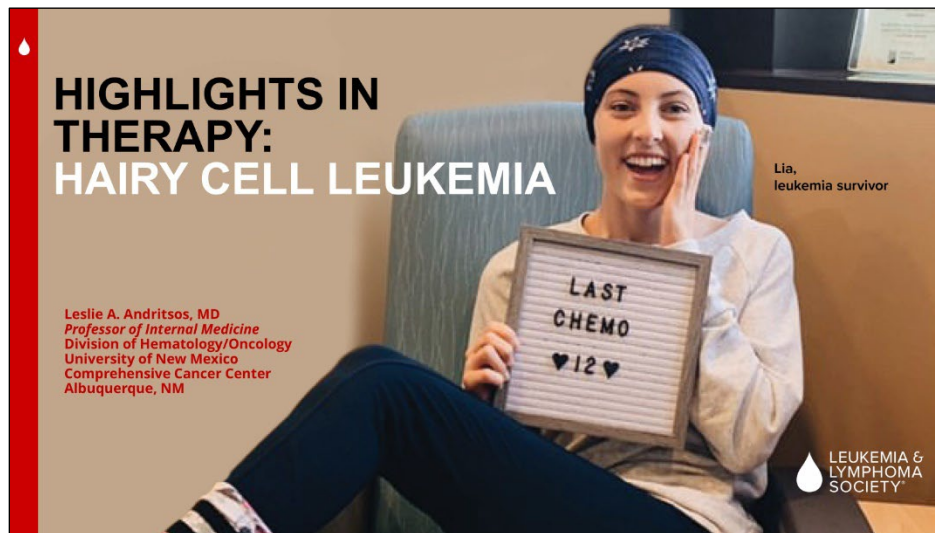


WELCOME AND INTRODUCTION



WELCOMING REMARKS

HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA



Lizette Figueroa-Rivera, MA
Senior Director, Education & Support
The Leukemia & Lymphoma Society
Rye Brook, NY

2



Lizette Figueroa-Rivera, MA

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. And special thanks to Dr. Leslie Andritsos for volunteering her time and expertise with us today.

LLS is the leading source of free education and support for blood cancer patients and families. We provide personalized one-on-one support, including assistance with identifying and enrolling in a clinical trial. The Leukemia & Lymphoma Society funds leading-edge research for every type of blood cancer. We are the largest nonprofit dedicated to creating a world without blood cancers.

Since 1949, we've invested more than \$1.8 billion in groundbreaking research pioneering many of today's most innovative approaches. The Hairy Cell Leukemia Foundation and The Leukemia & Lymphoma Society have joined forces to invest up to \$10 million over five years in targeted research to build a more comprehensive, foundational

Transcript

understanding of the molecular basis of hairy cell leukemia, develop additional therapies, and optimize outcomes for patients with hairy cell leukemia.

Following the presentation, we will take questions from the audience. We would like to also acknowledge and thank Genentech, a member of the Roche Group, for their support of today's program.

PRESENTATION



PRESENTATION
HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA



Leslie A. Andritsos, MD
Professor of Internal Medicine
Division of Hematology/Oncology
University of New Mexico Comprehensive Cancer Center
Albuquerque, NM



3

Lizette Figueroa-Rivera, MA

I'm now pleased to introduce Dr. Andritsos, Professor of Internal Medicine in the Division of Hematology/Oncology at the University of New Mexico Comprehensive Cancer Care Center in Albuquerque, New Mexico.



DISCLOSURES
HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA

- Research support from the Hairy Cell Leukemia Foundation
- Discussing off-label use of:
 - Vemurafenib, Dabrafenib
 - Rituximab, Obinutuzumab
 - Ibrutinib, additional BTK inhibitors
 - MEK inhibitors
 - Chimeric antigen receptor therapy (CAR T)



4

Leslie Andritsos, MD

Thank you. It is an honor to be here today. These are my disclosures. I do receive research support from the Hairy Cell Leukemia Foundation, and I will be discussing off-label use of a number of agents that have been studied in hairy cell leukemia.



OVERVIEW

- HCL epidemiology
- Diagnostic criteria
- Consensus guidelines for treatment and response assessments
- Highlights of therapy
- Complications
- Clinical trials
- Patient resources

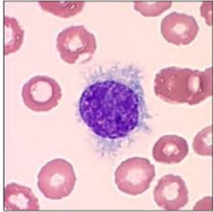


Photo courtesy of Gerard Lozanski, MD.



5

A quick overview of the discussion for today. Just a brief review of epidemiology, diagnostic criteria, and the most recent consensus guidelines. And then we'll get onto highlights of therapy. I'll touch briefly on complications of treatment and hairy cell, but I thought that might be something that people would have specific questions for in the question and answer. And so, we will address those more specifically at the end if needed. I wanted to briefly highlight a couple of clinical trials and some places to obtain patient resources.



A BRIEF HISTORY OF HCL

- 1923: HCL-like cells first observed
- First termed "leukemic reticuloendotheliosis"
- Further characterized by Dr. B. Bouroncle in 1958¹
- Uniformly fatal until development of interferon alfa in 1984
- Cladribine and Pentostatin in 1980s/1990s – transformed HCL into a chronic disease with near normal life expectancy²





6 ¹Bouroncle B et al. *Blood* 1958; ²Eise et al. *Br J Haematol* 2006.

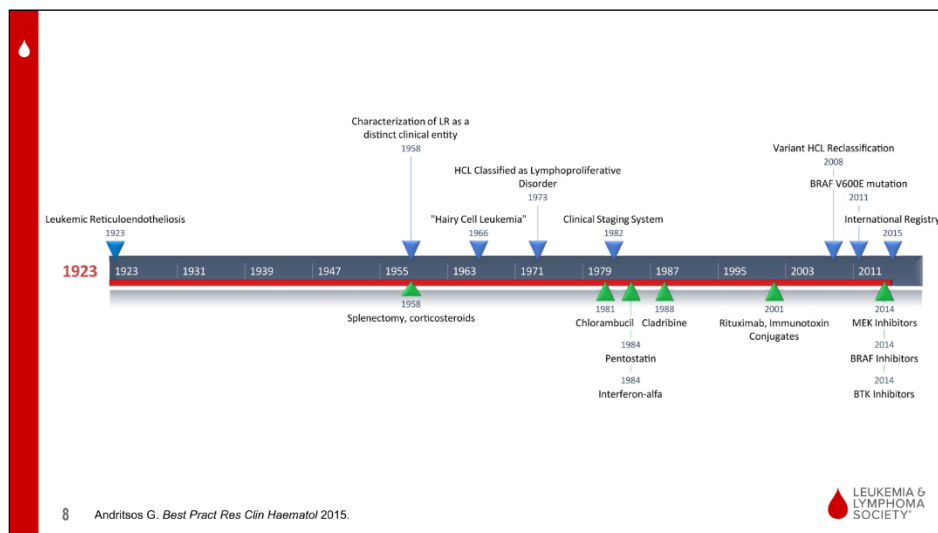
I love to show this picture of Dr. Bertha Bouroncle. She was the real pioneer in discovering what hairy cell leukemia is. This was first observed in 1923 and called

Transcript

leukemic reticuloendotheliosis, but it wasn't until 1958 that Dr. Bouroncle described it as a standalone disease with very specific features. And one thing I like to remind myself of is that until we had the development of effective therapies, this was a uniformly fatal disease. And that didn't happen until 1984 with the median survival being only four years until that development. And then, we quickly had the development of cladribine and pentostatin, which are still in use, which transformed hairy cell into a chronic disease with a near normal life expectancy. And I actually believe with some of the newer discoveries and treatments, we probably will be saying a normal life expectancy in the near future when compared to unaffected other people.

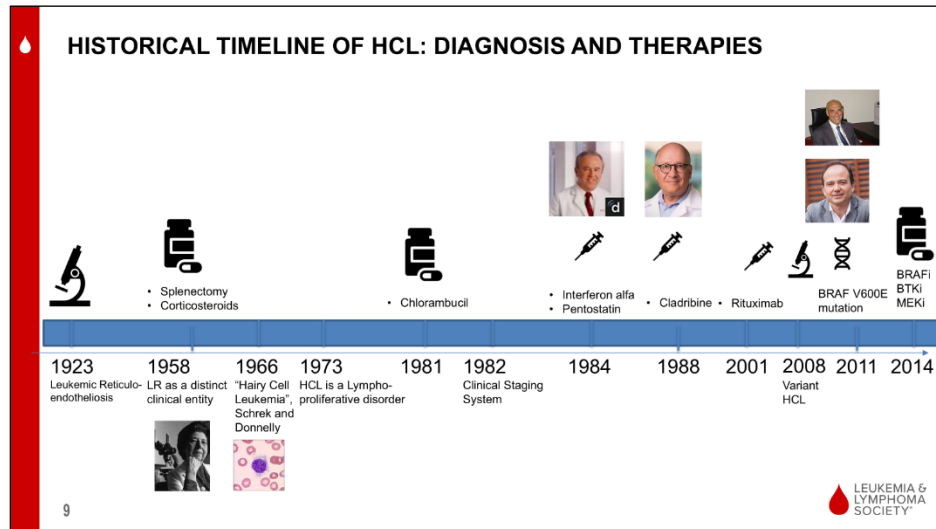


This was the first national report of a new treatment for hairy cell. This was in *The New York Times* discussing a new drug for hairy cell called cladribine. And I actually have a patient who was on this study and is still doing great. And I think it's very interesting that the situation was so dire for patients that it was really national news whenever we had effective therapies.



Transcript

I made this timeline back in 2015 and I was going to update it for this lecture, but so much has happened since 2014 and 2015 that I actually had to make a new timeline.

