Lizette Figueroa-Rivera:
Greetings and welcome to The Leukemia & Lymphoma Society’s Living with Hairy Cell Leukemia (HCL) education program. On behalf of The Leukemia & Lymphoma Society (LLS), I’d like to welcome you.

Introduction to Hairy Cell Leukemia

Michael Grever, MD
Professor Emeritus, Internal Medicine/Hematology
The Ohio State University
Columbus, OH
We’re fortunate to have as our presenter Dr. Michael Grever, one of the nation’s leading experts in hairy cell leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. We would like to thank AstraZeneca for their support of this program.

Dr. Michael Grever is Professor Emeritus, Internal Medicine, Hematology at The Ohio State University in Columbus, Ohio. We thank Dr. Grever for volunteering his time and sharing his knowledge with us.

Dr. Grever, I am now privileged to turn the program over to you.

**Michael R Grever, MD:**
Well, thank you and this is a wonderful opportunity to discuss all the progress that has been made in the management of patients with this disease.

**Financial Disclosures**

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

**Financial Disclosures**

On this slide, I'm presenting my financial disclosures in the interest of transparency.
First Descriptions of Hairy Cell Leukemia


First Descriptions of Hairy Cell Leukemia:

Hairy cell leukemia is a rare form of adult chronic leukemia. Over the past 60 years, we have witnessed tremendous progress in the management of patients with this illness. While the average survival in 1984 was approximately four to five years, as a result of our current medications, most patients achieve a remission. Once remission has been achieved the quality of life is much as it was before they had leukemia. In fact many of the patients with a remission can live almost as long as they would have if they did not have leukemia at all.

The first descriptions of this disease were initially reported in 1956 by Dr. Gosselin and colleagues. Dr. Bertha Bouroncle and colleagues at Ohio State University described the multiple features of this disease and established the fact that this is a separate clinical entity in 1958.
Dr. Bertha Bouroncle

This is a picture of Dr. Bertha Bouroncle, who was a Professor of Internal Medicine and Hematology at The Ohio State University when she described this illness.

Typical hairy cells among red blood cells

(Dr. Gerard Lozanski, OSU)
On this slide, we can see the characteristic leukemic cells, and I would like to just point out that the edges of these cells have irregular projections that have been the reason that this disease was called hairy cell leukemia. These two white blood cells are presented from the peripheral blood smear and you can see the red blood cells that are surrounding these two leukemic cells.

Clinical Features of Hairy Cell Leukemia

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

Clinical Features of Hairy Cell Leukemia

The clinical features of this disease are listed on this slide. There’s an unexplained remarkable male predominance, with approximately four men to every woman who has this disease. The median age of patients who are diagnosed with this disease is 55 years, but patients are actually diagnosed with the entire spectrum going from early 20s all the way up to the 80s. But, the median age is 55 years.

The symptoms are often related to fatigue and frequently related to infection. Infection is one of the leading causes of death in patients with hairy cell leukemia and, therefore, it’s important that we realize that some patients, approximately 15%, will present with infection at the time of the diagnosis. On physical examination, we often find an enlarged spleen. In the original description of this disease, the spleen was massively enlarged in approximately 90% of the patients. In the current era, there is earlier diagnosis and so many patients now present with a spleen that’s only mildly enlarged or not enlarged at all.

Patients often present with low blood counts, and this is referred to as cytopenia. The low blood counts will involve the red blood cells, and that’s anemia. The white blood cells, which fight infection, are often low; as well are the platelets, which are important to prevent bleeding.

The diagnosis is made by looking at the blood smears we’ve shown you in a few slides ago and then also to do a bone marrow biopsy to document the extent of involvement of the hairy cell leukemia in the bone marrow. It’s very important that the diagnosis is confirmed by looking for markers on the surface of those cells, and this is done by the use of the flow cytometer. The blood is characteristically showing the four markers identified on this slide: CD11c, CD25, CD103, and CD123. In 2011, another marker of this disease was identified.
called the BRAF mutation, and we’ll talk about that a little bit later. However, essentially all cases of classic hairy cell leukemia demonstrate this characteristic BRAFV600E mutation. In contrast, this is not expressed on the leukemic cells of patients with the variant form of hairy cell leukemia.

Manifestations of Hairy Cell Leukemia

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

The manifestation of hairy cell leukemia at the time the patients present are listed on this slide. Fatigue and symptoms related to anemia are often gradual in onset, and so patients can present with significant anemia that has come on gradually. Fatigue, however, is one of the most common symptoms. Because the platelets are often low at the time of diagnosis, the patient may experience easy bruising or bleeding. As I stated before, infection is one of the most serious consequences of the low infection-fighting cell called a granulocyte, and these cells are often referred to as neutrophils. And so, infection is one of the presenting symptoms in many patients whenever they come and present to the doctor.

One other infection that can present a problem for patients is the reactivation of herpes zoster or shingles. This viral illness is often experienced as chickenpox in patients whenever they were children. When patients with hairy cell leukemia present to their doctor, their immune system is compromised and they, therefore, sometimes will have a reactivation of this viral infection in the form of painful blisters called shingles.

There are other symptoms and signs of hairy cell leukemia that are less frequent at the time of diagnosis. Some of these are listed on this slide as vasculitis, which can present as a rash on various parts of the body. There’s also a rheumatoid-like arthritis and patients can sometimes present with painful joints, and this inflammation in the joints can be migratory or present in several different locations.

