks after completion of therapy
- Measurable residual disease (MRD) after treatment:
  - No studies have shown benefit of consolidation therapy in patients with residual MRD after treatment; used as a prognostic test at this time

Relapsed HCL: Vemurafenib based therapy

- Single-agent vemurafenib (960 mg BID) was given to 36 patients with relapsed hairy cell leukemia (median 3 prior lines of therapy) for at least 3 months; and extending to 6 months if residual disease was noted at 3 months
- Median duration of treatment = 6 months; ORR: 86%; CR: 33%; and PR: 58%





Handa; *Blood*; epub August 2022

Median relapse free survival = 19 months

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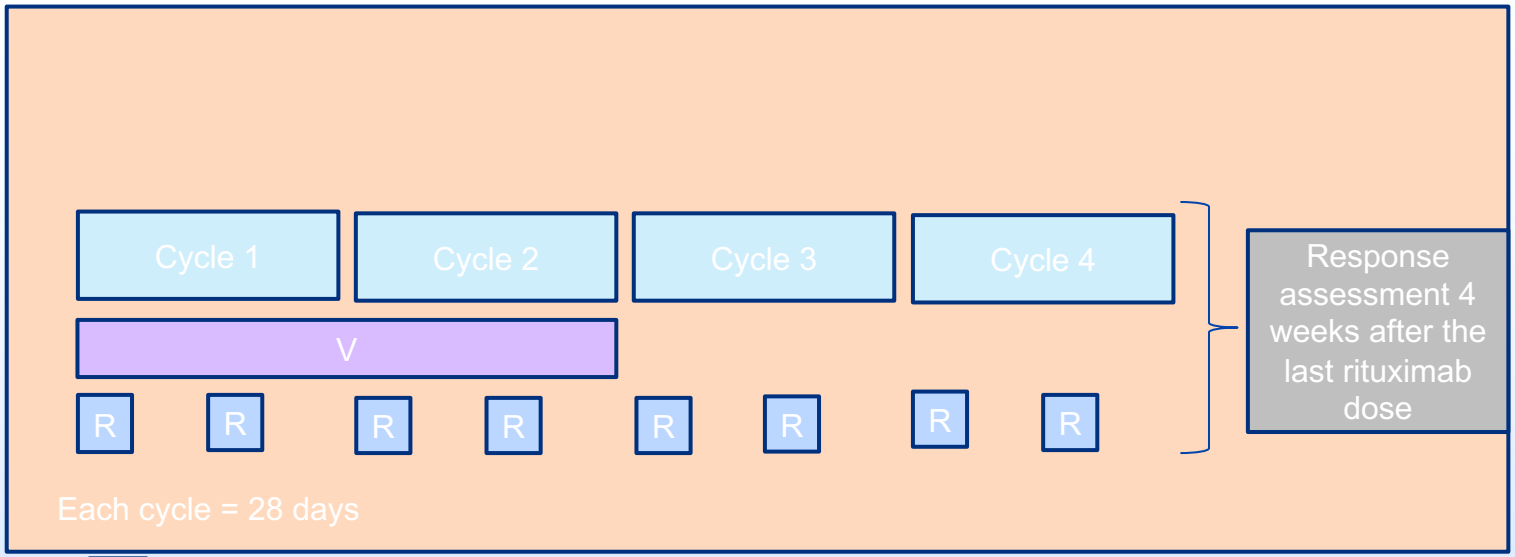
Vemurafenib + rituximab in relapsed HCL



- 31 patients enrolled
- Median age = 61 years; 28 men
- Median 3 prior lines of therapy

Tiacci; *NEJM*; 2021;384:1810

Update ASH 2023: A CR was observed in 30/32 evaluable cases (94%). At a median follow-up of 21 months after the end of treatment, RFS was high among the 31 responding pts, with just 1 relapse (3%), Tiacci Abstract #3027