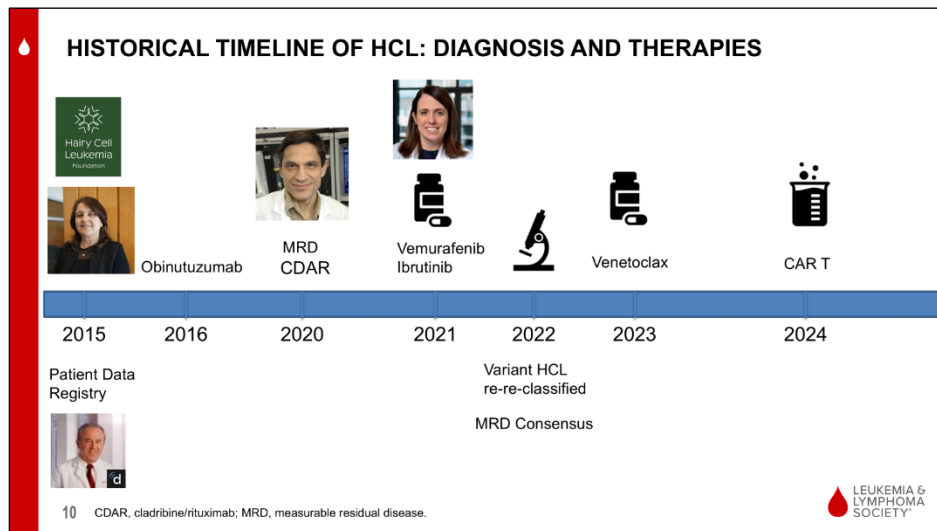


I thought I would take everyone through the historical timeline of hairy cell diagnosis and therapies. It has been over 100 years since leukemic reticuloendotheliosis was first described. When Dr. Bouroncle was really showing that this is a distinct clinical entity, the only treatments available were steroids and having your spleen removed. Shrek and Donnelly realized looking under the microscope that there's these hairy projections, but it wasn't until 1973 that it was clear that it was a type of lymphoma. So, hairy cell leukemia is a lymphoproliferative disorder, and you can't treat a disease until you know what it is. And so, once the lymphoproliferative disorder classification was arrived at, people started using chlorambucil, which was an oral alkylating chemotherapy that was sort of already in use, started treating people with that in about 1981. Then we had a clinical staging system. And then things really got better in 1984 and 1988 when cladribine and pentostatin were developed. And I wanted to put up pictures of people because I thought it might help everybody to realize that all of the people that you see are still doing hairy cell leukemia research and still see patients and are part of the recent discoveries in hairy cell.

Under 1984, pentostatin is Dr. Michael Grever. He is the Medical Director of the Hairy Cell Leukemia Foundation and is still very active in hairy cell research. Dr. Alan Saven is out at Scripps and helped to develop cladribine. And then, around 2001, we had rituximab. I wanted to draw your attention to the fact that in 2008 there was a separate classification of variant hairy cell leukemia. So, up until that time it was kind of lumped in with hairy cell leukemia and then it got moved over into a different section of indolent lymphomas in the diagnostic workbooks that we use. Prior to that time, any data that you would see with results in hairy cell leukemia also included the variant, which tends to have a more aggressive clinical course that may have skewed some of the results.

In 2011, Drs. Tiacci and Falini had this groundbreaking discovery that hairy cell leukemia is driven by a mutation in the BRAF gene. And that then led to the development of targeted therapies. We can now target BRAF because there were already drugs available

for use in melanoma where BRAF mutations are very common. And then, we also saw the start of use of BTK inhibitors and MEK inhibitors.



In 2015, we launched the Hairy Cell Leukemia Foundation Patient Data Registry. I wanted to show everybody Dr. Mirela Anghelina's picture. She really got this done and spearheaded the efforts along with me, and Dr. Grever. Some of the data that you see coming out today, and hopefully much more in the near future, came from the registry data. If you send an email query to the registry, it either goes to Mirela or one of her counterparts in the registry and she will respond to your email. So, it's always nice to put a name to a face.

In 2016, we had obinutuzumab being used for the first time in hairy cell. And then really, the biggest, I think, practice-changing event was when Dr. Kreitman published his results of the randomized trial using cladribine and Rituxan® (rituximab), either starting them together or delaying Rituxan until later. And he also used minimal or measurable residual disease to look at response assessments. And that was really the first time that has been done in a systematic way in a randomized trial in hairy cell leukemia. And that really has changed the landscape.

And then moving on, moving forward, a lot of it has been about targeted therapies and immunotherapies. Dr. Kerry Rogers, you see here, published her results of the ibrutinib study. Then we had Drs. Falini and Tiacci publishing their venetoclax data. And now, currently, Dr. Kreitman has a CAR-T study open. The World Health Organization just again reclassified variant hairy cell leukemia; I'll talk a little bit about that too. But the same year we had our first consensus paper regarding use of minimal or measurable residual disease (MRD) testing. I'll call it MRD from here. And this is one of the biggest areas of focus that we have in the future because we want this to be something that is done routinely for patients so we know how to predict outcomes a little bit better.



EPIDEMIOLOGY

- ~2% of all lymphomas
- Median age at diagnosis ~55–60 years of age
- ~4:1 male predominance
- Higher incidence among Caucasians¹
- Lower incidence among Asian, African, and Arab populations¹
- Higher incidence in first degree relatives of patients with HCL²
- Improved progression-free survival in women after treatment³
- Possible associations:
 - Farming^{4,5}
 - Exposures to pesticides and herbicides^{6,7}
 - Diesel exposure^{5,6}
 - Exposure to ionizing radiation⁶

¹Bernstein L et al. *Cancer Res* 1990;50:3605–9; ²Sud A et al. *Blood* 2019;134(12):960–9; ³Titmarsh GJ et al. *Am J Hematol* 2023;98(5):E116–8; ⁴Monnereau A et al. *J Natl Cancer Inst Monogr* 2014;48:115–24; ⁵Clavel J et al. *Br J Haematol* 1995;91(1):154–61; ⁶Hardell L et al. *Leuk Lymphoma* 2002;43(5):1043–9; ⁷Federal Register 2010.



As everybody knows, hairy cell is a rare leukemia/lymphoma. It technically is a lymphoma. The median age at diagnosis is 55 to 60 years of age. We know that many more men than women are diagnosed with this disease. We don't exactly know why. There is a higher incidence among Caucasians, lower incidence among Asian, African, and Arab populations.

There is a clear set of patients who have familial hairy cell leukemia. There is a higher incidence in first-degree relatives, and there have been about 20 case reports of families with more than one family member with hairy cell leukemia. And recent studies show that that is probably related to a change in the immune system that is heritable, but that work is still ongoing, and I expect to see more about that as time goes on. But clearly, there is a familial hairy cell.

We know, although we don't know why, that there is improved progression-free survival in women after they receive treatment. So, when we looked at patients starting treatment for the first time, the women stayed in remission much longer than the men. And we are still looking at why that may be the case.

I get a lot of questions about, "Why did I get hairy cell leukemia?" And most of the time the answer is, "We don't know why." There have been publications of possible associations with farming, exposures to pesticides and herbicides, diesel exposure, and ionizing radiation. I think that time will tell, and this is another area that we'll probably use the patient data registry to figure this out a little bit better. Soldiers who were exposed to Agent Orange, which is an herbicide, that's now considered a service-connected illness by the military.

HCL BIOLOGY

- Lymphoproliferative disorder, circulates in the blood in 10%–15% of patients ("leukemia")
- Characterized by the accumulation of clonal B cells with surface hairy projections
- Cell of origin felt to be a late-activated memory B cell
- However, BRAF mutant stem cells have been identified in the bone marrow of some patients¹

B-cell development

12 ¹Chung SS et al. *Sci Transl Med* 2014;28:6(238):238ra71.

Quick overview of hairy cell biology, it is a lymphoproliferative disorder that sometimes circulates in the blood, so that's why we call it a leukemia. This can be confusing, I think, sometimes for people when they're first diagnosed, but it's only about 10% to 15% of patients who actually will have circulating hairy cells. You get the accumulation of these clonal B cells, meaning they're all the same, with surface hairy projections. And the cell is felt to be a late-activated memory B cell. So, if you look to the right, this is the B-cell development spectrum starting with HSC, which is hematopoietic stem cell, and it goes through, and you see the activated B cell right before your germinal center.

It has been shown that some hairy cell patients actually have BRAF mutations in their stem cells. And I think that there will be a lot more work showing when in blood development that mutation starts showing up. And that will be very helpful in, I think, treatment and targeting it more specifically.

HCL BIOLOGY

- Majority of classic HCL cases have common BRAF V600E mutation
- Acquired driver mutation
- Present in the entire tumor clone, with high stability at relapse
- Alternative mutations may act as driver mutations
 - Alternative BRAF mutations
 - MAP2K1 mutations
 - Others
- Consider next-generation sequencing if clinical course is more aggressive

13 Tiaocci E et al. *N Engl J Med* 2011.

Transcript

The majority of the classic hairy cell cases have this common BRAF V600E mutation. This is an acquired driver mutation. So, basically the mutated BRAF gene encodes a BRAF protein, and the protein was what drives the cancer cell through the cell cycle. And one of the ways we know that the BRAF mutation is involved in development and perpetuation of hairy cells, it is present in the entire tumor clone. So, all the hairy cells will have the mutation. And if the disease does relapse, it should again have the BRAF mutation.

We also know that there are alternative mutations that can act as driver mutations. There are other BRAF mutations. There are MAP2K1 mutations and others, which I'll show in just a second. And so, if there is controversy or uncertainty about the diagnosis, that would be a good time to consider next-generation sequencing.