Patients can also present with low platelets that are due to antibodies directed against the platelets, and this is called immune thrombocytopenia. Finally, we do see patients who have bone pain and there can be some destructive lesions within the skeleton, and this has to be carefully evaluated to rule out other diseases that can affect the bone.
Clinical Judgement in Treatment Decisions

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

Clinical Judgement in Treatment Decisions

When the decision is made to treat, an extensive clinical judgment is involved. First of all, it’s extremely important to confirm the diagnosis. Classic hairy cell leukemia is identified by those markers on the leukemic cells that we discussed earlier. The other marker, which is found in essentially all patients with classic hairy cell leukemia, is the expression of this BRAFV600E mutation. The patients who have the variant of hairy cell leukemia have different markers and are negative for the BRAF mutation.

The reason it’s very important to make this distinction is that the response and the duration of remission for the patients with the more common classic hairy cell leukemia is much better than for patients who have the variant of hairy cell leukemia. Patients with the variant of hairy cell leukemia can still be effectively treated, but they run into problems with relapse and failure to achieve the sustained remissions that we see in patients with classic hairy cell leukemia.

In general, it’s felt that the frequency of hairy cell leukemia breaks down as follows: about 10% of the patients will have the variant of hairy cell leukemia and about 90% of the patients will have classic hairy cell leukemia. The distinction of these two entities is so important that the World Health Organization (WHO) actually declared that the hairy cell leukemia variant is a completely separate entity and is not the same as classic hairy cell leukemia. So, these are two separate entities and it’s very important to define which of the entities is involved with your patient’s case.

About 10% of patients with hairy cell leukemia do not require immediate treatment; however, though, they do require close follow-up. This is sometimes concerning to the patients because they were told that they have a diagnosis of leukemia and we then tell them, about 10% of the patients, we’re going to follow you very closely, but we don’t think we need to initiate therapy right now. One of the reasons that this is hard for patients to understand is that as they get the diagnosis of leukemia they want to make sure that they get things treated and get things under control.
What we tell them is that the earlier treatment is not going to cure them of the disease; however, we do have effective therapy that controls the disease. The chemotherapy and the treatments that we use further can suppress the immune system and the blood counts. And therefore, if patients present with hairy cell leukemia and have a reasonable blood count, we follow them closely because we don’t want to add further immunosuppressive therapy until it is necessary. When we follow them, though, we follow their blood counts, because if we see that they’re trending down, we want to initiate therapy before they get to be too low.

Patients with active infection need to be approached very carefully and the infection should be treated first, if possible, before initiating any therapy for the hairy cell leukemia. The treatments that are used for hairy cell leukemia, either cladribine or pentostatin, can further lower the blood counts. And so, if somebody has an active infection, you want to get the infection under control if possible before compounding the situation by lowering their infection-fighting cells.

When cladribine is used to treat this disease, it has a very high response rate and success rate. Patients will, however, see a decline in their infection-fighting cells that can last for weeks and sometimes beyond a month. Therefore, when the initial studies with cladribine were done, patients who had an active infection were not enrolled in those studies.

Therefore, we believe that cladribine is a highly-effective treatment for most patients with hairy cell leukemia. However, if patients have an active infection, we don’t recommend initiating cladribine until the infection is either cleared or controlled, and then we would think of other treatment strategies to try and get the disease under control if the infection can’t be actively eradicated. The other planning could involve the use of other agents that are effective in hairy cell leukemia that don’t lower the blood count quite as much as cladribine.

It’s important before starting therapy to get a careful assessment of the kidney function and this can be done through checking blood work. Also, it’s important to know whether or not the patient ever had a history of hepatitis. In patients who’ve had a prior history of hepatitis, their clinical course needs to be followed very carefully because the treatment of hairy cell leukemia is immunosuppressive and sometimes that can reactivate the hepatitis and would require cooperation with a hepatologist to manage the patient carefully.

We believe that bone marrow biopsies at the beginning of treatment and after completion of therapy have value. The reason that we do the bone marrow at the initial point of treatment is to confirm the diagnosis and to make sure that we understand everything that could possibly contribute to the lowered blood counts. After completing therapy, we want to know how much residual disease is left.

A complete remission is defined as seeing no hairy cell leukemia in the bone marrow biopsy and restoration of normal blood counts. There’s also a term called minimal residual disease (MRD), where small amounts of hairy cell leukemia can be identified in a bone marrow with the use of special stains called immunohistochemical stains. Definition of the extent of minimal residual disease is important because the more disease that’s present in the bone marrow after therapy may predict the duration of remission. The optimal management of minimal residual disease is under discussion and requires additional investigation.
Natural History of HCL Prior to 1984

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

The natural history of this disease before 1984 was that it was clearly incurable and it did not respond to the chemotherapies that were available at that time. And the reason for this was that the chemotherapy agents were called DNA-damaging agents or alkylating agents. The bone marrow involvement with hairy cell leukemia at the time of diagnosis is usually very extensive and so the use of alkylating agents, which can damage the DNA of the normal cells, would really make the blood counts go very low and the leukemia did not respond very well. And so, patients were often harmed by using intensive chemotherapy.

At that time, the approach to patients who had low blood counts was to remove the spleen. Removal of the spleen would result in improvement of the blood counts in many of the patients and also relieve some of the pressure and abdominal discomfort that the patients experienced from an enlarged spleen. This was the most commonly used treatment up until 1984. In the timeframe of the 1980s, the median survival of patients was between four and five years, and as we’ve stated before, most of the deaths were due to either infection or very low blood counts and bleeding. There was also an awareness that there was an increase in second malignancies in about 3% to 10% of patients with hairy cell leukemia, probably resulting from the immune suppression that goes along with the disease itself.
Treatments

Historical Approach to HCL Treatment

- Early attempts with chemotherapy unsuccessful; splenectomy became the frontline approach.

- While this temporarily improved blood counts, ultimately patients needed more treatment as disease progressed in the bone marrow.

- In 1984, the use of interferon alpha was successfully introduced, improving blood counts.

- Overall response to interferon challenged need for splenectomy.