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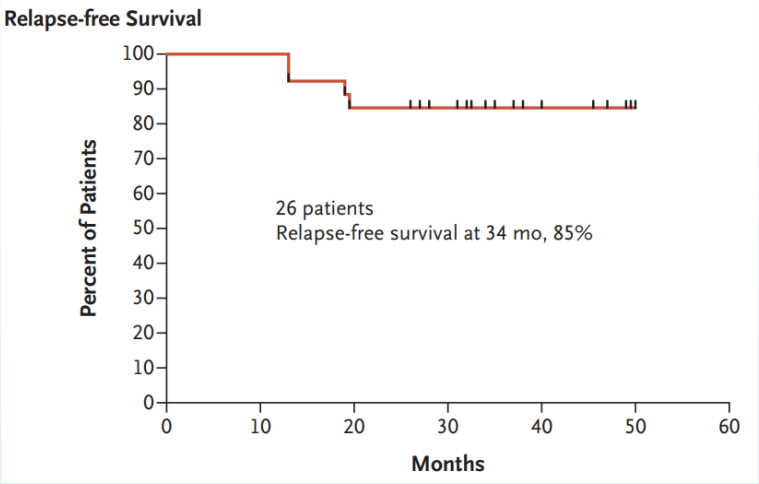
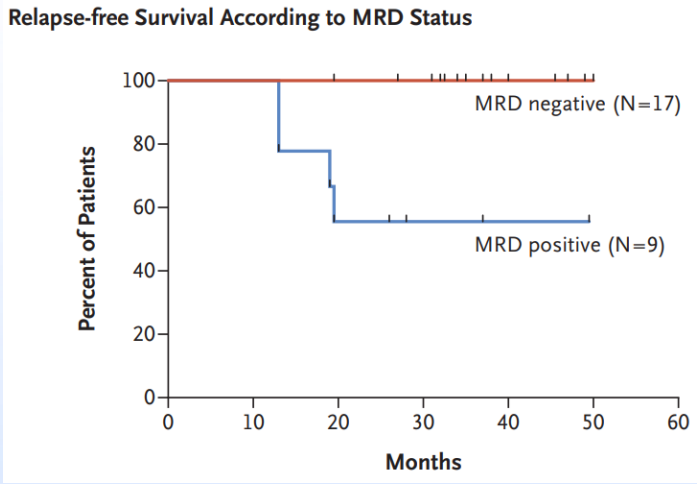
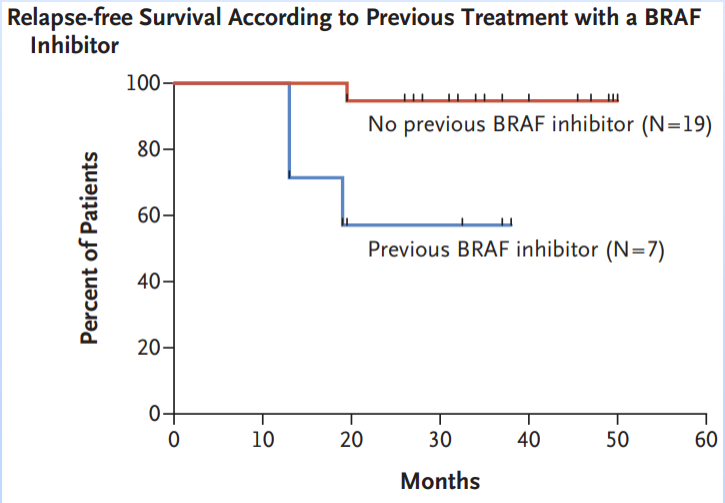
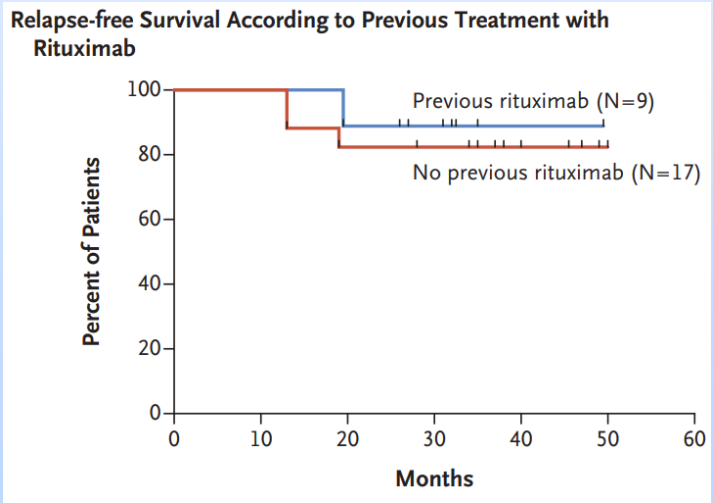
Outcomes with vem + Rituximab in relapsed hcl