GENOMIC ALTERATIONS

TABLE 1 Genomic alterations in hairy cell leukemia (HCL), hairy cell leukemia-variant (HCL-V), splenic diffuse red pulp lymphoma (SDRPL) and splenic marginal zone lymphoma (SMZL)

	HCL	HCL-V	SDRPL	SMZL
MAPK pathway				
BRAF V600E	70% ²¹ -100% ²²⁻²⁵	0% ^{22,23,25}	0% ^{22,27} -2% (G46V) ²⁴	0% ²² -2% ²⁴
MAP2K1*	0% ^{22,23,27} -22% ²¹	38% ²¹ -42% ²¹	7% (V14-34) ²⁷ , 12% ²⁸	0% ²¹
Cell cycle				
CDKN1B (p27)	11% ²¹ -16% ²²	0% ^{22,23}	4% ²⁸	
CCND3	0% ²¹	13% ²³	21% ²¹ -24% ²⁶	13% ²⁴
NF-κB pathway				
MYD88	0% ²¹		0% ²¹	9% ²⁴
TNFAIP3	0% ²¹		0% ²¹	20% ²⁴
Spliceosome				
UGAF1	0% ^{21,23}	13% ^{23,29}		
TP53		8% ²¹ -38% ²³	0% ²¹	
Notch pathway				
NOTCH1	4% ²¹ -13% ²⁴	0% ²¹	2% ²¹	9% ²⁴
NOTCH2	0% ^{21,28} -4% ²³	0% ²¹	10% ²⁴	17% ²¹ -25% ²⁸
Epigenetic regulators				
DOT1L (histone methyltransferase)	13% ²¹	23% ²³		
ARID1A (SWI/SNF family)	4% ²¹	4% ²¹	8% ²⁴	
Transcription factors (TF)				
TFN	4% ²¹	4% ²¹	8% ²⁴	
KLF2	13% ²¹ -16% ²⁴	0% ²¹	2% ²¹	30% ²¹ -30% ²⁸
TF repressor				
BCL6	0% ²¹		24% ²⁴	2% ²⁴

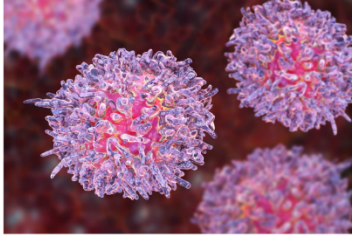
*MAP2K1 mutations in 6/7 VH4-34+ HCL patients and in 4/10 VH4-34+ HCL-V patients.²¹

14 Waterfall JJ et al. *Nat Genet* 2014;46:8-10.

As I'll show in this table, there are several sort of look-alike diseases that can look like hairy cell, and sometimes the best way to figure out if they are hairy cell or something else is by doing sequencing, especially if the BRAF mutation is in question. But as you'll see here, the BRAF is the first in the line and it should pretty much always be present in what we used to call classical hairy cell leukemia, and it should never be present in variant. It's pretty much a rare mutation in other types of lymphoma. And then, there are a number of mutations that are sometimes or even commonly seen in other either variant hairy cells or other types of indolent lymphomas.

WHY ARE THEY HAIRY?

- Cells develop membrane ruffling and microvilli formation
- Early clue into biology of HCL with constitutive activation of RAF-MEK-ERK pathway¹
- Indication of ongoing cellular activation
- External portion of the cell is in a state of constant reorganization



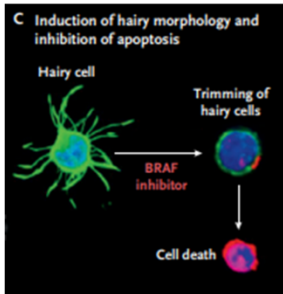
www.HairyCellLeukemia.org

15 ¹Kamiguti AS et al. *Oncogene* 2003;17:22(15):2272-84.

LEUKEMIA &
LYMPHOMA
SOCIETY®

This is another question I get asked, so I thought I would quickly address it because people want to know why are they hairy? So, the cells develop membrane ruffling and microvilli formation because of the activation of the RAF-MEK-ERK pathway. And there was a group back in 2003 that published a paper saying, "Hey, we think that hairy cell leukemia is driven by an alteration in this pathway," which is where BRAF comes in. And so, before there was mutation testing for that in hairy cell, this hairiness was kind of a clue to how this all got started because it's an indication of ongoing cellular activation. And the outside of the cell is in a state of constant reorganization.

HAIR LOSS PRECEDES CELL DEATH



C Induction of hairy morphology and inhibition of apoptosis

Hairy cell

Trimming of hairy cells

BRAF inhibitor

Cell death

16 Falini B and Tiacci E. *N Engl J Med* 2024;391:14.

LEUKEMIA &
LYMPHOMA
SOCIETY®

And also, interestingly, the hair loss precedes cell death. This little picture shows a hairy cell being treated with a BRAF inhibitor, but actually any treatment that's effective that you apply to a hairy cell will cause it to lose its hairs and undergo apoptosis. The cell will die without its hairs, or that's a marker that the cell is dying.

DIAGNOSIS

17



INDICATORS OF POSSIBLE HCL

- Pancytopenia
- Monocytopenia
- Splenomegaly
- Presence of infection, especially unusual infection
- Constitutional symptoms (fevers, unintentional weight loss)
- Circulating hairy cells (less common)
- Need a bone marrow biopsy for definitive diagnosis

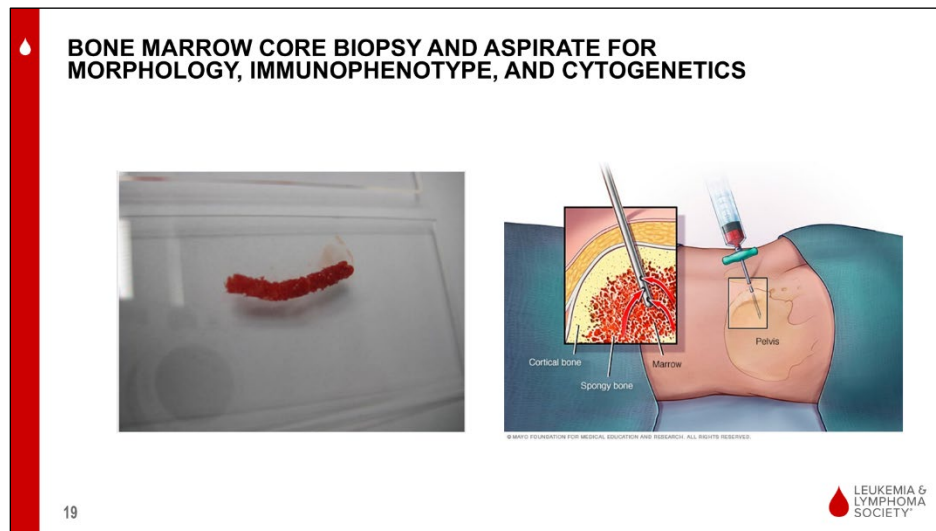
18



I wanted to quickly run through diagnosis. Most people are diagnosed with hairy cell when they are found to have low blood counts, usually more than one lineage of blood counts being low, so we would call that pancytopenia. Also, it is very characteristic for people to have absent monocytes, and we don't see that hardly in any other diseases. So, monocytopenia can be a real indicator of hairy cell leukemia. A lot of people end up with a big spleen. They may show up to the emergency room with an infection and be found to have an unusually severe pneumonia or an unusual type of infection.

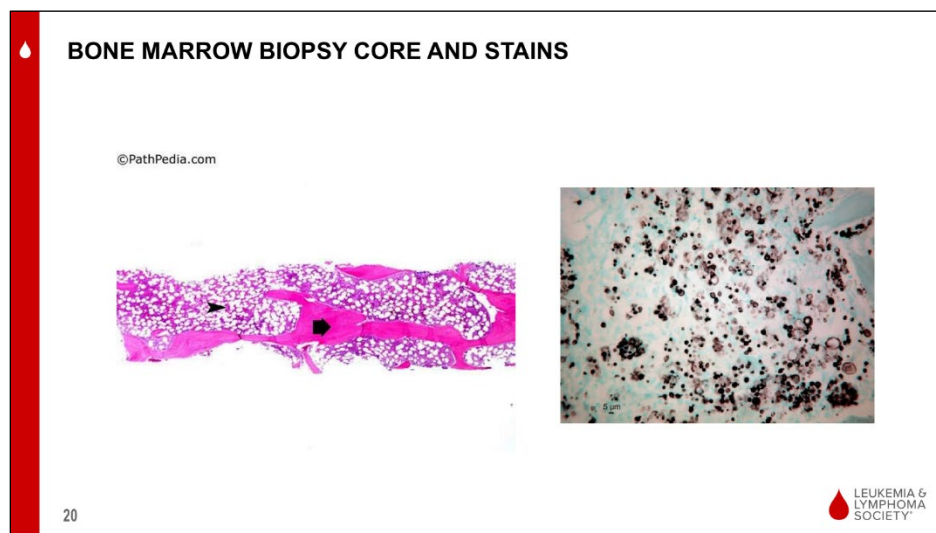
A lot of people do get flu-like symptoms, fevers, unintentional weight loss, and then very occasionally the diagnosis will be made on a blood test when circulating hairy cells are seen. That is far less common because they don't really circulate and 100% of people need a bone marrow biopsy for a definitive diagnosis.

My next slide is going to actually have a picture of a bone marrow core biopsy specimen and also a cartoon of a bone marrow biopsy being performed.



On the left is the little worm-looking core biopsy specimen, and on the right is a depiction of how we get the aspirate out of the bone marrow. And so, both of these parts of the test are critically important. They give us different information.

The reason the core biopsy is so important to get is because most people, their hairy cells don't come out very efficiently when you do the aspiration, you will get some, but it's not going to be fully representative of what's going on in the bone marrow. So, we need to get this little piece of bone marrow. This bone marrow has to be processed. Once it's obtained, it has to be decalcified, it has to be sliced and then it has to be stained. And that's why when you have your biopsy, it can easily take a week to even have any preliminary information about what the numbers are looking like in there.



This is a couple of pictures of the bone marrow, how it looks under the microscope. So, this pink stain on the left is an H&E (hematoxylin and eosin) stain and that gives very

Transcript

basic information about cell burden, and types, and numbers of cells. And then, we can further use immunohistochemical stains to see what types of cells are in there. On the right is the CD20 stain, so most people with hairy cell are positive for CD20 and when it's positive it looks like little chocolate donuts and that's what you see here.