Historical Approach to Hairy Cell Leukemia

The early attempts with chemotherapy, as I said, were unsuccessful and removing the spleen became the front-line approach. While this approach improved the blood counts temporarily because this disease is extensively involving the bone marrow, the disease would eventually progress and require some additional
therapy which was very challenging before 1984. In 1984, the use of interferon alpha was identified as showing improvement in the blood counts of these patients, and the overall response to interferon actually challenged the need for removing the spleen. And this was important and good for the patients because removing the spleen also increased the risk of infection.

The therapies that were introduced then that actually changed the natural history of this rare disease are listed on this slide. In 1984, Dr. Quesada at M.D. Anderson reported in the New England Journal of Medicine that interferon alpha in seven patients resulted in three complete remissions and four partial remissions. This was really exciting and subsequent studies showed that many of the patients really only achieved a partial response, but nevertheless, the ability for interferon to improve the blood counts was a real step forward in the management of these patients. Part of the problem associated with interferon was that it required continuous administration to maintain the response and it also was associated with symptoms of the flu and patients frequently didn’t feel very energetic while they were taking the interferon.

In 1984, there was also an early report of deoxycoformycin producing a complete response in patients with hairy cell leukemia. In 1986, Dr. Kraut, Dr. Bouroncle, and myself reported that 9 of 10 patients with hairy cell leukemia responded to low-dose deoxycoformycin (pentostatin). This was a major breakthrough because interferon was associated with more partial responses. In contrast, patients who were getting treated with pentostatin achieved a complete response.

In 1990, Dr. Piro had a landmark paper in the New England Journal of Medicine showing that 11 of 12 patients had complete responses with cladribine. As I said before, patients who were placed on the cladribine studies were not having active infection. Those patients were not eligible. But if patients were not infected, it turned out to be a very exciting new therapy as well. There were extensive additional studies with both pentostatin and cladribine, either alone or in comparison to interferon, and then subsequently in combination with an antibody called rituximab.
Pentostatin Studies in HCL

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DOSE (i.v.)</th>
<th>Complete Response %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIERS (ECOG)</td>
<td>5 mg/m² for 2 days every 2 weeks</td>
<td>59</td>
</tr>
<tr>
<td>JOHNSTON (NCIC)</td>
<td>4 mg/m² per week for 3 weeks, repeat every 8 weeks</td>
<td>89</td>
</tr>
<tr>
<td>HO (EORTC)*</td>
<td>4 mg/m² per week for 3 weeks, then every 2 weeks X 3</td>
<td>33</td>
</tr>
<tr>
<td>GREM (NCI)</td>
<td>4 mg/m² every 2 weeks (variable schedule of drug administration)</td>
<td>56</td>
</tr>
<tr>
<td>KRAUT</td>
<td>4 mg/m² every 2 weeks</td>
<td>87</td>
</tr>
</tbody>
</table>

*RESTRICT TO INF FAILURES

Pentostatin Studies in HCL

On this slide there's a number of the early studies that were presented with pentostatin, and between 1984 and 1990 many of the patients entered these trials with pentostatin. As you can see that the complete response rate here varied from 33% up to 87% or 89%. And one of the unusual things here was that the lower the dose that was used, the higher the complete remission rate. And this illustrates that this disease is very sensitive to pentostatin, and using lower doses of pentostatin and using it on an intermittent schedule decreased the lowering of the normal infection-fighting cells, making it easier to achieve a good remission.

In several of the patients in these various studies, there were prior attempts with interferon, and so we found that in patients who were treated upfront with pentostatin there was a very high complete remission rate.
Cladribine in Hairy Cell Leukemia

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

Cladribine, as I indicated, in 1990 was introduced as a very effective agent through the work of Dr. Piro and his colleagues at Scripps Clinic, where they gave seven days of continuous intravenous infusion of cladribine, resulting in a very high complete remission rate. Dr. Tallman also approached the patients with a seven-day continuous infusion. 80% of the patients achieved a complete remission with one cycle and there were several additional patients who initially had only achieved a partial remission that were converted to a complete remission with some additional therapy.

Dr. Juliusson, in Europe in the 1990s, introduced a concept of subcutaneous administration of cladribine, and this resulted in 81% of the patients achieving complete remission. It was also easier to administer because it was a subcutaneous injection and avoided the necessity for an indwelling intravenous catheter for a week-long period. So, those patients were effectively treated with a subcutaneous administration of the drug every day for seven days.

Exploration of the administration of different routes and schedules of administration of cladribine were pursued in Europe. In addition hematologists in the United States have delivered cladribine intravenously over five days. These administrations which usually are two hours each day for five days, have resulted in a high complete remission rate.
In the 1990s, I had the opportunity to conduct a large study comparing interferon to pentostatin. And the interferon was given three days a week as a subcutaneous injection and the pentostatin was given intravenously every two weeks, and we were able to titrate the dose of pentostatin to try and avoid suppression of the normal white blood cell count. And this randomized trial was done to tell whether or not the pentostatin was a major improvement over interferon.

If the patients achieved a good response, but not a complete remission, they would then get an additional six months. If there was no response, the patients on interferon would cross over to pentostatin. Likewise, patients who were receiving the pentostatin, the goal was to achieve a complete remission. If that was not achieved, then they would get six months of additional therapy. If there was no response at six months, the patients would cross over to the alpha interferon.
HCL Intergroup Study (Grever et al. JCO, 1995)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Initial Pentostatin</th>
<th>Crossover to Pentostatin</th>
<th>Initial IFN-alpha</th>
</tr>
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<tbody>
<tr>
<td>Evaluable Patients</td>
<td>154</td>
<td>86</td>
<td>159</td>
</tr>
<tr>
<td>Complete Remission (%)</td>
<td>76</td>
<td>66</td>
<td>11</td>
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This slide shows that there were equal numbers of patients who were initially entered onto this trial. It was a large study which had over 350 patients administering therapy for their newly-diagnosed hairy cell leukemia. As you can see the majority of patient's crossed over from interferon to pentostatin if they didn't have a good response.