Tiacci; *NEJM*; 2021;384:1810

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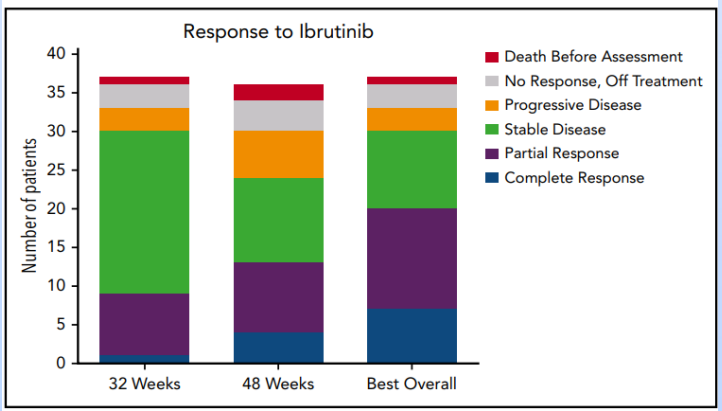
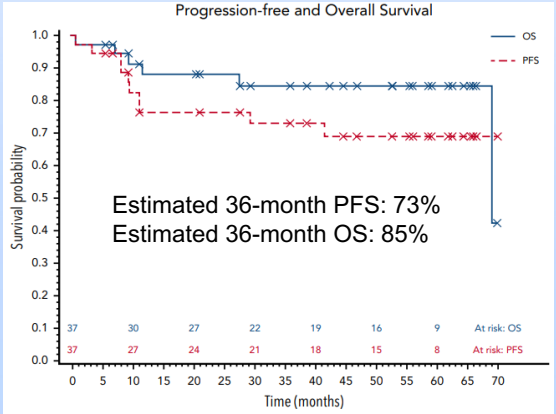
Adverse events (side effects)

- Cladribine
  - Myelosuppression (low blood counts)
  - Immune suppression(can last for 1+ years)
  - Minimal nausea
- Rituximab/Obinutuzumab
  - Allergic reaction
  - Infusion reaction
- Vemurafinib
  - Myalgias (can adjust dose downward)
  - Skin changes(rash, warts/skin cancers/pigmentation-usually temporary) (can adjust dose downward)
  - Pancreatitis(rare)

Ibrutinib in relapsed hcl

- 37 patients with relapsed HCL (median 4 prior lines of treatment)
  - 9 patients had hairy cell leukemia variant
- Ibrutinib was given at 420 mg daily (n=24) and 840 mg daily (n=13)
- AE's: Afib in 16%; atrial flutter: 5%; hypertension: 43%; 7 patients discontinued ibrutinib due to toxicity