CONSENSUS GUIDELINES FOR DIAGNOSIS, RESPONSE ASSESSMENT, AND TREATMENT OF HCL

Review Article • blood

Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia

Michael R. Grever,¹ Omar Abdel-Wahab,² Leslie A. Andritsos,¹ Versha Banerji,³ Jacqueline Barrientos,⁴ James S. Blachly,¹ Timothy G. Call,⁵ Daniel Catovsky,⁶ Claire Dearden,⁷ Judit Demeter,⁸ Monica Else,⁶ Francesco Forconi,⁹ Alessandro Gozzetti,¹⁰ Anthony D. Ho,¹¹ James B. Johnston,⁷ Jeffrey Jones,¹ Gunnar Juliusson,¹² Eric Kraut,¹ Robert J. Kreitman,¹³ Loree Larrat,¹⁴ Francesco Lauria,¹⁵ Gerard Lozanski,¹⁶ Emili Montserrat,¹⁶ Sameer A. Parikh,⁵ Jee H. Park,³ Aaron Pollack,¹⁷ Graeme R. Quest,¹⁸ Kamal R. Rai,⁴ Farhad Ravandi,¹⁹ Tadeusz Robak,²⁰ Alan Saven,²¹ John F. Seymour,²² Tamar Tadmor,²³ Martin S. Tallman,² Constantine Tam,²² Enrico Tiaoli,²⁴ Xavier Troussard,²⁵ Clive S. Zent,²⁶ Thorsten Zenz,²⁷ Pier Luigi Zinzani,²⁸ and Brunangelo Falini²⁴

- Established first standards for:
 - Diagnosis
 - Indications for treatment
 - Response assessments
 - Recommendations for first-line therapy
 - Treatment at relapse

21 Grever MR et al. *Blood* 2017;129(5):553–60.

LEUKEMIA & LYMPHOMA SOCIETY®

Moving on to the consensus guidelines that were published in 2017. This was the first time this group had come together and established the standards for diagnosis, indications for treatment, response assessments, recommendations for first-line therapy, and treatment at relapse. This document is currently being revised, and you will hopefully see an updated publication in the next year or two, because it must incorporate so many new discoveries and there's a lot to add, which is a really great feeling in such a short time.

CONSENSUS GUIDELINES FOR DIAGNOSIS

Immunophenotype:

Clonal B cells positive for CD19, CD20, CD22, PAX5, CD79a, CD11c, CD25, CD103, CD123, CD200, DBA44, FMC7

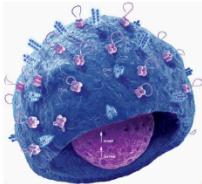
Immunohistochemical stains:

Annexin-1, VE1 (BRAF)

BRAF testing:

BRAF V600E mutation positive by PCR or IHC (VE1/BRAF)

In the case of an atypical phenotype, diagnosis is based on the most diagnostic features



22

LEUKEMIA & LYMPHOMA SOCIETY®

I'm not going to read all of these, but suffice it to say that for a diagnosis of hairy cell leukemia, there should be the right combination of positive features, the right

Transcript

combination of things that are not there. BRAF testing of some kind should be positive, whether that's like a PCR genetic test or immunohistochemical staining, it can be found either way. And the hairy cells should be positive for the majority of the diagnostic proteins that are on the outside of the cell.

If there is a very atypical phenotype or something that would not be expected, that's there, a lot of times the pathologist will make a diagnosis based on the most diagnostic features. But I think I would say if the diagnosis is in question, it would be good to be sure that a hematopathologist has reviewed the diagnosis. And a lot of times this can be done at one of the centers of excellence, and I'll show you how to find that as well, especially for people who may not have a hospital in their city with a hematopathology consulting team.

 **IMAGING NOT REQUIRED BUT USEFUL IN SOME CIRCUMSTANCES**

- Ultrasound of spleen to obtain measurements
- CT scans to evaluate for presence of enlarged lymph nodes and/or enlarged spleen
- PET/CT scan to look for involvement in extranodal areas; currently no consensus on standard features in HCL
- Imaging would be recommended prior to starting treatment

 **LEUKEMIA &
LYMPHOMA
SOCIETY®**

23

Imaging is not required at the time of diagnosis, but we do recommend it prior to starting treatment because that may end up being part of the response assessment and we definitely would want to see some type of measurement of the spleen to be sure that the spleen is getting smaller with treatment. That's really important to know if a response is happening. If there is a question of something else going on (for example, maybe your doctor noticed that you had enlarged lymph nodes in your neck or something like that, they would probably want to get some type of scan to more fully assess that). That could either be CT scans or some people get PET/CTs, but I would caution that that is still an area of active scientific investigation because we don't know what brightness is characteristic of hairy cell.

And so, the PET/CT may be a little bit confusing if it's showing activity in places that it is not expected. And so, that can be helpful for looking at other types of cancers or maybe a coexisting lymphoma, which can happen in some people. Most of the time we recommend an ultrasound or basic CT scans.

 **VARIANT HCL**

- Now termed splenic B-cell lymphoma/leukemia with prominent nucleoli¹
- Typically has a more aggressive clinical course than cHCL
- By definition BRAF-V600E negative
- Originally felt to always be CD25 negative
- Considered a separate disease from HCL
- Treatment will not be addressed in this discussion; however, there is a great deal of overlap

24 ¹WHO Classification 2022.



Just a quick word about variant hairy cell leukemia. I'm not really going to touch on this with treatment. I don't know if people know that it was reclassified and is now termed splenic B-cell lymphoma/leukemia with prominent nucleoli. This has been a little bit controversial because then you have to tell people their diagnosis changed again.

But it typically does have a more aggressive clinical course. By definition, this disease is BRAF negative, and so, BRAF inhibitors would not be a treatment option in this case. This is considered just a completely separate disease from hairy cell leukemia. I'm not going to address treatment in this discussion, but there is a great deal of overlap. And with the exception of BRAF inhibitors, I would say the majority of other available treatments for hairy cell have also been used in SPLPN.

 **INDICATIONS FOR TREATMENT**

- Most HCL patients need treatment at the time of diagnosis
- Around 10% of patients can be monitored on observation at the time of diagnosis¹
- Consider treatment when:
 - Hemoglobin <11 g/dL
 - Platelet count <100,000/ μ L
 - Absolute neutrophil count <1,000/ μ L
 - Splenomegaly, especially if symptomatic

25 ¹Golomb HM. *J Clin Oncol* 1983;1(10):652-6.



Most people do need treatment at the time of diagnosis. About 10% of patients can be monitored on observation, but ultimately, the majority of people do end up getting treated. We say consider treatment when one of the following is present, so that would

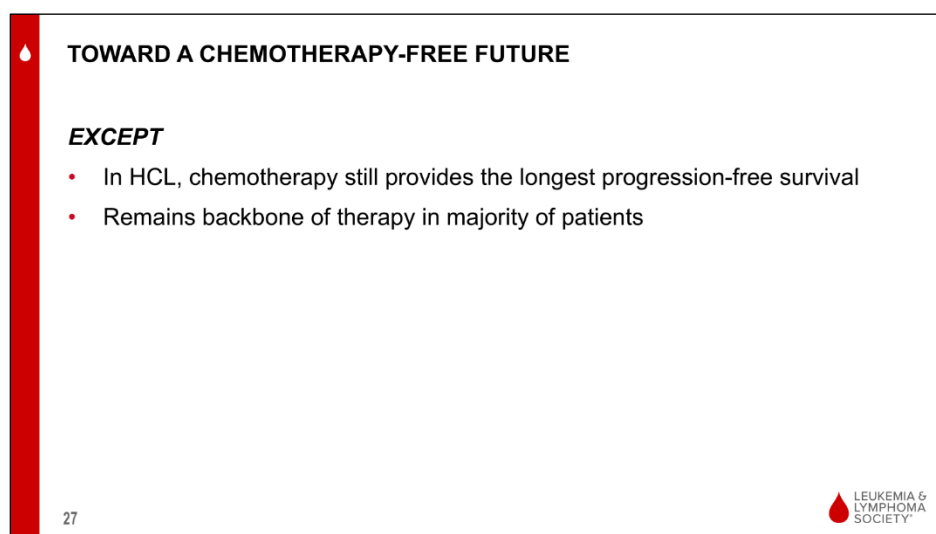
Transcript

be anemia, a low platelet count, a low absolute neutrophil count, or if the spleen is enlarged and especially if it's symptomatic.

One word of caution is that as many of you probably already know, sometimes these numbers can bounce around. You may go to your doctor's appointment one day and have a platelet count of 88 and then there's a discussion about treatment, but the next time you have it checked, it's 120. Some of these blood counts are variable depending on what else is going on with your health. This is one of the reasons why we want to see a trend, a couple of abnormal values, before deciding to do treatment, and also, a bone marrow biopsy to be sure we know exactly what's going on in the bone marrow before treatment is initiated.



Now moving on to treatment.



Transcript

In general, in hematology and oncology, everybody is moving towards a chemotherapy-free future. So, trying to get away from chemotherapy in the situations where we can, because chemotherapy has off-target effects, it can affect other body parts, especially the bone marrow function. We do try to avoid that if there's a better or equivalent available non-chemotherapy treatment option.

The big exception is in hairy cell leukemia. Chemotherapy still provides the longest progression-free survival and remains a backbone of therapy in the majority of patients. The caveat to that is some people cannot get chemotherapy for various reasons, and so, it becomes very important to have chemotherapy-free options.

**CHEMOTHERAPY ALONE**

- Cladribine or pentostatin
- Highly effective in both the upfront and relapsed setting
- Equivalent response and long-term outcomes¹
- Up front ~100% overall response rates, 70%–90% complete response rates
- Identification of residual disease more sophisticated but remissions remain the same
- 5-year progression-free survival around 70%
- Has resulted in near normalization of life expectancy²
- Still ~40% of patients relapse

28 ¹Eise et al. *BJH* 1999; ²Yazan et al. *Clin Lymph Myel* 2017.



I'm going to start the discussion with a review of chemotherapy, so that will be cladribine or pentostatin. Those are the two big ones. We know that they are highly effective in both the upfront and relapse setting. They provide equivalent response and long-term remissions. And so, I don't want to say they're interchangeable, there may be reasons to do one or the other which we'll discuss, but neither one is wrong as a choice, especially in the first-line.

In general, there is about a 100% overall response rate meaning either a complete or partial remission, and with either of these about a 70% to 90% complete response rate. Nowadays, we have a greater ability to identify residual disease because of more sophisticated testing, but their remissions remain the same. They have equivalent five-year progression-free survival, which is about 70% of patients. And again, the near normalization of life expectancy. But the problem is still about 40% of people will ultimately relapse and some people will relapse quite early in their treatment course, within two years of getting treated. And so, there is definitely a need to improve the treatment landscape.