The complete remission rate in this very large study was at least 76% for pentostatin. In contrast, the complete remission rate for interferon was 11%. What this shows is if you went from interferon to pentostatin, there still was a high complete remission rate. We had very strict criteria in this study and the definition of a complete remission required doing two bone marrow biopsies to confirm that there was no evidence of hairy cell leukemia. So, this is one of the most stringent criteria for complete remission in any of the published studies. There were some patients who didn’t get a second bone marrow biopsy, and so we believe that the complete remission rate may have been higher than 76%.
Long-Term Results: Pentostatin in HCL
(Flinn et al., Blood, 2000)

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

The long-term results of pentostatin were published in 2000 by Dr. Flinn and myself. We had long-term data on 241 patients. The median duration of follow-up in these patients was over nine years. We had a projected 10-year overall survival being 81% and the relapse-free survival was estimated to be 67%. When we looked at these patients, we felt that the patients with hairy cell leukemia who achieved a complete remission were probably projected to live as long as they would have if they hadn’t developed leukemia.

This relapse-free survival being 67% is consistent with many other studies that have been published, showing that the percentage of patients who ultimately may relapse is around 40%. So, we don’t believe that we can claim that we’ve cured this disease, but we’ve put it into a long-term remission and patients who do relapse can be effectively retreated.
This was another very extensive study by our European colleagues. Monica Else, in 2009, reported on 233 patients with hairy cell leukemia who were treated at the Royal Marsden Hospital and their collaborating institutions. There were 188 patients treated with pentostatin and 45 of the patients received cladribine, and they were followed for a period of about 16 years. So, very good, long-term follow-up study.

They came to the conclusion that these agents were essentially interchangeable, being equal in effectiveness. The patients achieving a complete remission had longer periods of relapse-free survival, and that’s one of the reason why we tried to achieve a complete remission in patients. It’s also one of the reasons it’s important to look at the bone marrow to determine whether or not you’ve completely eradicated the hairy cell leukemia or not.

The complete remission rates in this group of patients was 80% of the patients went into a complete remission on their first treatment. In those patients who relapsed, 69% of the patients were able to achieve a second remission, and if they relapsed again, 50% of the patients were able to achieve a complete remission again. So, the remission durations got shorter with each subsequent relapse and the retreatment period was capable of producing sustained remissions, as you can see on this slide, being 16 years on the average after the first remission, 11 years after the second remission, and a little over six years on the third remission.

So, the majority of the patients have a near normal life expectancy with this disease. And while they may relapse there is a high percentage of the patients who can be salvaged and still go on to have a highly-functional life.
Considerations in Clinical Decisions

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

Considerations in Clinical Decisions

So, the considerations in clinical decision-making. It’s important to control active infection before starting the leukemia-directed therapy, if possible. It’s important to improve the infection-fighting cells, or the granulocyte count, in patients with an active infection. That’s one of the reasons that we do not favor using drugs in actively-infected patients that can decrease the granulocyte count, because it’s so important to get the infection under control.

Cladribine, as I said earlier, was not initially utilized in the treatment of hairy cell leukemia in the early studies in those patients with infection, but it is used most often in noninfected patients and is probably the drug that’s most frequently used by practicing hematologists in patients who don’t have an active infection. Some of the features that are associated with a higher complete remission rate are listed here. If you have a lower hemoglobin or a lower platelet count, if you’re older or have a massively enlarged spleen, this has been, in general, more challenging to get a complete remission, but not impossible.
When to Initiate Therapy

When do you start therapy? We talked about 10% of the patients just being closely followed. After you have confirmed the correct diagnosis and taken a look at the extent of bone marrow involvement, you need to follow the blood counts and you need to follow this closely on patients. If there is a progressive decrease in the blood counts with the neutrophils or granulocytes going less than 1,000, or the platelet counts going less than 100,000 or if the hemoglobin is less than 11, it’s time to initiate therapy. Now, some judgment has to be exercised here, and it is important to realize it’s a progressive decline in your blood count that should trigger initiation of therapy.

The important aspect of close follow-up is not to let this decline to extremely low levels, because that increases the risks of infection. So, patients, if they’re not treated and they’re being followed closely, should not be lost to follow-up because if they come back with very low counts, it’s going to make it more dangerous to treat them.

The other indication for treating patients would be related to symptoms of an enlarged spleen. Patients who have an enlarged spleen frequently can have what’s called early satiety, or they have a decrease in their ability to complete their meal because of the pressure exerted from the spleen on the stomach. The other thing that an enlarged spleen can do, it can become painful, and that would be an indication for starting treatment, particularly if there was a lot of pressure in the abdomen being exerted by an enlargement of the spleen.

The other symptoms that we talked about, anemia or infection or bleeding, have already been addressed in the last bullet point.

In this past year of 2017, we had a number of investigators from across the globe agree on the guidelines for the diagnosis and the management of hairy cell leukemia. We published this in Blood and this gives advice
to practicing hematologists on when to initiate therapy and how to select the best way to approach making the diagnosis and ensuring the best management for the patients.

Long-Term Consequences of Therapy for HCL

- Prolonged immunosuppression with reduced CD4 and CD8 T-cells
- Most common long-term infection is shingles
- Careful assessment of risk for secondary malignancies reveals either a slight increase in lymphoid malignancies or no increase related to treatment.
- Bone marrow toxicity can result from excessive therapy
The long-term consequences of therapy are related not only to the disease, but also its treatment. The drug of cladribine, as well as pentostatin, are both immunosuppressive. They can reduce the lymphocytes that are called CD4 cells and CD8 T cells. This can increase the risk of infection.