Rogers; *Blood (2021);*137 (25): 3473–3483

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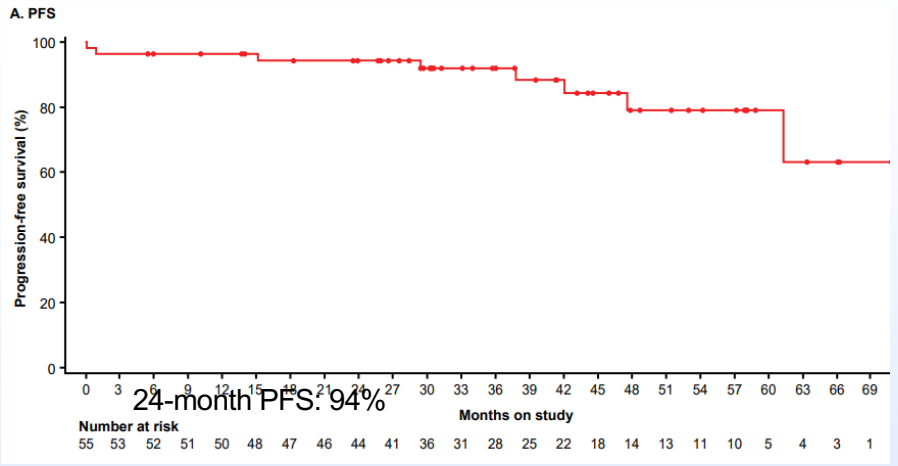
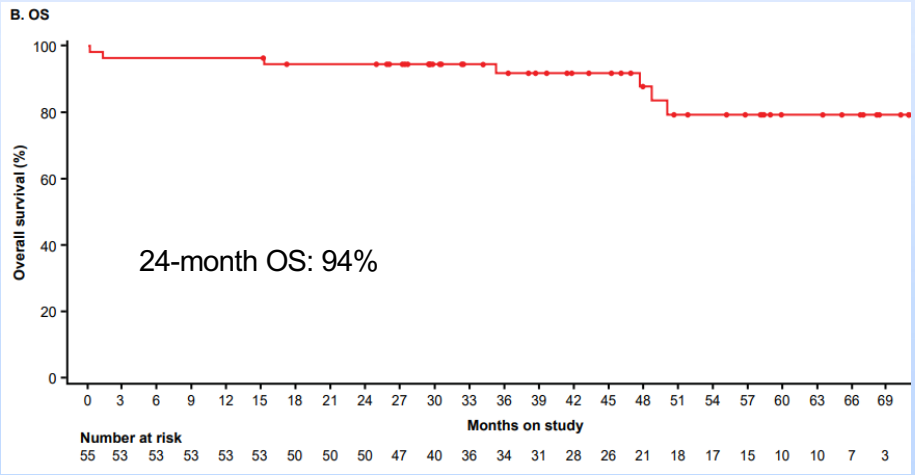
Dabrafenib and trametinib in relapsed hcl

- 55 patients with relapsed hairy cell leukemia (median 3 prior lines of therapy) were treated with oral dabrafenib 150 mg twice daily and oral trametinib 2 mg once daily until disease progression, unacceptable toxicity or death
- Median follow-up was 43 months
- Best response was CR in 65% patients (including 49% who achieved uMRD); and the ORR was 89%
- Most common AEs, any grade, included fever and chills (47-58%), hyperglycemia (40%), aceniform dermatitis (38%), maculopapular rash (29%), ALT, AST and alkaline phosphatase increase (25-32%), and peripheral edema (31%).
- The most common grade ≥3 AEs were hyperglycemia (9.1%), pyrexia, neutropenia, and pneumonia (each 7.3%)





Kreitman, *Blood, epub*, September 2022

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Other treatments in hairy cell leukemia

- Splenectomy
- Pegylated interferon α

Follow up post HCL therapy

- Monitor counts every 1-2 weeks, until counts are recovered to near normal. Then periodically. Sometimes the counts may recover more slowly.
- Monitor for any signs of opportunistic infections. (fever, cough, etc)
- Bone marrow biopsy
  - Not mandatory if good count recovery
  - **Debated:**
    - Will it change management?
    - Could it lead to un-needed extra Rx?
      - The increased sensitivity of testing (flow cytometry) can pick up minute populations of cells down to 1:10,000
    - Yet can be good to know for follow up.
  - **Not debated:** *Do not do the marrow too early*. Can see further response deepening up to 12-18 months. Not before 4-6 months, I use 6-9 months, unless signs of inadequate marrow recovery.