CLADRIBINE

- A purine nucleoside analog chemotherapy
- Multiple ways to administer:
 - 0.1 mg/kg/day continuous IV infusion for 7 days
 - 0.14 mg/kg/day IV over 2 hours for 5 days
 - 0.1–0.14 mg/kg/day subcutaneously daily for 5 days
 - 0.15 mg/kg/day IV once weekly for 6 weeks
- Route and duration of administration may depend on available facilities and patient preference
- No significant differences observed in responses based on regimen
- May have less neutropenia with weekly dosing



29

I wanted to talk a little bit about cladribine because it does get confusing because there are so many ways to administer it. It is a purine nucleoside analog chemotherapy, meaning it does affect the DNA of the cells. It can be given either by continuous IV infusion for seven days, which has to be done in the hospital. It can be done intravenously over two hours for five days, which is typically administered in an infusion center. It can be administered subcutaneously for five days, which is a nice option if the setting is more rural, or there is not an infusion suite available, it can still be given subcutaneously. And then, it has also been studied once weekly for six weeks. So, that was given IV once weekly for six weeks.

It turns out that there is no significant difference observed in responses based on the treatment regimen, but there may be less neutropenia if you do the weekly dosing. So, that's obviously the most inconvenient dosing option, but there may be less neutropenia.



PENTOSTATIN

- Purine nucleoside analog chemotherapy
- Administered 4 mg/m² IV every two weeks × 12 doses
- Two additional doses if CR achieved after 12 doses
- Dose can be reduced
- Treatment interval can be lengthened
- Treatment can be held if complications arise
- Previously unavailable due to manufacturing delays, currently listed as available



30

Pentostatin is also a purine nucleoside analog chemotherapy. It works very similarly to cladribine in how it affects the DNA of the cell. There's really kind of just one way that we give this. It's given IV every two weeks for 12 doses. So, it's about six months of therapy. In the original randomized trial that Dr. Grever did with SWOG [Cancer Research Network] comparing it to interferon – I'm not going to talk about that study, but I can always come back and do that – but, two additional doses were given to the patients who achieved complete remission and then they went on to observation.

One of the nice things about pentostatin is obviously the dose can be reduced, you can reduce the dose if there's a problem with tolerating treatment, the treatment interval can be lengthened. It can go from every two weeks to every three weeks if the peripheral blood counts are struggling. Treatment can be held. So, for example, if somebody got COVID or influenza in the middle of treatment, you can just hold it and not give it, and give the person some time to recover and then come back and restart and try to get those 12 doses in.

Recently it was unavailable. There was a manufacturing issue, but I looked on their website and they say it's currently available. And so, there's certainly different reasons to do one or the other treatment. I would say probably cladribine is the most commonly administered purine analog in the United States and probably Europe.

**PENTOSTATIN VS CLADRIBINE**

Long-term results for pentostatin and cladribine treatment of hairy cell leukemia

CLAIRE E. DEARDEN, MONICA ELSE, & DANIEL CATOVSKY
The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, UK

Abstract
Over the past 25 years we have collected data at our institution from 242 patients with hairy cell leukemia (HCL), treated with pentostatin ($n=188$) or cladribine ($n=54$), with a median follow-up of 16 years. From this we have been able to conclude that there is no significant difference in outcome between the two agents either at first or subsequent lines of therapy. Overall, the complete response (CR) rate is 81% and the median disease-free survival (DFS) is 16 years. After relapse or non-response patients can be successfully retreated with pentostatin or cladribine achieving a lower rate of CRs with each line of therapy, although these remain equally durable. Complete response and pretreatment counts of hemoglobin >10 g/dL together with platelets $>100 \times 10^9/L$ are associated with the longest DFS. Importantly, for patients achieving a CR the DFS is five times as long as for those achieving a partial response (PR). Patients still in CR at 5 years have only a 25% risk of relapse by 15 years. Outcomes for patients with recurrent disease have improved with the addition of rituximab to either purine analog. Overall, only eight patients have died of HCL-related causes. Patients with HCL who achieve a CR can expect a normal lifespan.

Keywords: Hairy cell leukemia, pentostatin, cladribine

31 Dearden CE et al. *Leuk Lymphoma* 2011;52(S2):21-4.

 LEUKEMIA &
LYMPHOMA
SOCIETY®

Here is a really nice paper that was done, published back in 2011 by the group at Royal Marsden. They looked at their 25-year institutional experience, 242 patients with hairy cell that were treated with either pentostatin or cladribine. This sort of established some of our world view in terms of these drugs being basically equivalent and understanding their use of single agents.

COMPARISON OF RESPONSES

Table I. Single-agent cladribine and pentostatin treatment of 242 patients with hairy cell leukemia: response and disease-free survival by line of treatment.

	No. of patients	CR	PR	NR	DFS at 5 years
First line					
Pentostatin	188	82%	14%	4%	77%
Cladribine	54	76%	24%	0%	
Second line					
Pentostatin	28	59%	33%	8%	68%
Cladribine	60	69%	31%	0%	
Third line					
Pentostatin	4*	100%	0%	0%	58%
Cladribine	18*	38%	62%	0%	

*Only 16/22 patients were evaluable for response (three pentostatin, 13 cladribine).
CR, complete response; PR, partial response; NR, no response; DFS, disease-free survival.

32 Dearden CE et al. *Leuk Lymphoma* 2011;52(S2):21-4.



This was studied in the first-line, second-line, and third-line. They looked at who got what. In the first-line, you'll see that almost 100% response rate except for 4% of patients who did not respond. There were responses seen in both different types of diseases, with a disease-free survival at five years of 77%. But it turns out if you treat people again, they still can have a great response with a large percentage of patients achieving a complete response, almost 70% in the cladribine group. And maintaining those responses at five years, almost 70% of patients are still in remission. And then again in the third-line. The reason why this study exists is because there was very little treatment available and this is one of the most effective therapies, and so, many patients got it multiple times. And you can see that even in the third-line, people can still respond to this chemotherapy, making it a very powerful option if there's not a reason to not give chemotherapy.

DISEASE-FREE SURVIVAL ACCORDING TO RESPONSE

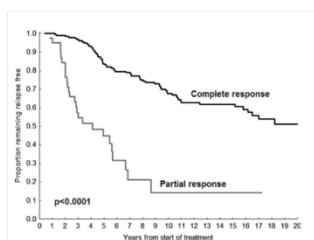


Figure 1. Disease-free survival by response to first-line single-agent treatment with either pentostatin or cladribine, showing a significant difference between patients achieving a complete response (CR) versus a partial response (PR). The median disease-free survival was 16 years overall; 20+ years (not reached) for patients attaining a CR and 4 years after a PR ($p < 0.0001$). There was no difference in DFS by type of treatment (pentostatin or cladribine).

33 Dearden CE et al. *Leuk Lymphoma* 2011;52(S2):21-4.



This graph I wanted to show, from the same study, because I think this really opened our eyes to the differences in outcomes between patients who achieve either a complete

Transcript

response, which is great, versus a partial response. You can see on the left part of the curve, this is the proportion of patients remaining free of relapse and then years from the start of treatment. So, in the first two years, there were a fair number of patients who experienced disease relapse. The median progression-free survival was only between three and four years. Certainly, this encourages us to continue finding better treatments because people who achieve a complete response do great and people who achieve a partial response will relapse.

RITUXIMAB

- Anti-CD20 immunotherapy
- Limited data for use in up-front setting as a single agent
- Multiple studies for use during relapse

34 Salles G et al. *Adv Ther* 2017;34:2232-73.

This brings us to the first non-chemotherapy treatment I'd like to discuss, which is rituximab. On the right is a figure with kind of just a generic B cell, and I'm sorry it's a little bit light, but on the surface of the B cell are these tan projections which represent the CD20 receptor. And so, because all these proteins stick out from the B cell, you can target them because CD20 is very important for the cell to stay alive.

The purple, triangle looking things are the anti-CD20 monoclonal antibody. Those kind of float through the bloodstream, find B cells, find the CD20 protein on the surface of the B cells, bind to it, and then start a sequence of events that leads to cell death. And a lot of times that involves other cells of the immune system that come over to kill the tumor cell.

There are limited data for its use in upfront settings as a single agent, but I know that there are places where this is done fairly routinely with very good responses. But we do have studies for use during relapse, and I wanted to present the most recent one.

TO THE EDITOR:

Single-agent rituximab is an effective salvage therapy in pretreated patients with hairy cell leukemia

Alessandro Broccoli,^{1,2} Lisa Argani,² Laura Nanni,^{1,2} Vittorio Stefoni,^{1,2} Cinzia Pellegrini,¹ Beatrice Casadei,¹ Gabriele Gugliotta,¹ Matteo Carella,^{1,2} Paolo Elia Coppola,^{1,2} Gianmarco Bagnato,^{1,2} and Pier Luigi Zinzani^{1,2}

¹IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Serafini," Bologna, Italy; and ²Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy

35 Broccoli A et al. *Blood Adv* 2023;7:6762-6.

This was just from 2023 using Rituxan just by itself as a treatment for people who had already received other types of treatments. And this was from the Italian group out of Bologna.