One of the most common infections that’s potentially at risk for these patients is shingles. Shingles can be very dangerous in an immune compromised patient and so we often put patients who are receiving these purine nucleoside analogues, cladribine or pentostatin, we often put patients on prophylactic doses of an antiviral agent, either acyclovir or Valtrex, in an attempt to prevent reactivation of shingles. We often follow the CD4 counts until they have recovered and use that information when we decide when to stop the prophylactic medication.

The CD4 and the CD8 cells take a very long period of time to recover. The white blood cell count may have recovered, the hemoglobin may have recovered, and the platelet count may have recovered as the patients are in remission, but it can take over a year or more for the immunosuppressive effects to go away. So, patients who are being followed after treatment, we usually recommend a yearly flu shot. However, we do not recommend getting any vaccination with a live virus, because if your immune system is suppressed, you might be at more risk for getting the infection until your blood counts have completely normalized in the compartment called the lymphocyte compartment, which contains the T cells.

So, careful assessment of the risk for secondary malignancies is also important in patients who are on drugs that can cause suppression of the immune system. We realized from the one of the earlier slides that there’s an increased risk for second malignancies in patients with hairy cell leukemia because of their intrinsic suppression of their immune system from the disease, but the chemotherapy that gets them into a complete remission can contribute to this immunosuppression. And so, patients need to be followed by a dermatologist. Any suspicious lesions on the skin need to be evaluated effectively and completely. And all of the methods for cancer surveillance should be followed that are normally followed in a healthy patient, but they have to be carefully monitored for other second malignancies.

Bone marrow toxicity long-term can also result from the agents that are used to put people into a complete remission, and so that’s one of the reasons why we’re very careful about selecting agents for second induction or third induction, because there can be a cumulative bone marrow toxicity that results from the use of these drugs, cladribine and pentostatin.
Remaining Questions

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

There are a lot of remaining questions. Even though we’ve made tremendous progress over the last 60 years, there are still some remaining questions because, the disease being so rare, it’s hard to accumulate enough patients to answer all these questions. Some of the questions are listed on this slide.

When should rituximab be added to the treatment? It does add further immunosuppression and so we need to define what would be the best therapy. Several of the studies, like Dr. Ravandi from M.D. Anderson, has suggested that the addition of rituximab after cladribine will increase the percentage of patients that are in a complete remission with negative residual disease in the bone marrow. We have to assess whether or not the additional immunosuppression from adding two agents is likely to be a worthwhile investment considering everything we add to the cladribine or the pentostatin can increase the risk of immunosuppression.

On the other hand, when patients relapse, one strategy has been to add rituximab to either pentostatin or cladribine to increase the chances of getting more durable remission. So, there’s a lot of questions about when should rituximab be optimally added. Dr. Kreitman at the NIH is trying to determine whether or not these antibodies should be given simultaneously with the cladribine or the pentostatin or whether they should be done in sequence. What’s the optimal duration? How many doses of the rituximab are really needed? Is it four or eight?

Some of these questions are being addressed. On the other hand, there’s many physicians and practicing hematologists who have selected a current regimen and just gone with the best evidence that’s available.

How important is minimal residual disease? It depends on the extent of the minimal residual disease that is observed after therapy. Is the eradication of that residual disease worth the additional immunosuppression?
When should the patient be referred for an investigational drug? What order of investigational agents should be pursued? What new combinations of agents are effective and well-tolerated? What therapy is best for the variant of hairy cell leukemia? This is a very challenging question.

Many other clinical management questions exist. For example, what’s the optimal schedule and dose of infection prophylaxis that should be utilized? We have been asked on a number of occasions what impact hairy cell leukemia will have on pregnancy. We have less official data here because, as we’ve indicated, this is a disease that’s much more frequently found in men. However, patients who have been diagnosed with hairy cell leukemia have successfully been able to have children after they’re in remission. There are a lot of unanswered questions about that, but we do know we’ve seen examples of that.

We’ve also been asked how to manage patients who are diagnosed with hairy cell leukemia in the middle of a pregnancy. And this requires extensive advice from physicians who have had experience using these agents. This can become complicated, but it can be successfully managed as long as the experts are working with the primary hematologist.

One of the things that we’re engaging in is a long-term quality-of-life study. We’re very gratified and excited that we’ve extended the life of patients with hairy cell leukemia to be a near-normal achievement, but it’s also important to think about what are the long-term effects of treatment, what are the long-term effects of living with this disease even if it’s in remission. So, we’re in the process of doing a long-term quality-of-life study, which we believe is very important.

So, living with hairy cell leukemia does present some challenges. We’ve indicated that approximately 10% of patients may not require immediate treatment, but need close follow-up. Most patients, however, will require treatment at the time of diagnosis.
About 40% of patients eventually will relapse. We don’t have any way right now predicting when that will occur. 40% of patients not only will relapse, but may then require retreatment. We try to use the same criteria for initiating the retreatment as we did for the initial indications for starting therapy.

Living with a rare and chronic disease can produce anxiety and depression, and so we try and encourage people to make use of the healthy years that we are able to achieve with the successful treatment of the leukemia and provide careful follow-up every two to three months for the first couple of years. And then we extend that period of time out after their remission lasts longer than the second year.

There are ongoing challenges with medical insurance, life insurance, employment decisions related to the diagnosis of a chronic leukemia. We have also seen patients who have difficulty identifying a medical team that has the sufficient experience in treating this rare disease, and this can add to the anxiety of patients who are wanting to make sure that they are getting the best treatment.

Successes and Challenges

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

Successes and Challenges

Both pentostatin and cladribine have changed the natural history of hairy cell leukemia. We’re far beyond the four to five years projected survival from 1984. We now can tell patients that they may live nearly as long as they would have without this disease. They may experience multiple relapses, and that may require retreatment.