HCLF guidelines: May 2021

Leukemia (2021) 35:1864–1872
https://doi.org/10.1038/s41375-021-01257-7

REVIEW ARTICLE

INFECTIOUS MEDICINE, VIROLOGY

Hairy cell leukemia and COVID-19 adaptation of treatment guidelines

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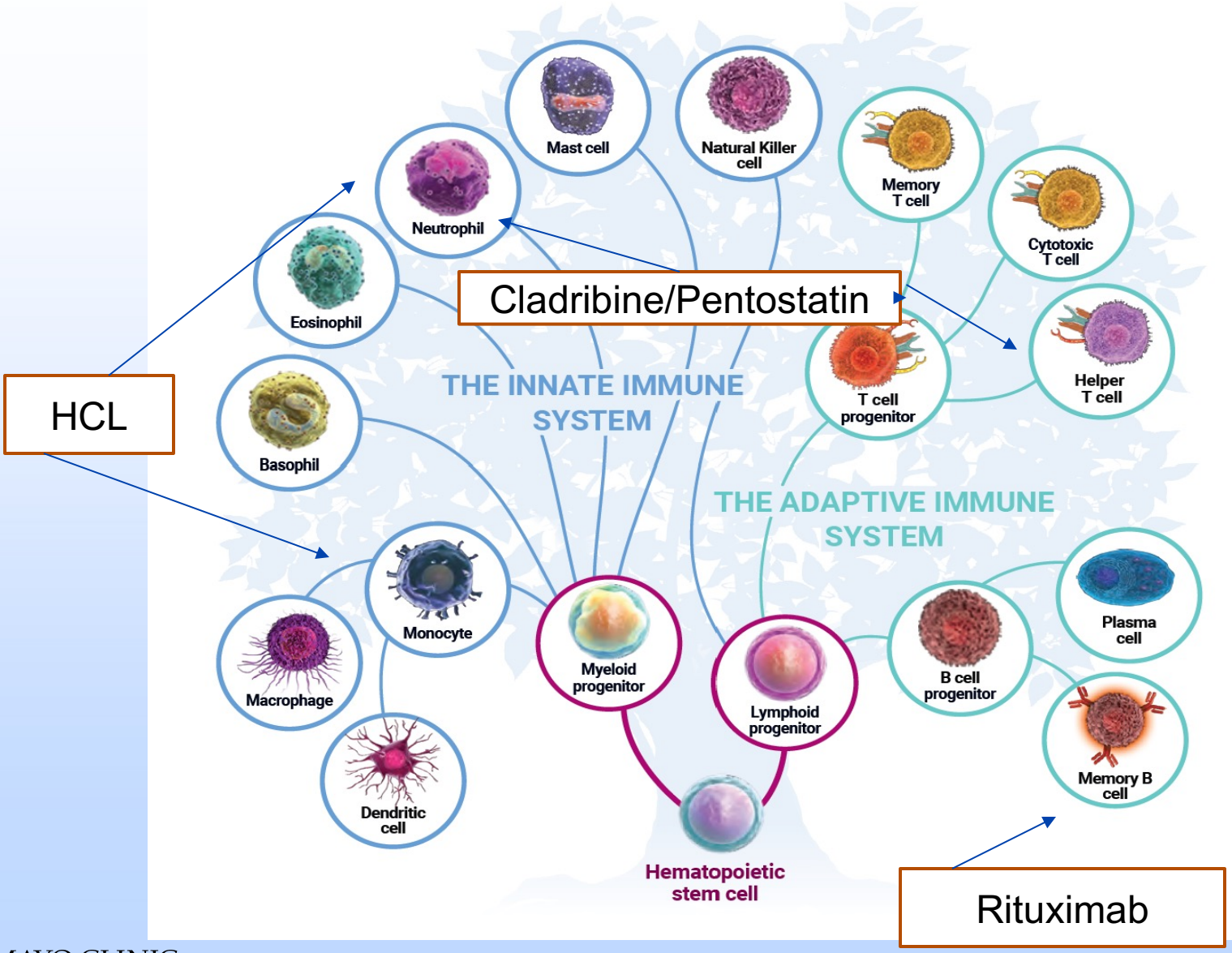
Received: 26 February 2021 / Revised: 11 March 2021 / Accepted: 12 April 2021 / Published online: 4 May 2021

Abstract

Immune System: Innate vs Adaptive



https://lab-a-porter.com/2019/12/cells-of-the-immune-system/

Caveats regarding HCL and immunity

- Following cladribine or pentostatin Rx, the CD4 T-cell count may be low for 6-24 months
  - Therefore most centers will give Bactrim(or alternate) to decrease risk of Pneumocystis pneumonia.
  - Also consider acyclovir(or alternate) to decrease risk of shingles
- For patients presenting with HCL and significant infection, many centers will consider initiating vemurafenib, or sometimes interferon until the infection is under control and the patient is eligible for a more definitive therapy with cladribine or pentostatin.
- No definitive studies, but immunization results may be suboptimal (in terms of % achieving immunity) but still considered beneficial in HCL.

Thank you!

Questions?