RITUXIMAB ONCE WEEKLY × 4 WEEKS

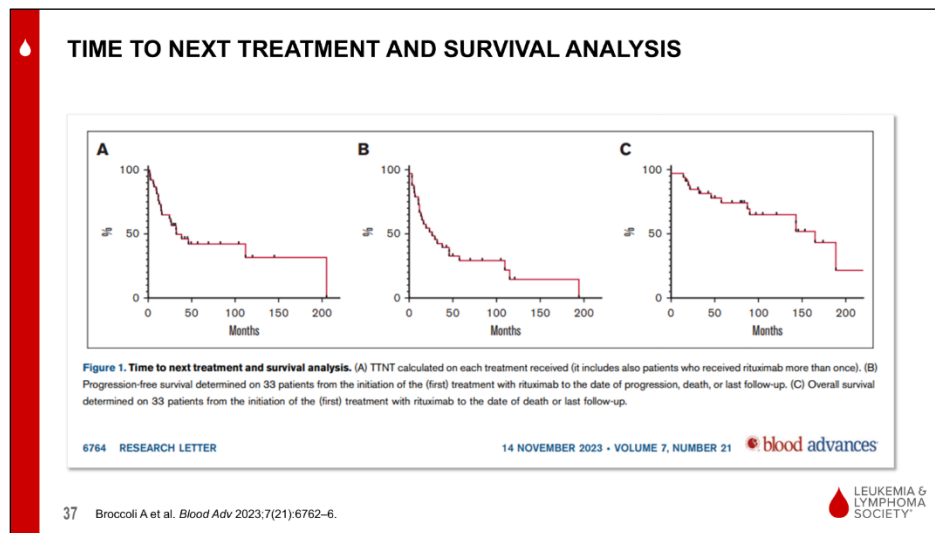
Table 1. Clinical details and outcomes by line of treatment

	Second line	Third line	Fourth line	Fifth line	Sixth line	Seventh line	Eighth line
Patients, n	12	9	7	5	4	1	1
Male, n	12/12	8/9	6/7	5/5	4/4	1/1	1/1
Leukocytes (mm ³)	2 250	1 740	2 600	1 800	2 950	1 800	5 900
Neutrophils (mm ³)	660	1 160	1 300	740	1 350	1 072	2 000
Hemoglobin (g/dL)	13.4	11.3	13.1	11.6	12.7	11.7	7.6
Platelets (mm ³)	72 000	89 000	58 000	100 000	97 000	77 000	21 000
Splenomegaly	33%	33%	0	20%	0	0	0
Last therapy before rituximab	Clofazimine (100%)	Clofazimine (89%) Rituximab (11%)	Clofazimine (86%) Interferon (14%)	Clofazimine (80%) Interferon (40%)	Rituximab (50%) Clofazimine (25%) Pentostatin (25%)	Rituximab (100%)	Clofazimine (100%)
Early interruption of rituximab, n	1 (death)	None	1 (splenial)	None	1 (splenial)	None	None
Next therapy after rituximab	Clofazimine (50%) Rituximab (25%) Venetoclax (25%)	Clofazimine (80%) Interferon (20%) Rituximab + venetoclax (20%)	Venetoclax (20%) Pentostatin (40%) Clofazimine (20%)	Rituximab (50%) Clofazimine (25%) Interferon (25%)	Interferon (50%) Clofazimine (25%) Rituximab (25%)	None	None
Overall response	75.0%	88.9%	85.7%	80.0%	50.0%	100%	0
Complete response	41.7%	33.3%	0	20.0%	25.0%	100%	0
Further treatment	36.4%	55.6%	71.4%	80.0%	100%	0	0*
Month to relapse, range	2.6-24.9	2.5-105.0	1.2-28.8	10.0-37.5	1.5-193.7	N/A	N/A*

N/A, not assessable.
*Patient deceased in the post-rituximab follow-up.

36 *Blood Adv* 2023;7:6762-6.

I thought it was important to show how many lines of therapy some of these patients have had. This one person is out on their eighth line of treatment, and so, there are a lot of people who will receive multiple treatments for hairy cell leukemia. If you look towards the bottom, you'll see a place that says overall response. If you go all the way across, you'll see that the overall response rate, even in patients who have had multiple prior lines of therapy, is relatively high. That means either they got into a complete remission or a partial remission, and a reasonable percentage of patients achieved a complete response. So, on that second-line of therapy, you're looking at 41% of patients getting into a complete remission. They also looked at how long it was until people needed treatment again, and I'll show that graph next, but the remissions were longer than I was expecting to see.



If you look at the A column, that is the calculated to next treatment received. So, looks like the median progression-free survival was about 40 to 50 months. If you look at the overall survival, which was calculated from the first dose of Rituxan until the date of death or the last follow-up, that's getting out to about 150 months. And so, even though we don't really think of rituximab just by itself as being a backbone of therapy, there may be times where this is a useful and important treatment to have available. There's certainly a role for Rituxan if you need to avoid chemotherapy for some reason.

OBINUTUZUMAB

- Anti-CD20 monoclonal antibody
- Similar mechanism of action as rituximab
- Fully humanized
- Developed to be more potent than rituximab
- Better responses when given with chemotherapy than rituximab in other indolent lymphomas¹

38 ¹Townsend W et al. *HemaSphere* 2023;7(7):e919.

I also wanted to talk about obinutuzumab. This is also an anti-CD20 monoclonal antibody. It has a similar mechanism of action as Rituxan in that it binds to the CD20 protein. It's different in that it's fully humanized and it was developed to be more potent than rituximab. And it seems like it is more potent than rituximab, because we know that in pretty much the majority of the lymphomas where it has been studied, the responses were better when it was given with chemotherapy as compared to Rituxan.

OBINUTUZUMAB

Efficacy and Safety of Obinutuzumab in Relapsed or Refractory Hairy Cell Leukemia (R/R HCL): An Italian Multicenter Phase-2 Academic Trial (HCL-PG04)

Enrico Tiacci, Luca De Carolis, Monia Capponi, Flavio Falcinelli, Francesco Zaja, Alessandro Pulsoni, Edoardo Simonetti, Elisa Montechiarello, Alessandra Romano, Jacopo Olivieri, Alessandro Mancini, Gianna Maria D'Elia, Robin Foa, Maurizio Frezzato, Brunangelo Falini



Blood (2023) 142 (Supplement 1): 4398.
<https://doi.org/10.1182/blood-2023-180035>

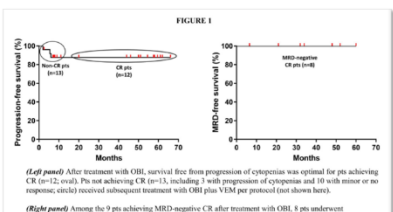
39

LEUKEMIA &
LYMPHOMA
SOCIETY®

Drs. Tiacci and Falini just recently published their paper at the American Society of Hematology (ASH) [annual] meeting. This is currently just in abstract data, but I'm told that it will be updated in manuscript form and there will be more information about patients that got obinutuzumab in the setting of having relapsed or refractory hairy cell.

OBINUTUZUMAB – RELAPSED HCL

FIGURE 1



Left panel: After treatment with OBI, survival free from progression of cytopenias was optimal for pts achieving CR (n=12; oval). Pts not achieving CR (n=14, including 1 with progression of cytopenias and 10 with minor or no response; circle) received subsequent treatment with OBI plus VEM per protocol (not shown here).

Right panel: Among the 9 pts achieving MRD-negative CR after treatment with OBI, 8 pts underwent subsequent bone marrow evaluations during follow-up and showed durable MRD-free survival.

- Phase 2 multicenter trial in relapsed HCL
- Schedule:
 - 1000 mg IV days 1, 8, and 15 of cycle 1 and on day 1, cycles 2–6 (1 cycle = 28 days)
- 26 patients treated
- 12 of 25 achieved a CR
- In CR patients, OS and PFS were 100% at 56 months
- In non-CR patients, vemurafenib was added at time of progression

40 Tiacci E et al. *Blood* 2023;142(Suppl_1):4398.

LEUKEMIA &
LYMPHOMA
SOCIETY®

It was a Phase 2 multicenter trial. I like to show the schedule because patients who are going to be getting obinutuzumab always want to know when they're going to be getting treatment. So, it's given days 1, 8, and 15 of the first cycle. And then, just on the first day of the subsequent five cycles.

Twenty-six (26) patients were treated, and 12 of them achieved a complete response. In the patients that had a complete remission, the overall [survival] and progression-free survival was 100% at 56 months. In the non-complete remission patients, vemurafenib, which is the BRAF inhibitor, was added at the time of remission. And so, in the first part of the figure you see some circles and the first one is circling the patients who did not

Transcript

achieve a complete remission. And you'll see that some of them had relatively early disease progression, and the patients that achieved complete remission stayed in remission a long time. So, again, that is being borne out that the depth of the remission is very important for the duration of their remission.

 **CHEMO-IMMUNOTHERAPY**

Randomized Phase II Study of First-Line Cladribine With Concurrent or Delayed Rituximab in Patients With Hairy Cell Leukemia

Dai Chihara, MD, PhD¹; Evgeny Arons, PhD²; Maryalice Stetler-Stevenson, MD, PhD³; Constance M. Yuan, MD, PhD³; Hao-Wei Wang, MD, PhD³; Hong Zhou, BS²; Mark Raffeld, MD³; Liqiang Xi, MD³; Seth M. Steinberg, PhD⁴; Julie Feurtado, RN⁵; Lacey James, CRNP²; Wyndham Wilson, MD, PhD⁶; Raul C. Braylan, MD⁷; Katherine R. Calvo, MD, PhD⁷; Irina Maric, MD⁷; Alina Dulau-Florea, MD⁷; and Robert J. Kreitman, MD^{1,2}

41 Chihara D et al. *J Clin Oncol* 38:1527–38. © 2020.

 LEUKEMIA &
LYMPHOMA
SOCIETY®

There will be more to come on obinutuzumab hopefully soon. This is the randomized trial. It was a randomized Phase 2 study of initial treatment. So, first-line treatment with cladribine either given with Rituxan at the time of starting cladribine or delaying it until later. And I love this study. It is practice-changing. I think most of us have readjusted our standard practice to include Rituxan in the concurrent strategy if possible, unless there's a reason not to.

 **RANDOMIZATION**

- 68 patients randomly assigned 1:1 to concurrent cladribine plus rituximab vs cladribine followed by delayed rituximab
- Concurrent: Cladribine 0.15 mg/kg/day IV days 1–5 PLUS rituximab 375 mg/m² beginning day 1 × 8 weekly doses
- Delayed: Cladribine 0.15 mg/kg/day IV days 1–5 followed by rituximab 375 mg/m² × 8 weekly doses if MRD detected

42 Chihara D et al. *J Clin Oncol* 38:1527–38. © 2020.

 LEUKEMIA &
LYMPHOMA
SOCIETY®

Sixty-eight patients were randomly assigned one-to-one to either get cladribine with Rituxan out of the gate or followed by delayed Rituxan. This is the schedule for the concurrent Rituxan, it is given IV infusion over two hours days 1 through 5, and then the

Transcript

first day of the cycle, and then weekly for a total of eight doses it's given in addition. The delayed Rituxan patients, it was cladribine given the same way, but followed by Rituxan down the road if MRD was detected.