We have also seen that in some patients the disease becomes resistant to the treatment and therefore, continued research to find novel agents and combinations are needed. We need to define the optimal way to manage infection because it still remains one of the most serious complications of the disease. And managing patients with an active infection requires very close attention and should involve, not only the hematologist, but also infectious disease experts to make sure that the best care is delivered to the patients.
Experimental Approaches to Relapsed HCL

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

(Tiacci E et al., Targeting mutant BRAF in relapsed or refractory hairy cell leukemia, MEJ 373(18):1733-47, 2015)

Experimental Approaches to Relapsed HCL

In some of the patients who are no longer responding to standard therapy, there have been some remarkable advances made. As I indicated earlier, the identification of the BRAF mutation in approximately all patients with classic hairy cell leukemia is associated with the expression of a marker on the cell called the BRAF V600E mutation. And this would indicate that the agent called vemurafenib, which is an inhibitor of the BRAF mutation, would have a potential benefit for the patient. Vemurafenib can induce complete remissions in approximately 40% of patients. Overall, close to 100% of the patients have some improvement with a partial remission. The remissions however are limited in terms of the duration, but the value in using vemurafenib is that you can get a rapid improvement in the blood counts and it does not tend to lower the good infection fighting cells. This is an “off-label” or investigational use of this agent.

There have been several case reports where vemurafenib has been used for patients who have a serious infection and need to get the hairy cell leukemia under control to improve the infection fighting cells. And so, their treatment may have been initiated with vemurafenib to get the improvement necessary to control the infection. Only then, after the infection is under good control, to go and get consolidation with the standard chemotherapy that’s used.

There are also ongoing studies by Dr. Tiacci of Italy right now combining vemurafenib plus rituximab to see how the combination of agents could be used in patients with relapsed disease. Dr. Kreitman, at the NIH, has also done extensive work studying immunotoxin conjugates that are directed against CD22 on the hairy cells. And this has been capable of getting responses in many patients with relapse disease. There’s been an ongoing study, looking at the use of ibrutinib in patients with hairy cell leukemia that has become unresponsive to standard therapy. This agent has been able to control the disease in a number of patients. And, while the complete remission rate is not very high, the patients that do have hematologic improvement is very encouraging.
There are a number of other targeted agents that are currently undergoing investigation. For example, the inhibitors of a target called MEK. And there’s combination of agents that are being studied. Pentostatin or cladribine with a monoclonal antibody and the monoclonal antibody armamentarium includes even more than just rituximab. So, there’s a lot of work that still needs to be done.

Novel agents with monoclonal antibodies, we indicated the studies that have been started in Italy using vemurafenib plus rituximab are very encouraging. Combinations of novel agents that are effective in the treatment of resistant disease and also for the treatment of the variant of hairy cell leukemia are extremely important research projects that are ongoing.

The Hairy Cell Leukemia Foundation is another group of investigators and patients with this disease who have joined forces. They provide information to patients. They also have peer reviewed research funding, and the website that they have developed is listed on this slide.
This just shows that the Hairy Cell Leukemia Foundation does support an annual patient seminar along with a scientific meeting, and, like many organizations, including The Leukemia & Lymphoma Society, are working very hard to continue to improve the outcome of patients with this rare form of adult leukemia.

So, thank you very much for your attention.
Lizette Figueroa-Rivera:
Thank you so much Dr. Grever for you very clear and informative presentation. We received some pre-submitted questions from patients and caregivers that have contacted us through our online community or spoken to one of our information specialists.

Dr. Michael Grever:
I would be delighted to take some questions.

Lizette Figueroa-Rivera:
First question, Dr. Grever. How did I get this disease? Does my gender and age affect the risk of hairy cell leukemia?

Dr. Michael Grever:
That’s a very important question. We hear it frequently. We don’t know what causes hairy cell leukemia. There have been large studies that show that patients with hairy cell leukemia have a higher exposure, in general, to organic chemicals like in farming or insecticides. And so, prior exposure to chemical agents have been thought to be associated with hairy cell leukemia.

The fact that there’s more men that get the disease than women has defied an explanation. We don’t understand why that happens. But, it doesn’t necessarily affect the outcome, at least as far as we know. There are some studies that are planned to actually look at hairy cell leukemia in women to see what kind of new information we might get. We’ve put together a patient registry so that we can answer some of these important questions.

But, we don’t know why people get it. We don’t know why men are more frequently involved with the disease than women. The only thing that we think may be related may be a prior exposure to chemical agents.
We don’t believe that there’s necessarily a genetic predisposition. But, there are patients who have hairy cell leukemia who tend to have a higher incidence of other forms of lymphoma and leukemia in their family. But, that is an area that’s not been well explored.

Lizette Figueroa-Rivera:
I’m glad that you mentioned the registry because somebody else is asking, is this something I need to worry about with my kids? Will my kids also get hairy cell leukemia?

Dr. Michael Grever:
We tell people that it’s very, very unlikely that this disease will be transmitted to children of the patients. While families may have an increased incidence of an underlying lymphoma or leukemia, this does not mean that the children of patients are going to have this disease by any means.

Lizette Figueroa-Rivera:
And I know that you published the guidelines for physicians, which is great. I do have somebody asking, do I need a hairy cell leukemia specialist or simply a leukemia doctor to help me manage my disease?

Dr. Michael Grever:
Most leukemia doctors can manage the disease. We get a lot of questions from excellent hematologists who are running into some of the difficult cases. So, we believe that many hematologists who treat leukemia are quite capable of taking care of hairy cell leukemia.

However, if they run into complications, it’s really important that the doctor consults with somebody who has extensive experience. We have identified about 25 different institutions across the globe where we get together with these investigators every year for the last nine years just to review progress and new ideas. So, if we have hematologists who are confronted with a difficult case, we are always willing and anxious to talk with them.