**CDAR RESULTS**

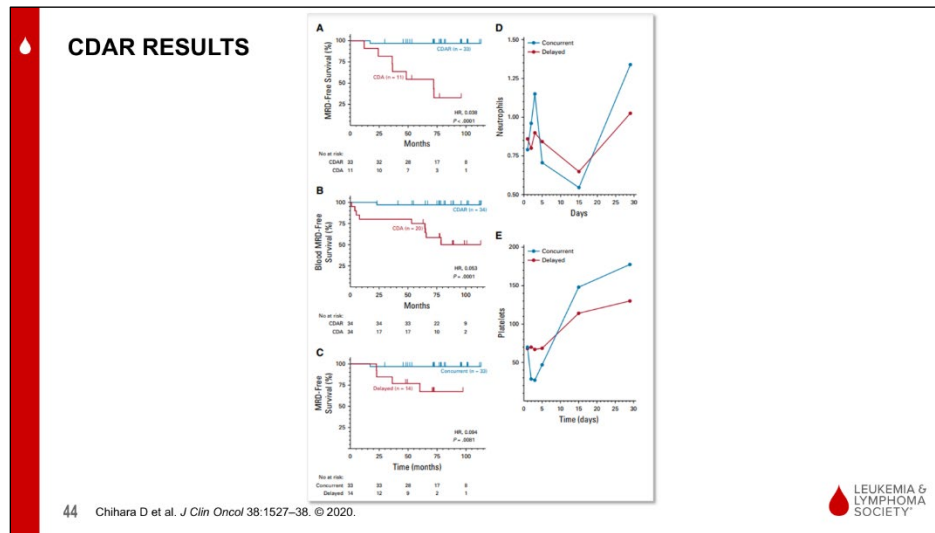
- 6 months posttreatment:
 - CDAR: 100% CR; MRD negative 97%
 - Cladribine alone: 88% CR; MRD negative 24%
 - Statistically significant differences in MRD negativity
- 96 months median follow-up posttreatment:
 - CDAR: MRD negative 94%
 - Cladribine alone: MRD negative 12%
 - Delayed rituximab led to lower rate and durability of MRD negativity
- CDAR associated with higher rates of thrombocytopenia and need for platelet transfusions but faster blood count recovery overall

43 Chihara D et al. *J Clin Oncol* 38:1527–38. © 2020.

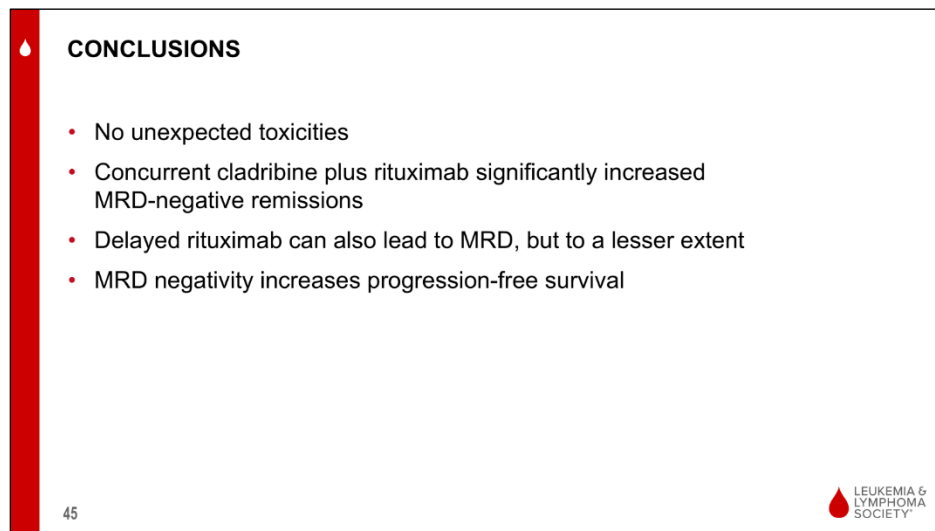


So, really great results. Six months post-treatment the patients that got the concurrent treatment were still in a complete remission. Ninety-seven percent (97%) of them were MRD negative compared to 88% who got cladribine alone and only 24% of them were MRD negative. So, it was statistically significant differences in MRD negativity. They followed these patients out to 96 months and 94% of the CDAR (receiving concurrent c-rituximab) patients were still MRD negative compared to only 12% of the cladribine delayed. They did note that giving the delayed Rituxan led to a lower rate and durability of MRD negativity. So, giving it later doesn't really make up for the issue of MRD negativity. It needs to be given upfront to see those same results.

One thing I would like to point out is that the CDAR concurrent regimen was associated with higher rates of low platelets and need for platelet transfusion, but there was actually faster blood count recovery overall.



And this is just showing that. In Kaplan-Meier curve form, looking at the MRD-free survival, you can see in blue the CDAR group is doing much better looking at both the blood and bone marrow. If you look over to the right, this is the blood count recovery, the top boxes are neutrophils, and the bottom box is platelets. And the CDAR patients seem to dip a little bit lower with their blood counts, but then rebound faster and with higher peripheral blood counts.



My takeaway from this is that there were no unexpected toxicities. Everybody worried about giving Rituxan with cladribine in newly-diagnosed patients because of the concern it might increase the risk of infection, but there did not seem to be a problem with that. And it definitely significantly increased MRD-negative remissions. And we know that MRD negativity increases progression-free survival. And so, when I'm seeing a patient who needs treatment, this is one of the things that we're discussing because even though it's harder upfront, it may lead to much longer progression-free survival.



USE OF MRD IN TREATMENT ASSESSMENT

- Minimal/measurable residual disease (MRD)
 - The lowest level of HCL cells that can be detected accurately and reproducibly using validated methods
 - Can be measured in bone marrow or peripheral blood; marrow most accurate
- Methods for measuring MRD:
 - Immunohistochemical analysis
 - Multiparameter flow cytometry
 - Allele-specific PCR for BRAF
 - Currently no standardization for testing in HCL¹
 - Future clinical practice guidelines will likely contain recommendations for MRD testing

46 ¹Ravandi F et al. *Blood Cancer J* 2022;12:165.



I just wanted to give a word about MRD in hairy cell and the treatment assessment. So, just as people need a bone marrow biopsy before treatment, you need another bone marrow biopsy after treatment. MRD is basically defined as the lowest level of hairy cells that can be detected accurately and reproducibly using validated methods. The marrow is most accurate for assessing this.

There are a lot of different ways to measure MRD and there's currently no standardization for testing. And so, one of our challenges is that across clinical trials there will be different methods for testing MRD. We would really like to standardize that, and that's one of the things that the Hairy Cell Leukemia Foundation researchers are looking at doing into the future.



TARGETED THERAPIES

47



BRAF INHIBITORS

The activated BRAF pathway provides oncogenic signaling to the leukemic hairy cell through the MEK-ERK cascade.

48 Grever MR et al. *Blood* 2016;127:2784–5.

This is showing the BRAF pathway. I borrowed this from Dr. Grever's paper in *Blood*. And so again, you have the receptor on the cell surface and then through a sequence of events there are critical points in the cell cycle pathway that you can target to try to kill the cell.

BRAF INHIBITORS GIVEN AS SINGLE AGENTS

- Vemurafenib and Dabrafenib
- Four phase 2 trials evaluating BRAFi as single agents
- Duration of therapy 3–5 months
- Overall response rates across studies: 90%
- Complete response rates: 30%–35%
- Duration of responses: median 1.5 years

49 Taccioli E et al. *Leukemia* 2021;35:3314–8; Taccioli E et al. *N Engl J Med* 2015;373:1733–47; Handa S et al. *Blood* 2022;140:2663–71; Blay JY et al. *ESMO Open* 2023;8:102038.

There have been a number of studies looking at BRAF inhibitors given just as single agents, just by themselves, mostly vemurafenib and dabrafenib. The duration of therapy ranges from three to five months across the studies and there is an overall response rate of 90%, with a complete response rate of 30% to 35%. The duration of response is also not as high as we would prefer. However, there are very specific situations where just vemurafenib by itself is very important. One of those being if somebody has a life-threatening infection and needs treatment for hairy cell leukemia. This can very quickly raise the blood counts to get somebody safely through an infection, and then, you can go on later and do something a little bit more intensive if needed.

 **VEMURAFENIB WITH RITUXIMAB**

- No established dose of vemurafenib in treating HCL
- Has been studied in combination with rituximab
- Phase 2 study of 30 patients with relapsed HCL
- Vemurafenib 960 mg twice daily plus rituximab IV × 8 doses over 18 weeks
- 26 patients (87%) achieved a complete response, 17 (65%) were MRD negative
- Median time to count recovery was 2 weeks for platelets and 4 weeks for neutropenia
- 78% of all patients were still in remission at 37 months after therapy
- Early results comparable to single-agent chemotherapy

50 Tiacci E et al. *N Engl J Med* 2021;384:1810–23.



So, vemurafenib with rituximab. Vemurafenib has been studied in combination with both rituximab and obinutuzumab. I'll get to that in just a second. There was a paper in 2021 from Drs. Tiacci and Falini looking at vemurafenib combined with rituximab. This was a Phase 2 trial, 30 patients, and the dose that was used was the melanoma dosing. And so, this is a relatively high dose, 960 mg twice daily plus rituximab IV for eight doses over 18 weeks.

The majority of patients achieved a complete response and 65% of those were MRD negative. Count recovery was relatively rapid, so two weeks for platelets, four weeks for neutrophils, and 78% of patients were still in remission at 37 months of therapy. So, this is certainly a treatment option, especially in the setting of relapse for people who are BRAF mutated.

 **VEMURAFENIB WITH RITUXIMAB**

ORIGINAL ARTICLE

Vemurafenib and Obinutuzumab as Frontline Therapy for Hairy Cell Leukemia

Jae H. Park, M.D.,^{1,2} Sean Devlin, Ph.D.,³ Benjamin H. Durham, M.D.,⁴ Eric S. Winer, M.D.,⁵ Scott Huntington, M.D.,⁶ Gottfried von Keudell, M.D.,^{6,7} Shreya Vemuri, M.P.H.,⁸ Madhulika Shukla, B.A.,⁸ Victoria Falco, R.N.,⁸ Bernadette Cuello, N.P.,¹ Steven Gore, M.D.,^{6,9} Richard Stone, M.D.,⁵ Omar Abdel-Wahab, M.D.,^{1,10} and Martin S. Tallman, M.D.^{1,11,12}

51 Park JH et al. *NEJM Evid* 2023;2(10):EVID02300074.



The more recent study is looking at vemurafenib with obinutuzumab, and the reason why everybody's pretty excited about this is it's being used as frontline therapy. So, these are

Transcript

people who never got chemotherapy who are getting a non-chemotherapy-based regimen, and I'll show you the results.

**STUDY**

- Phase 2 single-arm, multicenter study
- A total of 30 patients were enrolled
- All had indications for treatment per guidelines
- Treatment regimen:
 - Oral vemurafenib 960 mg twice daily × four 28-day cycles
 - Obinutuzumab beginning cycle 2
 - 1000 mg IV days 1, 8, and 15 of cycle 2
 - 1000 mg IV day 1 of cycles 3 and 4
 - Vemurafenib dose reductions allowed

52 Park JH et al. *NEJM Evid* 2023;2(10):EVIDoa2300074.



So, again, a Phase 2 single-arm study, 30 patients enrolled, they got vemurafenib 960 mg twice daily for basically four months. And then, during the second cycle, obinutuzumab was added in the standard treatment approach. Vemurafenib dose reductions were allowed because some people had rashes or joint pain.

**RESULTS**

- Responses assessed at end of cycle 4
- MRD assessed with multiparameter flow cytometry
- 27 patients achieved a CR (90%)
- 96% of CRs were MRD negative
- Median duration of remission >2 years
- 3 patients withdrew due to toxicities
- 26 patients required dose reductions of vemurafenib
- Most common toxicities: rash, joint pain, fatigue
- Only 7% developed febrile neutropenia

53 Park JH et al. *NEJM Evid* 2023;2(10):EVIDoa2300074.



The responses were great. Twenty-seven or 90% of the patients achieved a complete response. Ninety-six percent (96%) of those were MRD negative. And it's a relatively recent study. And so, the median duration of remission is more than two years, but the follow-up is still ongoing. Some patients had to withdraw from the study due to toxicities, or needed dose reductions. I would say the majority of patients ended up getting a dose reduction because of side effects with vemurafenib.

Lizette Figueroa-Rivera, MA

Thank you, Doctor. I know that this is very timely. Do they have less side effects than the older medications that have been used for hairy cell leukemia?

Leslie Andritsos, MD

So, it depends on the side effect. The main advantage is there is not as much risk of long-term bone marrow suppression and immunosuppression. So, there's two different types of infection risk. One is just from low blood counts and that can be from a direct side effect of the drug causing a low white count, but then also the rest of the immune system, especially the T cells, are very suppressed for up to a year or sometimes beyond after chemotherapy. And so, this avoids that situation.

Some people who get purine analogs do get a rash. It's a different type of rash than what we see with vemurafenib, but there's a lot of fatigue and joint pain also. And so, you kind of have to gauge what your biggest priority is when you start treatment. If there's a real need to avoid chemotherapy, this is an excellent strategy. If the goal is to be in the longest remission possible, I think the chemotherapy combinations are still, as far as we know, going to give the longest remission.

Lizette Figueroa-Rivera, MA

Thank you. And I know that we're getting to the Q&A portion.

Leslie Andritsos, MD

We are.



ASK A QUESTION
HIGHLIGHTS IN THERAPY:
HAIRY CELL LEUKEMIA

Ask a question by **phone:**
Press star (*) then the number 1 on your keypad.

Ask a question by **web:**
Click "Ask a question"
Type your question
Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

 **LEUKEMIA &
LYMPHOMA
SOCIETY®**

Lizette Figueroa-Rivera, MA

And I know that you have more about BTK inhibitors and other treatments. Is there something that you're very excited about? You had mentioned ASH, the American Association of Hematology [annual] meeting where a lot of results come out of. Is there something that you're very excited about with hairy cell leukemia treatments?

Leslie Andritsos, MD

At this most recent ASH, there was an update on the CDAR regimen, so like a longer follow-up, and again, showing that patients are maintaining excellent remissions that are MRD negative. We also have had the novel development of immunotherapy for hairy cell in the form of CAR T [chimeric antigen receptor T-cell therapy]. And that's one place where I really wanted to thank The Leukemia & Lymphoma Society, because you guys have sponsored the majority of that research. And so, we now have a CAR-T study that's open and enrolling. That's with Dr. Kreitman. The target is CD22, and there are two other centers who are looking at development of novel CAR T for hairy cell targets.

Lizette Figueroa-Rivera, MA

That's great to hear. Thank you. And thank you, Doctor, for being so clear with your presentation. We have a lot of questions; I just want to get to some of them right now. Alex is asking, "What is the best way to deal with bone pain?"

Leslie Andritsos, MD

Oh, that is a really good question. So, this is a common problem. We don't always know what's causing it. There have been a number of different things that have been studied for bone pain in other hem-malignancies, particularly myelofibrosis. One of the most successful treatments is actually some of those antidepressant-type therapies that also work on things like neuropathy. And sometimes that really deep bone pain is hard to fix with just pain medication like Advil® (ibuprofen) or Tylenol® (acetaminophen), but some of the drugs targeted towards nerve pain are effective for that. So, that would be something to try.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take the next question from our telephone audience, please.

John from Pennsylvania

Yes. I've been on Rituxan, and so far I've had it for about four years, I've had pretty good results. How much longer can I expect to be able to maintain the Rituxan regimen?

Leslie Andritsos, MD

A lot of that is going to depend on the depth of the response and whether you've had MRD testing that's showing positive or negative. But in Dr. Broccoli's study, he found that people were out as far as five years still in remission.

Another thing I would also like to emphasize that I didn't get a chance to talk about earlier, but even if the disease comes back, does not mean that you necessarily have to go back on treatment. It's whether the disease is causing a problem that necessitates it. So, if the blood counts are getting too low or the spleen is growing or something else is going on.

Transcript

Lizette Figueroa-Rivera, MA

Thank you so much. And our next question comes from Natalia. Natalia asks, "What causes the loss of BRAF mutation and what significance does the loss of the BRAF mutation have in treating refractory hairy cell leukemia?"

Leslie Andritsos, MD

If the BRAF mutation is not present at the time of relapse, then I would look and make sure that it's still the same type of lymphoma. So, we know not as commonly in hairy cell, but in other types of lymphoma, sometimes at the time of relapse, the lymphoma is a new subtype of lymphoma. And so, if the original testing showed that BRAF was positive, it should still be positive at relapse. And if it's not, that would tell me that perhaps the test is not working and a more sensitive or different type of test needs to be checked. And it might be a good time to have another bone marrow biopsy to confirm that. Or, as we talked about, sometimes there's alternative BRAF mutations that are not picked up on the routine testing and would have to be tested specifically. And that would probably be a send out to a specialty lab that does that type of sequencing.

Lizette Figueroa-Rivera, MA

Thank you. And speaking about testing, Tim is asking, "In 2001, I was diagnosed through a blood test, not a bone marrow test. Has the protocol changed since 2001 or perhaps the results from my blood test were clear for me?"

Leslie Andritsos, MD

Yes. So, that's a lucky situation. That means that probably you do have circulating hairy cells, so only about 10% of people do, and so, it makes it very easy to test them. There are definitely new types of tests available since you were originally diagnosed, but I don't think you would need to have any of those performed unless it was time to start treatment. And then, you would definitely want to have the bone marrow biopsy, have the modern testing and make sure everything is done before treatment.

Lizette Figueroa-Rivera, MA

Well, thank you, Tim, for that question. And thank you all for your questions. And thank you so much, Dr. Andritsos, for your continued dedication to patients and for being able to present this webcast for us today.

LLS EDUCATION & SUPPORT RESOURCES



HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: www.LLS.org/InformationSpecialist
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: www.LLS.org/ContactUs

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical trial process.
www.LLS.org/Navigation



Personalized Nutrition Consultations
Talk to a registered dietitian about nutrition and cancer.

NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLSNutrition.org

66

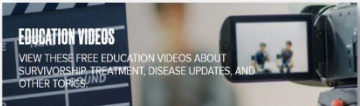
Now, if we weren't able to answer your question today, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. Information Specialists are available to speak with you from 9:00 AM to 9:00 PM Eastern Time, or you can reach out to us by emailing us at LLS.org/ContactUs. Also, patients as well as caregivers can schedule a free personalized nutrition consultation with our dietitians at LLS.org/Consult.

LLS EDUCATION & SUPPORT RESOURCES



ONLINE CHATS

Online Chats
Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**.



EDUCATION VIDEOS
VIEW THESE FREE EDUCATION VIDEOS ABOUT SURVIVORSHIP, TREATMENT, DISEASE UPDATES, AND OTHER TOPICS.

Education Videos
View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**.



Exploring Hairy Cell Leukemia

Patient Podcast
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**.

67

We did get a question in regards to the registry, and if you would like to register for the Hairy Cell Leukemia Registry, you can contact the Hairy Cell Leukemia Foundation at HairyCellLeukemia.org.

LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers:
www.LLS.org/Finances



To order free materials: **www.LLS.org/Booklets**

68

The Leukemia & Lymphoma Society offers financial assistance to help individuals with blood cancer. Please visit our LLS.org/Finances webpage for more information.

THANK YOU

This program is supported by
Genentech
A Member of the Roche Group

Please complete our program evaluation



**LEUKEMIA &
LYMPHOMA
SOCIETY**

We have one goal: A world without blood cancers

Please note that continuing education credit is not being offered for this program. Again, we'd like to acknowledge and thank Genentech, a member of the Roche Group, for their support of today's program, as well as Dr. Andritsos. And to all the patients, caregivers and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you so much for sharing your time with us. Have a happy new year and we wish you well. Thank you.