Lizette Figueroa-Rivera:
Great and thank you. And the next question is, what is the role of autologous or allogeneic stem cell transplant for a hairy cell leukemia patient?

Dr. Michael Grever:
Well, that is a good question. Very few patients with hairy cell leukemia have had a stem cell transplantation. Autologous transplantation has many potential problems. Because hairy cell leukemia is primarily a bone marrow disease autologous transplantation may result in reintroducing the leukemic cells into the patient.

In contrast, an allogeneic bone marrow transplantation would not result in transplantation of leukemic cells, but the majority of patients who have this disease have been successfully treated with either cladribine or pentostatin therapy. In patients who have had allogeneic bone marrow transplantations in the past, the majority of these patients were limited to younger patients. Since this is a disease that often effects older patients there’s not very much experience with the use of allogeneic bone marrow transplantation in this disease.

Fortunately, chemotherapy has resulted in successful achievement of a complete remission in most patients, therefore transplantation has not been required. The complications associated with allogeneic bone marrow transplantation would also be avoided by successfully treating the patient with chemotherapy rather than resorting to a stem cell transplantation.
Lizette Figueroa-Rivera:
Thank you, doctor. And since hairy cell leukemia is a chronic type of leukemia, usually the goal for treatment is to manage the disease, not to cure the disease. You did mention 40% will relapse. What about the other 60% or so?

Dr. Michael Grever:
Well, the other 60% may relapse as you get out beyond the ten-year interval. The other thing that happens to people is that they die from other causes. So, we think that the word “cure” here would be great if we could do it. But, we really put people into deep remissions. We don’t really cure the disease. We just control the disease.

We believe, if we can control the disease and keep people living as healthy as they were before they got leukemia that, even if there is some residual hairy cell leukemia in the bone marrow, it would be better to have them not compromise by adding extensive additional therapy to impact the function of the bone marrow and also to further immunosuppress them.

So, that’s why I always say it’s a challenge to make a decision about when you’re going to try and get rid of minimal residual disease and whether or not the cost of doing it, not the financial cost, but the cost in terms of the health of the patient, merit trying to eradicate the last residual leukemic cells. So, these are some of the unanswered questions.

We do believe that the more residual disease is left, the higher the chance for relapse. But, we’ve seen patients that have hairy cell leukemia in the bone marrow for years, and they’re living perfectly normal lives. So, it’s a judgment call about when you push to try and get rid of the residual disease. And there’s a lot of unanswered questions there.

Lizette Figueroa-Rivera:
And along the same lines, the next question is asking if it’s true that increased risk of infection is one of the leading causes of illness and death for patients with hairy cell leukemia.

Dr. Michael Grever:
Well, unfortunately that’s true. Most of the patients do well once they get into remission, but the initial time after being treated poses to some additional risk for opportunistic infections that are a result both of their disease related immunosuppression as well as the additional risks from the chemotherapy that are necessary to place the patient into remission. Therefore, they go through a period where their counts are lower before they get better. And so, up front there is additional risks for infection. And these risks have resulted in the death of some patients if the infection cannot be controlled.

This is one of the reasons why, if somebody’s actively infected, we are major proponents of using pentostatin because the intermittent administration allows you to titrate it so you try not to lower the neutrophil count too low. After people are in remission, most of the patients do pretty well. But, they do need to be followed, and anybody who develops an infection has to be seen and treated appropriately and quickly. We think that the long-term consequences can last for a year, and so, infection can still be a problem after people are in remission. But, it gets progressively better the longer they’re in remission.
Lizette Figueroa-Rivera:
And somebody is asking about long-term effects. They’re asking, do I need to worry about any long-term effects from treatment?

Dr. Michael Grever:
Well, there are long-term possible consequences from the treatment. In patients who receive chemotherapy you suppress the immune system, and this raises the risk of infection or the possibility of the development of a second malignancy. We follow patients carefully, and recommend that they be followed by a dermatologist to make sure that there’s no skin cancers that are developed. And they need to make sure that they follow the routine health screening recommendations like their colonoscopy according to the guidelines, and also making sure that they get mammograms on schedule and other annual physical examinations. While there is a risk of long-term side-effects from the therapy, these risks are certainly less than the risks of hairy cell leukemia being ineffectively treated. Patients with untreated hairy cell leukemia can also develop serious infections and are also at risk for the development of secondary malignancies. Therefore, the long-term risks from effective therapy are less than not effectively treating the hairy cell leukemia.

Lizette Figueroa-Rivera:
And the next question is asking, how long do I need follow up care after remission, and what tests should that be?

Dr. Michael Grever:
Well, we recommend for the first five years we follow patients pretty carefully. For the first two years after being in remission, we usually follow them at every two to three-month intervals because, even though we showed here results of people in long-term remission, there are people whose remission only lasts for a year or two. And if the relapse occurs relatively soon after the remission, then, it’s possible that the patient can still get back into another remission. But, we feel it’s important to follow them carefully every three months at least for the first two years. And then, after that we start to extend it out to every four months or every six months.

We initially do a bone marrow biopsy after we’re done. We don’t like to do it too soon though because, once you finish treatment, there can be some continual improvement for three or four months. And so, I know a lot of people recommend if you’re going to do a bone marrow after cladribine that you don’t do it too soon after you’ve completed therapy. But, after somebody’s in remission, you may want to wait three to four months before you do the bone marrow because there can be some continual improvement in their bone marrow picture.

So, we recommend waiting for a couple months afterwards to get the confirmatory bone marrow biopsy. With the pentostatin a lot of times, we use it to decide when we’re going to stop therapy. And so, we tend to get that a little bit earlier.

When we’re following patients though after they’re in remission, we get a CBC and differential and look underneath the microscope to make sure that there’s no circulating hairy cells and to make sure the infection fighting cells and the platelets are good. So, we get a blood count basically every three months on these patients after they’re in remission.

We have also followed some other aspects too. I mean, if there’s any chance that they might have previously been exposed to hepatitis, we follow their liver enzymes for a little while after completing therapy. And there
are other strategies that have been used to predict that somebody’s relapsing. But, the main way that we follow people is with their blood counts every three months.

Lizette Figueroa-Rivera:
Thank you. And what are the typical side effects of cladribine?

Dr. Michael Grever:
It’s usually pretty well tolerated. The biggest thing that we worry about is that it can lower the infection fighting cells. And most strategies for giving cladribine give it over five days to seven days. And there have been some studies where they give it once a week for five to six weeks. But, most of the time it’s given as a five to seven day treatment. And what happens when you give all the medicine all at once, then you don’t have to worry about coming back to get more treatment. But, you have to be followed very carefully because the bone marrows are sensitive at the initiation therapy. They’re usually very heavily infiltrated with the leukemic cells. And when you get all the treatment at once, the counts are going to be lower, and they can be lower for longer.

So, patients have to be evaluated very quickly and carefully if they developed a fever after being treated with either cladribine or pentostatin to ensure that they do not have an active infection that needs to be treated.

Lizette Figueroa-Rivera:
Sure, and do you find that most patients right now are on some kind of (Rituxan®) rituximab maintenance?

Dr. Michael Grever:
No, we don’t normally do (Rituxan®) rituximab maintenance. Dr. Rivandi has done some studies and several others have done studies using (Rituxan®) rituximab as part of the induction regimen. After they go into a complete remission, they may get four to eight cycles weekly rituximab. But then, they don’t continue to get rituximab for maintenance therapy, in general.

Lizette Figueroa-Rivera:
And somebody is asking about clinical trials. Since hairy cell leukemia is such a rare diagnosis, are there many clinical trials available or a lot of new treatments in the pipeline?

Dr. Michael Grever:
Well, there are new treatments in the pipeline. As I previously indicated there are questions that involve standard therapy as well as looking at new therapies. We’re trying to develop clinical trials that would address all of these questions. We’ve seen impressive results from the participation of patients in ongoing clinical trials. Because many patients do well with the treatment under their local hematologists some of the patients are not interested in enrolling in ongoing studies, however we believe that there’s still room for improvement and would encourage patients to at least consider participating in ongoing clinical trials.

One of the biggest studies that was randomized that I had the opportunity to perform back in the 90s was the randomization between interferon and pentostatin and that study we were able to accrue 356 patients in a little over three years. And one of the reasons it was so easy to accrue is because pentostatin was not commercially available. It was only available through the National Institutes of Health (NIH) study, National Cancer Institute sponsored study. And when access to new promising agents is only available in a study, it usually gets easier to get people to enroll.
So, as some of these newer drugs become available, like MEK inhibitors and some of the other strategies that may be more capable of inducing a uniform sustained remission, then maybe we’ll be able to get people more interested in participating in studies. We’re trying to put together a frontline study for patients who have active infection, and we’re trying to work through the Hairy Cell Leukemia Foundation to come up with a study to explore how we can treat patients who have an active infection yet need to have their leukemia treated. Right now, there’s a lot of studies that are being designed and usually they can be identified through the government clinical trial network.

Lizette Figueroa-Rivera:
Thank you. And our last question today, what can I do, what’s in my control to do to help ensure that I have a positive outcome? Anything I can do with nutrition, exercise, et cetera?

Dr. Michael Grever:
Well, we think exercise is helpful. It’s hard to really use a lot of evidence there to prove this.

Nutrition is hard because there are a number of individuals who want to boost the immune system by using nutritional strategies. And there’s not a lot of evidence in this rare disease of which approach would be supported by clinical evidence. So, this is another area that could be subject to important studies.

Lizette Figueroa-Rivera:
Sure, thank you. And that concludes the question and answer portion of our program. Thanks again to Dr. Grever for sharing his knowledge with us.

Dr. Michael Grever:
Thanks for your interest in this important disease.

Lizette Figueroa-Rivera:
Of course.
Closing Comments

The Leukemia & Lymphoma Society Offers:

- **Information Resource Center:** Information Specialists, who are master’s level oncology professionals, are available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - EMAIL: infocenter@LLS.org
  - TOLL-FREE PHONE: 1-800-955-4572

- **Free Education Booklets:**
  - www.LLS.org/booklets

- **Free Telephone/Web Programs:**
  - www.LLS.org/programs

- **Live, weekly Online Chats:**
  - www.LLS.org/chat

Lizette Figueroa-Rivera:
If you have additional questions, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. Information Specialists are available to speak with you from nine AM to nine PM Eastern time.
Or you can reach us by email at infocenter@LLS.org. We can provide information about treatment, including clinical trials, or answer other questions you may have about support, including questions about financial assistance for treatments.

The Leukemia & Lymphoma Society Offers:

• Support Resources: LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support

• LLS Podcast, The Bloodline with LLS: Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.LLS.org/thebloodline

• Education Video: Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

• Patti Robinson Kaufmann First Connection Program: Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

• Free Nutrition Consults: Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

• What to ask: Questions to ask your treatment team: www.LLS.org/whatask

The Leukemia & Lymphoma Society Offers:

Lizette Figueroa-Rivera:
LLS does have a copay assistance program to assist patients with financial support toward the cost of insurance copayments and/or insurance premium costs for prescription drugs. To learn more about our copay program and to see if funds are currently available for hairy cell leukemia, please visit www.LLS.org/copay.
Thank you:

We would like to thank and acknowledge AstraZeneca for their support of this program. On behalf of The Leukemia & Lymphoma Society, thank you for listening and we wish you well.